Strategies for Defibrillation during Out-of-Hospital Cardiac Arrest – A Randomized Clinical Trial

Acronym: STRAT-DEFI

TRIAL PROTOCOL

Version 1.3

November 28, 2025

ClinicalTrials.gov number: NCT06781892

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Content

Preface

The “Strategies for Defibrillation during Out-of-Hospital Cardiac Arrest - A Randomized Clinical Trial” (STRAT-DEFI) 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] and Danish regulations[2]. The protocol was created in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[3,4] Bertram Lahn Kirkegaard, Mikael Fink Vallentin, and Lars W. Andersen initiated the trial and 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. The protocol generally describes procedures for the trial in Denmark. Any deviations from these general procedures used in other countries are described in appendices.

Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc. November 28, 2025

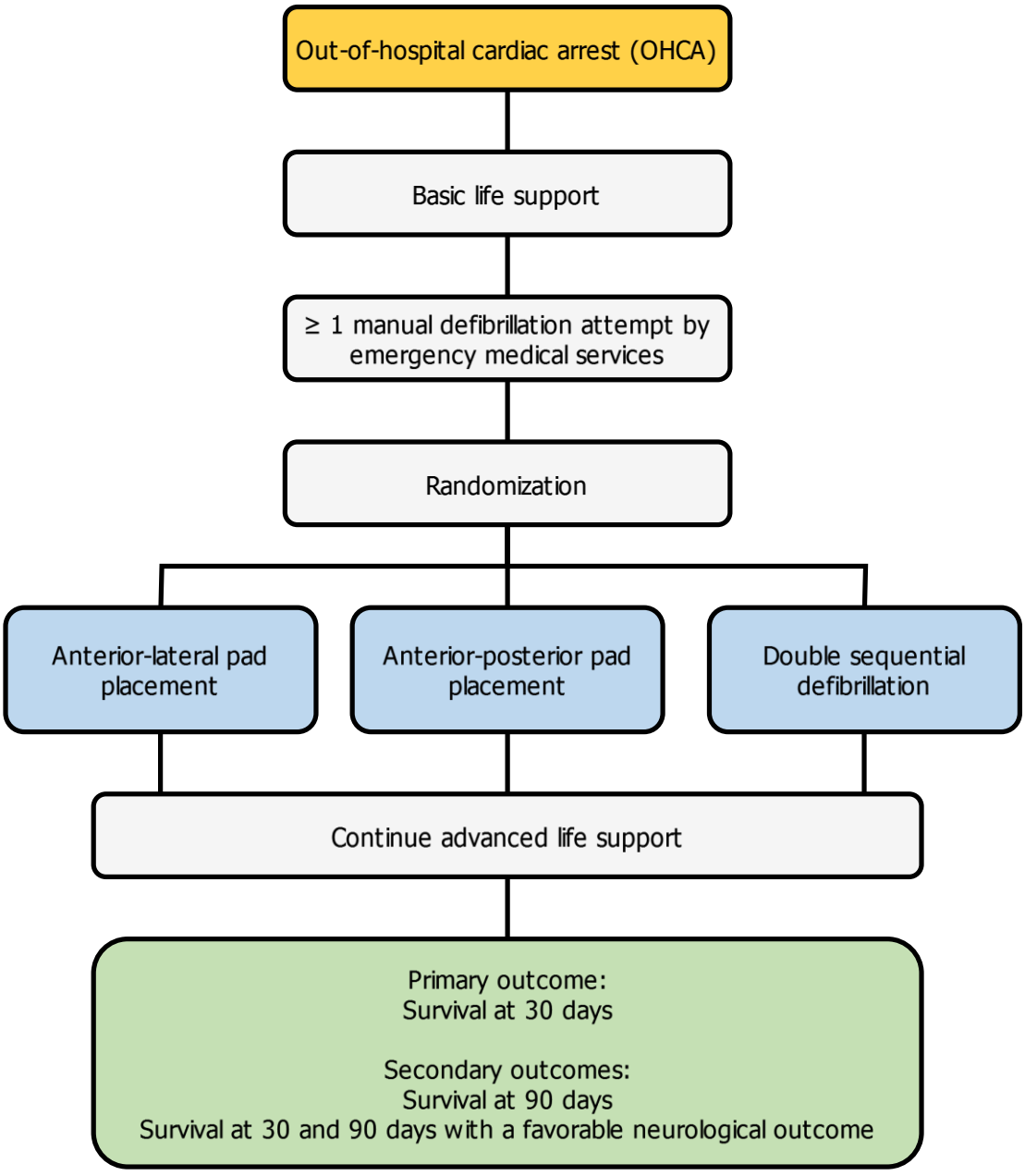
List of abbreviations

AED:	Automated external defibrillator
CONSORT:	Consolidated Standards of Reporting Trials
COSCA:	Core Outcome Set for Cardiac Arrest
CPC:	Cerebral performance category
EMS:	Emergency medical services
ERC:	European Resuscitation Council
ILCOR:	International Liaison Committee on Resuscitation
mRS:	modified Rankin Scale
OHCA:	Out-of-hospital cardiac arrest
pVT:	Pulseless ventricular tachycardia
REDCap:	Research Electronic Data Capture
ROSC:	Return of spontaneous circulation
SPIRIT:	Standard Protocol Items: Recommendations for Interventional Trials
VF:	Ventricular fibrillation

Overview

Registry and trial number	ClinicalTrials.gov number: NCT06781892
Date of registration	ClinicalTrials.gov: 14/01/2025
Funding	The Independent Research Fund Denmark, Novo Nordisk Foundation, Danish Heart Foundation
Sponsor	Lars W. Andersen, Aarhus University
Contact	Lars W. Andersen, lwandersen@clin.au.dk
Title	Strategies for Defibrillation during Out-of-Hospital Cardiac Arrest - A Randomized Clinical Trial
Countries of recruitment	Denmark, Finland, and Belgium
Condition studied	Out-of-hospital cardiac arrest
Intervention	Anterior-posterior pad placement or double sequential defibrillation
Comparator	Anterior-lateral pad placement
Inclusion criteria	1) Out-of-hospital cardiac arrest 2) Age ≥ 18 years 3) ≥ 1 defibrillation attempt by emergency medical services 4) Shockable rhythm as the last known rhythm 5) Two manual defibrillators present on-site
Exclusion criteria	1) Blunt trauma, penetrating trauma, or burn injury suspected to be the cause of the cardiac arrest 2) Prior enrollment in the trial 3) Posterior pad placement not deemed possible by on-site clinician
Study type	Interventional Allocation: Randomized (1:1:1) Intervention model: Parallel group Masking: Patients and certain outcome assessors will be blinded
Date of first screening	To be added
Target sample size	909
Recruitment status	Not yet recruiting
Primary outcome	Survival at 30 days
Key secondary outcome	Survival at 30 and 90 days with a favorable neurological outcome (modified Rankin Scale of 0-3), survival at 90 days

Trial flow chart



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Conflicts of interest

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

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Additional sites will be added in a later version

Ireland

To be added in a later version.

Amendments

Version 1.0 to 1.1

- Added the names of the initiators (Preface)
- Added details for the data collection process (section 7.2.1 and 7.5).
- Clarified the reason for why the Utstein data variables were chosen for data collection and disclosure details. (section 7.2.1).
- Added details regarding consent procedures (section 9.3.2).
- Added a section 9.3.3 describing procedures for when a patient dies prior to obtainment of any consent
- Added funding amount from each funding agency (section 14).

Version 1.1 to 1.2

- Corrected error in overview.
- Updated figure 1.
- Removed name of investigator (section 3.1).
- Added details regarding energy settings of the defibrillator (section 3.3.3).
- Changed the wording of the data access section to clarify what access is granted after consent is obtained (section 7.2.1).
- Added research ethical committee number to appendix 6.

Version 1.2 to 1.3

- Added ClinicalTrials.gov registration number and date (Front page)
- Added additional investigators to the steering committee (Steering committee)
- Added details regarding sites in Finland and Belgium (Sites)
- Added Ireland as a country for sites (Sites)
- Removed the word manual from inclusion criteria #3 (Section 4.2)
- Added details regarding the sample size (Section 6.1)
- Added information regarding a new grant. (Section 14)
- Updated Conflict of interest disclosures (Appendix 1)
- Added the international appendix (Appendix 3)

1. BACKGROUND

1.1 Out-of-hospital cardiac arrest

1.1.1 Incidence and mortality

Out-of-hospital cardiac arrest (OHCA) occurs in an estimated 4 million people each year globally of which approximately 5000 are in Denmark.[5,6] OHCA is a detrimental condition with only approximately 15% being alive after 30 days in Denmark.[5,7] Twenty percent of cardiac arrest patients have an initial shockable rhythm (i.e., ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT)). These patients have higher rates of survival compared to patients with an initial non-shockable rhythm (i.e., asystole or pulseless electrical activity).[8] However, approximately 75% of patients with a shockable rhythm do not respond to initial defibrillation and these patients are unlikely to survive.[9,10] In our previous and ongoing trials in Denmark,[11,12] patients with out-of-hospital cardiac arrest who did not respond to the initial defibrillation attempt by emergency medical services (EMS) only had a 20% chance of surviving to 30 days.

1.1.2 Pathophysiology

In broad terms, cardiac arrest can be divided into two phases: intra-cardiac arrest and post-cardiac arrest, where intra-cardiac arrest can be further divided into a no-flow (no circulation) and a low-flow (circulation induced by chest compressions) phase. One of the main drivers of poor outcomes after cardiac arrest is the duration of the intra-cardiac arrest phase (i.e., no-flow and low-flow time); for each minute increase in the length of the cardiac arrest, mortality substantially increases.[13,14] Because of this, and since return of spontaneous circulation (ROSC) is a prerequisite for long-term survival, the main goal of intra-cardiac arrest interventions is to establish ROSC and limit the duration of the cardiac arrest.

The pathophysiology of cardiac arrest and the post-cardiac arrest syndrome is complex and have been described in extensive detail elsewhere.[15-17] 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.[15] Consequently, this leads to a clinical state with potential global brain injury, impaired myocardial function, hemodynamic instability, and increased susceptibility to infections known as the "post-cardiac arrest syndrome".[15]

1.2 Defibrillation during cardiac arrest

1.2.1 Electrophysiology

VF is a malignant arrhythmia involving the ventricular myocardial tissue. Unorganized electrical activity results in insufficient contractions of the heart and thus no circulation. The underlying pathologies that cause VF are numerous and include ischemic heart disease, cardiomyopathies, and electrolyte disorders.[18]

The initial mechanisms related to sustained VF were first conceptualized by Wiggers in 1940 and has been refined throughout the 20th century,[19] though they are still not clearly understood. Several theories have been proposed, but no clear consensus exist regarding the mechanisms for initiation and maintenance of the electric pattern of VF.[20-22]

The effect of defibrillation is believed to be mediated by a change in myocardial transmembrane potential, hereby stunning the tissue and making it unexcitable and thus eliminating the unorganized electric pattern of VF. Defibrillation characteristics, such as waveforms (i.e., monophasic or biphasic), energy used, and transthoracic impedance, have all been shown to play a role in the success of defibrillation.[23,24] Animal models have demonstrated that failed defibrillation attempts may alter the electric pattern that maintains VF.[21]

Two different presentations are possible when a defibrillation attempt fails in a cardiac arrest setting: recurrent or refractory VF. Observational data have shown that up to 90% of patients respond to initial defibrillation but approximately 75% of these patients experience refibrillation (i.e., recurrent VF). True shock-refractory VF is thus less common. It is virtually impossible to distinguish between the two during a cardiac arrest as the cardiac rhythm is only analyzed every other minute.[9,25-27] In clinical practice, the term ”refractory VF” is therefore used for both refractory and recurrent VF and is often operationalized as continued VF after a given number of shocks (e.g., after 3 shocks).

The second shockable rhythm is pVT, which is much rarer than VF. Data from our research group’s previous out-of-hospital cardiac arrest trial found that 2% of the initial rhythms were pVT, corresponding to 9% of those with a shockable rhythm.[12] Recent data suggest that most patients with pVT respond to initial shocks making it less likely to become a refractory shockable rhythm.[28]

1.2.2 The history of defibrillation

The first description of the potential for affecting the heart using electric shocks was made in 1899; Jean-Louis Prévost and Frédéric Batelli found that small electric shocks induced ventricular fibrillation in dogs and larger shocks restored the heart to a normal rhythm. During the early 20th century, the concept of using electric shocks to alter the cardiac rhythm was explored further. The defibrillator, as we know it today, was developed by William Kouwenhoven in 1930, and the first use in humans was performed by Claude Beck in 1947. The

defibrillator continued to undergo development that made it more practical for clinical use and it has since become an essential tool in resuscitation.[29]

The electric current used in defibrillators has evolved over time. The waveform used in early defibrillators had a monophasic pattern. In the late 20th century, a biphasic waveform was found to be more effective and is being used today.[29-31]

1.2.3 Pad placement

There is a lack of evidence regarding which pad placement during resuscitative defibrillation is the most effective. The most detailed descriptions and theories for mechanisms originate from atrial fibrillation cardioversion studies. One theory is that the difference in pad placement mediates better conversion rates because of the amount of cardiac tissue that is being shocked.[32] Additionally, some believe the mechanism to be dependent on which angle you shock the atrial tissue from.[32] Systematic reviews of the efficacy of pad placement in atrial fibrillation/flutter cardioversion have found that anterior-lateral pad placement is more effective than anterior-posterior pad placement.[33,34] The transferability from atrial cardioversion to shockable rhythms in cardiac arrest is unclear.

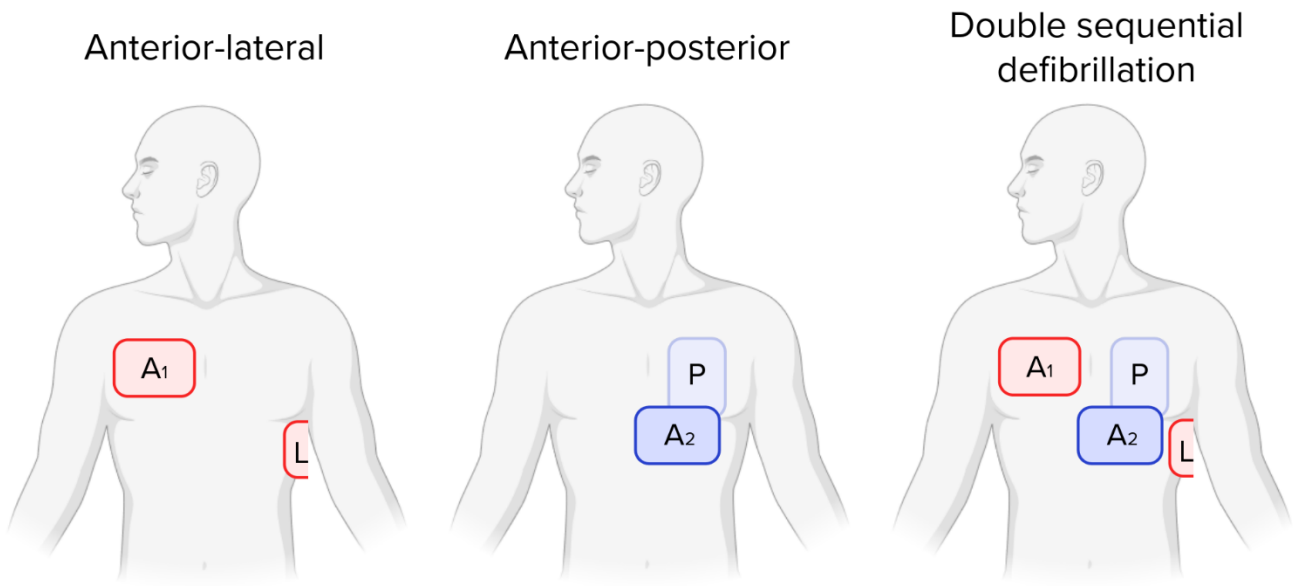


Figure 1: Defibrillator pad placements (created with BioRender.com)

1.2.4 Double sequential defibrillation

Double sequential defibrillation is a defibrillation strategy, where patients are shocked two times in immediate succession with pads placed anterior-lateral and anterior-posterior using two separate defibrillators.
This technique was first reported to be effective in patients with refractory VF in 1994.[35] The mechanism is unclear, but it is hypothesized that the increase in total energy applied to the myocardium leads to higher conversion rates. Another theory is that the first shock acts as a conditioning shock, altering the electric pattern of VF such that the second shock becomes more efficient.[36,37] The two shocks from different angles could also increase the probability for the electric vector to have the most ideal angle.

1.3 Current evidence regarding pad placement in cardiac arrest

1.3.1 Randomized clinical trials

There is only one randomized clinical trial comparing different pad placements for defibrillation in out-of-hospital cardiac arrest. The Defibrillation Strategies for Refractory Ventricular Fibrillation (DOSE-VF) trial included patients with refractory VF, defined as 3 failed defibrillation attempts, and compared anterior-lateral positioning (the standard approach) with anterior-posterior positioning, and double sequential defibrillation. The trial was stopped early after inclusion of 405 patients of the planned 930. The results were striking, with only 13% surviving to hospital discharge in the standard anterior-lateral group, while 22% survived to discharge in the anterior-posterior group, resulting in a relative risk of 1.71 (95% CI, 1.01 ; 2.88) and 30% survived to discharge in the double sequential defibrillation group, with a relative risk of 2.21 (95% CI, 1.33 ; 3.67).[36]
Because of numerous limitations, the trial results have been met with skeptisms. First, the trial was stopped early, which may lead to overestimation of effect sizes.[38] Second, the trial was cluster-randomized without allocation concealment, which could result in important bias.[39] Third, the trial was relatively small resulting in large uncertainty in the results. Fourth, survival in the standard anterior-lateral group was lower than reported in similar populations, thus making generalizability unclear.[36]

1.3.2 Observational studies

An observational before and after study from the Unites States comparing 1020 anterior-lateral shocks and 1023 anterior-posterior shocks during OHCA, found similar conversion rates for the two groups.[40] A recent observational study from the United States found a higher proportion of patients with ROSC when anterior-posterior pad placement was used as compared to anterior-lateral pas placement as the initial strategi for OHCA.[41] There was no statistically significant difference in survival to hospital discharge.[41]

Multiple case-series have reported the use of double sequential defibrillation. Evidence from these studies is of very low quality and thus cannot be used to determine the causal effect of this defibrillation strategy.[42,43]

In patients with refractory VF treated with double sequential defibrillation, the timing of the shocks administered is associated with the probability of achieving ROSC. A retrospective cohort study, using data in part from the DOSE-VF trial, investigated the optimal timing of the shocks delivered when using double sequential defibrillation.[44] The study reported an association between shock intervals <75 milliseconds and rates of termination of VF and ROSC. The evidence from this study is deemed to be of low quality due to serious limitations, such as the observational study design and very few patients included.

A survey aimed to investigate potential defibrillator equipment damage when using double defibrillation and found an incidence between 0.1% and 0.2% in an estimated 1130 cases, with between 2260 and 4520 shocks. The survey only reported damage when using the simultaneous technique, while there were no incidents reported for the sequential technique.[45]

1.4 Current guidelines

Defibrillation is a cornerstone in the treatment of cardiac arrest patients with a shockable rhythm and is recommended as soon as possible after a shockable rhythm is recognized. The European Resuscitation Council (ERC) guidelines recommend that the initial pad placement for adults with cardiac arrest is anterior-lateral.[46] The anterior pad must be placed to the right of the sternum and below the clavicle. The lateral pad is placed in the mid-axillary line in level with the bottom of the pectoralis muscle for men, and below the breast for women. The lateral pad must be placed sufficiently lateral to clear breast tissue and remain under the armpit.

ERC guidelines recommend checking for correct pad placement when defibrillation is performed, as well as to consider an alternate pad placement, e.g. anterior-posterior for refractory VF.[46] The current 2021 ERC Adult Advanced Life Support guidelines states that double sequential defibrillation should not be used outside of a research setting in patients with recurring or refractory VF.[46]

The 2023 International Liaison Committee on Resuscitation (ILCOR) treatment recommendations state that double sequential defibrillation may be considered when VF or pulseless ventricular tachycardia remains present after ≥ 3 consecutive shocks (weak recommendation, low certainty of evidence). A single operator approach is recommended.[47] Recent ILCOR recommendations state that it is essential to ensure proper pad placement before considering a change to double sequential defibrillation or an anterior-posterior pad position.[48]

American guidelines states that both anterior-lateral and anterior-posterior are viable options for pad placements.[49]

1.5 Current practice

National and regional Danish out-of-hospital guidelines do not recommend either anterior-posterior or double sequential defibrillation.

From previous and ongoing trials conducted by our group, no reports have been made of anterior-posterior or a double sequential defibrillation strategy in out-of-hospital cardiac arrests in Denmark.[11,12] Similarly, neither anterior-posterior pad placement nor double sequential defibrillation are routinely used in any other participating country.

1.6 Standard of care

The participating sites' standard of care protocols during adult cardiac arrest follow the guidelines of the ERC.[46,50,51] Defibrillator pads must be placed as soon as possible without pausing chest compressions. The initial recommended pad placement is anterior-lateral, while ensuring that the lateral pad is placed correctly below the armpit. The precharge method for defibrillation is used in Denmark. In the precharge algorithm, the defibrillator is charged prior to all rhythm checks, and a shock is delivered immediately if a shockable rhythm is recognized.[52]

All included patients in this trial will – apart from patients allocated to anterior-posterior and double sequential defibrillation – receive the established basic and advanced life support standard of care.

2. TRIAL OBJECTIVES AND HYPOTHESES

The objective of the current trial is to determine whether there is a difference in outcomes depending on the type of defibrillation strategy used in adult OHCA with a refractory shockable rhythm. The specific objectives are:

1) To determine whether there is a difference in outcomes when using anterior-posterior defibrillation as compared to standard anterior-lateral defibrillation in adult OHCA with a refractory shockable rhythm.

2) To determine whether there is a difference in outcomes when using double sequential defibrillation as compared to standard anterior-lateral defibrillation in adult OHCA with a refractory shockable rhythm.

The outcomes include survival at 30 and 90 days and survival with a favorable neurological outcome at 30 and 90 days (see section 5 for details).

Hypotheses:

1) We hypothesize that anterior-posterior defibrillation, in adult OHCA with a refractory shockable rhythm, will result in improved outcomes compared to standard anterior-lateral defibrillation.

2) We hypothesize that double sequential defibrillation, in adult OHCA with a refractory shockable rhythm, will result in improved outcomes compared to standard anterior-lateral defibrillation.

3. TRIAL DESIGN

3.1 Overview

The “Strategies for Defibrillation during Out-of-Hospital Cardiac Arrest” (STRAT-DEFI) trial is an investigator-initiated, individually randomized, 3-group clinical trial comparing standard anterior-lateral pad positioning with anterior-posterior positioning and double sequential defibrillation during adult out-of-hospital cardiac arrest. The trial will primarily be conducted in Denmark with additional participation from international sites.

The primary outcome will be survival at 30 days, and 909 patients will be included. The key secondary outcomes will be survival at 90 days and neurological outcomes at 30 and 90 days. Additional outcomes will include sustained ROSC, survival and neurological outcome at 180 and 365 days, as well as health-related quality of life at 30, 90, 180, and 365 days.

3.2 Allocation

Patients will be randomized to one of three defibrillation strategies, in a 1:1:1 ratio using blocks of 12, stratified by country. An independent statistician will create the randomized allocation list using a random number generator. The list will be shared exclusively with the personnel responsible for preparing the randomization envelopes, who will not be involved in clinical care or outcome assessment. As described in section 3.3 and section 3.4, stations where participating prehospital personnel can refill defibrillation equipment (henceforth “stations”) will be provided with continuously numbered opaque envelopes containing the allocation. These envelopes will be opened on site of the cardiac arrest when the patient is deemed to fulfill all inclusion criteria and none of the exclusion criteria, thus ensuring allocation concealment.

3.3 Interventions

3.3.1 Anterior-lateral defibrillation

At time of randomization, pads will be placed in the anterior-lateral position, as this is the current standard of care. Patients randomized to anterior-lateral pad placement must adhere to this strategy for all defibrillation attempts.

3.3.2 Anterior-posterior defibrillation

The intervention will alter the defibrillation pad placement from anterior-lateral to anterior-posterior. After randomization and as soon as possible, new defibrillation pads will be placed on the patient in the anterior-posterior position (see Figure 1). The posterior pad must be placed to the left of the thoracic spine and below

the spine of the scapula. To avoid interruptions in chest compressions, the pads can be placed when ventilations are performed.

After correct placement of the defibrillation pads in the anterior-posterior position, the prehospital personnel will use this pad placement for all subsequent defibrillation attempts. In the event of prehospital re-arrest after ROSC, the prehospital personnel will continue using the anterior-posterior pad placement for any additional defibrillation attempts.

3.3.3 Double sequential defibrillation

The intervention will alter the defibrillation method from single-shock anterior-lateral to double sequential defibrillation. As soon as possible after randomization, a second set of defibrillation pads will be placed in the anterior-posterior (section 3.3.2) position in addition to the original anterior-lateral position (section 3.3.1, Figure 1). When delivering the shocks, the two defibrillators must be operated by the same clinician. The second defibrillator's shock energy setting should be set corresponding to the joule amount given at maximum escalation. The shocks are administered separately but sequentially, ideally as close to each other as possible. The order in which the defibrillators are triggered is not protocolized.

After correct placement of the defibrillation pads in the anterior-posterior position, the prehospital personnel will use double sequential defibrillations for all subsequent defibrillation attempts. In the event of prehospital re-arrest after ROSC, the prehospital personnel will continue using double sequential defibrillation for any additional defibrillation attempts. If the patient is transported during the cardiac arrest, and it is not possible to transport the patient with two defibrillators, double sequential defibrillation will no longer be used. In this case, additional defibrillation attempts will be performed using the anterior-posterior pads.

3.3.4 Procedures

Specific trial materials in the prehospital clinician's equipment will be limited to a single opaque envelope for trial randomization. Once the patient meets all inclusion criteria and none of the exclusion criteria, the randomization envelope will be opened. Once opened, the patient is considered randomized. The note inside the envelope contains the unique trial ID along with the allocation (anterior-lateral, anterior-posterior, or double sequential defibrillation). We estimate that the randomization procedure will take approximately 5-10 seconds. The clinical team will then prepare the allocated defibrillation method, ideally before the next rhythm check. After the patient is randomized and the allocated pad placement has been prepared, it is required that at least one rhythm check is made, and a shock delivered if applicable. All manual defibrillators irrespective of the manufacturer may be used to deliver the intervention.

3.3.5 Randomization envelopes

Randomization envelopes will be prepared and packed by personnel independent of the trial, based on a randomization list made by an independent statistician. Only the independent statistician and these personnel will keep a copy of the randomization list during trial inclusion, thus ensuring allocation concealment for the trial's investigators and clinicians. The packed randomization envelopes will be sent to the coordinating investigator. The independent statistician will provide the allocation for 10 of the produced envelopes selected by a random number generator, and the coordinating investigator will open these envelopes to check that the inside text match the provided allocations. The remaining envelopes will then be stored centrally in a safe and locked location. From here, they will be shipped to participating stations based on their current tally and inclusion rate. A person appointed by the site investigator will oversee each station's setup and tally, and any problems will be referred to the coordinating investigator. Each participating clinician will obtain a new randomization envelope directly from the station when relevant. Each envelope's exterior will be clearly marked with trial name, a phone number, and the unique randomization ID (see Appendix 2). The inside paper slip will present the allocation both in text and visually.

3.3.6 Protocol deviations

Protocol deviations are entered into the database and will be handled on a case-by-case basis. This involves informing the sponsor as well as the relevant clinicians by e-mail. If deemed relevant, clinicians will be asked to review trial information including trial procedures.

3.4 Blinding

Due to the nature of the intervention, the clinicians performing the intervention cannot be blinded. Patients, along with any legally designated representatives, will be blinded. Prehospital personnel will be informed not to note the patient's allocation in the patient's in-hospital medical records, thus maximizing the likelihood of blinding of the in-hospital clinical personnel. Investigators involved in data entry will not be blinded meaning that outcomes such as survival are entered without blinding. There is little – if any – subjectivity in evaluating these outcomes and blinding is therefore of minor importance. Outcome assessors performing the follow-up interviews will be blinded as this involves outcomes with some degree of subjectivity.

A patient, or alternatively the consenting legally designated representatives, will not be informed of the allocation until the end of follow-up and only if indicated on the consent form.

3.5 Trial procedures

3.5.1 Patients

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

3.5.2 Clinical personnel

Clinical personnel involved in the inclusion and randomization of patients will be prehospital physicians, prehospital physician assistants, and paramedics. Other emergency medical services personnel can have the randomization task delegated during the cardiac arrest, but they will not be involved in the decision to include a patient.

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the participating clinicians (see section 4.1) will be informed and educated about the trial. This includes information about the trial's background, objectives, inclusion and exclusion criteria, interventions, and trial specific procedures (see section 3.3 and section 9.3.2). A demonstration of the correct procedures will be included, and in-person simulation training will be provided continuously when possible.

4. SETTING AND PATIENT POPULATION

4.1 Setting

The trial will be conducted in all five Danish regions and at additional international sites.

In Denmark, cardiac arrests are generally attended by a primary ambulance and a physician-manned unit.[53,54] The primary ambulance is manned by emergency medical technician assistants, emergency medical technicians, and/or paramedics. The physician-manned unit can be a car or helicopter and includes a board-certified anesthesiologist and a physician assistant. In rare cases, if the physician-manned unit is not available, an independent paramedic in a rapid response vehicle will attend the cardiac arrest as the second unit.

The setting for other countries is described in Appendix 3.

4.2 Inclusion criteria

Inclusion criteria:

1) Out-of-hospital cardiac arrest
2) Age ≥ 18 years
3) ≥ 1 defibrillation attempt by emergency medical services
4) Shockable rhythm as the last known rhythm
5) Two manual defibrillators present on-site

Cardiac arrest is defined as unconsciousness, abnormal breathing, and a loss of pulses requiring chest compressions and/or defibrillation.

OHCA is defined as any individual with a cardiac arrest where the prehospital system is activated. The trial will only include patients deemed or known by the prehospital clinicians to be 18 years or above, as pediatric OHCA is vastly different on several parameters including etiology, basic life support algorithm, guidelines for defibrillation energy, drug-dosing, and research ethics.[55]

At least one defibrillation attempt must be made by emergency medical services. Emergency medical services include all ambulance personnel, paramedics, and prehospital physicians. Shockable rhythms include VF or pVT, as determined by prehospital personnel, by a manual defibrillator analysis or a shock recommended and provided, when using the automated external defibrillator mode of the defibrillator. This inclusion criterion ensures that a verified shockable rhythm is present, and a standard shock has been administered correctly.

The underlying rhythm during chest compressions after a defibrillation attempt is not known to the personnel managing the cardiac arrest. Therefore, the last known rhythm will be assumed to still be present

during the subsequent cardiopulmonary resuscitation period. This will enable patients to be randomized, and for the intervention to be prepared, before the next rhythm check.

Two manual defibrillators must be present on-site for a patient to be included. This is to ensure that all three interventions can be performed at the time of randomization.

4.3 Exclusion criteria

Exclusion criteria:

1) Blunt trauma, penetrating trauma, or burn injury suspected to be the cause of the cardiac arrest
2) Prior enrollment in the trial
3) Posterior pad placement not deemed possible by on-site clinician

OHCA caused by blunt trauma, penetrating trauma, or burn injury will be excluded, because the patient population and the pathophysiology are vastly different from those of non-traumatic OHCA. Cardiac arrests caused by drowning, hanging, strangulation, and foreign body airway obstruction will not be excluded.

Patients previously included in the trial will be excluded to avoid statistical complexity related to correlated data. Since this is documented (but might not be known by the cardiac arrest team) prior to the cardiac arrest and the intervention, any post-randomization exclusions will not lead to bias.[56]

The posterior pad placement in both the anterior-posterior and the double sequential defibrillation arm of the trial, requires that the patient is turned or rotated. This may be impossible, e.g. due to patient size, location of the cardiac arrest, or available personnel. If this is the case prior to randomization, the patients will not be included.

The trial will not exclude females of childbearing age, nor will it exclude females with known or strong suspicion of pregnancy, as the trial does not introduce any additional teratogenic risk. International guidelines do not recommend a different approach to defibrillation in maternal cardiac arrest.[57]. Maternal cardiac arrest is exceedingly rare, with a British study estimating 1 in 36,000 maternities.[58] During two previous trials conducted by the research group none of the 5,839 OHCA patients assessed were pregnant.[11,12]

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.[59]

5. OUTCOMES

5.1 Primary outcome

5.1.1 Definition

The primary outcome will be survival at 30 days. Time point zero for this outcome will be time of sustained ROSC. In cases where extracorporeal circulation is initiated prior to sustained ROSC, time of established extracorporeal circulation will define time point zero.

5.1.2 Rationale

30-day survival after cardiac arrest is regarded as a meaningful outcome internationally and is highly valued by both clinicians and patients. This measurement is linked to long-term survival and the majority of 30-day survivors have a favorable functional outcome after one year.[60] Survival is an objective core outcome where missing data is rare.[11,12,61] Survival will be collected from electronic medical records or telephone follow-up.

5.2 Secondary outcomes

5.2.1 Definitions

The key secondary outcomes will be survival at 90 days and neurological outcome at 30 and 90 days. Neurological outcome will be assessed with the modified Rankin Scale (mRS, Table 1); scores 0-6 will be presented as counts and percentages, while the outcome will be dichotomized as favorable (mRS 0-3) vs. unfavorable (mRS 4-6).

Table 1. modified Rankin Scale (mRS)[62]

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 and 90 days with a favorable neurological outcome are considered key outcome measures in cardiac arrest research.[63] All follow-up data will be obtained from electronic medical records, the Danish Central Personal Register (Danish patients), and telephone follow-up interviews, which allows for accurate and virtually complete follow-up.[64]

A trained, blinded researcher will assess mRS using a standardized telephone interview, which ensures good reliability.[65-67] The dichotomy with favorable at 0-3 and unfavorable at 4-6 is widely used in cardiac arrest research.[11,12,68] In case the patient is still hospitalized, the interview can be conducted face-to-face. Assessment of neurological outcome by telephone is valid and reliable.[69] If the patient is not able to participate in the interview, the interview will be conducted with a close relative or secondarily with clinical personnel if the patient is admitted. The same standardized interview will be used.

In accordance with the Core Outcome Set for Cardiac Arrest (COSCA)-initiative, we will also assess the Cerebral Performance Category (CPC).[61] CPC will not be considered a key outcome of neurological status.

Survival at 90 days was chosen since it is unlikely that later mortality will be directly linked to the cardiac arrest or the trial intervention. The outcomes assessed at 90 days are also consistent with recommendations from the American Heart Association.[70]

5.3 Other outcomes

Other outcomes include any ROSC, ROSC at hospital arrival, sustained ROSC, health-related quality of life, and hospital disposition.

ROSC is defined as a palpable pulse or other signs of circulation without a need for chest compressions, and sustained means that ROSC is maintained for at least 20 minutes. The on-site clinician will decide if ROSC is present. If a patient is placed on extracorporeal circulation during the cardiac arrest and before reaching the aforementioned criteria, the patient will only be considered to have achieved ROSC if the criteria are reached after weaning from the extracorporeal circulation.

Health-related quality of life will be assessed by the questionnaire EQ-5D-5L,[71] which is supported by the American Heart Association as well as the COSCA-initiative.[61,70] EQ-5D-5L is a generic approach with five items covering symptomatic, physical, psychological, and social consequences of a disease. It is preferred to the McMaster Health Utilities Index Mark 3 and Short Form 36 because it is free to use and requires a shorter interview. Assessment of health-related quality of life by telephone is valid and reliable.[72] If the patient is not able to participate in the interview, the interview will be conducted with a close relative or secondarily with

clinical personnel in case of hospitalization. The same standardized interview will be used. EQ-5D-5L allows for potential future cost-effectiveness analyses and comparison to the background population.

In addition to the above, we will collect outcome data on hospital disposition. Hospital disposition (e.g., home or rehabilitation) will be defined at the time of discharge from an acute care hospital.

The primary trial and publication will be related to the trial outcomes after 30 and 90-days (see section 5.1, 5.2, and 5.3). However, extended follow-up at 180 days and 1 year, including overall survival, neurological outcomes, and health-related quality of life, will be collected and reported. Data will be collected and analyzed similarly to the 90-day outcomes but will be reported in a separate publication. Although the overall trial results will be published after the collection of the 90-day outcomes, the person(s) assessing 180-day and 1-year outcomes will remain blinded to the allocation.

5.4 Harm

5.4.1 General consideration

Patients with OHCA included in this trial have an expected mortality rate of approximately 70-80% in the first 30 days,[5] and survivors will in the adjacent time risk complications such as brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[15] Furthermore, OHCA patients have a high prevalence of pre-cardiac arrest morbidity with cardio- and cerebrovascular disease as well as chronic obstructive lung disease, diabetes, and psychiatric disease.[73] The immediately preceding cause may be circulatory failure (e.g. due to coronary heart disease, primary arrhythmia, pulmonary embolism, or hypovolemia), respiratory failure (e.g. due to a medical cause, drowning, or asphyxia), or more rarely neurologic disorders.[68] Given this, it is difficult, if not impossible, to comprehensively report all adverse events and assess their possible relationship with the intervention.

Administration of a shock by a defibrillator is a common procedure which is considered safe and is used routinely in patients with cardiac arrest and atrial fibrillation. Atrial fibrillation guidelines state that cardioversion using defibrillation may result in minor skin burns to the patient, while no other patient safety concerns are mentioned.[74] The current trial will evaluate the potential impact of alternative defibrillation strategies. The overall benefit and potential harm will be captured in our primary and secondary outcomes. Specific adverse events that could be related to the intervention, such as defibrillator damage and accidental shocks to someone other than the patient, will be documented.

5.4.2 Definitions

The following definitions[75] will be used for patients who received one of the trial's interventions:

Adverse event: any untoward medical occurrence which may or may not have suspected causal relationship with one of the trial's interventions but through available literature and/or safety information may be associated with one of the trial's interventions.

Serious adverse event: any untoward medical occurrence which may or may not have a suspected causal relationship with the intervention but through available literature and/or safety information may be associated with one of the trial's interventions – additionally, the occurrence must require either inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Unexpected adverse reaction: any untoward medical occurrence not included in the specific adverse event list and where a clinician suspects an association with one of the trial's interventions.

Unexpected serious adverse reaction: any untoward medical occurrence not included in the specific adverse event list and where a clinician suspects an association with one of the trial's interventions – additionally, the occurrence must require either inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

5.4.3 Data entry on adverse events and adverse reactions

Based on the available literature and safety information, we will define specific adverse events, which will be a part of the data entry for any included patient (see section 5.4.4). Data on other potential adverse events or serious adverse events will only be collected if a clinician suspects an event is associated with one of the trial's interventions (i.e., the event is a reaction).

5.4.4 Specific adverse events

Specific adverse events for the interventions will be defibrillator damage and accidental shock to anyone except the patient. Data on specific adverse events will be entered for all included patients no matter the allocated intervention. Assessment of specific adverse events will be based on available medical records and direct reports from the clinical personnel.

Chosen specific adverse events are based on the literature provided in section 5.4.5 and section 5.4.6.

5.4.5 Defibrillator damage

Damage to the defibrillation equipment is a theoretical concern with double sequential defibrillation. Data on the incidence of damage to equipment in cardiac arrest treatment are sparse. A study found low incidence rates of damage to defibrillators (0.1% - 0.2%) and damage have only been reported when using double simultaneous defibrillation, while there were no reported events for double sequential defibrillation.[45] A recent study, comparing single to dual cardioversion in atrial fibrillation, reported no damage to defibrillators when using a synchronized dual shock method.[76] We therefore consider this risk minimal, but will record any defibrillator damage during the cardiac arrest.

5.4.6 Accidental shock to a person other than the patient

Defibrillation attempts pose a small risk of harm to the EMS personnel delivering the shock. The frequency of this is reported to be very low (1 of 1700 shocks in one study).[77] Reports of simulated hands-on defibrillation with continued cardiopulmonary resuscitation while wearing plastic gloves, have shown no harm to personnel when in contact with the patient being shocked.[78] A potential increase in risk might arise from the increased handling of defibrillation pads in the trial interventional arms and the very small prolongation of defibrillation time when performing double sequential defibrillation. The same safety measures apply in this trial as in standard settings, where no persons are allowed to touch the patient during defibrillation. Both a verbal warning and visual check are performed before the electrical shock is delivered. The DOSE-VF trial did not report any events of accidental shock to a person other than the patient.[36] We therefore consider this risk minimal, but will record any accidental shocks during the cardiac arrest.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

Estimates used for the sample size calculation are based on data from the research group's previous and ongoing trials in Denmark[11,12] and the DOSE-VF trial[36]. We anticipate that 20% will survive to 30 days in the standard anterior-lateral pad placement group. An alpha of 4.5% for the final analysis was calculated based on the O'Brien-Fleming approach using an overall significance level of 5% (see section 6.2.10). Based on this, a 30-day survival of 30% in the intervention groups (corresponding to a risk ratio of 1.50), and a chi-squared test, we will need 303 patients that fulfill the modified intention to treat criteria (see section 6.2.1) per group (i.e., a total of 909 patients) to have 80% power to detect a statistically significant difference between either of the intervention groups and the standard group. The trial is not powered to detect a difference between the two intervention groups. The relative increase in survival of the interventional groups is based on the findings of the DOSE-VF trial (see section 1.3.1) reporting risk ratio estimates of 1.71 (95% CI: 1.01, 2.88) and 2.21 (95% CI: 1.33, 3.67) for anterior-posterior pad placement and double sequential defibrillation, respectively, as compared to anterior-lateral pad placement.[36] We chose a more conservative risk ratio of 1.50 based on the considerations outlined in section 1.3.1, and due to the uncertainty in the results from the DOSE-VF trial (i.e., wide confidence intervals). For risk ratios of 1.71 and 2.21, we have 97% and >99% power, respectively.

Given that the primary analysis will be adjusted for country stratification and strong prognostic factors (see section 6.2.2 and section 6.2.5), we will obtain additional power.[79,80]

6.2 Statistical analysis plan

6.2.1 General considerations

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

All analyses will, unless noted otherwise, be conducted on a modified intention-to-treat basis including all randomized patients that met all inclusion criteria as well as no exclusion criteria at the time of randomization. The patient is considered randomized once the randomization envelope has been opened. Patients will be analyzed according to their assigned group.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see Appendix 4 for a draft). Baseline patient and cardiac arrest characteristics will be presented using descriptive statistics (see Appendix 5 for a draft).

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).[81] 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).[81,82] If this fails to converge, results will be presented as odds ratios obtained from a logistic regression model. 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.[81]

To increase power, all models will include adjustment for country stratification and strong prognostic factors (see section 6.2.5).[83] 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.[84] In case none of these adjusted models are feasible, 95% confidence intervals will be obtained using methods described by Miettinen and Nurmimen without any adjustment.[85]

6.2.3 Continuous outcomes

Continuous data will be presented as means with standard deviations 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 and adjustment for country stratification and prognostic variables (see section 6.2.5). 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 Significance testing and type 1 error control

The trial will primarily be analyzed within a frequentist framework. Given the confirmatory nature of the trial, the trial will be designed with strong control of the family-wise type 1 error rate, which will be maintained at 5%. All statistical tests will be two-sided.

The trial has three potential sources of multiplicity: three interventional groups, interim analyses, and multiple outcomes.

The trial is designed with one control arm and two interventional arms with two distinct and independent hypotheses (see section 2). Since these two hypotheses are distinct, and conclusions will be made separately for each, multiplicity related to the use of a common control group is not a concern and there will be no adjustment of the significance level based on this.[86-90]

The trial will have two interim analyses for the primary outcome as a part of the independent data monitoring committee's (IDMC) oversight of the trial (see section 6.2.10 and section 10.1). To control the family-wise error rate, the O'Brien-Fleming approach will be used for each of the two distinct hypotheses (see section 6.2.10 and Table 2).

Null-hypothesis significance testing for the primary and key secondary outcomes will be performed in a sequential order such that the subsequent outcome will be tested for statistical significance only if the previous outcome had a P value ≤ 0.045 (see section 6.2.10). Otherwise, no tests will be performed.[91] The order of the outcomes will be: 30-day survival, 30-day survival with a favorable neurological outcome, 90-day survival, and 90-day survival with a favorable neurological outcome. There will be no statistical significance testing and reporting of P values for other outcomes.

All confidence intervals will have 95% coverage with no adjustment for multiplicity.

6.2.5 Adjustment for baseline characteristics

To increase power, we will adjust all outcome comparisons for country stratification and strong prognostic factors.[79,80,83,92] These will include age, whether the cardiac arrest was witnessed, and whether early cardiopulmonary resuscitation was initiated or not (i.e., bystander cardiopulmonary resuscitation or EMS-witnessed arrest). Age will be included as a linear continuous variable, and witness-status and early cardiopulmonary resuscitation will be included as binary variables (i.e., witnessed vs. unwitnessed, early cardiopulmonary resuscitation vs. no early cardiopulmonary resuscitation, respectively).

6.2.6 Sensitivity analyses

There will be three sensitivity analyses for the primary and the key secondary outcomes. Firstly, analyses will be performed excluding patients who were randomized but who never received a shock after the randomization. This analysis thus excludes patients who had ROSC, termination of resuscitation, or transitioned to and withheld a non-shockable rhythm after randomization but before a shock could be performed.

Secondly, per-protocol analyses will be conducted. These analyses will exclude patients that never received a shock after randomization and those who received one or more shocks with a defibrillation method other than the allocated one after randomization and before transport.

Thirdly, an intention-to-treat analysis including all randomized patients will be performed.

These analyses will also be adjusted for country stratification and prognostic factors (see section 6.2.5).

6.2.7 Other analyses and considerations

Health-related quality of life will only be assessed in those alive at the time of measurement.

Survival until 90 days will be presented graphically with Kaplan-Meier curves,[93] but will otherwise be analyzed as a binary outcome as described section 6.2.2.

Adverse events and hospital disposition will be presented descriptively.

6.2.8 Subgroup analyses

Subgroup analyses will be performed on both the absolute and relative scale.[94] The analyses will be performed according to the last known rhythm prior to randomization (VF or pVT), whether the OHCA was unwitnessed, witnessed by a bystander, or witnessed by emergency medical services personnel, whether bystander cardiopulmonary resuscitation was performed, the number of shocks administered before randomization (<3 or ≥3 shocks), and sex. The trial is not powered to detect subgroup differences, and these will be considered exploratory and hypothesis generating.

Predefined secondary subgroup analyses will be performed and reported in a separate manuscript. These analyses will consider the following variables: time after trial initiation, time interval between double sequential shocks, and refractory or recurrent VF.

6.2.9 Missing data

Missing data will be reported in the relevant publications. We expect very minimal missing data for the primary outcome and the key secondary outcomes consistent with recent randomized trials in the same setting with the same follow-up plan.[11,12] Multiple imputation using known risk factors for outcomes after OHCA will be used to impute values for patients with missing data if missing data is substantial (>5%). Otherwise, patients with missing data will not be included in the relevant analyses.

6.2.10 Interim analyses and statistical stopping criteria

Interim analyses on the primary outcome will take place as part of the IDMC's oversight of the trial (see section 10.1 and Appendix 6 for details). The trial will have predefined stopping criteria for benefit and harm but not for futility. Stopping criteria for harm and benefit will be binding.

There will be symmetrical stopping criteria for benefit and harm based on the primary outcome (survival at 30 days). The stopping bounds were calculated using the O'Brien-Fleming approach[95] with a total of three analyses (two interim and one final), a power of 80%, an overall significance level of 5%, 20% survival at 30 days in the control group, and 30% survival at 30 days in either of the interventional groups (Table 2). While we do not explicitly hypothesize that there will be a difference in outcomes between the two interventional groups, this comparison will be included in the interim analyses.

Table 2. O'Brien-Fleming stopping boundaries for benefit and harm		
Analysis (number)	**Number of patients**	**p-value**
Interim (1)	303	0.001
Interim (2)	606	0.014
Final analysis (3)	909	0.045

In the case of harm or benefit in an interim analysis, the trial may continue with the other trial arms depending on the specific scenario (Table 3), the overall status of the trial, and accumulating external evidence. Appropriate protocol amendments will be made as relevant.

There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow for detection of benefit in subgroups or in other outcomes even if there is no difference between groups in the primary outcome. Furthermore, since a previous randomized clinical trial found a difference between groups[36], a neutral trial with an adequate sample size will be important.

Table 3. Scenarios for meeting stopping boundaries and potential continuation of the trial			
Intervention 1 vs. Control	**Intervention 2 vs. Control**	**Intervention 1 vs. Intervention 2**	**Consequences for the trial**
Meeting stopping criteria for harm of intervention 1	Not meeting stopping criteria	Not meeting stopping criteria	Drop intervention 1, continue trial with intervention 2 vs. control.
Meeting stopping criteria for benefit of intervention 1	Not meeting stopping criteria	Not meeting stopping criteria	Drop control, continue trial with intervention 1 vs. intervention 2.
Not meeting stopping criteria	Not meeting stopping criteria	Meeting stopping criteria for benefit of intervention 1	Drop intervention 2, continue trial with intervention 1 vs. control.

6.2.11 Secondary Bayesian analyses

A separate manuscript will be published containing secondary Bayesian analyses for the primary and key secondary outcomes in order to aid interpretation of the results.[96] We will primarily use noninformative prior probability distributions and the results obtained from the trial to obtain posterior probability distributions for risk ratios. Standardized skeptical, neutral, and optimistic prior probability distributions will also be used consistent with a recent trial by our group.[11] We will also use priors obtained from the results from the DOSE-

VF trial.[36] 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 mean risk ratios with 95% credibility intervals.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data collection process

Trained members of the research team, along with site investigators, will be responsible for data collection and entry. Very limited data will be obtained by the prehospital team on an electronic case report form. This will include site, the patient identifier (i.e., the personal ID code or event number ID), study ID, allocation observed in the envelope, number of shocks before randomization, time of randomization, details on pad placement after the randomization, details on any shocks after the randomization, and name of the prehospital personnel responsible for inclusion. This, along with the telephone interviews for long-term follow-up, will be the only source data; all additional data will be obtained from pre- and in-hospital electronic medical records and will be based on measurements and assessments made by the clinical team.

7.2 Variables

7.2.1 Overview

Based on the definitions in section 4.2, all OHCAs with ≥ 1 manual defibrillation attempt by EMS at the participating sites will be entered into a screening log to provide data for a CONSORT diagram, which is used to describe the recruitment of participants and evaluate the trial's external validity. OHCAs will be identified by review of prehospital medical records as well as emergency dispatch logs, approximately 8000 records yearly. These records will be used to identify patients for the screening population of the trial. For OHCAs not randomized, a specific reason for non-inclusion/exclusion will be passed on to researchers along with the event number ID. At the end of follow-up, the screening log's non-randomized patients will be anonymized (i.e., the event number ID will be deleted from the database). All randomized patients will be entered into the primary database with full data registration. For these patients, the data passed on from medical records before consent is obtained will adhere to the variables stated in sections 7.2.2-7.2.5. After consent is obtained, the primary investigator, the sponsor, project employees, and regulatory authorities, will be able to directly access the patients' medical records to gather information regarding the health condition of the patient. This includes electronic medical records, which is necessary for the trial's conduct as well as lawfully mandated self-monitoring, external monitoring, and data quality control (details outlined in section 7.5).

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), source of the data, a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables.

The included variables largely follow the OHCA Utstein guidelines from 2024 which outlines recommended data reporting for trials in OHCA.[97] *Pre-cardiac arrest characteristics* are important for the unique identification of trial participants and for the baseline descriptive data necessary in cardiac arrest trials. *Pre-intervention variables* are important for the statistical adjustment for strong prognostic factors and to enable subgroup analyses. *Procedure-related variables and trial related variables* are source data, meaning that the clinicians responsible for inclusion will provide these data, and are essential to answer the primary and secondary hypotheses. *Post-intervention variables* will be used to evaluate tertiary outcomes. *Other variables* are collected to create a descriptive overview of the population. *Post-cardiac arrest characteristics* can influence outcomes for cardiac arrest patients thus making the data collection important to describe the three groups. *Outcomes* data variables are needed to answer the primary and secondary hypotheses of the study.

Below is provided a brief overview of the included variables. All data will be collected from pre- and in-hospital medical records unless the variable is marked as *source data* in which case the data will be provided directly by the prehospital clinician or through telephone interview follow-up. Further details are reserved for the data dictionary.

7.2.2 Pre-cardiac arrest characteristics

Patient demographics and characteristics

- Name
- Unique patient identifier
- Age
- Sex
- Height
- Weight

Conditions/medications prior to the cardiac arrest

- Co-morbidities
    - Cardiac
    - Non-cardiac
    - Previous cardiac arrest
- Estimated mRS prior to cardiac arrest
- Estimated clinical frailty scale score

7.2.3 Cardiac arrest characteristics

Pre-intervention variables

- Date and time of the cardiac arrest
- Location of the cardiac arrest
- Witnessed (bystander, EMS, none)
- Bystander cardiopulmonary resuscitation
- Bystander shock with automated external defibrillator (AED)
- Initial rhythm
- Last known rhythm prior to randomization
- Time of arrival on site by EMS
    - Primary ambulance
    - Physician-manned vehicle or helicopter

Procedure-related variables (the below are source data)

- Number of defibrillation attempts prior to randomization
- Date and time of first defibrillation attempt
- Date and time of randomization
- Defibrillation attempts after randomization
    - Number of defibrillation attempts after randomization
    - Defibrillation method for defibrillation attempts after randomization
    - Time of first defibrillation attempt after randomization

Post-intervention variables

- Transport during cardiac arrest
- Date and time of the end of resuscitation (sustained ROSC or time of death)
- Extracorporeal cardiopulmonary resuscitation

Other variables

- Presumed etiology
    - Medical
    - Drug overdose
    - Drowning

    - Electrocution
    - Asphyxia
    - Other/unknown
- Relevant medication during resuscitation: Adrenaline, amiodarone

Trial related variables (the below are source data)

- Study ID
- Site
- Inclusion criteria
- Exclusion criteria
- Allocation observed in the envelope
- Role of prehospital personnel responsible for patient inclusion (physician, physician-assistant, or paramedic)
- Date and time consent for data collection is obtained

7.2.4 Post-cardiac arrest characteristics

- Targeted temperature management (with target temperature / avoidance of fever / no)
    - If either with target temperature or avoidance of fever: Duration
    - If with target temperature: Temperature target
- Presence of ST-elevation myocardial infarction
- Cardiac interventions attempted
    - Coronary angiography
    - Percutaneous coronary intervention
    - Coronary artery bypass grafting
    - Ventricular assist device or Intravascular pumps
    - Veno-arterial extracorporeal membrane oxygenation
    - Veno-venous extracorporeal membrane oxygenation
- Specific adverse events (see section 5.4.4)

7.2.5 Outcomes

- Survival at 30 days, 90 days, 180 days, and 1 year
- mRS and CPC at 30 days, 90 days, 180 days, and 1 year (source data)

- ROSC
    - Sustained
    - Any
    - At hospital arrival
- EQ-5D-5L at 30 days, 90 days, 180 days and 1 year (source data)

7.3 Data storage and security

The database application will be Research Electronic Data Capture (REDCap, Vanderbilt, Tennessee, USA).[98] 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") as well as relevant laws in other participating countries. The project will be registered on the internal list of research projects at the Central Denmark Region and Aarhus University.

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

7.4 Data quality and validity

7.4.1 Central monitoring

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 (e.g., time and date of first defibrillation attempt after hospital admission); these data are assessed and – if relevant – corrected continuously throughout the inclusion period.

Given its limited utility, double-data entry will not be performed.[99,100]

7.4.2 On-site monitoring

The site investigator has the overall responsibility for on-site monitoring.

7.5 Data access

The primary investigator, the sponsor, and project employees (e.g., research assistants), will have full access to an included patient's medical records, including electronic medical records, which is necessary for the trial's conduct as well as lawfully mandated self-monitoring, external monitoring, and data quality control. Site investigators will have access to medical records for patients included at their site.

Regulatory authorities will be given access to an included patient's medical records and/or the trial database if requested.

During the trial, relevant members of the steering committee will have access to the entire database. Once the database is locked, a de-identified version of the database will be made available to the members of the steering committee.

8. CLINICAL TREATMENT

The clinical management of included patients (other than the interventions) will be at the complete discretion of the treating prehospital and in-hospital teams to test the interventions in a real-life clinical setting. In general, management will adhere to the intra- and post-cardiac arrest guidelines provided by the ERC[101] and, in Denmark, the Danish Resuscitation Council[102], but no specific treatments will be prohibited or mandated. The participating clinicians will be informed about the most recent guidelines for intra-cardiac arrest care and will be encouraged to limit premature termination of resuscitation efforts.[103] Hospitals will also be encouraged to follow ERC post-cardiac arrest guidelines including appropriate neurological prognostication.[104]

9. ETHICAL CONSIDERATIONS

9.1 Clinical equipoise

9.1.1 Potential benefits

Details about the potential benefits of the interventions are provided in the background section (see section 1.2 and section 1.3). In brief, a cluster-randomized clinical trial found that alternative defibrillation strategies (i.e., anterior-posterior pad placement and double sequential defibrillation) improved survival to hospital discharge in patients with refractory VF.[36] Due to these findings, ILCOR suggests that anterior-posterior or double sequential defibrillation may be considered in patients with refractory shockable rhythms. ILCOR calls for clarification regarding the benefits of these interventions and states that confirmatory findings are needed in different settings.[47]

9.1.2 Potential harms

Defibrillation is widely used and considered a safe intervention. The proposed new strategies for defibrillation have not raised concern for harm. Known potential complications to the interventions are outlined in section 5.4.4.

9.1.3 Risk/benefit ratio

From the data provided above in section 9.1.1 and section 9.1.2 and in the background section (see section 1.2 and section 1.3), the current risk/benefit ratio is encouraging for the trial as it will provide valuable data that are desired by the international community while introducing little risk of harm to the included patients.

9.2 Research in cardiac arrest

9.2.1 General considerations

Research in cardiac arrest is ethically challenging for two reasons: 1) Patients are unconscious and can therefore not provide informed consent and 2) treatment must be administered within minutes limiting the possibility of obtaining informed consent from legally designated representatives.[105,106] 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,[107] 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 Danish regulations

The Danish law allows for inclusion in research without informed consent in a setting where an acute intervention is required, and the following criteria are met[2]:

1. The research can only be conducted in an acute setting and the patient is acutely impaired in their ability to act, because of conditions such as: thrombosis, intracerebral hemorrhage, loss of consciousness, cardiac arrest, severe trauma, etc.
2. It is impossible to collect consent without wasting the opportunity to provide the intended intervention, given the urgency of the situation.
3. The research personnel collect informed consent from the patient or a surrogate as soon as feasible.
4. The intervention should have the opportunity to improve the health of the specific patient included in the study or improve the health of patients suffering from the same disease.

9.2.3 Conditions in relation to the current trial

Condition (1)

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

Condition (2)

Cardiac arrest often lasts less than 30 minutes. The intervention will be performed as soon as possible after randomization. Shocks are to be applied early and every two minutes in patients with shockable rhythms. Given these time frames, it would be impossible to obtain informed consent from legally designated representatives.

Condition (3)

Procedures described in section 9.3 are in place to ensure consent is obtained after the cardiac arrest.

Condition (4)

The interventions in this trial are specifically targeted for OHCA patients. Given the high morbidity and mortality of OHCA (see section 1.1.1), clinical trials are highly needed to improve patient outcomes. A previous trial (see section 1.3.1) indicates that the interventions planned in this trial have the potential to improve patient outcome. The intervention is not suspected to impose further harm than standard defibrillation. The trial also has the potential to improve the health of patients suffering from the same disease in the future.

9.3 Procedures

9.3.1 Ethical review committee

The trial will be sent for approval through relevant research ethics committees.

9.3.2 Trial-specific procedures

The decision to include and randomize an adult patient with OHCA will be up to the first on-site participating clinical personnel (physician, physician assistant, or paramedic). Interventional procedures are described thoroughly in section 3.3.

For patients who survive to intensive care unit admission, but remain unable to provide consent, written consent from the legally designated representatives will be obtained as soon as possible. The legally designated representatives are defined as both the closest relative and a legal guardian ("forsøgsværge" in Danish) in Denmark.[75,108] The legal guardian will be a physician that is independent from the principal investigator and the clinical trial.[108] The legal guardian will be site-specific and is chosen based on sufficient knowledge of cardiac arrest and patients in the intensive care unit, enabling assessment of whether the patient can participate in the current trial. The physician obtaining consent will be a member of the steering committee or a physician with sufficient knowledge about the patient, the condition, and the trial (e.g., a member of the clinical team who has been formally educated about the trial and relevant procedures). There will be made multiple attempts to contact the legally designated representative if this is not achieved in the first attempt. If there is no close relative to approach during the patient's first days of hospital admission, reasonable attempts will be made to gather contact information for a close relative. Trial information and the consent request will take place in an undisturbed room, and the patient or the legally designated representatives will have the opportunity to request an assessor. Between the trial information and the consent request, the patient or legally designated representatives will be offered at least 24 hours for consideration. Prior to written consent, a patient or the legally designated representatives will always be asked, whether he or she needs more time for consideration.

The patient, the legally designated representatives, and the person obtaining the consent will sign individual digital or paper consent forms as appropriate. If a patient dies before it is possible to obtain consent , patient data will be included in the trial.[109] If a patient denies future participation in the trial, no additional data will be collected but all data collected up until the point of withdrawal will be included consistent with Danish law.[110]

When approached, the patient or the legally designated representatives will be informed, verbally and in writing, about the background and significance of the trial, inclusion criteria, potential risks and benefits, as well as a brief description of the trial protocol. They will be informed that no additional interventions or procedures, except telephone interviews for long-term follow-up, will be performed and that future

participation will only include data collection. The patient or the legally designated representative will then provide written informed consent through the informed consent form approved by the relevant authorities. When consent is obtained from a participant or the legally designated representatives, information about potential de-identified data sharing will also be included.

The consent forms will primarily be digital, and signatures will be written on a smart phone, tablet or computer using REDCap which has dedicated functionalities for written consent. If the digital consent form is not available, a paper format will be used as backup and then uploaded as a scanned document to the REDCap-database.

Procedures for other countries that defer from the above are described in Appendix 3.

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 the legally designated representatives, an investigator will attempt to contact a relative, who is able to give consent. If no relative is readily available or if it is not possible to obtain contact information for the relative, 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 relative.[111] 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 the legally designated representatives denies ongoing 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.[112] 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.

9.3.5 Insurance

The Danish patients in the trial are covered by the Danish patient insurance.[113]

9.3.6 End of trial

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

9.3.7 Included patients without adequate local language proficiencies

The trial might include patients who do not have adequate language proficiencies to understand and comprehend local language trial information, as it is not possible to exclude these patients before inclusion. In

the setting of an OHCA, data on a patient's language skills are often unavailable, unreliable, and cannot be prioritized over collection of more important clinical information.

In case of inadequate local language proficiencies, 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.

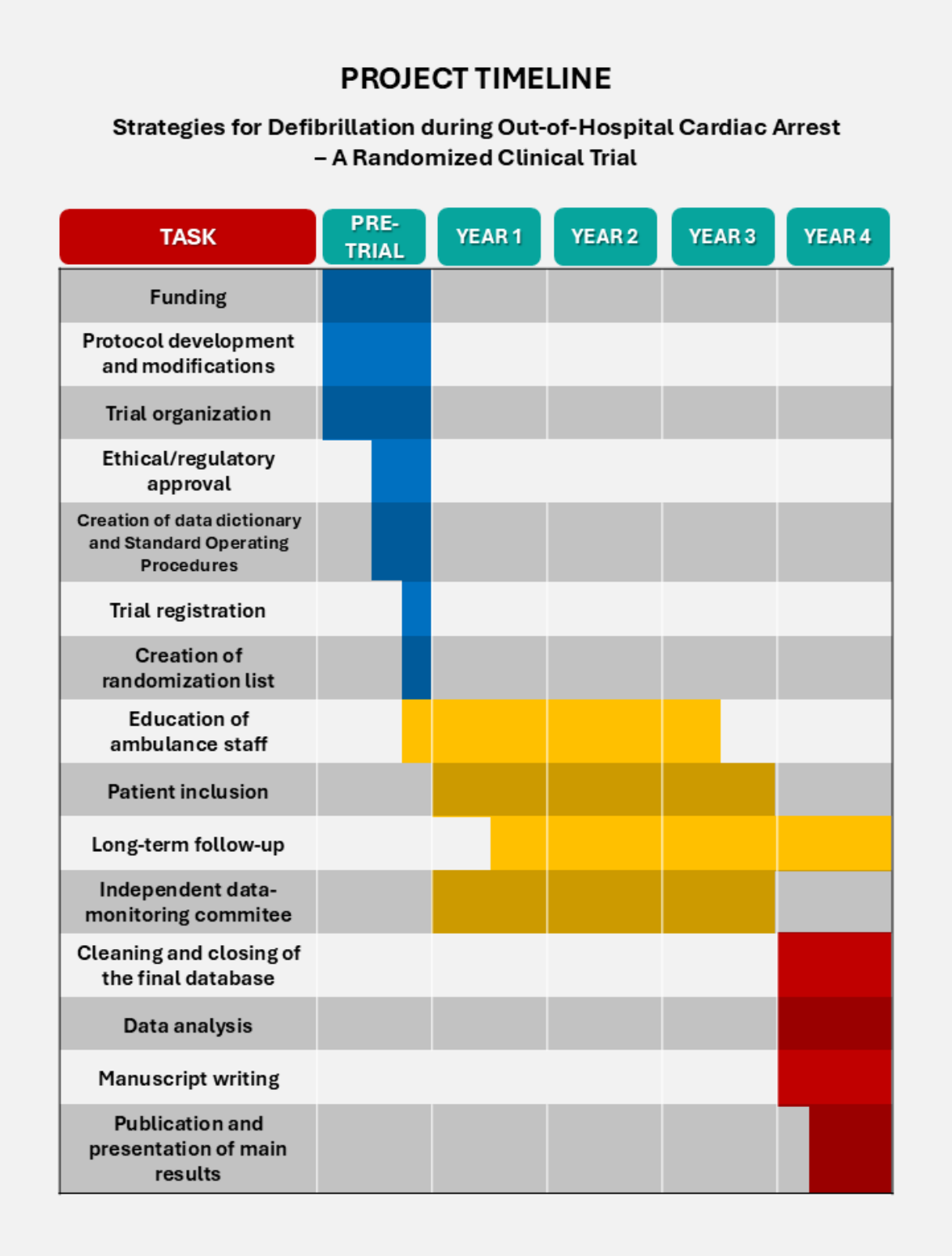
10. MONITORING

10.1 Independent data-monitoring committee (IDMC)

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the harm and benefit 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 cardiac arrest research. The IDMC members are chosen 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 predetermined milestones (303 and 606 enrolled patients, respectively), but can – at any time – require extra reviews. The IDMC will not be blinded to treatment groups. The trial will continue while the IDMC review data. After the reviews, the IDMC will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. Criteria for recommending termination will be at the discretion of the IDMC but will include the trial's predefined binding stopping criteria (see section 6.2.10). The final decision regarding potential modifications or termination of the trial will rest with the steering committee. A detailed charter for the IDMC is provided in Appendix 6.

11. TIMELINE AND ENROLLMENT

11.1 Timeline



11.2 Feasibility

There are approximately 800 patients with cardiac arrest and an initial shockable rhythm in Denmark each year.[8] Based on our inclusion and exclusion criteria, we anticipate that approximately 300 of these patients will be able to be included in the trial making this trial feasible within three years. The combined international sites have approximately 150-200 eligible cardiac arrests each year which increases feasibility further.

11.3 Enrollment

Enrollment will be continuously monitored by the site investigators, coordinating investigator, and the principal investigator. Formal reports outlining the number of OHCAs, and the proportion of those enrolled, will be shared with the steering committee regularly. In case multiple eligible OHCAs are not enrolled, a root cause analysis will be performed, and efforts will be made to avoid such issues in the future. Given the urgency of OHCA, we do not expect 100% enrollment rate. However, we will aim for enrollment of >70% of eligible OHCA. In case there is continuous underperformance at a specific site or station despite troubleshooting and feedback, the steering committee will evaluate whether enrollment will continue at that location.

12. PUBLICATION PLAN

At least four 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 up until 90 days. The coordinating investigator will be the first author, and the principal investigator will be the last and corresponding author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors[114] and will include members of the steering committee and clinical staff involved in the trial as appropriate. The trial results will be shared with participating staff and via press releases, as well as with participating patients if they requested so on their consent form.

The second manuscript will report Bayesian analyses of the outcomes reported in the main manuscript (see section 6.2.11).The third manuscript will report pre-specified secondary subgroup analyses (see section 6.2.8). The fourth manuscript will include long-term follow-up at 180 days and 1 year (see section 5.3).

Trial findings will be published irrespective of negative, positive, or inconclusive results. All manuscripts will adhere to the CONSORT guidelines.[115,116]

13. DATA SHARING

After publication of the last results (i.e., 1-year follow-up), all de-identified individual patient data will be made available for data sharing as allowed within Danish law.[117] Procedures, including re-coding of key variables, will be put in place to allow for de-identification of the data.

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 if required 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[114] 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 coordinating investigator: Overall responsibility for protocol development, funding, budget overview, data dictionary development, ethical approval, trial registration, daily management, trial oversight, contact to the independent data monitoring committee, assessment of overall recruitments, data entry and management, patient follow-up, data analysis, and dissemination and presentation of results.

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

Site investigator: Site-specific enrollment, education of personnel at participating sites, reporting of site-specific issues or challenges to the principal investigator, participant consent.

Clinical team: Decision to include a patient, randomization, perform the intervention, eCRF data entry.

IDMC: See section 10.1.

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Appendices

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

Lars W. Andersen

Industry:

- None

Other:

- None

Mikael Fink Vallentin

Industry:

- None

Other:

- None

Asger Granfeldt

Industry:

- None

Other:

- None

Bertram Lahn Kirkegaard

Industry:

- None

Other:

- None

Carsten Meilandt

Industry:

- None

Other:

- None

Christian Juhl Terkelsen

Industry:

- Edwards Lifesciences and Meril Life Science – teaching honorarium (heart valves)
- Terumo – teaching honorarium (ultrasound)
- Meril Life Sciences and Medtronic: Unrestricted research grants to perform studies in patients treated with TAVI.

Other:

- None

Steffen Christensen

Industry:

- None

Other:

- None

Thomas Dissing

Industry:

- None

Other:

- None

Allan Bach

Industry:

- None

Other:

- None

Kristian Blumensaadt Winther

Industry:

- None

Other:

- None

Thomas Lass Klitgaard

Industry:

- None

Other:

- None

Søren Mikkelsen

Industry:

- None

Other:

- None

Fredrik Folke

Industry:

- None

Other:

- None

Helle Collatz Christensen

Industry:

- None

Other:

- None

Jacob Steinmetz

Industry:

- None

Other:

- Professorship funding from Norwegian Air Ambulance Foundation.

Markus Skrifvars

Industry:

- BARD Medical (Ireland) – Speakers fees

Other:

- None

Cornelia Genbrugge

Industry:

- None

Other:

- None

Siobhan Masterson

Industry:

- None

Other:

- Member of the ILCOR Scientific Advisory Committee

Appendix 2: Randomization envelope and allocation paper slip

STRAT-DEFI RANDOMIZATION ENVELOPE

OPEN DURING ADULT NON-TRAUMATIC CARDIAC ARREST
IMMEDIATELY AFTER A MANUAL DEFIBRILLATION.
TWO MANUAL DEFIBRILLATORS MUST BE PRESENT ON-SITE AND
IT MUST BE POSSIBLE TO PLACE A PAD ON THE PATIENT'S BACK

Randomization number:
XXXX

Register all patients in REDCap, regardless of opening the envelope or not, if a manual defibrillation attempt was made. Use the link or QR-code below

redcap.link/strat.defi

Do not discard opened envelopes before REDCap registration

Contact: +45 91 17 43 23 Email: STRAT.DEFI@rm.dk

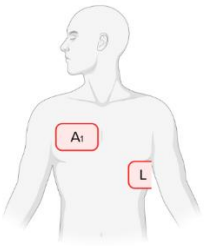
Randomization envelope: Outside text and design

Defibrillation strategy:

Anterior-lateral

Randomization number:
XXXX

Anterior-lateral



Randomization envelope: Inside text and design (example)

Appendix 3: International sites

Finland

Setting

In Finland, prehospital emergency medical services are based on a four-tiered system, including first responder units, basic life support units, advanced life support units, and physician-manned units (either vehicles or helicopters). First responder units are primarily staffed by firefighters or border guards. Advanced life support units consist of at least one paramedic nurse with a bachelor's degree, requiring four years of education. Physician-manned units are staffed by either anesthesiologists or emergency care physicians.

For cardiac arrest, first responder, advanced life support, and physician-manned units are dispatched to the scene. First responder units provide basic CPR and use automatic external defibrillators. Advanced life support and physician-manned units provide advanced life support interventions, identify and treat possible reversible causes of cardiac arrest, and provide immediate post-resuscitation care. Resuscitated patients are transported directly to hospitals with 24/7 access to emergent cardiac catheterization and intensive care.

Consent procedures

Emergency research in Finland is required to adhere to the following criteria, according to the Research Act.

- There are scientifically justified reasons to assume that the research subject's participation in the research can directly benefit their health.
- The research is directly related to the research subject's illness, injury, or change in health condition, making it impossible to provide information and obtain informed consent from the research subject or someone authorized to consent on their behalf.
- That the investigator is not aware that the research subject or someone authorized to consent on the research subject's behalf has objected to participation in the research.
- The nature of the research is such that it can only be conducted in emergency situations.
- The risk and burden to the research subject from the research are very small compared to the standard treatment for the research subject's disease, injury, or health condition.

Regulations regarding to informed consent:

- The researcher must provide information and request informed consent from the participant without undue delay, or if the participant is unable to give informed consent after the intervention, from a close relative or other close person.

- If informed consent has been obtained from a close relative or other close person, informed consent to continue participating in the research must be obtained from the participant immediately when they are able to provide it

The trial will adhere to these regulations. A detailed description of the ethical considerations and consent procedures in general is provided in Section 9 of the trial protocol.

Belgium

In addition to the Danish Setting

In Belgium, all cardiac arrests are generally attended by a primary ambulance and a unit staffed by a board-certified emergency physician and nurse. The primary ambulance is manned by two emergency medical technicians or by an emergency medical technician and a nurse. In Belgium only physicians are allowed to include patients in the trial, so the primary ambulance is often the first present but will not be able to include patients.

Consent procedures

In Belgium, when prior written or oral consent from a participant is not possible due to their critical condition, enrollment may proceed without consent under the following regulations. The investigator must, as soon as possible after enrollment, contact a legally acceptable representative to obtain consent on behalf of the participant if the patient achieves return of spontaneous circulation. A legally acceptable representative may include immediate family members, or legal guardians. If the participant regains the capacity to consent, the investigator must promptly obtain direct consent from the participant, regardless of any previous consent given by a legally acceptable representative.

The consent request process must be carried out accordingly. An informed consent form should be presented to either the participant or the legally acceptable representative by a clinician formally trained in the trial and its relevant procedures. This informed consent form is a comprehensive document detailing all aspects of the study, including the critical elements required by the ICH GCP Guidelines. The participant or legally acceptable representative must be given adequate time and opportunity to ask questions about the study before deciding whether to sign the consent form. These forms will be provided in Dutch, English, and French. If a family member or a legal guardian of the participant or the participant does not understand one of these three languages, an official translator will be contacted by phone.

The consent form will be signed manually on paper, this document will be scanned and added to REDCap.

During the trial, participants must be informed of any new information that could impact on their willingness to continue participation. This information should be reflected in an updated version of the informed consent form, which must be signed by all new participants and by currently enrolled participants (i.e., through a re-consenting process). Participants who have completed the follow-up phase are not required to re-consent. When re-consenting is necessary, the process must be documented in the electronic patient dossier, and the participant identification log must be updated.

When a participant withdraws consent, no more data will be collected from this person or the medical file. All previously collected data can still be used for the trial.

Safety

In addition to the Danish definition of an adverse event, in Belgium there is added for the definition of (Serious) Adverse event: Important medical events that may be considered an SAE when, based on appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes.

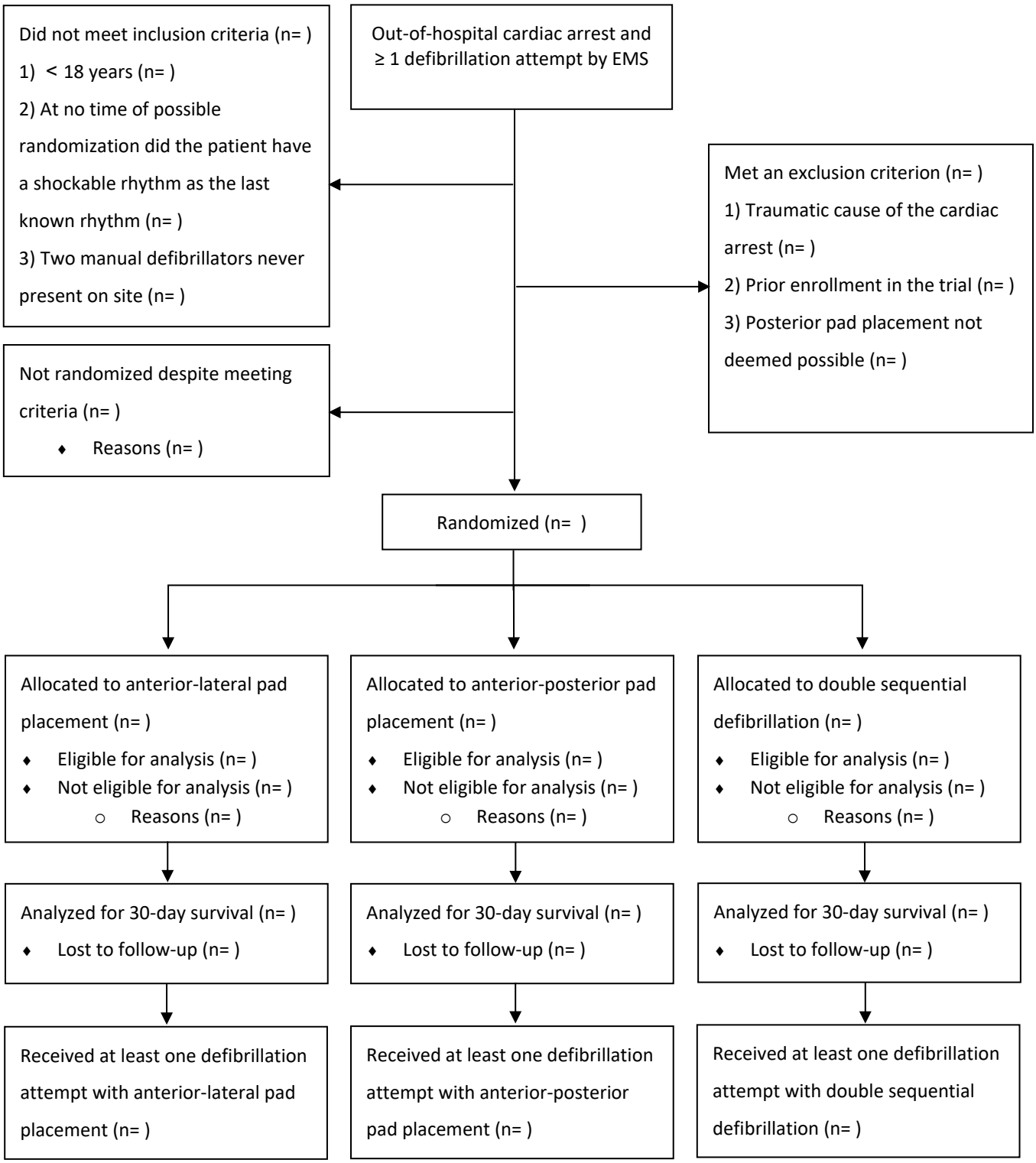
The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the Ethics Committee (EC).

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC containing an overview of all SARs (Serious Adverse Reactions) that occurred during the reporting period and to take into account all new available safety information received during that reporting period.

Any unexpected death of a participating patient occurring at the local site will be reported, as soon as possible after becoming aware, to the local EC (applicable when the local EC demands this). Section 9.2 describes that OHCA is an unpredictable and sudden event with a high morbidity and mortality. So not every death of a participant will be reported, only unexpected deaths. This SAE will be reported to the Danish sponsor via REDCap.

The trial will adhere to these regulations. A detailed description of the ethical considerations and general consent procedures is provided in Section 9 of the trial protocol.

Appendix 4: Draft of CONSORT flow diagram



Appendix 5: Draft of table 1 for main publication

	Anterior-posterior (n = XXX)	Double sequential (n = XXX)	Anterior-lateral (n = XXX)
Patient characteristics			
Age - years			
Male sex - no. (%)			
Body mass index – kg/m^2			
Past medical history - no. (%)			
Coronary artery disease			
Chronic heart failure			
Atrial fibrillation			
Stroke			
Venous thromboembolism			
Hypertension			
Diabetes			
Pulmonary disease			
Renal disease			
Liver disease			
Cancer			
Dementia			
Previous cardiac arrest			
Cardiac arrest characteristics			
Location – no. (%)			
Home			
Public area			
Witnessed – no. (%)			
Bystander			
EMS			
Unwitnessed			
Bystander cardiopulmonary resuscitation – no. (%)			
Bystander AED – no. (%)			
AED shock			
AED attached but no shock			
No record of AED attached			
Response time, first unit on site - minutes			
Initial rhythm – no. (%)			
Shockable			
Ventricular fibrillation			
Pulseless ventricular tachycardia			
Non-shockable			
Pulseless electrical activity			
Asystole			
Last known rhythm prior to randomization – no. (%)			
Ventricular fibrillation			
Pulseless ventricular tachycardia			
Time to first manual defibrillation - minutes			
Number of shocks prior to randomization – no. (%)			
Time to randomization - minutes			

Appendix 6: Charter for the independent data-monitoring committee (IDMC)

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

Trial name: Strategies for Defibrillation during Out-of-Hospital Cardiac Arrest – A Randomized Clinical Trial (STRAT-DEFI)

Principal investigator: Professor Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc.

Research ethical committee no.: 1-10-72-135-24

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 harm and benefit 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. This recommendation will be made in accordance with the predefined binding stopping criteria for benefit and harm. To contribute to enhancing the integrity of the trial, the IDMC may also decide to formulate recommendations relating to the recruitment of participants, 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 terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

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

The members of the IDMC will be unpaid.

Members of the IDMC

The IDMC is an independent multidisciplinary group consisting of physicians with epidemiological/statistical expertise 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:

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

Peter J. Kudenchuk, M.D.
Professor
Section of Electrophysiology
University of Washington, Seattle, Washington

Niklas Nielsen, M.D., Ph.D.
Professor
Department of Clinical Sciences
Lund University, Helsingborg, Sweden

Conflicts of interest

IDMC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The IDMC members will disclose to fellow members any consulting agreements or financial interests they have with the trial's primary investigator or with 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 benefit and harm at two predetermined milestones (303 and 606 enrolled patients, respectively), but can – at any time – require extra reviews. The IDMC will not 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. The trial will have formal stopping criteria for benefit and harm. A detailed description of the relevant statistical analyses can be found in the trial protocol (see section 6.2.10).
There will be no formal stopping criteria for futility.

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

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

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

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

The values of the following variables will be included:
1: id: a number that uniquely identifies the patient.
2: allocation: Allocation as decided by the randomization (1: anterior-lateral, 2: anterior-posterior, 3: double sequential defibrillation)
3: survival_30d: Survival at 30 days (1: yes, 0: no)
4: mrs_30d: modified Rankin Scale (mRS) at 30 days (integer, range: 0-6)
5: rosc_sustained_binary: Return of spontaneous circulation with palpable pulse for ≥20 minutes (1: yes, 0: no)
6: intervention_n: How many shocks were administered after randomization (integer)
7: crossover: Did the patient receive a defibrillation attempt with a different pad placement than the one allocated after randomization (1: yes, 0: no)

Specific adverse events (see sections 5.4.4-5.4.10 in the protocol):
8: defib_damage: Defibrillator damage (1: yes, 0: no)
9: accident_shock: Accidental shock to any personnel (1: yes, 0: no)

All variables will be provided by the steering committee.

An independent biostatistician or a member of the IDMC will provide aggregate data for each of the variables #3-9 stratified by treatment group (variable #2).

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

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

Meeting, communication, and reports

The steering committee, along with the IDMC chairman, will be responsible for scheduling and arranging the IDMC meetings. The meeting will start with a trial overview including status on recruitment as well as potential problems and issues. The remainder of the meeting, which will only be attended by the IDMC members, will be related to evaluations of trial data as described above.

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

The IDMC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the IDMC meeting, including the listing of recommendations by the committee. The IDMC and the independent biostatistician are obligated to keep all patient-level data confidential.