CLINICAL INVESTIGATION PLAN

DOUBLE-D TRIAL

Early Double sequential Defibrillation in Out-of-Hospital Cardiac Arrest
- A Randomised study

"A randomised trial assessing the effect of early double sequential defibrillation with anterior-posterior and anterior lateral pad placement and sequential defibrillation compared to standard pad placement and single defibrillation in patients with Out-of-Hospital Cardiac Arrest with initial shockable rhythm and at least one failed standard defibrillation"

CIV-25-01-051015

Date: 2025 - 12 – 05

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Document version	Date of Issue	Summary of Change
2.0	2025-12--05	-

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Signatures

Sponsor
I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical investigation. I will submit the CIP and all other important clinical investigation-related information to the responsible investigator(s) so that they can conduct the clinical investigation correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical investigation informed and trained.

Sponsor's signature Date: 2025-12-12

Gabriel Riva (digital signature at the bottom)

Coordinating Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.
I will submit this CIP and all other important clinical investigation-related information to the staff members and investigators who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this clinical investigation informed and trained.
I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Coordinating Investigator's signature Date: 2025-12-12

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Funding and research agreement

This is an academic design and financed study. Participating sites will in this trial take own economic responsibilities in taking their own costs. For this purpose, a resource certificate is signed. The defibrillators used in this trial are part of the participating sites standard equipment. A minor economical deal covering education, data management and defibrillation electrode pads used in the trial will be provided.

List of used acronyms and abbreviations

Abbreviation	Term/Explanation
ALS	Advanced Life Support
ADE	Adverse Device Effect
AE	Adverse Event
A-L	Anterior - Lateral
A-P	Anterior - Posterior
AE	Adverse Event
CIP	Clinical Investigation Plan
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
DD	Device Deficiency
DSD	Double Sequential Defibrillation
DMC	Data Monitoring Committee
ECMO	ExtraCorporeal Membrane Oxygenation
ECG	ElectroCardioGram
EMS	Emergency Medical Services
GCP	Good Clinical Practice
GSPR	General Safety and Performance Requirements
IFU	Instructions for Use
ILCOR	International Liaison Committee on Resuscitation
SS-EN ISO	Swedish Standard - European standard International Organisation for Standardisation
ISF	Investigator Site File
ITT	Intention-to-treat = including all data from all subjects who have participated in the clinical investigation
MDCG	Medical Device Coordination Group
mRS	Modified Rankin Scale
OHCA	Out-Of-Hospital Cardiac Arrest

PP	Per Protocol analysis = including only data from subjects who have completed the clinical investigation completely in accordance with the CIP, with no deviations from the CIP
ROSC	Return Of Spontaneous Circulation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1. Synopsis

Background and rationale and design:	**Background:** Out-of-hospital cardiac arrest (OHCA) affects about 270,000 individuals in Europe annually.[1] In OHCA, presenting with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) amendable to defibrillation are among the strongest predictors of survival.[2] If defibrillation can be performed successfully within the first 3-5 minutes, survival can be as high as 70%.[3] However, some patients in VT/VF do not respond to initial defibrillation, and survival decreases with an increasing number of defibrillations required to terminate VT/VF.[4] In 2022, one prospective cluster randomised trial showed increased survival among OHCA patients in refractory VF using an alternative defibrillation strategy; either switching to anterior-posterior defibrillation pad placement (A-P) or Double Sequential Defibrillation "DSD" (using two defibrillators, one in the standard anterior-lateral position (A-L) and one in A-P position and defibrillation in rapid sequence), as compared to standard defibrillation pad placement.[5] Refractory VF was defined as VF that persisted despite three consecutive defibrillations with the defibrillation pads in the standard position. These results prompted the International Liaison Committee on Resuscitation (ILCOR) to release a statement of treatment recommendation on DSD on March 6, 2023. It suggested that "…either vector change or DSD may be considered for adults with cardiac arrest who remain in VF or pulseless VT despite three defibrillations (weak recommendation, low certainty of evidence)." [6] Furthermore, if DSD was to be used, it should be performed with a methodology similar to that described in the trial by Cheskes et al. However, several questions remain. Knowledge gaps highlighted in the ILCOR statement included whether the results from this one cluster randomised trial could be reproduced in any other setting. Furthermore, since survival is inversely associated with the number of defibrillation shocks, if earlier application of DSD could lead

to even higher survival for patients not in refractory VF has never been studied.

Study rationale: To evaluate whether an early DSD-strategy could benefit all patients with VT/VF after the first shock, including those not in refractory VF, the Double-D trial was designed. If DSD proves to be superior to standard defibrillation in a broader cardiac arrest population, also among those not in refractory VF, it would have a large impact on how Advanced Cardiac Life Support (ACLS) should be performed.

Design: This is an academic, investigator initiated, open-label study with a randomised controlled trial (RCT) design and 1:1 allocation (1 DSD: 1 standard). Screening for inclusion will be performed in all cardiac arrests by participating EMS units when there are two study-specific defibrillators available on site.

Study population: Adult OHCA patients with pulseless VT/VF at initial rhythm analysis, at least one defibrillation performed in standard A-L position without return of spontaneous circulation (ROSC).

P: Adult patients, 18 years or older, with OHCA, initial shockable rhythm (VT/VF) and, at least, one defibrillation performed in standard position and ongoing CPR (no ROSC).

I: Application of a second defibrillator with pad placement in the anterior-posterior (A-P) position as early as possible after the first shock and double sequential defibrillation after the following rhythm analysis if the patient is still in VT/VF.

C: Standard defibrillation electrode placement (A-L) and routine defibrillation with one defibrillator after the following rhythm analysis if the patient is still in VT/VF.

O: The primary outcome is 30-day survival.

The trial will be conducted by participating ambulance units attending OHCAs. These units will perform screening for inclusion, randomisation, intervention or control treatment, and initial follow up.

Investigational device:	Two Corpuls3 defibrillators ***OR*** two Stryker LifePak15 defibrillators used together in a double sequential defibrillation
Number of subjects:	916
Inclusion criteria:	- OHCA patients with VT/VF and at least one defibrillation performed in standard (A-L) position
Exclusion criteria:	- Age < 18 years - Obvious pregnancy - Known preexisting Do Not Attempt Resuscitation order
Study objectives:	**Primary objective:** To compare 30-day survival with early double sequential defibrillation in OHCA patients with initial shockable rhythm, at least one defibrillation performed and ongoing CPR, to standard defibrillation. **Secondary objective:** To compare the proportion of ROSC, survival to hospital admission, survival to hospital discharge with favourable neurological function and long-term survival with a strategy of early double sequential defibrillation, compared to standard defibrillation. **Safety objective:** To assess the safety of an early DSD strategy in terms of defibrillation performance.
Study endpoints:	<u>Primary endpoint</u>: - 30-day survival <u>Secondary endpoints:</u> - Any ROSC - Survival to hospital admission, defined as a patient admitted alive to a hospital ward (ICU or CCU unit) with spontaneous circulation - Survival to hospital discharge - Neurological function at hospital discharge (mRS) <u>Other outcomes:</u> - Survival to 90 days - Neurological function (mRS and CPC) at 30 days - Neurological function (mRS and CPC) and Health-related Quality of Life at 90 and 180 days - Termination of ventricular fibrillation

	- Total time in ventricular fibrillation
Planned duration of the clinical investigation:	Q2 2025 – Q4 2029

2. *Identification and description of the investigational device*

2.1. Description of the investigational devices

The standard treatment for OHCA to terminate VT or VF is external defibrillation in order to restore spontaneous circulation. According to the ERC guidelines, the electrodes are placed in an anterior-lateral (A-L) position. The defibrillators used in this trial will be Corpuls3 (used in Sweden and Spain) and LIFEPAK15 (used in The Netherlands and Spain).

Corpuls3

Corpuls3 is a defibrillator with functions including monitoring of cardiac rhythm and vital parameters, but also defibrillation, cardioversion, and pacing. It is part of the standard equipment in the EMS units in the participating sites stated above.

The risk classification of Corpuls3 is non-invasive IIb.

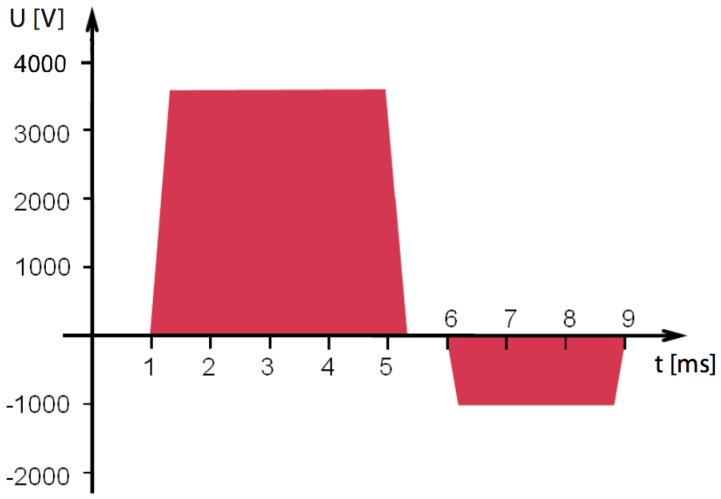
Image: Corpuls3

The Corpuls3 provides monitoring of cardiac rhythm and vital parameters as well as diagnostic and therapeutic functions for the treatment of emergency and intensive care patients. A 12 lead ECG function provides the user a comprehensive ECG, which can be optionally supplemented by ECG analysis software.

Further monitoring functions include oxygen saturation measurement (pulse oximetry), carbon dioxide measurement (capnometry) and temperature measurement, in addition to non-invasive and invasive blood pressure monitoring. Corpuls3 provides the following therapeutic functions:

- defibrillation
- cardioversion
- pacing

Defibrillation with corpuls3 is performed with a Biphasic, positive rectangular waveform 4 msec. (90 % energy) and a negative rectangular waveform 3 msec. (10 % energy) pulse.



The defibrillator which operates with the Corpuls3-specific biphasic pulse has two operating modes:

- automatic external defibrillation (AED mode)
- manual defibrillation and cardioversion (manual mode)

In AED mode, the user is assisted by an automated ECG analysis, verbal instructions (configurable) and a metronome (configurable). The defibrillation pulse is triggered by the user.

In manual defibrillation mode, the user has full freedom of action and decision-making.

Defibrillation is performed by applying disposable adhesive electrodes, so-called corPatch electrodes.

The standard position of the corPatch electrodes is the A-L Position, but alternative electrode positioning, including A-P should be considered in refractory VF.

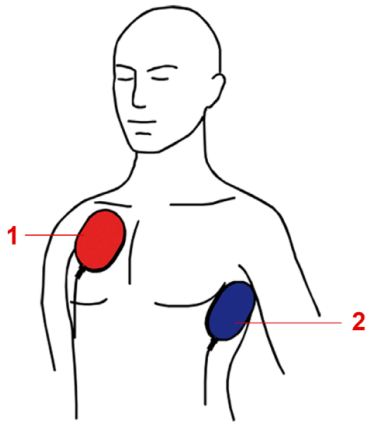


Image: Anterior-lateral (A-L, standard) corPatch electrode placement from Corpuls3 user manual

The Corpuls3 is intended for measurement and monitoring of vital parameters in addition to defibrillation, cardioversion or cardiac pacing of patients in the preclinical and clinical field by qualified medical staff trained in the use of the device.

Corpuls3 may only be operated by trained medical staff of, for example, hospitals, doctor's offices and emergency medical services, as well as of authorities and public safety organisations.

The qualified staff must be

• trained in proper handling, use and operation of the device and of the approved accessories as well as be

• trained in basic and advanced resuscitation measures (Basic Life Support and Advanced Cardiac Life Support).

For further information please see attached Description and intended purpose Corpuls3.

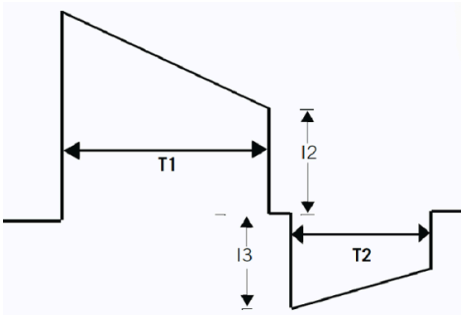
LIFEPAK15

LIFEPAK®15 is a defibrillator with functions including monitoring of cardiac rhythm and vital parameters, defibrillation, cardioversion, and pacing.[1, 2] LIFEPAK®15 devices are part of the standard equipment in the EMS units at the participating sites stated above.

The risk classification of LIFEPAK®15 is non-invasive IIb.[3]

The LIFEPAK®15 provides monitoring of cardiac rhythm and vital parameters as well as diagnostic and therapeutic functions for the treatment of emergency or critically ill patients. Further monitoring functions include oxygen saturation measurement (pulse oximetry), carbon dioxide measurement (capnometry) and temperature measurement, in addition to non-invasive and invasive blood pressure monitoring.

Defibrillation is performed with a biphasic truncated exponential waveform.



Biphasic Waveform

The defibrillator which operates with the LIFEPAK®15 has two operating modes:

- automatic external defibrillation (AED mode)
- manual defibrillation and cardioversion (manual mode)

In AED mode, the user is assisted by an automated ECG analysis, verbal instructions (configurable) and a metronome (configurable). The defibrillation pulse is triggered by the user. In manual defibrillation mode, the user has full freedom of action and decision-making. Defibrillation is performed by applying disposable adhesive electrodes.

LIFEPAK®15 may only be operated by trained medical staff of, for example, hospitals, doctor's offices and emergency medical services, as well as of authorities and public safety organisations. The qualified staff must be:

- trained in proper handling, use and operation of the device and of the approved accessories
- trained in basic and advanced resuscitation measures (Basic Life Support and Advanced Cardiac Life Support).

The LIFEPAK®15 is CE marked for defibrillation in OHCA. The usage of this device with the DSD strategy falls under "use outside of intended purpose" and is therefore deemed "off-label". The device manufacturer was contacted to evaluate potential risks associated with the use of this device within the DSD approach. According to the statement by the manufacturer, usage of this device for a DSD strategy incurs a theoretic chance of device damage or malfunction. The device-associated risks of DSD are further analysed in section 4.2 and 4.3.

For further information please see attached statement regarding LIFEPAK15. "3314911-030_int-eng_lifepak_15_operating_instructions "

2.2. Intended purpose

The intended purpose of defibrillators in cardiac arrest is to terminate VT or VF with external defibrillation to restore spontaneous circulation. This can be done by electrodes placed in standard anterior-lateral (A-L) position, but in some circumstances in the anterior-posterior (A-P) position. Using one defibrillator with either electrode position (A-L or A-P) is within the scope of the CE-mark of the investigational devices. This is all part of standard clinical practice and within the intended use of the investigational device.

An alternative strategy is to use two defibrillators (both A-L and A-P electrode position) and to perform two defibrillations in rapid sequence, as soon as possible but not simultaneously, so called double sequential defibrillation (DSD). This strategy is, at least partially, outside the CE-mark.

The intended purpose of the investigational device in this clinical trial is to terminate VT/VF by performing DSD as early as possible after the first defibrillation. To our knowledge this is the first clinical trial evaluating an early DSD strategy in cardiac arrest.

2.2.1 Performing DSD within the Double-D trial:

In this trial, all patients will be connected to defibrillators with adhesive electrodes in standard A-L position (se image above).

If another defibrillator (AED) is already attached to the patient at EMS arrival the EMS will remove the electrodes from the other defibrillator and attach electrodes in standard A-L position and connect them to Corpuls3 or LIFEPAK15 in all cases. This is all part of current routine practice.

2.2.2. If randomised to intervention

The electrodes from a second defibrillator (Corpuls3 or LIFEPAK15) are placed in the A-P posterior position during interruptions in chest compressions for ventilation, thus not interfering with the electrodes from the first defibrillator. Attachment of the second defibrillator electrodes shall be performed as soon as possible after randomisation.

If the patient has VT/VF at the subsequent rhythm analysis (every two minutes during CPR) both defibrillators are charged simultaneously during chest compressions and shocks from the two defibrillators are delivered by one healthcare professional in rapid sequence, as soon as possible but not simultaneously, (A-L first, A-P second when possible) and CPR is immediately resumed (DSD strategy). A DSD strategy will be used for all subsequent defibrillations if the patient remains in VT/VF, until termination of resuscitation or a decision to transfer the patient to hospital. The total shock pause (hands off interval where no compressions are performed) is recommended to be less than 5 seconds.

In summary:
- First defibrillator is attached in A-L position.
- Second defibrillator is attached in A-P position.
- Both defibrillators are set to manual mode.
- If VT/VF is present at the next rhythm analysis, chest compressions are resumed and both defibrillators are charged to maximal energy (200J Biphasic for Corpuls3, 360J for LIFEPAK15)
- Defibrillations are performed sequentially (as soon as possible but not simultaneously, preferably A-L first, A-P second.

2.2.3 If randomised to the control group,

The ambulance crew team will continue Advanced Cardiac Life Support in accordance with the European Resuscitation Council (ERC) guidelines and local protocols. Defibrillation is performed with standard A-L electrode placement using one Corpuls3 or LIFEPAK15 defibrillator. Maximal energy output should be used for second shock and beyond (200J Biphasic for Corpuls3, 360J Biphasic for LIFEPAK15). The 2025 ERC guidelines suggest that shifting the placement of electrodes to the anterior-posterior position (so called vector change) may be considered after three unsuccessful standard A-L shocks and refractory VT/VF. It lies within the decision capacity of the ambulance nurse or physician on site and local protocols to determine whether a vector change strategy may be conducted after three non-successful standard A-L shocks.

For both groups, in accordance with 2025 ERC guidelines, charging the defibrillator(s) before the rhythm check is an acceptable alternative, if this is in accordance with local practice and protocols.

2.3. Manufacturer of the investigational device

Corpuls3 (Sweden and Spain)

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LIFEPAK15 (the Netherlands and Spain)

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Mail: medicalcustomerservice@stryker.com

2.4. Model/type

- Corpuls3 / LIFEPAK15

2.5. Target population

The target population for this trial is patients with OHCA and VT/VF after one defibrillation in standard A-L position. The defibrillators deliver energy through electrodes attached to the patient in A-L or A-P position. Defibrillation with Corpuls3 or LIFEPAK15 is compliant with relevant GSPR, please see attached files.

2.6. Summary of required training/experience needed

Corpuls3 or LIFEPAK 15 may only be operated by trained medical staff of, for example, hospitals, doctor's offices and emergency medical services, as well as of authorities and public safety organisations. The qualified staff must be:

• trained in proper handling, use and operation of the device and of the approved accessories as well as be

• trained in basic and advanced resuscitator measures (Basic Life Support and Advanced Cardiac Life Support).

All EMS units in this trial provide ACLS care for OHCA and are trained in ACLS. In addition to this, all EMS organisations included in the study ensure that EMS crews are trained in double sequential defibrillation prior to participating in the trial.

This is in practice done by:

a) “Theoretical study concept course”. All EMS crews take a 20-minutes obligatory web-course providing theory and methodology for the study and the intervention.

b) Practical training. All EMS crews shall under the supervision of a certified ALS-instructor undergo practical training. This training includes application of defibrillation pads in the anterior-posterior position while making sure to minimise interruptions in chest compressions, performing defibrillation in manual mode and charging and defibrillating with two defibrillators in a sequential manner. During this training special attention will be given to delayed (sequential) defibrillation by one individual. All participants shall in front of an instructor demonstrate correct practical performance. Finally, to perform team training in ALS scenarios using the Double-D algorithm.

The scenarios shall facilitate the early provision of a DSD with maintained safety for all personnel, while minimizing interruptions in chest compressions. All EMS crews will rehearse the CPR training including DSD training once a year.

For details on EMS training protocol, please see attached “Double-D training prerequisites and procedure 250922_Final”

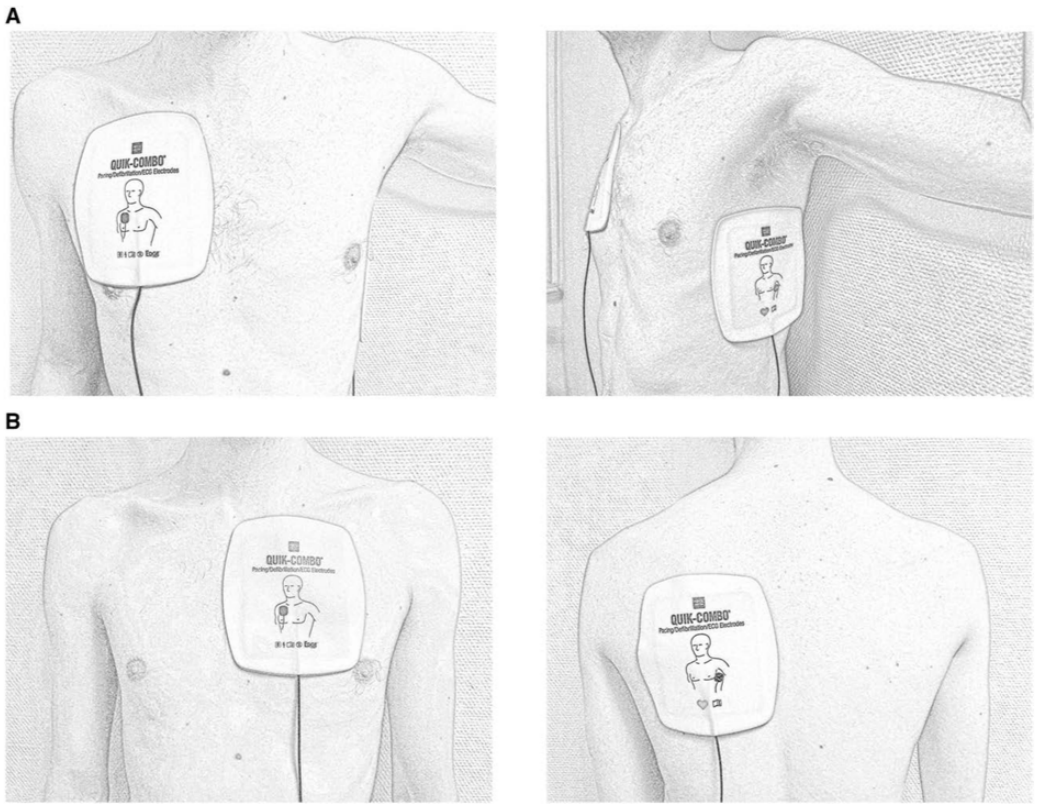
3. *Background and justification for the design of the clinical investigation*

3.1. Background

Out-of-Hospital Cardiac Arrest is a major health issue affecting approximately 380 000 persons in the U.S. and 270 000 in Europe each year.[4] Presence of VT or VF, which are amendable to defibrillation, at the first rhythm analysis is one of the strongest predictors of survival, with survival rates up to 10 times higher compared to patients found in asystole or pulseless electrical activity.[5, 6]

However, not all patients presenting with VT/VF will respond to defibrillation. The term “refractory ventricular fibrillation” is used for cardiac arrest patients who remain in VT/VF despite 3 consecutive defibrillation shocks. Treatment recommendations for this condition include administration of drugs such as epinephrine and amiodarone, continuous CPR, and where available, consideration of transport with ongoing CPR to a facility capable of ECMO-assisted CPR.[7] Importantly, survival of patients with VT/VF is inversely associated with the number of defibrillations required to terminate VT/VF.[8] Therefore, an intervention that could increase the rate of conversion from VT/VF into a perfusing rhythm earlier has the theoretical potential to increase survival.

Standard external defibrillation is provided by applying defibrillator pads in the anterior-lateral position (A-L) with the anterior pad placed to the right of the sternum, just below the clavicle and the lateral pad in the left mid-axillary line, approximately in level with a V6 ECG electrode. This position should be clear of any breast tissue, see fig A.[9]

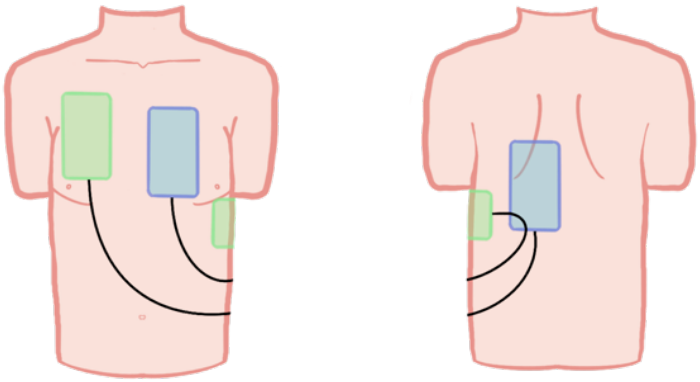


An alternative pad placement is the so-called anterior-posterior position (A-P) where the anterior pad is placed on the left side of the sternum, below the clavicle, and the second posterior pad is placed on the back, to the left of the spine, below the left scapula, see fig B. Advantages with A-L position include the possibility to perform defibrillation without adhesive defibrillation pads (not recommended during CPR since 2010), but it is also relatively easy to apply defibrillation pads during CPR without the need to move the patient, and application can be done while chest compressions are ongoing.

One advantage with A-P position is the theoretical closer proximity between pads resulting in lower thoracic impedance, and that the pads are encircling the heart, i.e. more current is transmitted through the posterior parts of the heart. Disadvantages include the need to move the patient to apply the posterior pad, interruptions in chest compressions during application, and no visual control over the posterior pad during chest compressions.

A-L pad placement has been compared to A-P placement in elective cardioversion of atrial fibrillation with conflicting results. However, more recent studies comparing A-L to A-P using modern biphasic rectilinear or truncated defibrillation waveforms have found A-L placement superior in this setting.[10]

An alternative defibrillation strategy with double sequential defibrillation includes the use of two defibrillators, one in the A-L position and one in the A-P position and defibrillation shocks in rapid sequence “Double Sequential Defibrillation” (DSD).



Electrode pad placement in DSD

Double sequential defibrillation was described in 1994 to treat induced ventricular fibrillation during electro-physiology studies, that where refractory to standard defibrillation.[11] Observational studies and case reports of DSD has provided conflicting results, but usually DSD was used as an “last resort” when all other therapies had failed [12]. However, in 2022, the first and only randomised trial demonstrated increased survival with a strategy of either switching from A-L to A-P or from A-L to DSD in refractory VF (defined as VF at three consecutive rhythm analysis despite standard A-L defibrillation).

These results prompted the International Liaison Committee on Resuscitation ILCOR to release a statement of treatment recommendation on DSD on March 6, 2023. It *suggested* that “either vector change or DSD *may be considered for adults with cardiac arrest who remain in ventricular fibrillation or pulseless ventricular tachycardia despite three defibrillations* (weak recommendation, low certainty of evidence).” Further, if DSD would be used it should be performed with a methodology similar to that described Canadian trial.

However, several questions remain. Knowledge gaps highlighted in the ILCOR statement included whether the results from this one cluster randomised trial could be reproduced in any other setting. Furthermore, since survival is inversely associated with the number of defibrillation shocks, whether earlier application of DSD could lead to even higher survival for patients not in refractory VF has never been studied. Finally, no randomised trial on DSD has evaluated neurological function at 90 and 180 days or Health related quality of life.

3.2. Evaluation of results of prior testing, assessments and clinical investigations

As stated above, DSD has already been tested in a previous randomised controlled trial in humans and may be considered in refractory VT/VF according to international guidelines.

The difference in this trial is to apply DSD after one failed defibrillation, before the VT/VF is considered refractory.

DSD with Corpuls3 is considered to be technically safe according to manufacturer, please see attached file “231130_DSED_eng_Corpuls”.

Double-D Pilot trial

We have performed a pilot study (CIV-25-01-051015) using Corpuls3 including 40 patients with the aim of assessing the feasibility and safety of a randomised trial comparing early DSD to standard defibrillation at 4 pilot sites (Clinical trials NCT06447805).
Randomisation in the pilot trial was 3:1 (3 DSD, 1 standard). The primary feasibility outcome was proportion of patients randomised before three defibrillations (target >80%). The primary safety outcome was defibrillation malfunction.

In total, 40 patients were included between June 2024 and April 2025, 29 were randomised to DSD and 11 to standard. Of all patients, 32/40 were randomised before three defibrillations (80%). Cross-over occurred in 1 patient in the control group after five standard defibrillations and in one patient in the control group. Follow-up was 100%.

In the pilot study, all defibrillators were checked for functionality via a self-test immediately after resuscitation and a test defibrillation as soon as possible after resuscitation following each DSD use. We have not had any reported adverse events or technical problems. No alarming safety risks regarding defibrillators or time delays have been observed.

In conclusion, we found that randomisation to a strategy of early DSD was feasible and appears safe. Therefore, the Double-D main trial will use same methodology for ambulance training and intervention as in the pilot trial.

In the pilot trial, patients who had received one defibrillation at any point during resuscitation, irrespective of first presenting rhythm, were included. This resulted in the inclusion of 14 patients who had an initial non-shockable rhythm that later transitioned to a shockable rhythm during resuscitation and were included. The rate of ROSC among those patients was very low and only one patient survived to hospital admission. The low rate of survival in this group is also supported by observational data (3). Therefore, we do not believe this group will benefit significantly from DSD and therefore, to increase homogeneity of the study population in the main trial, we will only include patients with an initial shockable rhythm.

3.3. Evaluation of clinical data

Please see 3.1 above

4. Risks and clinical benefits of the investigational device and clinical investigation

4.1. Expected clinical benefits

The novel strategy of DSD might have a higher probability of terminating VT/VF and restoring spontaneous circulation. Based on the results from one major previous trial, there is a strong signal that DSD is superior to continuous standard defibrillation in refractory VT/VF in terms of saving more lives and neurological recovery. The clinical situation, to be in a cardiac arrest, is highly time critical, and every minute that passes without restoration of spontaneous circulation is associated with lower survival. Every minute in delay without defibrillation and CPR raise mortality by 10%. Part of this outcome is due to irreversible brain damage that is caused by cerebral hypoperfusion during the cardiac arrest. The earlier VT/VF can be terminated, and spontaneous circulation be restored, the higher the probability of survival.

We therefore believe that a DSD strategy a soon as possible has a high potential to save more lives through a dual effect since:
a) A larger proportion of patients will have their VT/VF terminated and spontaneous circulation restored, e.g. higher survival,
b) The termination of VT/VF could occur sooner, leading to shorter duration of brain hypoperfusion and ischemia, and eventually better neurological function among survivors.

4.2. Anticipated adverse device effects

Possible adverse device effects with DSD compared to standard defibrillation include:

1. Higher energy delivery
A DSD strategy delivers double the amount of energy with each defibrillation. This may result in injuries such as superficial burns to the skin.

2. Failure to deliver energy during defibrillation / or defibrillation malfunction
There may be a theoretical risk of potential damage to defibrillators due to no synchronised shocks.[13] There is a theoretical risk that synchronised defibrillation could lead to high voltage and cause damage to the defibrillators. This risk may be higher if the defibrillator pads from the two defibrillators are placed linearly, as opposed to a 90-degree angle, and if defibrillation is synchronised. In this trial, the second pair of defibrillation electrodes will be placed at an almost 90-degree angle and defibrillation will be performed sequentially, meaning approximately a one second delay between defibrillation using the two defibrillators, with one person pressing both defibrillators in sequence. In the trial by Cheskes et al., there were no reports of defibrillation malfunction despite more than 130 patients treated using DSD. Also, in a recent survey on defibrillator damage during DSD use in clinical practice, the rate of defibrillator damage seemed to be exceedingly low.[14] In our pilot trial, there was no report of defibrillation malfunction or deficiencies, see above.

4.3. Risks associated with participation in the clinical investigation

The application of the second pair of defibrillation electrodes is associated with a short interruption in chest compression at the moment of placement of the posterior electrode. Long interruptions in chest compressions have been found to be associated with poorer outcome. However, short interruptions for ventilation have not been found to be worse than continuous chest compressions. In the trial by Cheskes et al., the application of the posterior

electrode was done in a standardised way, using the interruption in chest compressions for ventilation and simultaneously move the patient and apply the posterior electrode. They could also report guideline compliant CPR quality regardless of the treatment strategy (standard, Vector Change or DSD).[15] In order to minimise this risk there will be mandatory training for all participating ambulance crew on how to synchronise posterior defibrillation electrode placement to pauses in ventilation. The extra moment should not take longer than 10-15 seconds.

4.4. Possible interactions with concomitant medical treatments

This is strictly a defibrillator management/strategy trial, and no medication are involved. All other medical treatments, e.g., adrenalin, amiodarone, airway management and ventilation strategies and the use of mechanical CPR-devices follow standard routine for ALS.

During the course of the trial, it is possible that two other RCTs from ARREST (the Netherlands) are initiated in the same study region as this study. If the study period of these two other RCTs (REVIVE-PEEP and LUCASVP) would overlap with the current study, patients might be included in several RCTs simultaneously. Because neither of the selection, randomisation or treatment procedures interact with/influence each other's selection, this would not influence or bias any of these studies' results.

4.5. Steps to be taken to control or mitigate risks

1. Ambulance crew training. As mentioned above, the main risk with the DSD strategy, as far as we know, relates to the application of defibrillation electrodes and defibrillation. Therefore, all participating ambulance units must be trained and certified before participation in the trial. This is to minimise the risk of long interruptions in chest compressions and ensure correct electrode placement.

2. During the pilot study, we had individual assessment and early feed-back of EMS intervention for every included patient to allow for early detection of unanticipated adverse events. In the main trial we will continue to have close monitoring, with early assessment and feedback with regular intervals, or if requested by EMS personnel in CRF1. Please also see the attached monitoring plan.

3. Evaluation of defibrillators after each and every use. The Corpuls3 performs a complete system check each time it is switched on. This internal automatic self-test checks the system components. LIFEPAK 15 performs an internal self-test every time it is switched on and an automatic self-test daily at 03:00 AM.

If error messages appear during automatic self-test, these are displayed in the status line and listed in the event history. After each use of DSD, the defibrillators will be checked for malfunction by performing an automatic self-test to ensure functionality. Furthermore, all Corpuls3 defibrillators used in the study will be tested by using a test box and performing a test discharge at least once weekly during the study period (part of current

routine) and as soon as possible after each DSD use, and a “User Test” as described in the operating instructions for LIFEPAK15.

4. Stepwise escalation of including sites to uncover unknown risks. In order to perform monitoring of included patients and feedback from participating ambulance crew the trial will have an escalation strategy. The training protocol can be modified during trial to mitigate potential risks. For all significant modifications, the Swedish Medical Product Agency and the Swedish Ethical Review Authority will be notified. Please see also 9. Amendments to CIP.

4.6. Rationale for benefit-risk ratio

Cardiac arrest is a highly critical medical emergency. Only approximately 1/3 of all patients with VT/VF will survive to 30 days with standard ACLS treatment. Patients that survive the initial resuscitation phase and are transferred to hospital may still suffer from anoxic brain injury, cardiogenic shock, multiorgan failure and traumatic injuries from chest compressions. It is therefore highly important to convert patients in VF/VT to a sustained spontaneous circulation as soon as possible.

In cardiac arrest situation with VT/VF, early defibrillation within 3-5 minutes is the most important therapeutic treatment to terminate the arrythmia and based on the results from previous trials there is a strong signal that DSD is superior to standard defibrillation in refractory VT/VF. In terms of survival. The risk with DSD includes a theoretical risk of defibrillation damage but this risk appears to be exceedingly low. Another physical risk is worse CPR quality. However, to be in a cardiac arrest is highly time critical, and every minute that passes without restoration of spontaneous circulation is associated with lower survival. Part of this is due to irreversible brain damage that is caused by cerebral hypoperfusion during the cardiac arrest. The earlier VT/VF can be terminated, and spontaneous circulation be restored, the higher the probability of survival. We believe that a DSD strategy a soon as possible can have a potential dual positive effect since

a) a larger proportion of patients will have their VT/VF terminated and spontaneous circulation restored, which could potentially lead to higher survival,

b) the termination of VT/VF will occur sooner, leading to shorter duration of brain hypoperfusion and ischemia, which could potentially lead to better neurological function among survivors.

In summary, we believe that this novel method to use defibrillators has a strong potential benefit that largely outweighs the potential risks, and that the intervention can have a direct positive effect on the study participants. The net benefit is likely to be determined by efficacy of the intervention rather than safety aspects.

5. Objectives and hypotheses of the clinical investigation

5.1. Objectives

5.2.1. *Primary objective*

To compare 30-day survival with early double sequential defibrillation in OHCA patients with initial shockable rhythm, at least one defibrillation performed and ongoing CPR, to standard defibrillation.

5.2.2. *Secondary objective(s)*

To compare the proportion of ROSC, survival to hospital admission, survival to hospital discharge with favourable neurological function and long-term survival with a strategy of early double sequential defibrillation, compared to standard defibrillation.

5.2.3. *Safety objectives*

To assess safety of an early DSD strategy in terms and defibrillation performance.

5.2. Hypotheses

5.3.1. *Primary hypothesis*

In OHCA patients with an initial shockable rhythm who have undergone at least one defibrillation and still require CPR, switching to an early DSD strategy leads to higher 30-day survival rates compared to standard defibrillation.

6. Design of the clinical investigation

6.1. General information

Design: This is an academic, investigator initiated, open-label randomised controlled trial (RCT) design and 1:1 allocation (1 DSD: 1 standard). Screening for inclusion will be performed in all cardiac arrests by participating EMS units where there are two study-specific defibrillators available on site: one Corpuls3 + one Corpuls3 ***OR*** one LIFEPAK15 + one LIFEPAK15

Study population: All adult OHCA patients (≥18 years) with VT/VF at initial rhythm analysis and at least one defibrillation performed in standard A-L position and ongoing CPR (no ROSC).

Study setting: The study is conducted in the prehospital emergency medical services, i.e. ambulance organisations. The trial will be conducted by participating ambulance units attending OHCAs staffed with special nurses. These units will perform screening for inclusion, randomisation, intervention or control treatment and initial follow-up. All ambulance units in Sweden, the Netherlands and Spain follow the European Resuscitation Council (ERC) guidelines, published in 2021 and 2025 [7], and perform team training on an annual basis for high quality provision of ALS care in OHCA.

6.2. Endpoints

6.2.1. Primary endpoints

The primary endpoint of this trial will be survival to 30 days after the cardiac arrest.

6.2.2. Key secondary endpoint (s)

The secondary endpoints will, in chronological order be:
- Any prehospital ROSC, defined as confirmed ROSC by EMS personnel, in accordance with latest Utstein definition [16]
- Survival to hospital Admission, defined as a patient admitted alive to a hospital ward (ICU or CCU unit) with spontaneous circulation
- Survival to hospital discharge
- Neurological function at hospital discharge (mRS) using the modified Rankin Scale (mRS) scale.[17]

6.2.3. Other endpoints (optional)

- Neurological function (CPC) at hospital discharge
- Survival at 90 days
- Neurological function (mRS and CPC) at 30 days
- Neurological function (mRS and CPC) and Health-related Quality of Life at 90 days
- Neurological function (mRS and CPC) and Health-related Quality of Life at 180 days
- Termination of shockable rhythm, defined as the presence as a non-shockable rhythm 5 seconds after defibrillation
- Total time in ventricular fibrillation
- Total number of shocks (each DSD or STD count as one)
- Time from shock to re-fibrillation and time to first organised rhythm
- Time to first ROSC
- CPR quality measures (chest compression fraction, longest pause, chest compression depth)

Data to assess the listed other endpoints above, such as long-term survival, Health-related Quality of Life and ECG-outcomes for mechanistic and explanatory sub studies are not mandatory to collect at all participating sites (optional).

6.2.4. Description of the intervention and comparator

Please see 6.6.

6.3. Subjects

6.3.1. Inclusion criteria

- OHCA patients in VT/VF at initial rhythm analysis, and at least one defibrillation performed in standard (A-L) position and still ongoing CPR.

6.3.2. Exclusion criteria

- Age < 18 years
- Obvious pregnancy
- Known preexisting Do Not Attempt Resuscitation order

6.3.3. Investigation population

The goal is to include 916 patients (458 in each group)

6.3.4. Criteria and procedures for subject withdrawal or discontinuation.

If DSD by any reasons cannot be performed due to any expected/unexpected circumstances at the scene EMS shall at once proceed with standard defibrillation according to routine practice. All randomised patients will be included in the intention to treat ITT analysis.

6.4. Methods to minimise bias

Study participants will be randomised at the individual patient level, therefore minimising confounding and allocation bias.

Due to the nature of the intervention, blinding is not possible for providers, therefore there is a theoretical risk for performance bias (duration of CPR). Neurological and HRQoL follow-up at 90 and 180 days will be collected by research staff in a blinded way.

6.5. Unblinding

This is an open-label trial. However, the neurological long-term follow-up will be performed in a blinded way. The persons collecting the neurological follow-up data at 90 and 180 days will not be aware of the randomised allocation.

6.6. Description of the clinical procedures and diagnostic methods relating to the clinical investigation

The study will be conducted by prehospital emergency medical services, i.e. ambulance organisations. The trial will be conducted by participating ambulance units attending OHCAs. These units will perform screening for inclusion, randomisation, intervention or control treatment and initial follow-up. All ambulance units in Sweden, the Netherlands and Spain follow European resuscitation council (ERC) guidelines [18] and perform team training on an annual basis for high quality provision of ALS care in OHCA.

In clinical practice, a cardiac arrest is confirmed by the absence of consciousness and absence of normal or no breathing. In this clinical situation cardiac arrest shall be suspected and CPR initiated. In all cases of OHCA a defibrillator should always be attached with the standard pad placement first (A-L position) in accordance with standard of care and ERC guidelines. If there is VT/VF or an AED suggests defibrillation, defibrillation should be performed, and immediate chest compressions resumed.

Thereafter, the patient can be screened for inclusion. If two study specific defibrillators are on site, and no exclusion criteria is present the patient can be included and randomised. Randomisation will be performed by opening an opaque envelope with concealed allocation that will be stored with the EMS defibrillators. All envelopes will be pre-randomised in a 1:1 ratio in blocks consisting of 4-6-8 and stratified by region and ambulance provider.

Defibrillator requirements:
In this study all participating EMS units will have Corpuls3 or LIFEPAK15 defibrillators.

A prerequisite for inclusion in this trial is that there are two study specific defibrillators on site; this means that either one EMS unit with two defibrillators (Corpuls3 or LIFEPAK15) or two EMS units with one device each shall be on site.

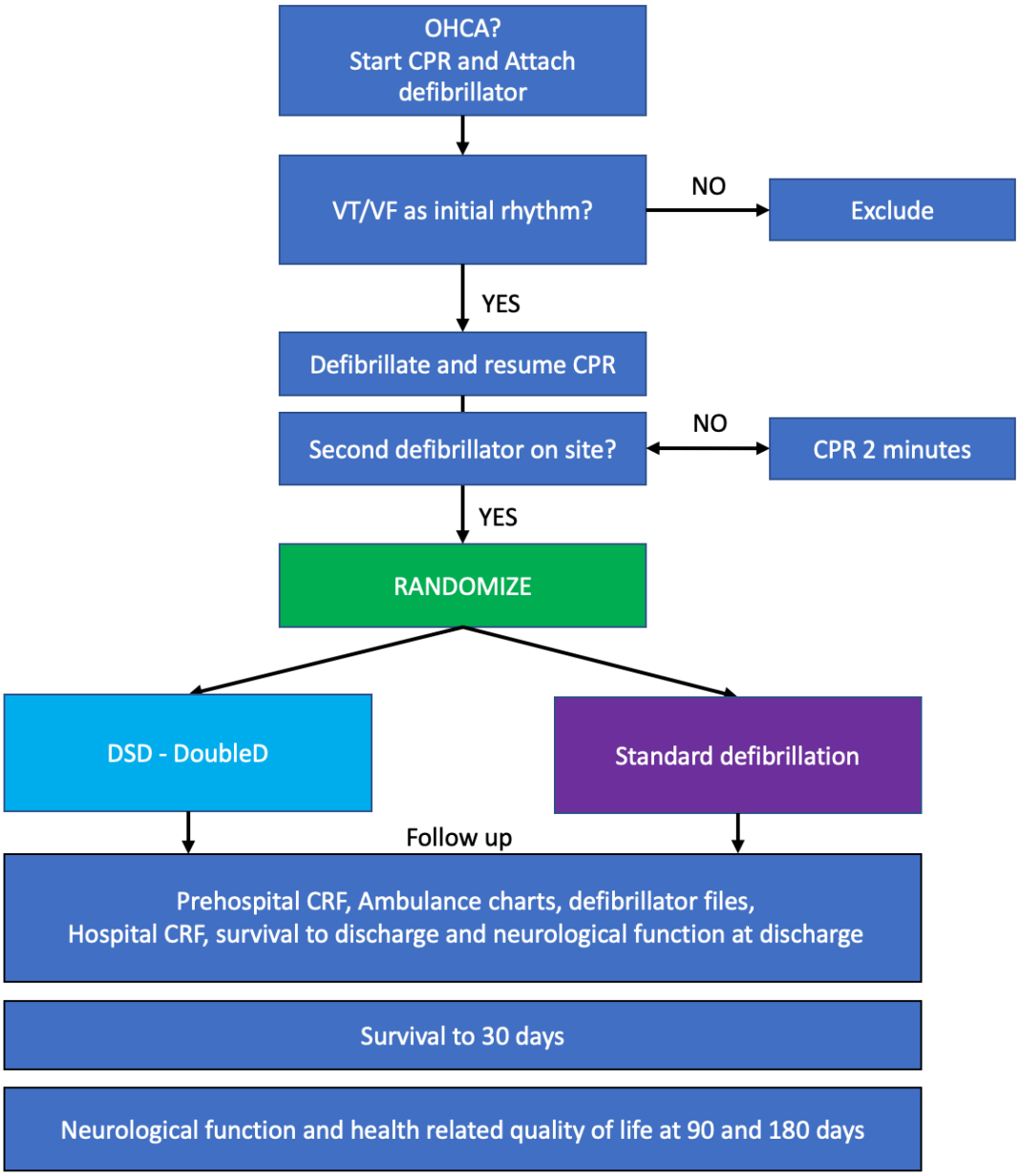
In situations where the first EMS unit only has one defibrillator, but a second EMS unit arrives, the patient can still be included as soon as the second defibrillator is on site. Therefore, in clinical practice the inclusion of patients will follow the flow-chart below.

If there is another defibrillator attached to the patient at EMS arrival (a public access AED or an AED from firefighters or police), that AED will be removed and the electrodes from Corpuls3 or LIFEPAK15 will be attached to the patient and connected to Corpuls3 or LIFEPAK15 in all cases (in accordance with routine practice).

Intervention
If the patient is randomised to the intervention group, the ambulance crew team will apply the second defibrillator with electrodes placed in the A-P position as soon as possible in the next CPR cycle (2 minutes) while trying to minimise interruptions in chest compressions. Defibrillation is performed by one person defibrillating both defibrillators in a sequential manner “Double Sequential Defibrillation” (DSD). All consecutive defibrillations will thereafter be performed with the DSD strategy until ROSC, termination of resuscitation or decision to move the patient to hospital. See also 2.2.2 *Intervention group.*

Control
If randomised to the control group, the ambulance crew team will continue ACLS in accordance with standard of care. Defibrillation is performed with standard electrode placement using a single defibrillator. If an AED is the first defibrillator attached to the patient, the ambulance crew should shift from an AED to their own manual defibrillator, but the mode of defibrillation should follow standard treatment in A-L position and only one defibrillation from one defibrillator should be used for each defibrillation attempt, and continued until ROSC, termination of resuscitation or decision to move the patient to hospital. Due to the

updated European guidelines in 2025, it lies within the decision capacity of each EMS unit to shift from A-L to A-P after three failed defibrillations. See also 2.2.3 *Control group*



OHCA = Out-of-Hospital Cardiac Arrest, VT/VF = pulseless Ventricular Tachycardia/Ventricular Fibrillation, CPR = Cardiopulmonary Resuscitation, DSD = Double Sequential Defibrillation, CRF = Clinical Report Form

Follow-up will be performed immediately after every resuscitation attempt (patient characteristics, pre-hospital treatment and short-term outcome and defibrillator files), at the hospital and long term follow up until 180 days. For details regarding data collection, se section 8.

6.7 Participating Trial sites

Sweden

1. Emergency medical services Sahlgrenska Universitetssjukhuset, Region Västra Götaland
Gullbergs Strandsgata 36C
411 04 Gothenburg
Phone: 0721-876236
Local PI: Carl Magnusson, R.N., Ph.D. Head of Research and Development

2. Emergency medical services Sjukhusen I Väster, Region Västra Götaland (Alingsås/Lerum and Kungälv)
Södra Ringgatan 30
441 83 Alingsås
Phone: 03232-22 60 00
Local PI: Andreas Claesson, R.N. Ph.D.

3. Emergency medical services Region Halland
Ambulans och Sjukresor I Halland (ASH) Skånegatan 59, plan 3
30238 Halmstad
Phone (+46) 076 72 14 007
Local PI: Kristoffer Wibring, R.N. Ph.D.

4. Emergency medical services Skaraborgs Sjukhus, Region Västra Götaland
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54949 Skövde
Phone: 0500 - 43 10 00
Local PI: Per Wennberg, R.N. Ph.D.

5. Emergency medical services NU-Sjukvården, Region Västra Götaland
Område ledning och stöd, NU-sjukvården
461 85 Trollhättan
Phone: 010-435 10 35
Local PI: Carl Magnusson, R.N. Ph.D.

6. Emergency medical services, Region Värmland
Älvgatan 39,
65230 Karlstad
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Local PI: Linus Lilja, M.D., Ph.D.

7. Emergency medical services, Södra Älvsborgs Sjukhus, Region Västra Götaland
Brämhultsvägen 53,
501 82 Borås
Phone: 033 - 616 10 00
Local PI Emil Bergerum, R.N.

8. Emergency medical services, Prehospital Intensive Care Unit Shalgrenska universitetssjukhuset / Östra Sjukhuset
Diagnosvägen 11
41 650 Göteborg
Phone: 031 - 343 40 43
Local PI: Patrik Martner., M.D.

9. Ambulanshelikoptern (HEMS) Västra Götalandsregionen, Kungälvs sjukhus
Lasarettsgatan 1
442 83 KUNGÄLV
Phone: 0046 (31) 55 63 85
Local PI: Knut Taxbro, M.D. Ph.D.

The Netherlands

10. ARREST (AmsteRdam REsuscitation STudies), Amsterdam UMC
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Spain

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Phone: (+34) 639 91 74 03
Local PI: Carlos Rubio Chacón M.D. Ph.D.

12. Centro de Emergencias 061 Andalucía,
Servicio Andaluz de Salud
Avda Severo Ochoa 28,
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Phone: (+34) 617 56 33 52
Local PI: María José Luque-Hernández M.D. Ph.D.

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Phone. (+34) 93 264 44 00 Ext. 12200 | Mòbil 616446068
Local PI: Dr. Xavier Jiménez Fàbrega, MD, PhD

14. Médico Emergencias Osakidetza EMERGENTZIAK, (Bilbao)
Maria Diaz de Haro 53, 48004 Bilbao
Baque Country. Spain
Phone: (+34) 99 68 11 82
Local PI, Cristian Fernández Barreras MD

Addition of new sites during the course of the clinical trial:

Additional sites can and will be added during the course of the clinical investigation. Before any addition of new sites approval must be sought by from relevant authorities, i.e., application of substantial modification to the Swedish medical product agency and Swedish ethical review authority, regarding new sites, must be approved.

6.8. End of the clinical investigation

The clinical investigation ends when the last subject has completed the last follow-up at 180 days. The sponsor will notify the Swedish Medical Products Agency within 15 days after the end of the clinical investigation and send the clinical investigation report within 1 year after the end of the clinical investigation, including an easily understandable summary.

6.9. Monitoring plan

The clinical investigation will be monitored by a monitor during the clinical investigation, and after the clinical investigation has been completed, so as to ensure that the clinical investigation is carried out according to the CIP, and that data is collected, documented, and reported according to SS-EN ISO 14155:2020 and applicable ethical and regulatory requirements. Monitoring is performed as per the investigation's monitoring plan and is intended to ensure that the subject's rights, safety, and wellbeing are met as well as data in the CRF are complete, correct, and consistent with the source data.

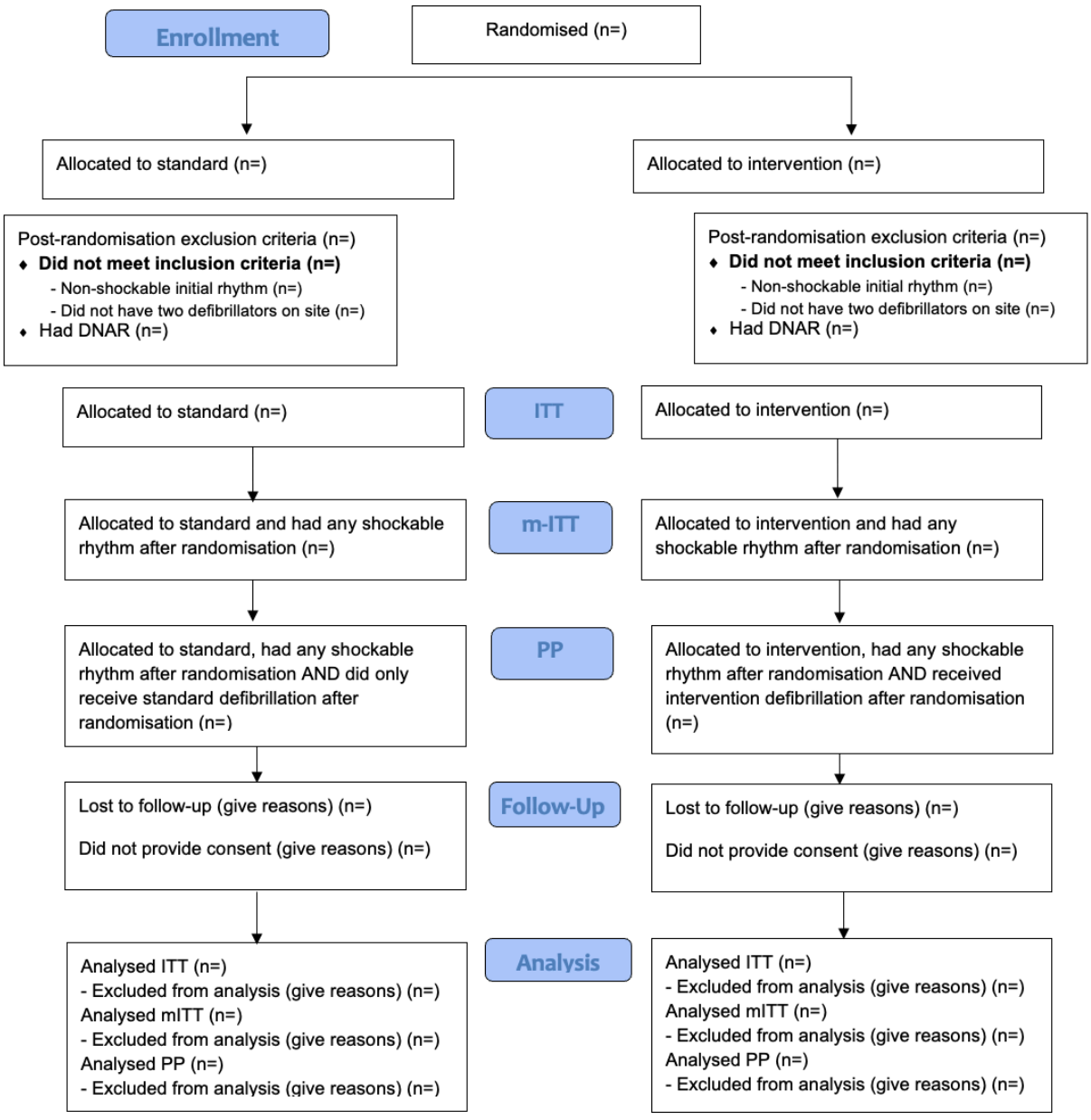
Please see appendix monitoring plan: "Monitoring plan DoubleD V. 250820-signed"

7. Statistical considerations.

7.1. Analysis population

The principal analysis strategy will be on an "intention to treat" (ITT) basis. All randomised patients who fulfilled inclusion criteria and no exclusion criteria will be included in this analysis. We will call this population ITT.
The modified intention to treat population mITT is defined as all patients in the ITT population that had shockable rhythm at any rhythm analysis after randomisation. In other words, the subgroup of ITT patients that are amendable to interventional or standard defibrillation. This will be defined as patients that received any kind of defibrillation after randomisation.
The per-protocol population is defined as the subset of the mITT population that received defibrillation according to allocated treatment.

Consort flow diagram



7.2. Descriptive statistics

Descriptive statistics will be presented as counts and proportions for categorial variables. For continuous variables the mean, standard deviation, medial and quartiles (Q1, Q3) will be presented. Balance between the treatment groups will be assessed using the standardised mean difference.

7.3. Analytical procedures

All primary analyses will be conducted on an intention-to-treat basis (ITT). The patient will be analysed based on their group allocation.

Secondary analyses will be performed on:

- Modified intention-to-treat (mITT)
- Per protocol (PP)

Primary outcome
- Survival to 30-days

Secondary outcome
- Neurological function (mRS) at hospital discharge
- Survival to hospital admission
- Any ROSC

Null-hypothesis significance testing for the primary outcome and the secondary outcomes of neurological function at discharge, survival to hospital admission and ROSC will be performed. Analyses will be conducted using logistic regression. The rationale behind this is to adjust for baseline characteristics to potentially increase power.

Adjustment for baseline characteristics

To increase power, we will adjust all outcome comparisons for strong prognostic factors. These will include number of defibrillations performed prior to randomisation, age and sex.

7.4. Sample size calculation

Baseline 30-day survival is based on data from the Swedish Register for Cardiopulmonary Resuscitation (SRCR). Among patients with shockable rhythm and > 1 defibrillation attempts, the 30-day survival was ~ 25%. We estimate that the survival rate could reach 33.5% in the intervention group (RR=1.34). The estimates are derived from the current survival SRCR (9) and the relative effect size in the Canadian trial (RR 2.21). However, we chose a more conservative relative risk.

With an alpha level of 0.05 and a beta level of 0.2, the estimated sample size would be 898 patients without interim analyses. The trial will have an adaptive parallel sequential design with interim-analysis and an independent data safety and monitoring board, with a priori stopping criteria for efficacy or harm but not for futility.

To adjust p-values for multiple looks, we use Lan and DeMets alpha-spending approximation of the O'Brien-Flemming boundaries.

Interim analyses will be conducted at different information rates (i.e. percentage of patients included in the study). Planned analyses are at 25% of included cases (229 patients), 50% of included cases (458 patients) and at 75% of included cases (686 patients). Critical values for superiority on the P-value scale are the following:

25%: 229: 0.00001
50%: 458: 0.00305
75%: 686: 0.01832

The P-value threshold for the final analysis (100%, 915 patients) is 0.044

7.5. Missing data

The aim is to minimise the missing data on core variables (treatment group, outcomes, number of defibrillations, age and sex). If some important data cannot be collected, we will consider using multiple imputation. The method will be multiple imputation with chained equations (mice). We assume that the missing will be at random (MAR).

7.6. Exploratory analysis and sensitivity analysis

The primary analysis will follow a frequentist approach, incorporating pre-specified interim analyses with appropriate alpha-spending adjustments to control the overall Type I error rate. These adjustments are necessary to ensure statistical rigor and regulatory compliance when conducting multiple looks at the data.

To aid in the interpretation of the primary and key secondary endpoints, a Bayesian analysis will be conducted to provide an additional probabilistic perspective on treatment effects, both in the overall study population and in relevant subgroups. This Bayesian approach allows for evaluating the probability of treatment benefits without requiring adjustments for multiple testing. The Bayesian analyses will use a conservative prior of normal (0, 0.5) on the log-odds scale and assume equal change of benefit and harm a priori.

The Bayesian analysis is intended to serve as a complementary assessment to the primary frequentist inference. A dedicated manuscript will report the Bayesian findings separately. 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. Exploratory sub-group analyses will be conducted on patients with a witnessed cardiac arrest, patient receiving bystander cardiopulmonary resuscitation, time to first defibrillation (below/above median) and stratified by age, sex and site.

Sub-studies:

Further sub-studies are planned to compare treatment effect in relation to subgroup exposure such as; a) EMS response time, b) if VF is refractory or recurrent, c) number of shocks before randomisation, d) AMSA, e) peri-shock pause, f) cause of cardiac arrest (cardiac / non-cardiac, STEMI / non-STEMI) and), g) chest compression fraction and h) Longitudinal follow up of neurological function and HRQoL. Other pre-specified sub studies may be added to this list during the course of the trial.

7.7. Data safety monitoring board (DSMB)

An independent data safety monitoring committee will be assigned by the steering group. An independent statistician will conduct the interim analyses. The data safety monitoring committee can recommend stopping or pause the trial if:

Superiority
Critical values for superiority are reached:
25%: 229: 0.00001
50%: 458: 0.00305
75%: 686: 0.01832

Harm
If the interim analysis shows a significant increase in risk (e.g., mortality) in the treatment arm compared to control, with $p \leq 0.05$, the monitoring committee shall recommend stopping the trial for harm.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the review committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

7.8. Reporting deviations

If deviations from the statistical analysis plan occur, we will present and explain these changes in the methods section of the paper.

7.9. Handling of imbalance of subjects per site

As each trial site have their own stratified randomisation list each site will have a balance of patients randomised to both groups.

8. Data management and protection

Subjects who participate in the clinical investigation will be coded with a specific clinical investigation identification number. All subjects will be registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a clinical investigation identification number.
All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

8.1. Data collection and Case Report Forms

Follow-up and data collection will be performed in three different and separate levels/occasions. All key primary data will be collected in all participating sites. The exact

methods for data collection and origin of source data may vary between sites in different participating countries and will be described in detail in the separate national applications.

A. For all patients after finished resuscitation:
- Prehospital Digital CRF 1 (see below)
- Ambulance charts, pre-hospital treatment, patient characteristics and short-term outcome
- ECG files from defibrillators used by including ambulance unit
- Time delays for EMS emergency dispatch (In Sweden, from the Swedish emergency dispatch organisation SOS-Alarm)

B. For all patients surviving to hospital admission:
- In-hospital treatment, survival to discharge and date of discharge
- For patients undergoing angiography, variables from the Swedish Coronary Angiography and angioplasty register, SCAAR (Sweden only)
- Medical charts, length of stay in hospital, if coronary angiography or ECMO was performed, date of discharge and ICD-codes at discharge (CRF 2)

C. All patients surviving to hospital discharge
- Neurological function (mRS and CPC) at hospital discharge

D. All patients surviving to 30 days
- Survival to 30 days,

E. For patients surviving to 30, 90 and 180 days (optional):
- Neurological function at 30 days (mRS and CPC)
- Survival to 90 days
- Neurological function (mRS, CPC), self-reported cognitive function (Single item) and Health-related quality of life (EQ-5D-5L, EQ VAS, PHQ-9, GAD, LiSAT-11, MFIS-21) at 90 days
- Survival to 180 days
- Neurological function (mRS, CPC), self-reported cognitive function (Single item) and Health-related quality of life (EQ-5D-5L, EQ VAS, PHQ-9, GAD, LiSAT-11, MFIS-21) at 180 days

8.1.1 Prehospital CRF1, Characteristics during the resuscitation phase

After completing the care of the patient, the study-responsible EMS unit will report a digital prehospital CRF. This is practically done by using and reading a study specific QR-code located on the back of the specific randomisation envelope/sheet using a smart-phone. This will open a webpage link to REDCap, automatic registration of time of registration and information to be filled in when opened.

The prehospital CRF will contain basic on-site information such as which ambulance that performed randomisation, randomisation study number, time and date of cardiac arrest, number of shocks prior to EMS arrival and number of shocks prior to randomisation, treatment allocation, if DSD was performed and number of DSD shock, estimated weight of patient, ROSC, if the patients survived the event and to what hospital the patients was

transferred. Furthermore, if the patient has a known identity, personal identification number will be included to enable follow-up. If the patients do not have a known identity, a temporary identification number will be used.

The prehospital CRF allows for real-time monitoring of randomisation and allows for early start of follow-up. If CRF1 is incomplete, missing variables can be collected from the ambulance charts.

Other core resuscitation characteristics will later be collected from ambulance medical charts and/or cardiac arrest registers. This data is standard and mandatory for all EMS personal to report and contains resuscitation and patient characteristics and is part of routine documentation.

ECG files from defibrillators. All data stored in the defibrillators after each use in the trial will be exported to a secure server and analysed for type of cardiac rhythms during resuscitation, type of defibrillation performed, result of defibrillation on cardiac rhythm as well as defibrillation safety.

For EMS units that use CPR quality feedback devices in their routine practice, information from those devices will be collected in the same way as ECG-files. All data above will be collected continuously during the course of the clinical trial and entered in the central REDCap database at Karolinska Institutet.

All key data will be collected in all participating sites but there may be national variations in the process of collecting data. Details regarding the data collection methods will be described in the applications (including ethics applications) of the different countries.

8.1.2 In-hospital CRF in-hospital treatment

The in-hospital CRF will cover core in-hospital treatment. The in-hospital CRF will collect core data such as length of stay, survival to hospital discharge, date of discharge, if coronary angiography was performed, target temperature management, if the patients received treatment with ECMO, and neurological function (mRS and CPC) at discharge. In addition, the mandatory SRCR part 2 will also be collected in Sweden. Neurological assessment at discharge can be performed either by research nurses at the hospital or the neurological follow-up team or by an assessment of medical charts (see below).

Please see supplemental file intrahospital CRF.

In Sweden, for the subset of patients that undergo coronary angiography, core variables regarding coronary anatomy, number of vessels with significant atherosclerotic stenosis and coronary intervention will be collected from the Swedish Coronary Angiography and angioplasty register (SCAAR).

8.1.3 Neurological and patient-reported follow-up at discharge, 30, 90 and 180 days

For patients who survive to hospital discharge and have signed an informed consent to further participation in the trial, a specific follow-up team, separated and blinded from the care and randomised allocation (intervention or control) will be responsible for neurological follow-up. Neurological function at hospital discharge will be assessed either by review of hospital charts or telephone follow-up. Neurological function will be assessed according to the modified Ranking Scale (mRS) and the Cerebral Performance Category (CPC) scale at hospital discharge, 30, 90 and 180 days.

The mRS scale includes categories 1-6, where higher numbers indicate more severe disability:

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 and/or unable to walk unassisted,
5 = severe disability—requires constant nursing care and attention, bedridden, incontinent, and
6 = dead.

The CPC scale includes categories 1-5, where higher numbers indicate more severe neurological impairment:
1 = Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities),
2 = Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes,
3 = Conscious. Dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the “locked in” syndrome,
4 = Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment, and
5 = Brain dead, circulation preserved. Death at discharge.

Patients that are alive at 90 and 180 days will also be evaluated for cognitive function and HRQoL using the self-reporting measures described below.

The single item for self-reported cognitive function is developed and used by the SRCR. It is formulated “How do you perceive your memory-, concentration- and/or planning ability today compared to before your cardiac arrest?”. The responses are rated on a five-point scale from “It is much better” to “It is much worse”.

The EuroQol 5D 5L (EQ-5D-5L) consists of 5 health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-point scale, ranging from 1 “no problems” to 5 “extreme problems”.

The EQ VAS is a single item measure evaluating “your health today”, using a visual analogue scale from 0 (“worst possible health”) to 100 (“best possible health”).

The 11-item Life Satisfaction questionnaire (LiSat-11) consists of 11 single items, one representing overall satisfaction with life (life as a whole) and 10 addressing specific domains of life satisfaction (vocation, economy, leisure, friends, sexual-life, self-care, family-life, partner relation, physical health, and psychological health). Each domain is assessed on a six-point scale ranging from “Very dissatisfied” to “Very satisfied”.

The Patient Health Questionnaire (PHQ-9) is a screening measure for symptoms of depression. It consists of 9 (+1) items with responses rated on a four-point scale from 0 “not at all” to 3 “nearly every day”. The item scores are summarised to a total score from 0-27, with higher scores indicating a more probable presence of depression. The last question addresses the possible impact on daily activities.

The Generalised Anxiety Disorder 7-item scale (GAD-7) is a screening measure for symptoms of anxiety. It consists of 7 (+1) items with responses rated on a four-point scale from 0 “not at all” to 3 “nearly every day”. The item scores are summarised to a total score from 0-21, with higher scores indicating a more probable presence of anxiety. The last question addresses the possible impact on daily activities.

The Modified Fatigue Impact Scale (MFIS) is a measure of how fatigue impacts life related to the respondents physical, cognitive, and psychosocial functioning. The original scale consists of 21 items. Responses are rated on a five-point scale from “never” (0) to “almost always” (4), resulting in a total score (0-84) and three subscale scores. Higher scores indicate a greater impact of fatigue on a person’s activities.

Variables from the neurological and HRQoL follow-up will be entered directly to a secure REDCap database at KI.

8.2. Data storage

All data reported from prehospital CRF, in-hospital CRF and neurological follow-up CRF will be digitally entered into a study-specific database (REDCap). The database will be stored on a secure server at the Karolinska Institute.

All essential documentation and trial records will be stored at in conformance with the applicable regulatory requirements. Access to stored information will be restricted to authorised personnel. Data will be stored in a secure area with access restricted to staff working on the trial. Any data that are transferred out of the secure environment (for example for statistical analysis) will adhere to standard procedures for secure data management.
All personal data will be handled according to the standard procedures for the current registries and medical records and in accordance with the General Data Protection Regulation (GDPR). Personal numbers and all other data that can lead to identification of

subjects included in the study will be coded and be accessible to key persons in the project to enable follow-up. The database will also only be accessible to key persons in the project.

8.3. Archiving

The PI and sponsor will maintain the essential clinical investigation documents in the investigation site files archive and sponsor files archive, respectively. The sponsor shall keep all documentation and data for at least 10 years after the clinical investigation has ended. The PI will archive all local investigation documentation for at least 10 years or as long as stipulated by the local institution.

8.4. Data protection

If any part of the data is handled by any other organisation, inside or outside the European Union, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (EU ordinance 2016/679, GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form shall comply with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their clinical investigation data will take place. The subject information and the informed consent form will explain how clinical investigation data are stored to maintain confidentiality in accordance with national data legislation.

The informed consent form will also explain that for verification of the data, authorised representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical investigation, including the subject's medical history.

Measures in the event of a personal data breach in the Double-D trial

1. Identify and document the incident
- Assess whether personal data is involved (e.g., code keys, study data, personal ID numbers).
- Document what happened, what data was affected, and the extent of the incident.

2. Assess risk to data subjects
- Analyse the potential risks: identity theft, discrimination, reputational harm, etc.
- If low risk: document internally, no notification required.
- If risk exists, proceed to steps 3 and 4.

3. Notify the Swedish Authority for Privacy Protection (IMY) within 72 hours
- Include a description of the incident, data affected, number of data subjects, contact information, and corrective actions.
- Use IMY's online reporting service.

4. Notify affected data subjects if there is a high risk
- Inform them without undue delay.
- Explain what happened and provide protective advice.
- Exception: e.g., if data was encrypted and risk is low.

5. Take technical and organisational measures
- Stop further data leakage.
- Restrict access and update security measures.
- Provide staff training if necessary.

6. Inform the sponsor and responsible investigator
- Notify according to protocol and contractual agreements.
- The sponsor is often the data controller responsible for regulatory communication.

9. Amendments to the CIP

Amendments to the CIP will be agreed upon between the coordinating investigator and the sponsor. Substantial modifications must be approved by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency before implementation.

10. Deviations from the CIP

Investigator(s) are not allowed to deviate from the CIP except if it is for the protection of the subject´s rights, safety, or well-being under emergency circumstances.
All such deviations shall be documented and reported to the sponsor, the Swedish Medical Products Agency and/or the Swedish Ethical Review Authority (as applicable) as soon as possible.

All deviations shall be documented with an explanation and reported to the sponsor. Deviations will be reviewed by the sponsor and reported to the appropriate regulatory bodies as required.

11. Device traceability and accountability

The investigational device(s) are part of the EMS standard equipment. The devices will only be used in the clinical investigation according to the clinical investigation plan. The sponsor provides the site with written instructions and training of DSD.

12. Statements of compliance

12.1. Compliance to the investigational plan, good clinical practice, and regulations

The clinical investigation will be conducted in accordance with the clinical investigation plan, the ethical principles of the Declaration of Helsinki, the principles of SS-EN ISO 14155:2020 and current national and international regulations governing this clinical investigation. This is to ensure the safety and integrity of the subjects as well as the quality of the data collected.

12.2. Ethical review of the clinical investigation

The clinical investigation will commence when written approval/favourable opinion from the Swedish Ethical Review Authority has been received and confirmation of validity has been received from the Swedish Medical Products Agency.

The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by the Swedish Ethical Review Authority or the Swedish Medical Products Agency. The Swedish Ethical Review Authority and the Swedish Medical Products Agency must be informed of any changes in the CIP in accordance with the current requirements. For each participating site outside of Sweden, a written approval/favourable opinion must be received from national and/or local ethical review boards and applicable authorities.

12.3. Insurance

Swedish Patient Insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, LÖF.

Separate national insurance agreements will be arranged for participating sites outside of Sweden.

13. Informed consent process

13.1. General process for informed consent

This study will be conducted according to the principles of the Declaration of Helsinki (version 2024, date 22-10-2024, see for the most recent version: www.wma.net). Informed consent for participating in the study cannot be obtained from the subject at the scene since the victim is unconscious. The cardiac arrest may be witnessed by family members, but to ask for consent form a relative or a legally representative in this scenario is not possible for both practical and ethical reasons. The time window to include and perform the intervention is within minutes. Therefore, informed consent cannot be obtained before the trial intervention.

According to the Helsinki Declaration paragraph 30;
“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorizes representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.”

According to MDR 2017/745 article 68, it possible to obtain informed consent to participate in a trial after the decision to include the patient if all other circumstances outlined in article 68 are fulfilled:
- The decision to include the patients is done in conjunction with the interventional treatment. The treatment in this trial must be provided during cardiopulmonary resuscitation, within minutes from the cardiac arrest.
- It´s not possible to obtain consent prior to inclusion since cardiac arrest is a sudden and unexpected life-threatening emergency event.
- There are scientific reasons to believe that participation in the trial can have direct clinical benefits for the participating patient/study subject.
- There is no possibility to inform or obtain consent from a legally representative since the interventional treatment must be provided within minutes from EMS arrival and during ongoing CPR.
- There is no way for the principal investigator to obtain information that the study subject has expressed an opposing view to participate in the trial beforehand, since cardiac arrest is a sudden, unexpected life-threatening emergency.
- The trial intervention has a direct connection to the medical condition (cardiac arrest) that renders the patient/study subject unable to give informed consent.

13.2. Consent process

The probability of surviving cardiac arrest is very low; overall, 90% of the patients die. In the OHCA sub-set of patients with VT/VF, survival at 30 days is about 30%. In a cardiac arrest scenario, treatment of CPR and defibrillation must be started immediately to increase the chance of survival.

Due to the nature of the condition of sudden cardiac arrest, informed consent for participating in the study cannot be obtained from the subject at the scene since the victim is unconscious at the time for study inclusion, and the EMS personnel or the sponsor has no previous information about the patients willing to participate in the study or not. The clinical course in patients that regains circulation after cardiac arrest shows a wide variety, from irreversible to reversible circulatory shock, and from irreversible brain damage and death to neurologically intact survival and fast recovery in cognitive functions. Therefore, the strategy for obtaining informed consent varies dependent on patient outcome.

The strategy for obtaining informed consent is as follows according to the patient's status

1. The patient who is not regaining circulation and is declared dead at the scene of the arrest or in the emergency department. No consent will be obtained.
2. The patient who survives the initial resuscitation phase, is transferred to hospital and is conscious and neurologically capable to provide informed consent. In Sweden, information about the study (both oral and written) will be given during hospital stay. The information includes the purpose of the study, the study intervention, possible risks and benefits from participating in the study and who is legal responsible for the study. In the information it is also clarified that all participation is voluntary, the right to

not participate in the study and the right to withdraw participation. The informed consent is obtained.

3. The patient who survives but is not fully conscious, GCS <14, has severe dementia, suffers from expressive and/or impressive aphasia, or is unable to write his or her signature. In this case, when the patient is not able to give an informed consent by his or her own, the consent shall as soon as possible be sought after by a legally representative without undue delay. If the patient does not have a legally representative, and still is unable to provide informed consent due to cognitive impairment after the ICU period, a renewed attempt will be made to inform the patient and obtain informed consent as soon as the patient can give informed consent. Attempts to inform the patient and obtain consent for this category of patients will continue during the entire follow-up period (180 days). In patients who die or do not regain neurological function to provide informed consent during the follow-up period (180 days), no consent will be obtained.

If informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the patient as soon as he or she can give informed consent.

The informed consent process is performed by local staff at each referring hospital.

There may be national variations in the process of informing the patient and obtaining informed consent. For details each participating site outside of Sweden, the informed consent process will follow national and local laws and regulations.

The principal investigator shall ensure that the subject is given full and adequate oral and written information about the clinical investigation, its purpose, any risks and benefits as well as inclusion and exclusion criteria.

Subjects must also be informed that they are free to discontinue their participation in the clinical investigation at any time without having to provide a reason. Subjects shall be given the opportunity to ask questions and be allowed time to consider the provided information and participation in the clinical investigation. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as a copy of the informed consent form shall be provided to the subject.

The process shall be documented in the subject’s source documents and the signed informed consents shall be maintained with the essential documents. If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If new information is added to the clinical investigation, the subject has the right to reconsider whether they will continue their participation. In patients that don’t want to participate or withdraw a given consent, there will be no more follow-ups. All patient data collected up to this point will be deleted with the exception of anonymised data regarding defibrillator safety (device deficiencies/damages).

14. Adverse events, adverse device effects and device deficiencies

14.1. Definitions

14.1.1. *Adverse Event*

An Adverse Event (AE) is untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
This definition includes events that are anticipated as well as unanticipated events.
This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

14.1.2. *Adverse Device Effect*

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.
This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes both the interventional and comparator.

14.1.3. *Serious Adverse Event*

A Serious Adverse Event (SAE) is any AE that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalization or prolongation of patient hospitalization,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

14.1.4. *Serious Adverse Device Effect*

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.
SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

14.1.5. *Unanticipated Serious Adverse Device Effect*

An Unanticipated SADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device shall be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.
For the anticipated adverse device effects, se section 4.2 above.

14.1.6. *Device Deficiency*

A Device Deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
This includes detected errors at defibrillator self-test after each use.

14.2. Recording and Reporting

14.2.1. *Recording*

As stated in section 13.3, cardiac arrest is associated with a probability of death of 70-80% in the first 30 days. Even among survivors this condition is associated with neurological, cardiac and multi-organ failure in the first post-cardiac arrest period. The standard treatment includes known side effects such as rib-cage fractures and lacerations to visceral organs due to CPR, infections and bleedings associated with invasive ventilation and other procedures during resuscitation and the post cardiac arrest intensive care period. In this population it is difficult, if not impossible, to report all AEs and SAEs and assess their relation to the intervention.

In this trial, two strategies of defibrillation will be compared but all other treatments will follow standard care. Therefore, adverse events related to the defibrillation process and intervention during resuscitation will be collected with emphasis on device deficiency (DD) and anticipated AE (se section 14.3).

The principal investigator or an authorised designee will record:

- - all SADEs;
- - all Device Deficiencies;
- - any new finding in relation to any of the above-mentioned events.

Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation should NOT be reported. These include but are not limited to:

- - Death
- - Hospitalization
- - Persistent or significant disability or incapacity
- - Organ failure
- - Rib fractures and bleeding related to CPR

In summary, due to the high amount of expected (serious) adverse events caused by the condition itself and the treatment of the patients as part of standard care, only study-related (S)AEs will be reported immediately. This means all (S)AEs related to participation in this

study protocol, meaning from double sequential defibrillation, will be reported. All other (S)AEs will not be reported.

14.2.2. *Reporting*

The investigators will report all SADEs and Device Deficiencies to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel's awareness of the event. This includes defibrillation malfunction during use or detected errors at defibrillator self-test after each use.

The sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

- any SADE that has a causal relationship with the investigational device, the comparator or the investigation procedure, or where such causal relationship is reasonably possible;
- any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and
- any new findings in relation to any event referred to above.

Reporting by the sponsor will be done by filling out the "Summary Reporting Form" (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

14.2.3. *Assessment of Causality*

The relationship between each adverse event and the investigational device, the comparator and the investigation procedure will be assessed and recorded by the investigator and sponsor.

The sponsor and investigator will distinguish between SAEs related to the investigational device and those related to the procedures, relatedness to both is possible.
Each SAE will be classified according to four different levels of causality:

1. Not related
   Relationship to the device, comparator or procedures can be excluded when:
   – the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

– the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;

– the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

– the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;

– the event involves a body-site or an organ that cannot be affected by the device or procedure;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. Possible
   The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.

3. Probable
   The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship
   The SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   – the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   – the event has a temporal relationship with investigational device use/application or procedures;
   – the event involves a body-site or organ that
      - the investigational device or procedures are applied to;
      - the investigational device or procedures have an effect on;
   – the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   – other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   – harm to the subject is due to error in use.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of the SAE.

14.3. List of foreseeable Adverse events

1. Device deficiency. The inability of one of the defibrillators to deliver energy at defibrillation or shut down/reboot. This risk is judged to be exceedingly low based on the preclinical testing and the results from the previous trials (likely incidence < 1/100). However, it is impossible to rule out. Defibrillation data will be analysed for each case and inability to defibrillate will be considered as a SADE. All defibrillator files will be analysed for energy delivery at each defibrillation.

2. Any device malfunction that becomes evident at defibrillator self-test or test defibrillations performed after each use. There is a theoretical risk that one defibrillator can be damaged by the current delivered from the other device during DSD. Please see also 4.2.

3. Perceived adverse event by participating EMS-units will also be collected in CRF1. All CRF1 forms with perceived adverse events will be followed up by the sponsor with undue delay, the monitor will be informed and the type of adverse event and its relationship with the intervention or the investigational device will be judged according to definitions in the CIP.

14.4. Monitoring

Monitoring will be performed by a monitor team according to the monitoring plan, please see 6.8 monitoring plan.

15. Premature termination of the clinical investigation

The sponsor may suspend or prematurely terminate either the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons. The Swedish Medical Products Agency may suspend or prematurely terminate the clinical investigation at the applicable investigation sites.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Medical Products Agency, the sponsor will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. The sponsor will inform all investigators.

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If, in the opinion of the investigator, the clinical observations in the clinical investigation suggest that it may be unsafe to continue the investigation at the site, the investigator may terminate participation in the investigation after consultation with the sponsor. A written statement fully documenting the reasons for such termination will be provided to the sponsor. If the clinical investigation is prematurely terminated, the investigators shall promptly inform the subjects and take necessary steps to finalise their engagement in the clinical investigation. All relevant investigation material must be collected, and accountability completed.

If the clinical investigation is interrupted or terminated prematurely the sponsor will report to the Medical Products Agency within 15 days together with a justification. If the sponsor has temporarily halted or prematurely terminated the clinical investigation on safety grounds, the Medical Products Agency will be informed within 24 hours. A clinical investigation report will be prepared within three months of the early termination or temporary halt, irrespective of the results. In the event that the clinical investigation is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed.

The final clinical investigation report shall include detail with respect to the temporary halt.

All patients included before the temporal halt or premature termination will be followed up until final planned follow-up after 180 days.

16. Publication policy

The clinical investigation will be registered in a publicly accessible database before the start of recruitment activities, and the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation. (www.clinicaltrials.org)

The results of the study will be published in international medical journals after study completion. Criteria for authorship will follow Vancouver guidelines. The coordinating PI will have full access to all data and make the final decision to submit for publication.

The first and primary manuscript will include the main results including pre-defined primary and secondary outcomes up until survival to 30 days.

Secondary publications include the pre-specified sub studies and an explanatory Bayesian analysis.

16.1 Authorship of the first publication

Coordinating PI Akil Awad will be first author of the main publication and Gabriel Riva will be last author. Additional authorship will be provided to members of the steering committee and clinical staff involved in the trial as appropriate.

A Double-D trial author consortium will be formed, including all other authors. The outline is that each participating site may list one author to this consortium, if a site includes over 20 patients 2 authors, and over 50 patients 3 authors can be added.

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