CLINICAL INVESTIGATION PLAN

DOUBLE D

Double sequential Defibrillation in OHCA ***- A Randomized Pilot study***

"A randomized pilot study assessing feasibility of a randomized trial comparing the effect of double defibrillation with anterior-posterior and anterior lateral pad placement and sequential defibrillation as soon as possible in all OHCA with a shockable rhythm (VT/VF) compared to standard pad placement and single defibrillation"

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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: 2024-09-28

Gabriel Riva

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: 2024-10-27

Akil Awad

Principal 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.
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I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature Date: 2024-10-27

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Funding and research agreement

This is an academic design and financed pilot 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 Corpuls3 defibrillators used in this trial are part of the participating sites standard equipment. Additional Corpuls1 defibrillators and CPR quality feed-back devices will be provided by the sponsor. 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**
ACLS	Advanced Cardiac Life Support
ADE	Adverse Device Effect
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
GCP	Good Clinical Practice
IB	Investigator's Brochure
IFU	Instructions for Use
ILCOR	International Liason Committee on Resuscitation
SS-EN ISO	Swedish Standard - European standard International Organization for Standardization
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 done 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 number of defibrillations required to terminate VT/VF.[4] In 2022, one prospective cluster randomized trial showed increased survival among OHCA patients in refractory VF using an alternative defibrillation strategy with either, switching to Anterior-Posterior defibrillation pad placements (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) compared to standard defibrillation pad placement.[5] Refractory VF was defined as VF that persisted despite three consecutive defibrillations with defibrillation pads in the standard position. These results prompted the International Liason Committee on Resuscitation (ILCOR) to release a statement of treatment recommendation on DSD in 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).” [6] Further, if DSD would 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 if the results from this one cluster randomized trial could be reproduced in any other setting. Further, 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: In order to evaluate if 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 is designed. The first phase of the Double D trial is a pilot-study assessing feasibility and defibrillation safety, presented here. If DSD would prove to be superior to standard defibrillation in a broader cardiac arrest population, also among those not in refractory VF, this would have a large impact on how Advanced Cardiac Life Support (ACLS) should be performed.

Design: This is an academic, investigator initiated, open-label pilot study with a randomized controlled trial (RCT) design and 3:1 allocation (3 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 (1) Corpuls3 + one (1) Corpuls3).

Study population: All OHCA patients (≥18 years) with VT/VF at rhythm analysis, at least one defibrillation performed in standard A-L position.

P: Adult patients, 18 years or older, with OHCA and a shockable rhythm (VT/VF) after ambulance arrival and at least one defibrillation in standard position

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 a double sequential defibrillation in the following rhythm analysis phase if the patient is still in VT/VF

C: Standard defibrillation electrode placement (A-L)

O: Assessment of feasibility in terms of inclusion, time to inclusion and randomization, adherence to protocol and safety in terms of adverse events and CPR quality.

The pilot study is conducted in the prehospital emergency medical services, i.e. ambulance organizations primary in Alingsås/Kungälv, Sahlgrenska, Gothenburg and Region Halland. Other areas/regions can be allocated later.

	The trial will be conducted by participating ambulance units attending OHCA´s. These units will perform screening for inclusion, randomization, intervention or control treatment and initial follow up.
Investigational device:	Corpuls3
Number of subjects:	40
Inclusion criteria:	- OHCA patients with VT/VF and at least one (1) 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 evaluate feasibility and defibrillation safety in a randomized pilot trial, comparing the effect of a double defibrillation strategy, initiated as soon as possible after the first shock has been delivered, among all patients with Out of Hospital Cardiac arrest (OHCA) remaining in a shockable rhythm (VT/VF) after the first defibrillation. The results from this pilot trial will inform design of a larger multicenter survival study. **Secondary objective:** To provide a power-calculation for a larger survival study **Safety objective:** To asses safety of an early DSD strategy in terms of CPR quality and defibrillation performance.
Study endpoints:	Primary endpoints are defined as feasibility and safety measures as described below: *Feasibility:* - Number of EMS defibrillations prior to randomization (target > 80% before third defibrillation) - Among patients randomized to DSD, proportion that received DSD (target > 80%) - Among patients randomized to standard, proportion that received DSD (target < 10%)

	- Proportion of eligible patients included and randomized (target > 80%) *Safety:* - Major adverse events (e.g. defibrillator malfunction) - Chest compression fraction (hands off time during CPR, target > 80% in both groups) *Secondary endpoint:* - Proportion of patients with sustained return of spontaneous circulation (ROSC) at hospital arrival - Total number of defibrillations to sustained ROSC *Tertiary Outcomes:* - Survival to hospital admission - Survival to hospital discharge - Survival at 30 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
Planned duration of the clinical investigation:	Q2 2024 – Q4 2025

2. Identification and description of the investigational device

2.1. Description of the investigational device

Corpuls3 and Corpuls1 are defibrillators with capabilities of monitoring of cardiac rhythm and vital functions but also defibrillation, cardioversion and pacing and are part of the standard equipment in the EMS units in the participating sites.

Corpuls3 is a portable device with a modular structure which can be used as a defibrillator/monitor or as a full patient monitor in its own right.

The risk classification of Corpuls3 and Corpuls1 are non-invasive IIb

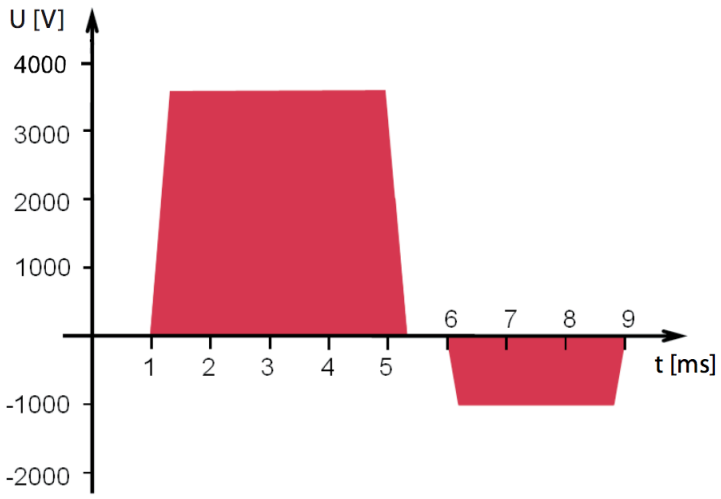
Image: Corpuls3

The corpuls3 provides monitoring of cardiac rhythm and vital functions, diagnostic and therapeutic functions for treatment of emergency and intensive-care patients. A 12 lead ECG function allows the user a comprehensive ECG diagnosis, 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 corpuls 3-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 since 2015.

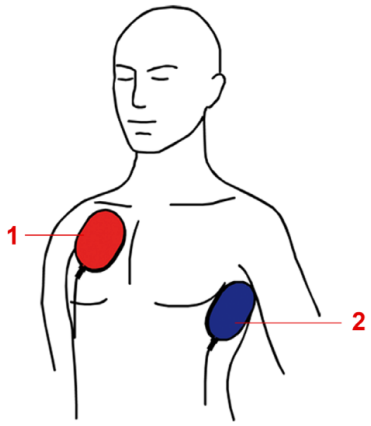


Image Anteriolatal (standard) corpatch electrode placement from corpuls3 user manual

The corpuls1 is a defibrillator/patient monitoring system/externalpacer and is intended for the following purposes for the treatment of emergency- and intensive-care patients:

- Monitoring patients.
- Measuring vital parameters.
- Performing defibrillations and cardioversions on adults, children and neonates.
- Performing external pacer therapy (option).
- Check the quality of thorax compressions in cardiopulmonary resuscitation (optional). The following therapy functions are available:

• Defibrillation (AED mode, manual mode)
• Cardioversion
• External pacer therapy (option)

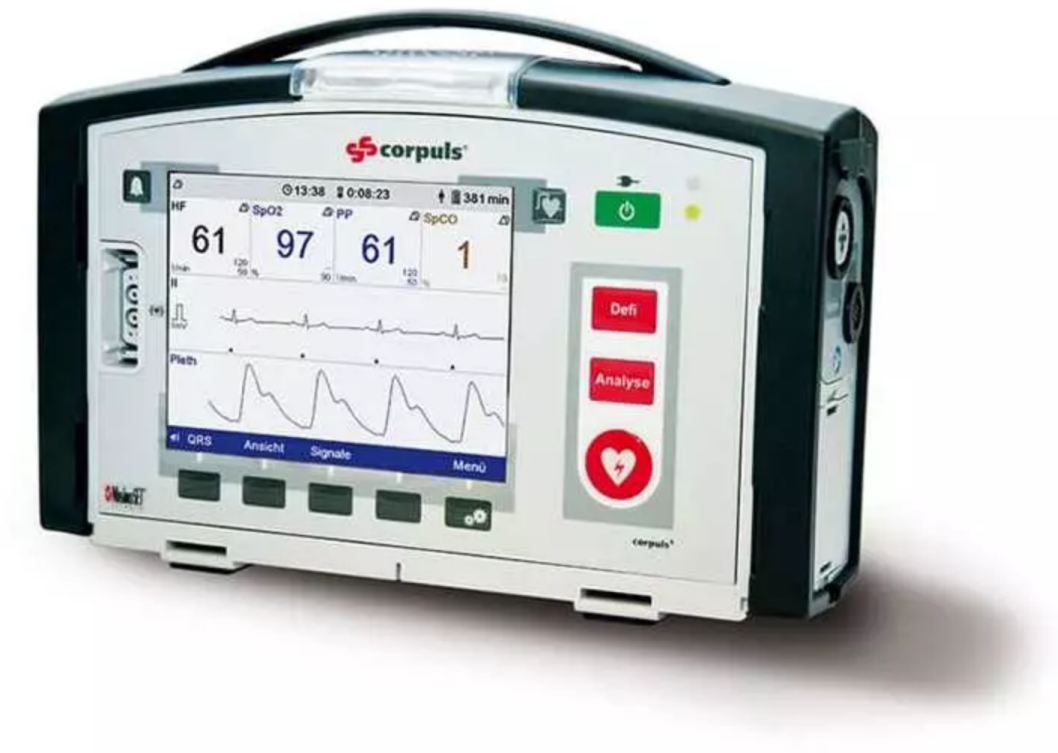


Image: Corpuls1

The corpuls3 and corpuls1 are intended for measurement and monitoring of vital functions 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 and Corpuls1 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 organizations.

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).

For further information please see attached Description and intended purpose Corpuls3 and Corpuls1

2.2. Intended purpose

The intended purpose of corpulse1 & 3 defibrillators in cardiac arrest is to terminate VT or VF with external defibrillation in order to restore spontaneous circulation. This can be done by electrodes placed in standard A-L position, but in some circumstances also A-P position (see above). I.e. using one defibrillator in with either electrode position (A-L or A-P) are 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, approximately 1 second apart, 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 pilot 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.

Performing DSD within the Double-D trial:

In this trial all patients will be connected to corpuls3 with electrodes in standard A - L electrode position.

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 cor-patch electrodes in standard A-L position and connect them to corpuls3 in all cases. This is all part of current routine practice.

If randomized to intervention, electrodes from a second defibrillator (corpuls3 or corpuls1) are placed in the anterior-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 made as soon as possible after randomization.

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 with approximately 1 second delay from each other (A-L first, A -P second when possible) and CPR immediately resumed (DSD strategy). For all consecutive defibrillations a DSD strategy will be used if the patient remains in VT/VF, termination of resuscitation or 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 (corpuls3) is attached in A-L position.
- Second defibrillator (corpuls3) is attached in A-P position.
- Both defibrillators are set in manual mode
- If VT/VF at next rhythm analysis, chest compressions are resumed and both defibrillators are charged to maximal energy (200J Biphasic for Corpuls3)
- Defibrillations are performed sequential (approximately 1s apart), preferably A-L first, A-P second

If randomized to the control group, the ambulance crew team will continue Advanced Cardiac Life Support (ALS) in accordance with standard of care. Defibrillation is performed with standard electrode placement using one corpuls3 defibrillator.

2.3. Manufacturer of the investigational device

Name: Corpuls**,** GS Elektromedizinische Geräte G. Stemple GmbH
Address: Hauswiesenstraße 26 86916 Kaufering, Germany
Contact, phone number: +49819165722-0,
Mail: info@corpuls.com

2.4. Model/type

- Corpuls3
- Corpuls1

2.5. Target population

Target population for defibrillation are patients with OHCA and VT/VF after one defibrillation in standard position. The defibrillators deliver energy through corpatch eletrodes attached to the patient in A-L or A-P position. Defibrillation with Corpuls3 and corpuls1 are complianent with relevant GSPR, please see attached files.

2.6. Summary of required training/experience needed

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 organizations. 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 organizations included in the study ensure that EMS-crews are trained in the Double defibrillation strategy 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. Participants shall reach 100% correct answers in order to be certified as Double D-users.

b) Practical training. All EMS-crews shall under the supervision of an ACLS-instructor (A-HLR) certified by the Swedish resuscitation council undergo practical training. This training includes application of defibrillation pads in the anterio-posterior position while making sure to minimize interruptions in chest compressions, performing defibrillation in manual mode and charging and defibrillating with two defibrillators in a sequential manner. Special attention during this training to delayed (sequential) defibrillation will be done. All participants shall in front of an instructor demonstrate correct practical performance. Finally, to perform ACLS scenarios with team training using the Double-D-algorithm during ongoing CPR.

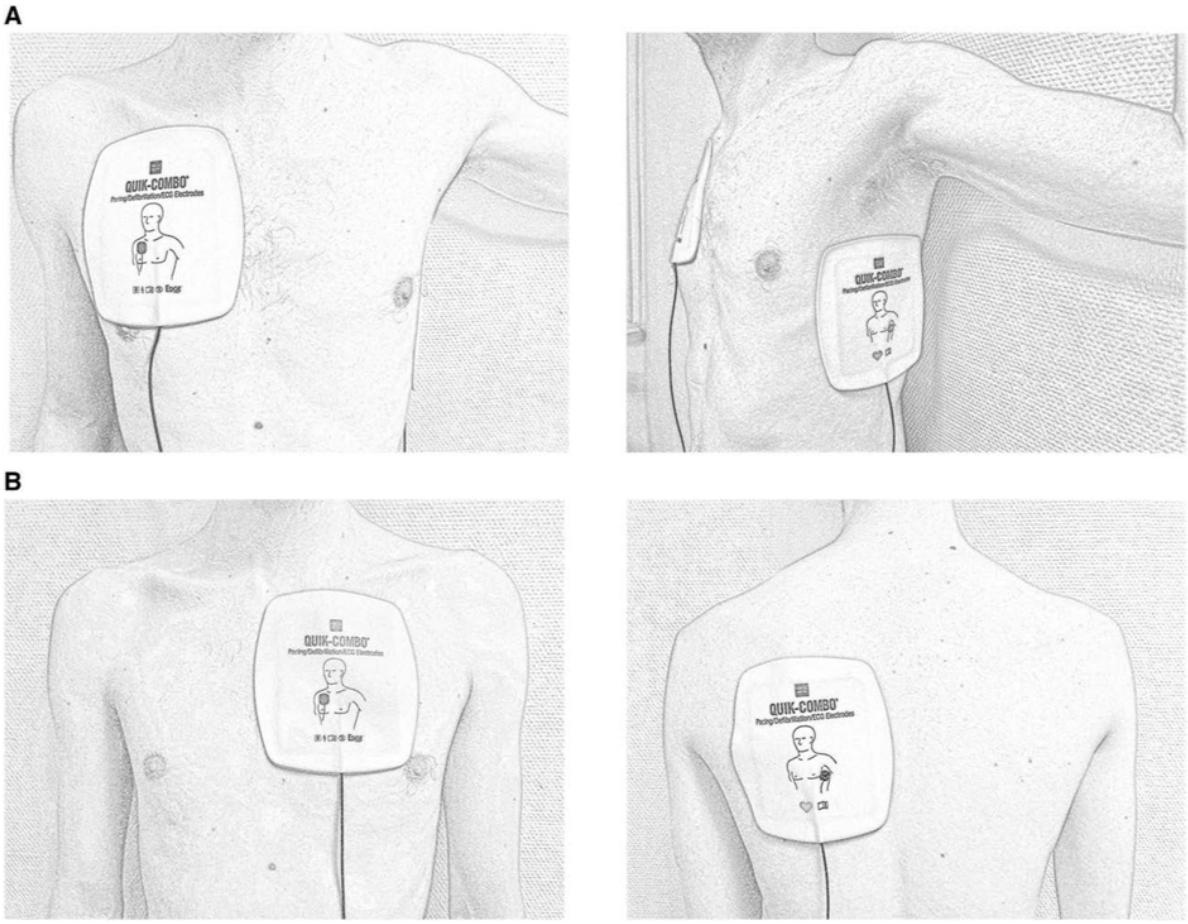
These scenarios shall facilitate the early provision of a DSD with maintained safety for all personnel, while minimizing interruptions in chest compressions. All EMS-crews will rehearse the CPR training including DSD training once a year.

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

3.1. Background

Out-of-Hospital Cardiac Arrest (OHCA) is a major health issue affecting approximately 380 000 persons in the U.S. and 270 000 in Europe each year.[1]. Presence of Pulseless Ventricular tachycardia (VT) or Ventricular Fibrillation (VF), amendable to defibrillation at 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.[2, 3] 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 VF despite 3 consecutive defibrillation shocks. Treatment recommendations for this condition include

administration of drugs such as Epinephrine and Amiodarone and continuous CPR, and in situations where available, consider transport during ongoing CPR to a facility capable of ECMO-assisted CPR.[4]
Importantly, survival of patients with VT/VF is inversely associated with the number of defibrillations required to terminate VT/VF.[5] 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 anterio-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.[6]



An alternative pad placement is the so-called anterio-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, se fig B.
Advantages with A-L position can be the possibility to perform defibrillation without adhesive defibrillation pads (not recommended during CPR since 2010), but it is also relatively ease to apply defibrillation pads during CPR, with no need to move the patient and application can be done while chest compressions are ongoing.
One advantage with A-P position is the theoretically closer proximity between pads (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 placements has been compared to A-P placements 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.[7]
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).
Double sequential defibrillation was described in 1994 to treat induced ventricular fibrillation during electro-physiology studies, that where refractory to standard defibrillation.[8]
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 [9]. However, in 2022 the first and only randomized 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 Liason Committee on Resuscitation ILCOR to release a statement of treatment recommendation on DSD in 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 in the trial by Cheskes et al.

However, several questions remain. Knowledge gaps highlighted in the ILCOR statement included if the results from this one cluster randomized trial could be reproduced in any other setting. Further, 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 and finally no randomized 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 randomize controlled trial in humans and may according to international guidelines be considered in refractory VT/VF. 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”. Currently, corpuls3 and corpuls1 are tested for combability and technical safety when used for DSD.

Before those results are final and an application for a substantial modification is approved by the Swedish Ethical Review Authority and the Swedish Medical Products Agency no combination of corpuls3 and corpuls1 will be used in this trial.

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

Potential benefit with the DSD strategy includes:

The novel strategy of DSD might have a higher probability of terminating VT/VF and restore 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 can have a high potential to save more lives and this effect is 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, e.g. 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 includes a double amount of energy to be delivered for each defibrillation. This may result in injuries such as superficial burns on 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 synchronized shocks.[10] There is a theoretical risk that synchronized 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 linear, as opposed to a 90-degree angle, and if defibrillation is synchronized. In this trial the second pair of defibrillation electrodes will be placed at an almost 90-degree angle and defibrillation will be performed sequential, meaning approximately one second delay between defibrillation using the two defibrillators, with one person pressing both defibrillators in sequnce. In the trial by Cheskes et al. there were no reports of defibrillation malfunction in spite of 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 seem to be exceedingly low.[11]

4.3. Risks associated with participation in the clinical investigation

Potential physical risks with the DSD strategy include:

1. 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 standardized 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 the patient was randomized to (standard, Vector Change or DSD).[12] In order to minimize this risk there will be a mandatory training for all participating ambulance crew on how to synchronize posterior defibrillation electrode placements to pauses in ventilation. This extra moment should not take longer than 10-15 seconds

4.4. Possible interactions with concomitant medical treatments

This is strictly a defibrillator manage/strategy study and no medication are involved. All other advance life support using adrenalin, amiodarone and other medical treatment follow standard routine for ACLS.

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, is connected with the application of defibrillation electrodes and defibrillation. Therefore, all participating ambulance units must be trained and certified before participation in the trial. This in order to minimize risk of long interruptions in chest compressions and correct electrode placement.

2. Close monitoring will be done by the sponsor and the monitoring team on a case to case base. During the pilot study individual assessment and early feed-back of EMS intervention for every included patient can allow the sponsor for early detection of unanticipated adverse events. Please see also 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.
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 defibrillators used in this DD study will be tested using a test-box and performing a test discharge will be performed once weekly during the study period (part of current routine) and as soon as possible after each DSD use.

4. Stepwise escalation of the pilot phase will be done in order to uncover unknown risks. In order to perform close monitoring of all included patients and feed-back from participating ambulance crew the trial will have an escalation strategy within the pilot study starting in two ambulance organizations and then escalate. The training protocol can be modified during the pilot study 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.

5. Testing of combability of corpuls3 devices (performed) and for corpuls3 and corpuls1 (ongoing). Before those results are final and an application for a substantial modification is approved by the Swedish Ethical Review Authority and the Swedish Medical Products Agency no combination of corpuls3 and corpuls1 will be used in this trial.

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 of highly importance to as soon as possible convert patients in VF/VT to sustain circulation

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 risks 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, e.g. higher survival
b) the termination of VT/VF will occur sooner, leading to shorter duration of brain hypoperfusion and ischemia, e.g. better neurological function among survivors.

In summary we believe that this novel method to use defibrillators have a strong potential benefit that largely outweighs the potential risk, 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

The overall aim of this pilot study is to evaluate feasibility of a Randomized Controlled Trial comparing a strategy with DSD defibrillation as soon as possible to standard defibrillation in OHCA patients who remain in VT/VF after the first shock.

5.2.2. Secondary objective(s)

To obtain data to inform design of the planned main study that will assess clinical outcomes

5.2.3. Safety objectives

To asses safety of an early DSD strategy in terms of CPR quality and defibrillation performance.

5.2. Hypotheses

5.3.1. Primary hypothesis

Randomization to a strategy of either early DSD or standard defibrillation is feasible and safe in terms of timely randomization, adherence to protocol, maintained CPR quality and defibrillation functionality.

6. Design of the clinical investigation

6.1. General information

Design: This is an academic, investigator initiated, open-label pilot study with a randomized controlled trial (RCT) design and 3:1 allocation (3 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 (1) Corpuls3 + one (1) Corpuls3 ***or*** one (1) Corpuls1).

Study population: All adult OHCA patients (≥18 years) with VT/VF at rhythm analysis after the first defibrillation.

Study setting: The study is conducted in the prehospital emergency medical services, i.e. ambulance organizations. The trial will be conducted by participating ambulance units attending OHCA´s staffed with special nurses. These units will perform screening for inclusion, randomization, intervention or control treatment and initial follow-up. All ambulance units in Sweden follow European resuscitation council (ERC) guidelines published in 2021 [4] and perform team training on an annual basis for high quality provision of ACLS care in OHCA.

6.2. Endpoints

6.2.1. Primary endpoints

The main feasibility endpoint is the proportion of included patients randomized before three EMS defibrillations.

In order to perform early DSD inclusion and randomization has to be quick, therefore the total number of EMS defibrillations prior to randomization was chosen as the main feasibility outcome. The goal is to perform randomization as soon as possible, however in clinical practice this can be challenging. A target of above 80% of included patients randomized before three EMS defibrillations is deemed acceptable. Other feasibility objectives will evaluate cross-over.

The main safety endpoints are related to CPR quality defined as chest compression fraction and any defibrillation malfunction defined as inability to defibrillate or any other defibrillator device deficiency (DD).

Feasibility:
- Number of EMS defibrillations prior to randomization (target > 80% before third defibrillation)
- Among patients randomized to DSD still in VF in the following rhythm analysis, proportion that received DSD (target > 80%)
- Among patients randomized to standard, proportion that received DSD (target < 10%)

Safety:
- Major adverse events (e.g. DD, skin burns)
- Chest compression fraction (hands off time during CPR, target > 80% in both groups)

6.2.2. Secondary endpoint (s)

- Proportion of patients receiving sustained return of spontaneous circulation (ROSC)
- Number of defibrillations to sustained ROSC

6.2.3. Tertiary endpoints

- Survival to hospital admission
- Survival to hospital discharge
- Survival at 30 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

The tertiary outcomes were chosen to comply with the “Core Outcome Set for Cardiac Arrest in Adults” advisory statement From the International Liaison Committee on Resuscitation.[13]

6.2.1. Description of the intervention

Please see 6.6

6.2.1. Description of the comparator

Please see 6.6. Standard defibrillation with Corpatch electrodes in the A-L position using one corpuls3 defibrillator (routine clinical praxis)

6.3. Subjects

6.3.1. Inclusion criteria

- OHCA patients in VT/VF at rhythm analysis after ambulance arrival and at least one defibrillation performed in standard (A-L) position

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 40 patients (30 randomized to DSD and 10 to standard treatment). The 3:1 ratio was chosen since our main focus in this pilot study is the interventional treatment but also to evaluate the randomization process and adherence to protocol.

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 randomized patients will be included in the ITT analysis.

6.4. Methods to minimize bias

Study participants will be randomized at the individual patient level, therefore minimizing 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). All clinical endpoints and follow-up will be collected by a research staff in a blinded way.

6.5. Unblinding

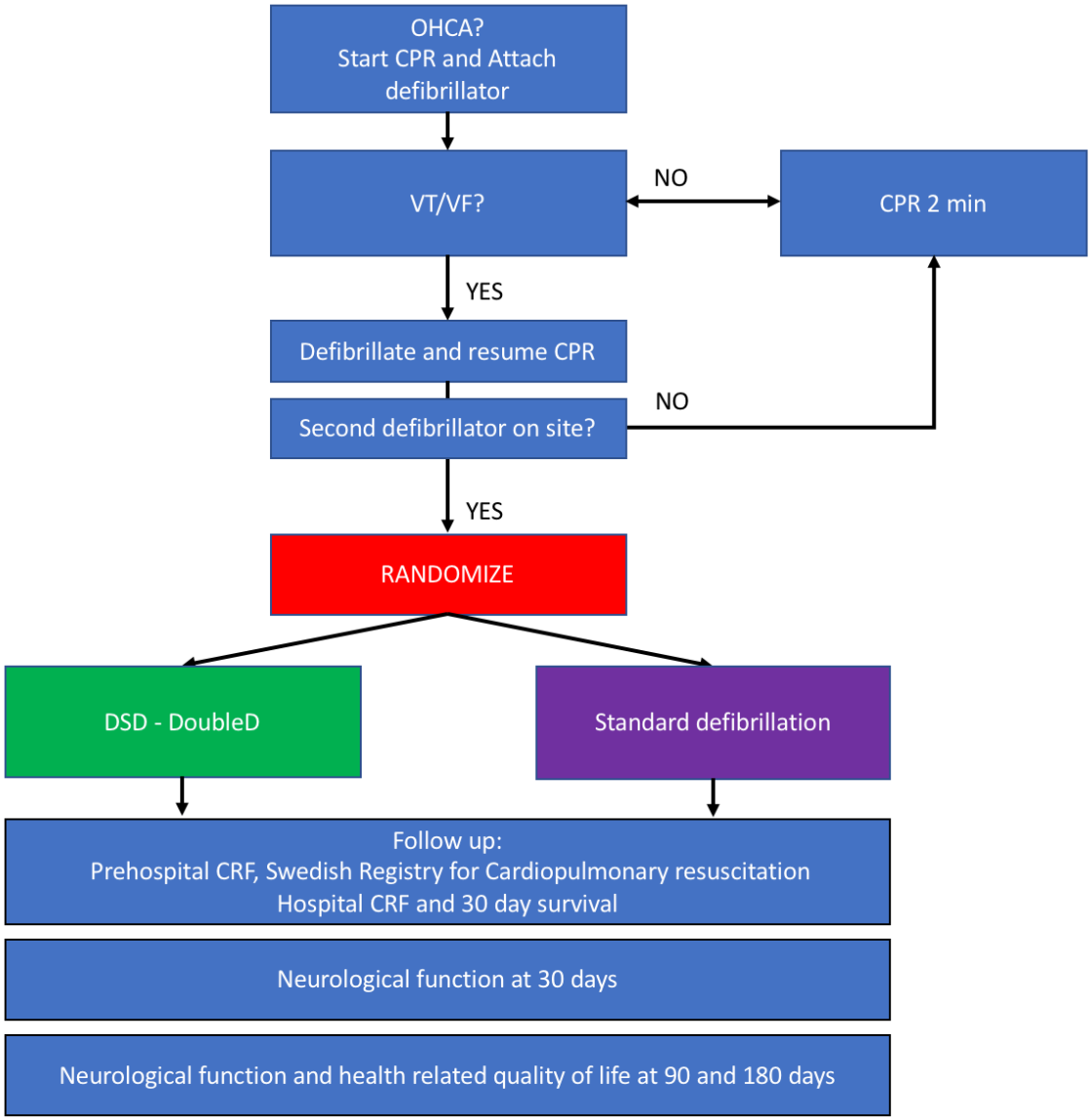
This is an open label pilot trial. The neurological follow-up will be performed in a blinded way. That is the persons collecting the follow-up data at 30, 90 and 180 days will not be aware of the randomized allocation.

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

The study is conducted in the prehospital emergency medical services, i.e. ambulance organizations. The trial will be conducted by participating ambulance units attending OHCA´s. These units will perform screening for inclusion, randomization, intervention or control treatment and initial follow-up. All ambulance units in Sweden follow European resuscitation council (ERC) guidelines published in 2021 [4] and perform team training on an annual basis for high quality provision of ACLS 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 defibrillators study specific defibrillators on site, and no exclusion criteria the patient can be included and randomized. Randomization will be performed by drawing a scratch-card with concealed allocation that will be stored with the EMS defibrillators. All scratch-cards will be pre-randomized in a 3:1 ratio in blocks consisting of 4-8-12 and stratified by region and ambulance provider.



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

Defibrillator requirements:

In this study all participating EMS units will have corpuls3 defibrillators.

A perquisite 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 two EMS units on site with one corpuls3 each.

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 above.

If there is another defibrillator attached to the patient at EMS arrival (a public access AED or a AED from fire-fighters or police) that AED will be removed and the corpatch electrodes from

corpuls3 will be attached to the patient and connected to corpuls3 in all cases (this is in accordance with routine practice).

Intervention
If the patient is randomized 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. 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.

Control
If randomized to the control group, the ambulance crew team will continue Advanced Life Support (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 remain in A-L position and only one defibrillation from one defibrillator should be used for each defibrillation and continue until ROSC, termination of resuscitation or decision to move the patient to hospital.

Follow up will be performed immediately after every resuscitation
- CRF1
- Swedish Register of Cardiopulmonary Resuscitation (SRCR) part 1, pre-hospital treatment, patient characteristics and short-term outcome.
At the hospital
- CRF2

Survival and neurological function at 30, 90 and 180 days.

PILOT trial sites

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: Carl Magnusson, R.N. Ph.D. Head of Research and Development

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

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. Care and business developer

6.7. 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.

6.8. Monitoring plan

The clinical investigation will be monitored by an independent monitor before the clinical investigation begins, during the clinical investigation conduct, 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 well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

Please see appendix monitoring plan

7. Statistical considerations.

7.1. Analysis population

The principal analysis strategy will be on an "intention to treat" basis. All randomized patients will be included in this analysis.
Further analysis will be performed after exclusion of patients with post randomization exclusion criteria (such as not in cardiac arrest, not VT/VF or exclusion criteria that were not evident at the time of randomization) in a modified intention to treat (mITT) analysis.

7.2. Descriptive statistics

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

7.3. Analytical procedures

The results will be presented as difference in proportions with 95% confidence intervals for categorial outcomes. For continuous outcomes the Wilcoxon rank-sum test will be used. In addition to these analyses, multilevel logistic regression analysis will be performed on categorial outcomes and multi-level ordinal regression for continuous outcomes. These results will be presented as odds ratios with 95% confidence intervals. The study site will be used as random effect.

7.4. Sample size calculation

No power or sample size calculation will be made in the pilot phase. The main reason is that it is a feasibility pilot study and no hypothesis testing will be performed.
The main purpose of the pilot study is to determine timely inclusion and randomization, measure adherence to protocol and assess safety aspects. The pilot study will also try to identify potential obstacles in conducting the study so they can be resolved prior to the main study.
The pilot phase of the study will continue until 40 patients (3:1 randomization) are included. The results from the pilot study will be of importance and used to inform a sample size calculation in a planned main study.

7.5. Missing data

The aim is to minimize the missing data to a minimum. If some important data cannot be collected, we will consider using multiple imputation. The method will be multiple imputation with chained equations (mice)

7.6. Exploratory analysis and sensitivity analysis

No exploratory or sensitivity analyses are planned due to the limited sample size.

7.7. Reporting deviations

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

7.8. Handling of imbalance of subjects per site

As the pilot study sites are in the same area, we will consider them to be one study site.

8. Data management and protection

Subjects who participate in the clinical investigation are coded with a specific clinical investigation identification number. All subjects are 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.

A. For all patients after finished resuscitation:
- Prehospital Digital CRF 1 (see below)
- Swedish Register of Cardiopulmonary Resuscitation (SRCR) part 1, pre-hospital treatment, patient characteristics and short-term outcome
- ECG files from corpuls3 used by including ambulance unit
- Ambulance charts
- EMS emergency dispatch organization time delays (from the Swedish emergency dispatch organization SOS-Alarm)

B. For all patients surviving to hospital admission:
- The SRCR part 2, in-hospital treatment survival to discharge and date of discharge
- For patients undergoing angiography, variables from the Swedish Coronary Angiography and angioplasty register (SCAAR)
- Medical charts, length of stay at ICU, length of stay in hospital and ICD-codes at discharge

C. All patients surviving to 30, 90 and 180 days:
- Neurological function (mRS, CPC) at 30 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
- 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 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 randomization envelope / sheet using a smart-phone. This will open a webpage 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 randomization, randomization study number, time and date of cardiac arrest, number of shocks prior to EMS arrival and number of shocks prior to randomization, treatment allocation, electrode placement for each defibrillation, number of defibrillations before DSD, ROSC and if the patients survived the event. Furthermore, if the patient has a known identity, personal id-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 randomization and allows for early start of follow-up.

Other core resuscitation characteristics will later be reported and collected from the SRCR part 1 and ambulance charts. This registry data is standard and mandatory for all EMS personal to report and contains resuscitation and patient characteristics and reporting to the register 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 analyzed for defibrillation safety and CPR quality.

8.2 In hospital CRF (See supplemental NN) in hospital treatment

In-hospital CRF will cover core in-hospital treatment. The in hospital CRF will collect core data from the mandatory SRCR part 2 such as length of stay and survival to hospital discharge.
Please see supplemental file intrahospital CRF.

For 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)

8.3 Neurological and patient reported Follow up CRF, 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 randomized allocation (intervention or control) will be responsible for neurological follow-up. Neurological function will be assessed according to the modified Ranking Scale (mRS) and the Cerebral Performance Category (CPC) scale at 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 health-related quality of life using the following self-reporting measures:
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 summarized 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.
Generalized 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 summarized 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 follow-up will be entered directly to a secure REDCap database at KI.

8.2. Data cleaning and database lock

All data reported from prehospital CRF, in-hospital CRF and neurological follow up CRF will be digitally entered to a study specific data base (red-Cap). The database will be stored at 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 authorized 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). In the study database all personal data will be pseudonymized and only handled on group level. Personal numbers and all other data that can lead to identification of subjects included in the study will be coded and keys for decoding will only be accessible to key persons in the project. 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 organization, 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, authorized 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.

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 emergency 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.

Any other deviations or waivers from the CIP are not permitted.

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) 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/favorable 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.

12.3. Insurance

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

13. Informed consent process

13.1. General process for informed consent

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 authorized 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 chance 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 in order 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. According to the EU:s Clinical Trials Regulation clinical course in patients that regains circulation after a in hospital cardiac arrest shows a wide variety, from irreversible to reversible circulatory shock, irreversible brain damage and death to neurological 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. No consent will be obtained
2. The patient who survives the initial resuscitation phase, is transferred to hospital and is conscious. 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 enough conscious, GCS <14, have severe dementia, suffer from expressive and/or impressive aphasia or are 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 the emergency situation, circulatory shock, (defined as no need for inotropics) is resolved. This informed consent will be sought by the investigator from the patients legally designated representative without undue delay, normally during or after the ICU period. If the patient still is unable to provide informed consent due to cognitive impairment after the ICU period, renewed contact to inform the patient and obtain informed consent as soon as the patient can give informed consent.

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.

If the incapacitated patient does not have a legally designated representative the investigator has to approach the lawcourt for this purpose.

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

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 he/she will continue their participation.

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) fetal distress, fetal 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 (DD) 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*

The principal investigator or an authorized designee will record:

- - all AEs except the events specified not to be recorded
- - all SAEs;
- - all DDs;
- - 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:

- - Death
- - Hospitalization
- - Persistent or significant disability or incapacity
- - Organ failure

14.2.2. *Reporting*

The investigators will report all SAEs and DDs to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel's awareness of the event. This includes 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 SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure, or where such causal relationship is reasonably possible;
- any DD 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. Compromised CPR-quality. There is a risk that application of a second defibrillator will be associated with interruptions in CPR-quality. Short interruptions are judged to be of no or less significance since they allow for an intervention with a potentially life-saving treatment. However, long interruptions in chest compressions might have an adverse impact on outcome. All interruption > 60s in the intervention-group detected at CRP-quality evaluation will be considered as an probable AE and the monitor / sponsor will be notified and actions taken in accordance with the monitoring plan.

2. 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´s impossible to rule out. Defibrillation data will be analyzed for each case and inability to defibrillate will be considered as a SADE. All defibrillator files will be analyzed for energy delivery at each defibrillation.

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 it´s 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 the monitor according to the monitoring plan, please see appendix “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 finalize 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 PI will have full access to all data and make the final decision to submit for publication.

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