DOUBLE-D MAIN TRIAL
MONITORING PLAN

Early Double sequential Defibrillation in Out of Hospital Cardiac Arrest
- **A Randomized Study**

This randomized trial examines whether giving early double sequential defibrillation — using both anterior–posterior and anterior–lateral pad positions — is more effective than the standard single defibrillation with standard pad placement. The study includes patients with out-of-hospital cardiac arrest who present with an initial shockable rhythm, have already received at least one standard shock, and still require ongoing CPR.

A Randomized Clinical Trial (RCT) - CIV 25-01-051015

Sponsor	Karolinska Institutet, Department of clinical science and education, Södersjukhuset, Sjukhusbacken 10, 118 83 Stockholm, Sweden
Sponsors Representative	Gabriel Riva, M.D., Ph.D., Center for resuscitation science, Karolinska Institutet, Department of clinical science and education, Södersjukhuset, Sjukhusbacken 10, 118 83 Stockholm gabriel.riva@ki.se Tel: +46 (0)8 58703647 / +46 (0)70 545 20 86
Head of Monitoring	Leif Svensson, professor Karolinska Institutet, Department of Medicine, Stockholm +46 (0)73 985 82 57 leif.svensson@ki.se
Coordinating Principal Investigator	Akil, Awad, M.D., Ph.D. Center for resuscitation science, Department of clinical science and education, Södersjukhuset, Karolinska Institutet Address: Sjukhusbacken 10, 118 83 Stockholm, Sweden akil.awad@ki.se +46 (0)70 400 13 63

Steering Committee

Gabriel Riva, M.D., Ph.D.,
Center for resuscitation science
Karolinska Institutet
gabriel.riva@ki.se
+46 (0)70 545 20 86

Akil Awad, M.D., Ph.D.
Center for resuscitation science
Karolinska Institutet
akil.awad@ki.se
+46 (0)70 400 13 63

Carl Magnusson, R.N., Ph.D.
Sahlgrenska University Hospital
carl.magnusson@vgregion.se
+46 (0)70 886 86 20

Andreas Claesson, R.N., Ph.D.
Södersjukhuset
andreas.claesson@ki.se
+46 (0)704940546

Index

GENERAL STUDY INFORMATION

Study summary

<u>Background</u>

Out-of-hospital cardiac arrest (OHCA) affects about 270,000 individuals in Europe annually. 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%. However, some patients in VT/VF do not respond to initial defibrillation, and survival decreases with number of defibrillations required to terminate VT/VF.

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. 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)."
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. 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.

<u>Study rationale</u>

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. 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.

<u>Design</u>

This is an academic, investigator initiated, open-label pilot study with a randomized 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.

Study population

All OHCA patients (≥18 years) with 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: Primary outcome is 30-day survival.

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
Primary objective	To compare 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 with favorable neurological function and long-term survival with a strategy of early double sequential defibrillation, compared to standard defibrillation.
Safety objective	To assess safety of an early DSD strategy in terms of defibrillation performance.
Primary endpoint	30-day survival
Secondary endpoints	Any ROSC Survival to hospital Admission Survival to hospital discharge
No of Subjects	916
No of sites	8
First Subject in *(anticipated)*	September 1st 2025
Estimated last Subject out	December 31st 2028

Definitions

Screening failure	A study Subject that does not fulfil all eligibility criteria
Randomized Subject	A study Subject that has been randomized
Withdrawn Subject	A randomized but not completed Subject (such as existing DNAR that become apparent after enrolment)
Completed Subject	A Subject who completed (all) follow-up after discharge or died prior to 180-day follow up

MONITORING CONDITIONS

This study is to be conducted according to globally accepted standards of Good Clinical Practice, and in agreement with the latest revision of the Declaration of Helsinki, EU directives and local Regulations.

This Monitoring Plan is based on the study protocol, CIP dated May 7th 2025 and has been written in full cooperation and understanding with the Sponsor representative and PI Gabriel Riva.
The monitoring activities described in this plan are in accordance with SOPs.

Overall monitoring aspects

The trial will be monitored where several monitoring offices and individuals will be involved, coordinated by the head of the monitoring team. The frequency of on site monitoring will depend on compliance with the protocol, number of enrolled patients and data handling. At a minimum, there will be a pre-study start-up visit, mandatory monitoring after the end of the trial and at least once during the trial period. All trial sites will be provided with sufficient information to participate in the trial. e-CRFs, log in to REDCap, instructions for registration of data in REDCap, checklists for inclusion/exclusion and randomisation, and a protocol for medical procedures and device control after use in the trial will be distributed to all sites. The site investigator (Local PI) will be fully responsible for that all relevant data is entered into the electronic CRFs (REDCap). The CRFs will be constructed in order to assure data quality with predefined values and ranges on all data entries. Data management activities will be performed and organised by the study coordinating team (Coordinating PI) and the head of the monitoring team.

More specific monitoring methods to be used

The primary focus of the monitoring plan of this study should be on processes that are critical to protecting human subjects, maintaining the integrity of study data and compliance with applicable regulations.

A risk evaluation of this project has been made to agree on the monitoring methodology (i.e. different aspects on-site and/or centralised monitoring) to be used. The study type and study population, characterization of the study endpoints, potential safety concern in the study, experience of PI and local investigators and data capture system has been considered. The methodologies agreed upon are described in following sections in this Monitoring Plan:

- On site monitoring activities (described in section 2.2)
- Centralized monitoring activities (described in section 2.3)

ON SITE MONITORING ACTIVITIES

Initiation (pre-study) visit

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 Double defibrillation prior to participating in the trial. This aspect is comprehensively addressed in the CIP, where further details are provided.
Following EMS personnel training, an initiation meeting will be held. This meeting includes 2–3 hours of education with hands-on training covering all study aspects and documents. The training will address procedures for performing DSD, data collection and reporting, as well as routines for reporting adverse events and device deficiencies in accordance with the CIP. The Local PI will receive all relevant documents and contact information. It is the responsibility of the Head Monitor to ensure that each Local PI has the necessary study information and that all study personnel have been adequately trained. In addition to the onsite/initiation meeting, a web-based training program will be held with each site before enrolment of their first Subject. At this initiating meeting the protocol, CRF/registry, study procedures are thoroughly explained and all practical issues are discussed with the site personnel. During the initiation visit the investigator sites files are checked to ensure that all essential documents are available to the local PI. All study documentation is also available for local PIs and distributed via a trial webpage: www.doubled-trial.org

Further on-site monitoring activities

The frequency of on-site monitoring will depend on compliance with the protocol, number of enrolled participants and data quality / handling. At a minimum, there will be one mandatory monitoring after the trial has started with at least one on-site meeting during the trial period. Preferably this first visit should take place after the first 1-3 patients have been randomized to be able to identify initial problems. Source data verification will be performed according to this monitoring plan of patient consent and key study variables which will be available to the trial monitors.

On-site monitoring could also be performed as digital meetings and will be performed in alliance with local/onsite PI investigators or upon demand, with sufficient notice.

It is the sponsors responsibility to provide all manuals, education and technical advice for all Local PIs. It is the Local PIs responsibility to ensure that all personnel involved in the trial are properly educated in the DSD procedure as well as trialspecific administrative processes, before start of inclusion of patients. The CRF system will be digital within the REDCap system and the REDCap system has error checking routines for range and consistency with immediate feedback to the caregiver. All participating centers are responsible to make arrangement to be able to use REDCap (user manuals will be provided), CRF definitions are easily understood and explained before data are entered. To ensure the correctness of the data entered in the CRF and database, regular contacts with the local investigator will be done during steering group meetings or via the study coordinator. The goal of agreement between key variables in the CRF and controlled medical records should be >90%.

How to handle presumed outliers and systematic errors

Outliers can be detected by central monitoring from available data in the study database and will be done at regular intervals by the study statistician with instructions from the study PI or his assistant and head of monitor. The outcome of any centralized monitoring review (e.g. for sites with systematically high error rate, high amount of outliers or high amount of lack compliance of entering data into the database) should be be highlighted and considered for early identification and close follow up. Those sites shall at once be reported to the steering group and PI for immidiate actions. Such actions can be: monthly/regular on-site visits or other action decied by the steering group/PI or by the head monitor if needed.

Definition of Source Data

Source Data is defined as original documents, data and records. This includes, but is not limited to, the following:
Ambulance records/documents/monitoring systems, defibrillator and CPR feed- back devices, Hospital records/documents/monitorings systems, Prehospital Cardiac arrest register data, other local register or different memorandum or memo sheeets, computer printouts and any other notes or documentation regarding the Subject.

For this study a Prehospital CRF is considered Source Data. The study period per patient ends at approximately 180 days (eg. after the follow up).

Informed Consent (IC)

Special attention during this study will be done to monitoring the specific and complicated process of gaining informed consent. In order to monitor the IC- process, all sites will compulsory log all completed informed consents. The local PI and his/her organization/assistant will check the log against the database for a random subset for each site with the aim to reach 100 % signed IC, from the patients who are capable of providing informed consents.

If the monitor found that inconsistencies are noted between the log and database, the site will be contacted first by the headmonitor or some one the head monitor assigned and if requied by the head PI (Gabriel Riva) or it´s assistant for clarification and to agree on any action required.

CRF and source data verification (SDV)

Study Subjects will be monitored throughout the whole study period, (i.e. study day 180).

Source Data Verification (SDV) will be done on approximately 5-10 % of the CRFs for enrolled patients. Increased level of SDV may be performed for reasons mentioned above, upon decision by sponsors representative, head of monitoring or the steering committee. This will be decided on a site-by-site basis, based on the outcome of all monitoring activities.

Investigational Medical Device Product

All adverse events associated with the defibrillator device that become apparent either during use or after use during mandatory immediate self-test after use (switching the device on and off) or during test defibrillations shall be documented and the local PI shall be contacted as soon as possible in accordance with the CIP.

Investigator Site File (ISF)

An ISF should be established at all sites before studystart

The Investigator Site File (ISF) shall contain all essential documents which shows that the clinical trial site and Investigator are following the regulatory requirements set out by the ICH GCP guidelines. According to the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, essential documents are defined as “documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced.” The ICH GCP 4.9.4 guideline states that “the Investigator and Institution should maintain the trial documents as specified in the ‘Essential Documents for the Conduct of a Clinical Trial’ guidelines.

An ISF plays a crucial role in the outcome of the clinical trial and should be established once a Clinical Trial site has been confirmed by the Sponsor. The Principal Investigator (PI) or an appointed delegate is responsible for setting up, maintaining and completing the ISF. It is the responsibility of the local PI or the delegate to ensure that all the essential documents are collected before the trial begins and that the ISF is updated throughout the duration of the study and archived as part of the Clinical Trial Agreement with the Sponsor.

All essential documents, including any correspondence should be placed in the ISF preferable within 5 business days of the receipt. The essential documents are to be made readily available for monitoring, sponsor audits and regulatory inspections upon demand, with reasonable notice.

The essential documents that should be included in the ISF include:

- CIP
- Participant Information Sheet and Consent Forms
- Regulatory documents, applications and approvals
- Delegation Logs
- Correspondence between delegated site staff and Sponsor
- CVs of all personnel involved
- Blank templates of essential documents
- Blank eCRF
- Patient identification list
- Contact list
- Instructions and manuals for all trial specific procedures
- Randomizational envelope log
- Training log
- Monitor visit log

In all contacts with the local clinic and at the DSD web-based initiation training it will be emphasized that updating of the Investigator File (IF) will be a mutual responsibility for the PI (or delegate) and the local investigator (or delegate).

CENTRALIZED MONITORING ACTIVITIES

The coordinating head monitor and the study statistician at Karolinska Institute will remotely check data from CRF on a regularly basis for outliers and systematic errors and completeness as described above. Furthermore, the monitor will document the CRFs reviewed on a CRF Review Log. This log will only document which patients/CRF-modules that have been checked. Items found where action is needed will be communicated to site via queries in REDCap (see below).

Queries
Queries will be submitted to site the database system (REDCap).

Clinical Event Adjudication (CEA)
All primary main endpoints and SAE to be reported according to the CIP shall be monitored and reported to 100%. For each and every one of them an adjudication of all those events shall be done. All relevant and important actions in regards to those events should be evaluated by a second person well trained in this kind of evaluations.

Close Out-visit

Close-out visits will be performed digitally and through REDCapfor each site. The Local PI at each site are responsible to assure that the ISF is complete, i.e lists and logs and randomization log-lists are properly filled in, signed and returned to the Sponsor. All remaining randomization envelopes should be collected and returned to the Sponsor. All other source documents (CRFs), loglists and ID-list will be archived at the site according to local procedures. When all queries are resolved the site is officially closed.

The Monitor documents the close out procedures in the Close out report. The report should be sent to Sponsor representative (or designee) for review and approval. Once finalized, the report is signed by both Monitor, head of monitoring and the Sponsors representative. The Monitor retains a copy of the signed report.

REFERENCES

Sources of information

1. ICH Topic E6, Guideline for Good Clinical Practice, CPMP/ICH/135/95
2. The Declaration of Helsinki, WMA General Assembly, Washington 2002, including notes of clarification up to 2004 (Tokyo)
3. EU Clinical Trial Directive 2001/20/EC and EU GCP Directive 2005/28/EC
4. MPA´s provisions and guidelines on clinical trials of medicinal products for human use (Läkemedelsverkets föreskrifter om kliniska läkemedelsprövningar på människor och tillhörande vägledning, LVFS 2011:19)
5. SFS 2008:355, Patientdatalagen

The following Monitor Plan is approved and will apply until updates are implemented

Date: ________________________________

Signature ________________________________
Gabriel Riva
Representing the Sponsor organisation

Date: ________________________________

Signature ________________________________
Leif Svensson
PM/Monitor,
Person responsible for compiling this monitoring plan