A randomized trial comparing the effect of a simplified form of cardiopulmonary resuscitation (CPR) consisting of compression-only, compared to CPR with compressions and rescue breaths

Trial Protocol

Version:	2.2
Date:	2025 12 20
Clinical Trials Identifier:	NCT02401633 (PILOT) / NCT03981107 (MAIN study)

Table of contents

List of abbreviations

ACLS	Advanced Cardiac Life Support
AREU	Agenzia Regionale Emergenza Urgenza
CARES	Cardiac Arrest Registry to Enhance Survival
CO-CPR	Compression-Only CPR
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
DA-CPR	Dispatch-assisted CPR
DSMB	Data Safety Monitoring Committee
EMDC	Emergency Medical Dispatch Centre
EMS	Emergency Medical Service
ERC	European Resuscitation Council
ILCOR	International Liaison Committee on Resuscitation
mITT	Modified intention to treat
KI	Karolinska Institute
OHCA	Out-of-Hospital Cardiac Arrest
PP	Per Protocol
PROM	Patient Reported Outcome Measures
REDCap	Research Electronic Data Capture
ROSC	Return of spontaneous circulation
SAP	Statistical analysis plan
SRCR	Swedish Register for Cardiopulmonary Resuscitation
S-CPR	Standard CPR (30:2)
SMD	Standardized mean difference

1. Summary

Title: TANGO2: A randomized trial comparing the effect of a simplified form of cardiopulmonary resuscitation (CPR) consisting of compression-only, compared to CPR with compressions and rescue breaths.

Background: In 2010, two large prospective, randomized trials showed no significant difference with respect to survival between instructions given by emergency medical dispatchers to bystanders without previous CPR training to administer compression-only CPR (CO-CPR) or standard CPR (S-CPR) in patients with witnessed out-of-hospital cardiac arrests (OHCA)(1, 2). Whether CO-CPR is no worse than, or even superior to, S-CPR when performed by bystanders with previous training in CPR remains unclear.

Purpose: To investigate whether CO-CPR is non-inferior to standard CPR (S-CPR) when performed by a bystander with previous CPR training in witnessed, non-asphyxic cases of OHCA. Superiority testing will also be performed for the purpose of demonstrating a possible increase in survival with CO-CPR.

Intervention: Cases of witnessed suspected OHCAs, where bystanders have previous training in CPR, will be randomized at the emergency medical dispatch centre to instructions to perform either CO-CPR (intervention) or S-CPR (control) until arrival of the emergency medical services (EMS). Upon EMS arrival, all patients will receive standard advanced cardiac life support in accordance with current guidelines.

Design: Interventional, prospective, open-label, multicentre randomized trial with 1:1 allocation. A non-inferiority design was decided since S-CPR is an established standard of care, and because a simplified form of CPR could lead to higher rates of bystander-CPR.

Inclusion criteria:

- Unconsciousness with no breathing, abnormal or agonal breathing (suspected OHCA)
- The OHCA is witnessed (seen or heard)
- Any bystander at the scene has previous training in CPR

Exclusion criteria:

- Age below 18 years
- Collapse is not witnessed
- Bystander has no prior CPR training
- Obvious asphyxia (i.e., hanging, foreign body, suffocation, strangulation)
- Obvious intoxication or drug overdose
- Pregnancy
- Trauma (penetrating, blunt, burn injury)

Post randomization exclusion:

- Not EMS-verified cardiac arrest
- Previous do not resuscitate (DNR) decision

Primary outcome: 30-day survival

Secondary outcomes: 1-day survival, 1-year survival, survival with good neurologic outcome at hospital discharge, defined as cerebral performance category (CPC) 1-2

Exploratory outcomes: Return of spontaneous circulation, ventricular fibrillation/ventricular tachycardia.

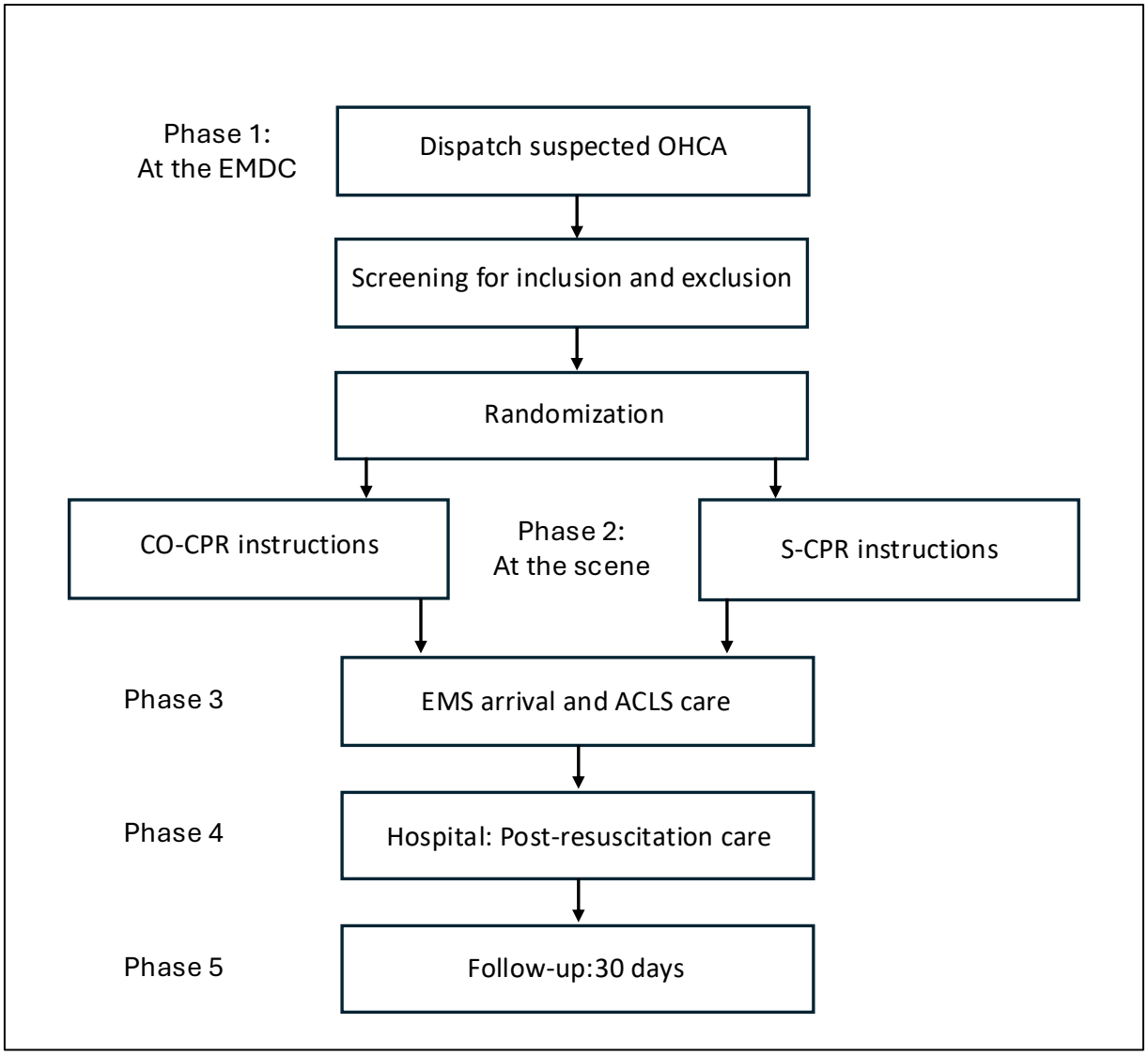
2. Trial overview

2.1. Flow chart

The trial flow-chart and the different study phases are presented below in Figure 1.

For a detailed description of the Study phases, please see Section 6.2 "*Trial phases and interventions".*

Figure 1. Trial overview



OHCA = Out of Hospital Cardiac Arrest, CO-CPR = Compression Only Cardiopulmonary Resuscitation, S-CPR = Standard Cardiopulmonary Resuscitation, EMS = Emergency Medical Services, ACLS = Advanced Cardiac Life Support

2.2 Principal investigator and sponsor

Jacob Hollenberg, MD, Professor
Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset
Director, Centre for Resuscitation Science
Department of Cardiology, Södersjukhuset
SE-118 83 Stockholm, Sweden
Phone: + 46 70413344
Mail: Jacob.Hollenberg@ki.se

2.3 Steering committee

Jacob Hollenberg, MD, PhD (Principal investigator and chair of steering committee)
jacob.hollenberg@ki.se

Giuseppe Ristagno, MD, PhD
giuseppe.ristagno@unimi.it

Markus Skrifvars, MD, PhD
markus.skrifvars@hus.fi

Gabriel Riva, MD, PhD
gabriel.riva@ki.se

Martin Jonsson, MSc, PhD
martin.k.jonsson@ki.se

Andreas Claesson, RN, PhD
andreas.claesson@ki.se

Per Nordberg, MD, PhD
per.nordberg@ki.se

Annette Nord, RN, PhD
anette.nord@ki.se

Mattias Ringh, MD, PhD
mattias.ringh@ki.se

2.4 Trial sites

SWEDEN:

All emergency medical dispatch centres (EMDC) in Sweden participate. This includes all dispatch centres at SOS Alarm AB as well as Sjukvårdens larmcentral.

SOS Alarm dispatch centres:

- Falun
- Göteborg
- Halmstad
- Helsingborg
- Jönköping
- Luleå
- Malmö
- Norrköping
- Stockholm
- Uppsala
- Sundsvall
- Västerås
- Växjö
- Örebro
- Östersund

Sjukvårdens larmcentral dispatch centres:

- Uppsala
- Västerås
- Eskilstuna
- Karlstad

ITALY:

Agenzia Regionale Emergenza Urgenza (AREU) dispatch centre:

- Bergamo
- Milan

2.4. Ethical approvals

The study has obtained ethical approval from both the Swedish Ethical Review Authority and the Italian Regional Ethics Committee (Lombardia 3).

Ethical approvals and amendments, Sweden:

Dnr 2014/97-31/2. Main approval

Dnr 2015/1833-32. Amendment

Dnr 2019-04897. Amendment

Dnr 2023/03361-02. Amendment

Dnr 2024/03712-02. Amendment

Ethical approval, Italy:

OSMAMI-19/09/2024-0036233-U

3. Introduction

3.1 Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of mortality in the industrialized world. The aetiology for OHCA is heterogeneous, but cardiovascular disease remains the most common underlying cause. In Sweden, the yearly incidence of EMS-treated OHCA is around 6,000, and overall survival has remained around 10-12 % over the last few years(3). Several factors increase the chance of survival and neurological intact survival in OHCA, of which bystander cardio-pulmonary-resuscitation (CPR), early defibrillation, and high-quality post-resuscitation care are among the most important ones(4, 5). Bystander CPR before arrival of the Emergency Medical Service (EMS) is a strong positive predictor of survival(6). During the last decade, the optimal form of bystander CPR has been debated(7-9). To perform rescue breaths is a complex task, and bystanders not recently trained in CPR are likely to have difficulties in delivering good rescue breaths. Chest compression only CPR (CO-CPR) has been advocated as a preferable method in situations where the bystander has no previous CPR training, both because it's believed to be equally efficient and also a simplified form of CPR that could lead to increased use of bystander-CPR(10). Furthermore, the CO-CPR method has already been well spread in several parts of the US and Japan(11, 12).

3.2 Preclinical results and data

Studies in porcine models show that CO-CPR increases the number of compressions given by the bystander per minute and minimizes interruptions in CPR(13, 14). Therefore, it is believed to maintain cerebral and cardiac blood flow over a greater period of time during resuscitation. It is also believed that rescue breaths may increase the risk of reflux of gastric content and cause aspiration. Rescue breaths increase the intrathoracic pressure and therefore decrease venous return of blood to the right ventricle, resulting in lower blood flow during compressions(15). Furthermore, it has been demonstrated that hands-off time (i.e., pauses of chest compressions) both before and after defibrillation is associated with worse outcome(16). On the other hand, CO-CPR leads to rescuer fatigue and poorer compressions(17). It is also believed that the withdrawal of rescue breaths leads to a faster decrease in saturation of arterial blood and therefore is believed not to give crucial oxygen delivery to vital organs, even though the blood flow to these organs is maintained(13).

3.3 Previously published clinical results

Several observational studies have shown similar or even increased survival rates with a simplified form of CPR, consisting of compressions only (CO-CPR), instead of standard CPR consisting of 30 compressions and two rescue breaths in non-traumatic/asphyxic OHCA(10, 18-21). In 2010, two large prospective, randomized trials showed no significant difference with respect to survival between instructions given by emergency medical dispatchers for CO-CPR and instructions for standard CPR (S-CPR) in patients with witnessed OHCA in cases where the bystanders had no previous CPR-training (1, 2). As a consequence, new guidelines recommend DA-CPR with compression-only for untrained

bystanders and trained bystanders unwilling or unable to perform rescue breaths(22, 23). The shift in recommendations is also based upon the assumption that a simplified CPR method would increase the number of bystanders performing CPR. In an initiative to increase CPR rates, the American Heart Association has launched public campaigns such as the “hands-only CPR,” promoting CO-CPR as an option to S-CPR for adult non-asphyxic cardiac arrest(11). In the 2015 update of the European Resuscitation Council guidelines, it states that the confidence in the equivalence between the two methods is not sufficient to change current practice(24). In Sweden, there have been no public campaigns promoting CO-CPR.

Whether CO-CPR leads to a survival rate no worse than S-CPR in situations where the bystander has previous CPR training remains unclear. This clinical question remains unanswered while millions of people are trained in CPR worldwide each year.

4. Overall aim and purpose

The overall purpose is to study whether CO-CPR is non-inferior to standard CPR when performed by bystanders with previous CPR training in witnessed, non-asphyxic cases of OHCA.

4.1 Primary objective

To evaluate whether survival at 30 days following dispatched instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR to bystanders with prior CPR training in witnessed, non-asphyxial OHCA. Superiority testing will also be performed to evaluate a possible increase in survival with CO-CPR.

4.2 Secondary objectives

To evaluate whether there is a difference between CO-CPR and S-CPR in 1-day survival and 1-year survival, and survival with good neurologic outcome at hospital discharge, defined as cerebral performance category (CPC) 1-2 across pre-specified subgroups (for details, see section 10.7).

4.3 Explorative objectives

To evaluate whether there is a difference between CO-CPR and S-CPR in return of spontaneous circulation (ROSC), ventricular fibrillation/ ventricular tachycardia, across the pre-specified subgroups (for details, see section 10.7)

4.4 PICO-question

P	Adult witnessed non-asphyxic OHCA (P),
I	Does instructions to perform CO-CPR performed by trained bystanders (I)
C	Compared to instructions to perform S-CPR (C)
O	Effect 30-day survival (O)

5. Eligibility

Witnessed cases of adult OHCAs with a non-asphyxic aetiology will be the principal study population. Patients will be eligible for enrolment if they meet all the following inclusion criteria and none of the exclusion criteria. Inclusion and exclusion criteria are unchanged throughout the different study phases (RUN-IN, PILOT, and MAIN study).

5.1 Inclusion criteria:

- Unconsciousness with no breathing, abnormal or agonal breathing (suspected OHCA)

- The OHCA is witnessed (seen or heard)

- Any bystander at the scene has previous training in CPR

5.2 Exclusion criteria:

- Age below 18 years

- Collapse is not witnessed

- Bystander has no prior CPR training

- Obvious asphyxia (i.e. hanging, foreign body, suffocation, strangulation)

- Obvious drug overdose / intoxication

- Pregnancy

- Trauma (penetrating, blunt, burn injury)

5.3: Post randomization exclusion from data analysis:

- Not EMS-verified cardiac arrest

- Previous do not resuscitate (DNR) decision

6. Trial design

This is an interventional, prospective, randomized, 1:1 open-label, multicentre trial comparing two different methods of bystander CPR in witnessed cases of OHCA. A non-inferiority design was chosen, as S-CPR is the established standard of care, and because a simplified form of CPR could lead to higher rates of bystander CPR. Superiority testing will also be performed to demonstrate a possible increase in survival with CO-CPR.

6.1 Principal study population and intervention

Adult witnessed cases of OHCAs with a non-asphyxic aetiology constitute the principal study population. According to current guidelines, an unresponsive patient with no breathing, abnormal or agonal breathing is indexed as a suspected case of OHCA at the EMDC. These cases will be screened for eligibility. If the case is witnessed, any bystander at the scene has previous training in CPR, and no exclusion criteria are present, the case can be randomized by the dispatcher and allocated to receive instructions to perform either CO-CPR (intervention) or S-CPR (control).

The intervention arm consists of instructions from a dispatcher at the dispatch centre to the bystanders to perform CO-CPR with chest compressions only.

The control arm consists of instructions from a dispatcher at the dispatch centre to the bystanders to perform S-CPR with chest compressions and rescue breaths in a 30:2 ratio.

6.2 Trial phases and intervention:

6.2.1. Phases 1 and 2: The work at the dispatch centre and CPR by a bystander

- Identification of cases
- Screening for eligibility
- Randomization
- Instructions according to the allocation

Suspected OHCAs identified at the EMDC, classified as unconscious with no breathing, abnormal or agonal breathing, are screened for eligibility. When a dispatcher suspects a case of OHCA, the inclusion criteria will automatically pop up on their computer screen. The inclusion criteria are assessed sequentially by the dispatcher. First, the dispatcher confirms that the victim is an adult (age ≥18 years). Age is a mandatory question for caller identification in the dispatch system. Second, the dispatcher assesses whether the collapse was witnessed (seen or heard). Third, the dispatcher evaluates whether the cardiac arrest is of presumed medical cause and non-asphyxic. All dispatchers have been trained in the study protocol and in this definition. As decision support, the exclusion criteria are accessible on their screen during the call. Fourth, the dispatcher assesses whether any bystander at the scene has previous CPR training. In accordance with current guidelines, if no bystander has previous CPR training, the dispatcher provides instructions for CO-CPR, and the case is not further screened for eligibility in

the study. If any bystander at the scene has previous CPR training (at any time) or if CPR is already ongoing, the case can be screened for eligibility in the study.

If any of the inclusion criteria are not met, the case is not randomized (and instead handled according to standard protocol). If no exclusion criteria are present, the case will undergo randomization (please see section 10.8). This will generate a randomized allocation to either intervention (CO-CPR) or control (S-CPR). A new pop-up will then appear on the dispatcher screen with detailed instructions to the caller/bystander in both groups. Simultaneously, the EMS will be dispatched.

The bystander will, in all randomized cases, obtain instructions from the dispatcher to provide either CO-CPR or S-CPR until arrival of the EMS.

The instructions from the dispatcher in the INTERVENTION arm include:

- An ambulance is dispatched and is on its way to you
- Perform CPR with chest compressions only
- Push hard on the chest with a pace of 110/minute without interruptions

The Instructions from the dispatcher in the CONTROL arm include:

- An ambulance is dispatched and is on its way to you
- Perform CPR with chest compressions and rescue breathing
- Push hard on the chest 30 times and give 2 rescue breaths.
- The pace of the compressions should be 110/minute.

Dispatchers are furthermore instructed to encourage all callers in both groups to stay in contact with the dispatcher until arrival of EMS or first responders, instruct callers to put the phone on speaker when possible, and to ask bystanders to count aloud while performing chest compressions. Dispatchers should try to aim for a compression rate of 100-120/minute and suggest switching CPR providers every two minutes if multiple rescuers are on the scene.

6.2.2. Phase 3: The work and action at EMS arrival

Upon arrival of the EMS or first responders, the intervention ends. The EMS will treat all patients with standard advanced cardiac life support recommended by the European Resuscitation Council (ERC) guidelines(24), including bag mask ventilation, advanced airway management with endotracheal tube or laryngeal mask, defibrillation, and intravenous drugs.

6.2.3. Phase 4: The work and action during hospital stay and care

If the patient is admitted to the hospital, patients are treated according to local hospital protocols and practice in accordance with ERC post-resuscitation care guidelines(25), including coronary angiography for ST-elevation or high suspicion of occlusion, intensive care with fever prevention, and multimodal prognostication strategy. Hospital clinicians will be blinded to the randomized treatment allocation.

6.2.4. Phase 5: Follow-up of survival and neurological function

Survival is evaluated for the primary endpoint at day 30 through the Swedish Register for Cardiopulmonary Resuscitation (SRCR) through linkage with the Swedish population register. For survivors, CPC is collected via standardized Patient-Reported Outcome Measures (PROM), including a neurological assessment conducted 30 to 90 days post-arrest by nurses blinded to treatment allocation, with results reported to the SRCR. This follow-up may not be feasible at all TANGO2 sites.

6.3. Blinding

Because of the inherent logistical problems with blinding of CPR techniques for dispatchers, the trial is considered as an “open labelled” trial.

Treatment allocation will be blinded to EMS crew, in all data management and follow-up, as well as for clinicians treating the patients at the hospitals, and for all responsible researchers.

6.4. Outcomes

6.4.1 Primary outcome:

- 30-day survival

6.4.2 Secondary outcomes:

- 1-day survival
- 1-year survival
- Survival with a good neurologic outcome at hospital discharge defined as cerebral performance category (CPC) 1-2

6.4.3 Exploratory outcomes:

- Ventricular fibrillation or ventricular tachycardia as the first rhythm
- Return of spontaneous circulation

7. Study phases: RUN-IN period, PILOT study, and MAIN study

7.1. Study Overview: RUN-IN period, PILOT and MAIN studies

The overall study project is conducted in three different phases:

1) RUN-IN period, for establishing logistical and technical study procedures (**completed**)

2) PILOT STUDY, with focus on feasibility, logistics, and safety (**completed**)

3) MAIN STUDY with focus on 30-day survival (primary end point) and other important clinical outcomes (secondary and exploratory outcomes)

7.1.1. Objective RUN-IN period

To test the technical inclusion procedures, logistics, feasibility, and data collection, a RUN-IN period started in Stockholm during 2015.

7.1.2. Objective PILOT study

The original aim of the PILOT study was to assess the safety and feasibility of the trial, as well as intermediate clinical outcomes of 1-day survival. The trial started recruitment of patients on January 1st, 2017. All patients from the PILOT study will be included in the MAIN STUDY in a seamless design (for details, see sections 7.2 and 7.3 below).

7.1.2. Objective MAIN study

The MAIN study aims to evaluate whether survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR for bystanders in witnessed, non-asphyxial OHCA where the bystander has previous CPR training. Secondary objectives include the evaluation of 1-day and 1-year survival as well as a neurological favourable survival (CPC 1-2). (for details, see section 10.7). The MAIN study will include patients from the RUN-IN and PILOT phase in a seamless design (for details, see sections 7.2 and 7.3 below).

7.2. Experiences from the RUN-IN period and implications for the PILOT and MAIN studies.

The RUN-IN period started in Stockholm County in 2015, and analyses were performed during 2016. After continuous technological adjustments, the randomization module was integrated within the digital dispatch system and was found to function well by the end of 2016. However, during the RUN-IN period, one major obstacle was identified. Due to unexpected technological difficulties and an unanticipated reorganization of the EMDCs in Sweden, only about 15% of the cardiac arrest calls in Stockholm were answered by dispatchers in Stockholm County; all other calls were transferred to different EMDCs throughout Sweden. This meant that the dispatchers had to consider the geographical site of the suspected cardiac arrest and remember if that area was part of the study

area. The reorganization, combined with logistical issues, where the call could be made in one county and answered and handled in another EMDC county during the RUN-IN period, resulted in a far slower inclusion rate than anticipated and made follow-up of patients unmanageable and unreliable. This made it impossible to conduct a PILOT study in Stockholm County only.

As a consequence, a decision was made by the steering committee:

A) To move the start of the PILOT study forward until completion of the national expansion of the study and not to start inclusion of patients into the PILOT study before January 1st 2017. The new length of the PILOT study was set to at least two years to ensure sufficient inclusion of patients to assess safety in terms of: time intervals for screening for eligibility and randomization, time to dispatch CPR instructions, time to first bystander chest compression, time to EMS dispatch, and intermediate clinical outcome defined as one day survival.

B) That the PILOT study will transition directly into the MAIN study in an inferentially seamless manner after the PILOT phase inclusion ended. This means that patients from the PILOT study will also be included in the MAIN survival study. The outcomes for the PILOT study were changed to not interfere with the primary endpoint of the main survival study (for details, see the section below). Inclusion and exclusion criteria have remained unchanged throughout the whole TANGO2 project.

7.3 Summary of changes in protocol after experiences from the pre-study RUN-IN period.

Previous changes from the original protocol (February 2019)

- As described above, the start and size of the PILOT study were modified.

- As a consequence of the national expansion, enlargement of the PILOT study, as well as the seamless design, the primary endpoints of the PILOT study were modified not only to assess feasibility but also to include assessment of safety as well as intermediate clinical outcome (1-day survival).

- The primary endpoint of 30-day survival is not evaluated in the PILOT study. The reason for this is not to interfere with the primary endpoint of the MAIN study.

- Inclusion and exclusion criteria and dispatch instructions have remained unchanged since the first initial protocol and throughout all phases of the TANGO2 project.

- In Stockholm, first responders are dispatched in parallel to EMS in suspected OHCA. The initial protocol included first responders as a part of the trial. However, due to the national expansion of the study together with the fact that the information of assigned treatment (CO-CPR or S-CPR) to first responders during dispatch in the RUN-IN phase was not feasible, the steering committee decided to remove first responders from participation in the PILOT study and the MAIN study.

- The initial protocol stated a randomization procedure through the opening of pre-printed envelopes with randomized allocation. This was changed before the start of the pre study RUN-IN period to an automated computerized randomization integrated in the dispatchers' software.

- For assessment of adherence to protocol, a decision was made by the Steering Committee to review all call audits during the PILOT study and MAIN study using a standardized template for evaluation of dispatch-assisted CPR (DA-CPR) provided by CARES (Cardiac Arrest Registry to Enhance Survival)(26). All audit reviewers will be blinded to allocation.

7.4 Effects of the COVID-19 pandemic

- Due to the outbreak of the COVID-19 pandemic, the ILCOR and the Swedish Resuscitation Council issued temporary guidelines for lay bystander CPR in OHCA, recommending only looking for signs of life and performing CO-CPR(27, 28). Therefore, this study was put on hold on date at the 3^{ed} of December 2020.

- The initial plan was to publish the PILOT study, including the years 2017 and 2018. Due to the uncertainty during the COVID-19 pandemic regarding whether the trial would be able to restart, a decision by the steering committee was made to postpone the pilot publication.

- During the pause due to the COVID-19 pandemic, an independent data monitoring committee reviewed all data up until 12-03-2020 (pre-COVID-19). Their recommendation was to continue the trial without modifications (for details, see section 11)

- When the temporary COVID-19 guidelines were removed the 1st April 2022, and the main trail was relaunched, inclusion re-started on 8th of August 2022.

- A decision was made to include all patients during the period pre-COVID-19 in the PILOT study, and the dates of the PILOT were changed accordingly.

- To ensure follow-up, all randomized suspected OHCA with no matching record in SRCR will be reviewed in the EMS records (for details, see section 8)

7.5 Expansion of the trial

- In October 2024, the AREU EMDC in Italy joined the trial.

8. Data collection

From the dispatch organizations, the following variables will be collected:

Time of emergency call, time of OHCA recognition (suspected), time of first chest compression, time of dispatch of EMS, time of dispatch of first responders when applicable, time for screening for eligibility, time of randomization, and time of arrival of EMS or first responders. Event times are automatically generated and stored in each EMDC database. The randomized allocation for each call is stored in a separate data file generated by both randomization modules.

Call audit review:

For evaluation of included calls and adherence to protocol, all randomized, EMS-treated OHCA dispatch calls will be reviewed. All call-audit reviewers will be blinded to the allocation. A standardized template for evaluation of dispatch-assisted-CPR will be used, provided by Cardiac Arrest Registry to Enhance Survival(CARES)(26). The study-specific inclusion criteria will be added as auxiliary variables to the call audit template.

From the Swedish register for Cardiopulmonary Resuscitation the following variables will be collected:

All EMS units report to the SRCR. For all EMS-treated OHCA, the following variables will be collected from the SRCR:

Date of OHCA, age, sex, location of OHCA, CPR before EMS arrival, highest educational level of CPR provider, first recorded rhythm, defibrillation, airway management, drug administration, and ROSC. Survival is collected for the primary endpoint at day 30 from SRCR through linkage with the Swedish population register.

1-day survival will be derived from the date of death recorded in SRCR. Because SRCR only provides the calendar date of death (and not the exact time), we cannot reliably determine the Utstein variable “survival to hospital admission”. We therefore will use 1-day survival as a proxy. If the SRCR date of death is the calendar day after the event date, the patient will be classified as still alive after 1-day. Separating survival to hospital admission from early in-hospital death will not be possible with the available SRCR data.

In randomized cases where there is no matching report in SRCR, EMS records will be reviewed; if EMS has performed CPR or the patient had been defibrillated by a public automated external defibrillator, the case will be classified as “EMS treated” and corresponding variables will be extracted from EMS records instead.

For survivors, CPC is collected via standardized PROM, including a neurological assessment conducted 30 to 90 days post-arrest by nurses blinded to treatment allocation, with results reported to the SRCR. This follow-up may not be feasible at all TANGO2 sites.

Italy:

In AREU, Italy, the same set of variables as in Sweden will be collected for all EMS-treated OHCA cases. Bergamo EMDC is part of the regional EMS organization (AREU). Data will be obtained directly from EMDC and EMS records within AREU, including dispatch data, call audit reviews, EMS, and resuscitation data. 1-day, 30-day survival, CPC, and 1-year survival will be collected separately from participating hospitals.

8.1 Data handling and record keeping

For each emergency call to the dispatch centre, a unique case number is automatically generated. This case number is stored at the dispatch centre and used to match randomized patients with the EMS record in SRCR. All case numbers and corresponding call audio will be saved and stored at SOS Alarm and Sjukvårdens Larmcentral. All patient data, including randomization, time variables, EMS treatment data, call audit review, informed consent, and follow-up, is stored and secured in the Research Electronic Data Capture (REDCap) application provided by Karolinska Institute(KI) for the TANGO2 specific study group at the Centre for Resuscitation Science KI. In KI REDCap, data is saved locally on KI servers and backed up every 24 hours. This system fulfils all criteria for handling patient data according to the European Union data protection regulation (GDPR). In REDCap, the allocation of each specific case will be blinded during the data collection to avoid bias in reporting or collecting data. Allocation concealment will be preserved. There will be manual cross-checking and completion of missing data through EMS organisations, SRCR, and hospital records.

Italy:
For the Italian site, patient data is managed in the same way and stored in a dedicated REDCap project within the same secure REDCap instance at KI. No patient-identifiable data are transferred between the Swedish and Italian REDCap systems.

9. Ethical considerations

9.1 Informed consent

This research group has a longstanding experience to perform studies in cardiac arrest patients, like the present, within the prehospital setting. In OHCA, the victim is unconscious and therefore incapable of providing informed consent. OHCA is however, also a medical emergency and treatment must be started immediately, making informed consent by a relative or legally authorized representative impossible due to practical reasons. As stated by the Helsinki Declaration 2008, 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. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative."

9.2 Potential risks

For the individual cardiac arrest patient, rapid actions by bystanders can lead to an increased chance of survival. Unless some form of life-support activity is performed before the arrival of the EMS, survival is dismal. CPR itself rarely leads to damage other than rib fractures. Any pain and discomfort after a successful survival is not proportional to the gain of being rescued to life. During CPR, the patient is unconscious and thus experiences no pain. The risk of injury associated with CPR is insignificant compared to the potential benefits of treatment. Those patients who survive 30 days after a cardiac arrest often have a good quality of life with only minor neurological disability. This contradicts the fear that an increased number of cases of successful resuscitation leads to many surviving patients with severe disabilities. For the helper, however, some discomfort can arise. Potential risks with this trial are the delayed start of CPR due to inclusion and randomization. These issues are separately evaluated in the RUN-IN and PILOT phase. Performing CPR is associated with great emotional stress. It is important to be prepared for the reactions that can arise among the lay volunteers. Fear of transmission of contagious diseases associated with CPR is greatly exaggerated. Only a few such cases have been reported worldwide. A small but important population of all OHCAs are due to asphyxia, drowning, drug overdose, and children (age below 18 years). These cases are excluded from the study as described in the study protocol. We believe that a small group of difficult cases that are not identified by either the bystander or by the dispatcher, e.g., Severe kidney failure, pulmonary embolism, haemorrhagic stroke, or chronic obstructive pulmonary disease, could

experience a small risk with this intervention. These cases are rare and already have a very poor prognosis.

9.3 Potential benefits

Survival after OHCA is very poor, in Sweden ranging between 10-12%(3). Experimental studies and previous randomized trials have shown that successful CPR can be achieved with CO-CPR(1, 2). Rescue breaths are technically difficult and take time from chest compressions. In non-cardiac causes of OHCA, rescue breathing might be more important. These cases are therefore excluded before randomization. CO-CPR could lead to an earlier start of CPR, and no interruptions in chest compressions could therefore be beneficial for more patients. In cases of OHCA, immediate chest compressions are of absolute necessity to increase the otherwise low chance of survival.

Today, Sweden has among the highest rates of bystander CPR in Europe, making a study like this possible for the first time. An additional simplification of the CPR algorithm, introducing CO-CPR could perhaps increase survival rates in Sweden and has the potential to increase bystander rates throughout Europe and beyond.

A simplified method of CPR with short CO-CPR courses will be more cost-effective in companies, schools, and throughout society and could enhance the care for this patient group nationally and internationally. In summary, whether CO-CPR leads to a survival rate no worse than standard CPR in situations where the bystander has previous CPR training remains unclear. This clinical question remains unanswered while millions of people are trained in CPR worldwide each year. The potential benefits of this study are two-fold in the sense that the results can lead to increased survival rates: 1) CO-CPR might be no worse or even better than traditional CPR, 2) CO-CPR could lead to more people performing it.

10. Data analytics and statistical analysis plan (SAP)

10.1 General statistical analysis plan

This trial is designed to investigate whether CO-CPR is non-inferior to S-CPR for bystanders with previous CPR training. The non-inferiority design was chosen since S-CPR is an established standard of care and because a simplified form of CPR could lead to higher rates of bystander-CPR.

Eligibility, inclusion, exclusion, randomization, and allocation will be displayed in the Consort diagram.

Baseline characteristics will be summarized by treatment group. Between-group differences in baseline variables will be described using standardized mean differences (SMDs), with values below 0.1 interpreted as a balanced baseline between treatment groups.

For the primary analysis, we will fit a binary logistic regression model for CO and S-CPR as the main exposure, adjusted for pre-specified baseline covariates* that are associated with the primary outcome. From this model, we will estimate the marginal risk difference of the primary outcome in each group. The absolute risk difference will then be calculated as the difference between the two marginal risks. CO-CPR will be declared non-inferior if the lower bound of the 95% confidence interval for the absolute risk difference is greater than −1.0 percentage points, corresponding to a one-sided alpha (0.025).

As a sensitivity analysis, the same approach will be applied using an unadjusted logistic regression model to estimate unadjusted marginal risks and marginal risk differences with corresponding 95% confidence intervals.

* Prespecified covariates to increase the precision of the primary efficacy outcome are age, sex, and EMS response time.

10.2 Statistical hypothesis for non-inferiority

10.2.1 The null hypothesis:

30-day survival rate with CO-CPR is more than 1.0 percentage point lower than S-CPR

10.2.2 The alternative hypothesis:

30-day survival rate with CO-CPR is no more than 1.0 percentage point lower than S-CPR

10.3 General statistical methods

All statistical analyses will be performed using R version 4.4.2 or higher. Continuous variables will be summarized with median (IQR), and categorical variables with counts and percentages.

10.4 Analysis strategy and steps for the overall study populations

The target population is adult, witnessed, non-asphyxial OHCA where any bystander at the scene has previous CPR training. All randomized calls of suspected OHCA will be included.

In this EMDC setting, dispatchers act on limited information at the time of randomization; therefore, non-OHCA cases are inevitable. Because randomization is based on dispatcher suspicion instead of a confirmed diagnosis, some randomized events will subsequently be determined not to be OHCA when assessed by EMS on scene.. Arrest status is verified upon EMS arrival. Non-arrest events such as syncope or low blood glucose will be excluded from the final analysis (i.e., cases not treated as cardiac arrest by the EMS personnel). The remaining randomized patients will constitute the modified intention-to-treat (mITT) population. Non-EMS-treated cases will be reported in the CONSORT flowchart (for details, see section 10.5). All excluded randomized cases and reasons for exclusion will be reported. Since randomization occurs at the level of a dispatch instruction, we will review all call audits using a standardized template for evaluation of dispatch-assisted CPR (CARES)(26), to verify the instructions delivered (CO-CPR vs S-CPR) and to assess if the bystander followed the dispatcher's instructions.

mITT analysis: The modified ITT population includes all randomized OHCA patients for whom treatment with CPR/ACLS was initiated. Patients are analysed according to the randomized dispatcher instruction (CO-CPR vs S-CPR), regardless of the CPR method actually delivered by the bystander.

Per protocol (PP): They are the subset of mITT in which the bystander delivered the randomized instruction, verified by the call audit. Protocol adherence-will be verified by PP.

As-Treated: Treatment actually received will be analysed with the As-Treated population that includes all randomized, EMS-treated OHCA patients, analysed according to the bystander action actually performed, as verified by call audit, regardless of the randomized assignment. The As-Treated analysis is supportive, non-conservative, as randomization is not preserved.

10.5 Power and sample size estimation

We estimated that 3260 patients (1630 per group) are required in the PP analysis to achieve 80% power to declare CO-CPR non-inferior to S-CPR. This is based on the assumption that 30-day survival is 11.0% with S-CPR (control) and 13.2% with CO-CPR (intervention), a two-sided alpha of 5%, and a non-inferiority margin of 1.0 percentage point (absolute risk difference).

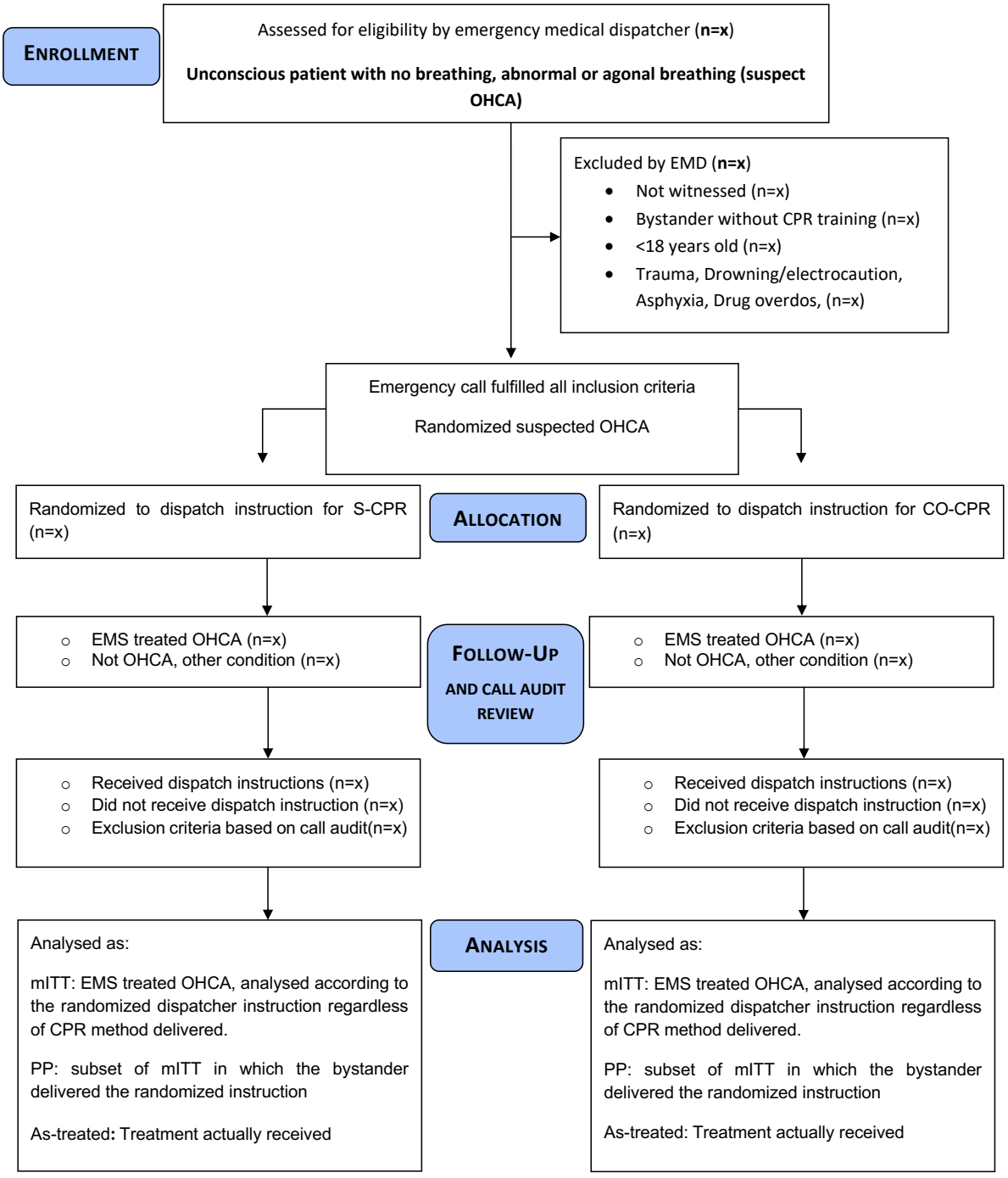
We defined the largest acceptable difference for the primary endpoint (30-day survival) as an absolute difference of 1.0 percentage point between CO-CPR and S-CPR. Any difference smaller than 1.0 percentage point (in either direction) is considered clinically acceptable.

The non-inferiority margin is an absolute difference of minus 1.0 percentage points, corresponding to a number-needed-harm of 100 (one additional death per 100 patients treated if CO-CPR were recommended instead of S-CPR). We consider this acceptable because CO-CPR is simpler to teach and perform and is expected to increase overall bystander rates.

We assume a 20% crossover between allocated and delivered CPR instruction, reflecting the expected mismatch between randomized instruction and CPR actually performed in a real-world setting.

CONSORT
TRANSPARENT REPORTING of TRIALS

2025 CONSORT Flow chart



10.6 Non-Inferiority and Superiority Testing

The primary analysis will be conducted in the PP population, consistent with the sample size calculation (for details, see section 10.5). If non-inferiority is demonstrated in PP, the same non-inferiority hypothesis will then be evaluated in the mITT population as a confirmatory analysis. If non-inferiority is established, the analysis will proceed with a pre-specified test for superiority. Non-inferiority will be concluded if the non-inferiority criterion is met in the PP population. The results from the mITT analysis will be presented alongside the PP population.

10.7 Subgroup analyses

Subgroup analyses of the primary outcome will be conducted using logistic regression models that include treatment, the subgroup variable, and their interaction term. The results will be presented as odds ratios with a 95% confidence interval for each predefined subgroup, together with a p-value for the interaction between treatment and subgroup

Subgroups will be analysed according to the following pre-defined variables:

- Sex
- Age
- Cause of OHCA
- Initial rhythm
- Location of cardiac arrest
- Time to start of CPR
- Time to arrival of EMS
- Neurological severity classification (CPC)

10.8 Randomization

Sweden:

Randomization will be performed by a random generator (Microsoft .NET Random Constructor (Int32) in a 1:1 allocation ratio, automatically within the dispatch system.

Italy:

Randomization will be carried out automatically within the digital dispatch system using permuted blocks with variable block sizes of 4, 6, and 8.

Screening for eligibility and randomization are integrated within the digital software at all EMDCs. For all dispatchers, randomization will generate a 1:1 allocation to either the intervention (CO-CPR) or the control (S-CPR), and a pop-up appears with allocation-specific instructions for the caller/bystander. After randomization, the allocation locks for 15 minutes to prevent reallocation by dispatchers.

11. Interim analysis and data monitoring committee

The trial will be monitored by an independent Data Safety Monitoring Board (DSMB), which will receive unblinded summaries of data at the two interim analyses scheduled at 750* and 1500 patients. The DSMB will have the mandate to evaluate specific safety concerns, as well as efficacy, with the option to either declare sufficient difference in the primary outcome variable or to recommend that the study be continued until 3260 patients have been enrolled. Early stopping for efficacy reasons will only be considered if primary outcome differences are observed between the groups, according to the Peto-Haybittle rule, with a p-value ≤ 0.001. The DSMB will be able to request unblinding of data if they find it necessary. The DSMB can initiate analysis at any time they request.

**In 2022, an interim analysis was performed after a total of 1250 patients (out of which 696 patients were included in the main PP population). For details, see Section 7: Study phases. The recommendation by the DSMB was to continue the trial without modification.*

12. Publication plan and author policy

The trial will be analysed by an independent statistician, and the results interpreted by the steering committee. The principal investigator, together with the steering committee, will prepare the manuscript before unblinding the treatment allocation. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will follow the Vancouver recommendations. The steering committee, via the principal investigator Jacob Hollenberg, will finally decide the list of authors and how these will be ordered in the final publication. The author list will include steering committee members, national investigators, and others. Publication of the principal results from any single-centre experience within the study is not allowed until both the preparation and publication of the multi-centre results. Thus, no publication or presentation of the data or results of the study may be presented until the principal investigator determines that the database for the study is clean and locked and that the primary and secondary endpoint analyses are consistent with the protocol.

13. Enrolment and timeline

Q1-2 2014	Application to the ethics committee
Q3-4 2014	Preparation
2015-2016	RUN-IN study
2017-2020	PILOT study
2022-2027	MAIN STUDY

14. Summary of changes from previous protocols

Version	Date	Reason
1.0	2015-01-01	Original manuscript
2.0	2019-05-01	RUN-IN adaption
2.1	2022-09-15	COVID-19 pause
2.2	2025-12-20	Statistical analysis plan (SAP) amendments, Italy joins the trial

Summary of changes in Protocol 2025

After the 2022 revision of the protocol, COVID-19 and a national EMS reorganization led to additional ethical amendments (for details, see section 2.4). In the current revision of the protocol, the following modifications have been made:

- Expansion of the trial with the addition of AREU in Italy.
- Clarification and updates about the Swedish national EMS reorganization and modification of active sites.
- Principal investigator, one instead of two.
- Steering committee, updated.
- Clarification of the statistical analysis plan to provide a more detailed description of the study design and the methods for conducting the primary analysis.
- The previously specified PP2 population has been replaced by an “as-treated” population, and explorative outcomes have been added.
- We corrected a typographical error in the power calculation where 13,1% was mistakenly reported instead of the correct value of 13,2%.
- The overall study design, including randomization, interventions, population, primary endpoint and follow-up, has remains unchanged compared with the initial plan.

15. References

1. Svensson L, Bohm K, Castrèn M, Pettersson H, Engerström L, Herlitz J, et al. Compression-only CPR or standard CPR in out-of-hospital cardiac arrest. N Engl J Med. 2010;363(5):434-42.
2. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, et al. CPR with chest compression alone or with rescue breathing. N Engl J Med. 2010;363(5):423-33.
3. Herlitz J. Annual report on Out-of-Hospital-Cardiac-Arrest https://docs.google.com/file/d/0B6j4zddszpvyUG9IWTNlbkFWemM/edit?pli=1: Swedish Cardiac Arrest Register; 2013 [
4. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital Cardiac Arrest A Systematic Review and Meta-Analysis. Circulation-Cardiovascular Quality and Outcomes. 2010;3(1):63-U111.
5. Valenzuela TD, Roe DJ, Nichol G, Clark LL, Spaite DW, Hardman RG. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med. 2000;343(17):1206-9.
6. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. N Engl J Med. 2015;372(24):2307-15.
7. Weisfeldt ML. In CPR, less may be better. N Engl J Med. 2010;363(5):481-3.
8. Anantharaman V. Chest compression-only CPR or good quality 30:2 CPR. Singapore medical journal. 2011;52(8):576-81.
9. Cabrini L, Biondi-Zoccai G, Landoni G, Greco M, Vinciguerra F, Greco T, et al. Bystander-initiated chest compression-only CPR is better than standard CPR in out-of-hospital cardiac arrest. HSR proceedings in intensive care & cardiovascular anesthesia. 2010;2(4):279-85.
10. Bobrow BJ, Spaite DW, Berg RA, Stolz U, Sanders AB, Kern KB, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. Jama. 2010;304(13):1447-54.
11. Sayre MR, Berg RA, Cave DM, Page RL, Potts J, White RD. Hands-only (compression-only) cardiopulmonary resuscitation: A call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest - A science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. Circulation. 2008;117(16):2162-7.
12. Iwami T, Kitamura T, Kiyohara K, Kawamura T. Dissemination of Chest Compression-Only Cardiopulmonary Resuscitation and Survival After Out-of-Hospital Cardiac Arrest. Circulation. 2015;132(5):415-22.
13. Sanders AB, Kern KB, Berg RA, Hilwig RW, Heidenrich J, Ewy GA. Survival and neurologic outcome after cardiopulmonary resuscitation with four different chest compression-ventilation ratios. Annals of emergency medicine. 2002;40(6):553-62.
14. Ewy GA, Zuercher M, Hilwig RW, Sanders AB, Berg RA, Otto CW, et al. Improved neurological outcome with continuous chest compressions compared with 30:2 compressions-to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest. Circulation. 2007;116(22):2525-30.
15. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, et al. Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. Circulation. 2001;104(20):2465-70.

16. Sell RE, Sarno R, Lawrence B, Castillo EM, Fisher R, Brainard C, et al. Minimizing pre- and post-defibrillation pauses increases the likelihood of return of spontaneous circulation (ROSC). Resuscitation. 2010;81(7):822-5.
17. Sugerman NT, Edelson DP, Leary M, Weidman EK, Herzberg DL, Vanden Hoek TL, et al. Rescuer fatigue during actual in-hospital cardiopulmonary resuscitation with audiovisual feedback: a prospective multicenter study. Resuscitation. 2009;80(9):981-4.
18. group S-Ks. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. Lancet. 2007;369(9565):920-6.
19. Iwami T, Kitamura T, Kawamura T, Mitamura H, Nagao K, Takayama M, et al. Chest compression-only cardiopulmonary resuscitation for out-of-hospital cardiac arrest with public-access defibrillation: a nationwide cohort study. Circulation. 2012;126(24):2844-51.
20. Bohm K, Rosenqvist M, Herlitz J, Hollenberg J, Svensson L. Survival is similar after standard treatment and chest compression only in out-of-hospital bystander cardiopulmonary resuscitation. Circulation. 2007;116(25):2908-12.
21. Japanese Circulation Society Resuscitation Science Study G. Chest-Compression-Only Bystander Cardiopulmonary Resuscitation in the 30:2 Compression-to-Ventilation Ratio Era. Circ J. 2013.
22. Travers AH, Rea TD, Bobrow BJ, Edelson DP, Berg RA, Sayre MR, et al. Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S676-84.
23. Council ER. Summary of the main changes in the resuscitation guidelines. European Resuscitation Council Secretariat vzw; 2010.
24. Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 1. Executive summary. Resuscitation. 2015;95:1-80.
25. Nolan JP, Sandroni C, Cariou A, Cronberg T, D'Arrigo S, Haywood K, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2025 Post-Resuscitation Care. Resuscitation. 2025;215.
26. Shah M, Bartram C, Irwin K, Vellano K, McNally B, Gallagher T, et al. Evaluating Dispatch-Assisted CPR Using the CARES Registry. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2018;22(2):222-8.
27. Couper K, Taylor-Phillips S, Grove A, Freeman K, Osokogu O, Court R, et al. COVID-19 in cardiac arrest and infection risk to rescuers: A systematic review. Resuscitation. 2020;151:59-66.
28. Council ER. Resuscitation practices during the COVID-19 pandemic (ENG202005) 2020 [Available from: https://cosy.erc.edu/en/online-course-preview/356a192b7913b04c54574d18c28d46e6395428ab/index#/lessons/DqAxkWGEKeM3V_Pc718KyrEVQ36bzQ1J.