AREU
Sistema Socio Sanitario
Regione Lombardia

DELIBERA DEL DIRETTORE GENERALE

91 / 2025 del 06/03/2025

***Oggetto*: PROGETTO DI RICERCA TANGO 2 - ACCORDO DI COLLABORAZIONE TRA AREU E KAROLINSKA INSTITUTET - APPROVAZIONE**

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OGGETTO: PROGETTO DI RICERCA TANGO 2 - ACCORDO DI COLLABORAZIONE TRA AREU E KAROLINSKA INSTITUTET - APPROVAZIONE

vista la seguente proposta di deliberazione avanzata dal Direttore della Struttura Complessa Affari Generali e Legali

IL DIRETTORE GENERALE

PREMESSO che l'Agenzia Regionale Emergenza Urgenza (AREU) è un Ente del S.S.R. disciplinato dall'art. 16 L.R. 30.12.2009 n. 33 e s.m.i. e attivato dalla DGR n. 2701/2019 e dalla DGR n. 4078/2020;

VISTA la deliberazione dell'Agenzia n. 1/2024 "PRESA D'ATTO DELLA D.G.R. N. XII/1650 DEL 21/12/2023 DETERMINAZIONI IN ORDINE ALLA DIREZIONE DELL'AGENZIA REGIONALE EMERGENZA URGENZA (AREU) – (DI CONCERTO CON L'ASSESSORE BERTOLASO)" di nomina del Dott. Massimo Lombardo a Direttore Generale dell'Agenzia Regionale Emergenza Urgenza (AREU);

DATO ATTO che l'Agenzia, ai sensi dell'art. 16, comma 1, della citata L.R. n. 33 del 2009 garantisce il coordinamento intraregionale e interregionale, l'indirizzo, la gestione, lo svolgimento, il monitoraggio della rete dell'emergenza urgenza extra ospedaliera e del Servizio NUE 112. Assicura inoltre il coordinamento delle attività trasfusionali dei flussi di scambio e compensazione di sangue, emocomponenti ed emoderivati, il coordinamento logistico delle attività di prelievo e di trapianto di organi e tessuti, il coordinamento dei trasporti sanitari e sanitari semplici disciplinati dalla Regione, il coordinamento delle centrali operative integrate per la continuità assistenziale;

VISTO il progetto di ricerca denominato "TANGO2", avviato dal Karolinska Institutet, con sede a Sjukhusbacken 10, 118 83 Stoccolma, Svezia ("KI"), identificato con i numeri NCT02401633 / NCT03981107 nel Clinical Trials Identifier, finanziato, tra gli altri, dal Consiglio Svedese per la Ricerca (Vetenskapsrådet);

PRESO ATTO che il Karolinska Institutet ha richiesto ad AREU di avviare una collaborazione nell'ambito del progetto sopra menzionato, in qualità di Collaborator;

CONSIDERATO che il progetto di ricerca riguarda il confronto dell'efficacia di una forma semplificata di rianimazione cardiopolmonare (CPR), consistente esclusivamente nelle compressioni toraciche, rispetto alla rianimazione cardiopolmonare tradizionale con compressioni e ventilazioni di soccorso;

DATO ATTO che il progetto è stato ricevuto l'approvazione del Comitato Etico di AREU;

DATO ATTO che AREU, nell'ambito dell'attività di emergenza urgenza territoriale, svolge pratiche del tipo di interesse del progetto e che rappresenta, quindi, un'attività di interesse comune tra il Karolinska Institutet e AREU;

CONSIDERATO, inoltre, AREU, potrà applicare direttamente le risultanze dello studio nella sua attività, in quanto volto a migliorare le pratiche di rianimazione cardiopolmonare e ad ottimizzare gli esiti clinici dei pazienti;

ACQUISITO il parere positivo del Direttore del Dipartimento Sanitario, individuato quale referente interno del progetto, e del Comitato Tecnico Scientifico;

RITENUTO pertanto opportuno avviare la collaborazione con il Karolinska Institutet e approvare l'accordo allegato, quale parte integrante e sostanziale del presente provvedimento;

PRECISATO che l'accordo di collaborazione decorre dalla data di sottoscrizione ed ha durata sino alla conclusione del progetto e presumibilmente fino al 31.12.2027;

PRECISATO, inoltre, che per l'adesione al progetto in qualità di collaborator, e per lo svolgimento delle attività di studio previste dall'accordo, è prevista la partecipazione al finanziamento stanziato dal Karolinska Institutet, nella seguente capacità:

- € 25.000,00 quale finanziamento per l'avvio del progetto;
- € 100,00 per ogni paziente per il quale sia trasmessa la documentazione di studio completa, sino ad un massimo di 1000 pazienti;

PRESO ATTO che il Proponente del procedimento attesta la completezza, la regolarità tecnica e la legittimità del presente provvedimento;

ACQUISITI i pareri favorevoli del Direttore Amministrativo e del Direttore Sanitario, resi per quanto di specifica competenza ai sensi dell'art. 3 del D.Lgs. n. 502/1992 e s.m.i.;

DELIBERA

Per tutti i motivi in premessa indicati e integralmente richiamati:

1. di approvare, autorizzandone la sottoscrizione, l'accordo di collaborazione tra AREU e il Karolinska Institutet, nell'ambito del progetto denominato TANGO2, allegato, quale parte integrante e sostanziale del presente provvedimento
2. di precisare che il progetto di ricerca riguarda il confronto dell'efficacia di una forma semplificata di rianimazione cardiopolmonare (CPR), consistente esclusivamente nelle compressioni toraciche, rispetto alla rianimazione cardiopolmonare tradizionale con compressioni e ventilazioni di soccorso;
3. di precisare che l'accordo di collaborazione decorre dalla data di sottoscrizione alla conclusione del progetto e presumibilmente fino al 31.12.2027;
4. di designare quale referente del progetto, il Direttore del Dipartimento Sanitario, dott. Maurizio Migliari, autorizzandolo alla sottoscrizione dell'accordo;
5. di dare atto che dall'adozione del presente provvedimento derivano proventi per la conduzione del progetto fino ad un massimo di € 125.000,00 da imputare nella contabilità dell'Agenzia al conto di ricavo n. 30101270 "Altri contributi in c/esercizio da privati" – codice: AREU – TANGO 2
6. di dare atto che, ai sensi della L. n. 241/1990, responsabile del presente procedimento è la Dott.ssa Domenica De Giorgio, Direttore S.C. Affari Generali e Legali;
7. di disporre che vengano rispettate tutte le prescrizioni inerenti alla pubblicazione sul portale web dell'Agenzia di tutte le informazioni e i documenti richiesti e necessari ai sensi del D.Lgs. n. 33/2013 e s.m.i., c.d. Amministrazione Trasparente;
8. di disporre la pubblicazione del presente provvedimento all'Albo Pretorio on line dell'Agenzia, dando atto che lo stesso è immediatamente esecutivo (ex art. 32 comma 5 L. n. 69/2009 s.m.i. e art. 17 comma 6 L.R. n. 33/2009).

La presente delibera è sottoscritta digitalmente, ai sensi dell'art. 21 D.Lgs. n. 82/2005 e s.m.i., da:

Il Direttore Amministrativo Andrea Albonico

Il Direttore Sanitario Gabriele Mario Perotti

Il Direttore Generale Massimo Lombardo

COLLABORATION AGREEMENT

for a Project

under the

Swedish Research Council funding

Project full title:

TANGO2

Project Leader: Jacob Hollenberg, MD, Professor

Collaborator: Maurizio Migliari, Head of Healthcare Department, AREU

This collaboration agreement (the “Agreement”) is entered into and made effective as of the date of its last signature by the Parties, hereinafter referred to as the “Effective Date”, by and between:

1. **Karolinska Institutet**, Department of Clinical Science and Education, Södersjukhuset , a medical university with org.nr 202100-2973 and registered address at Sjukhusbacken 10
2. 118 83 Stockholm, Sweden (“KI”), and

3. Agenzia Regionale Emergenza Urgenza (AREU), with its registered office at Viale Monza N. 223, 20126 Milan, and administrative office at Via A. Campanini No. 6, 20124 Milan, Tax Code/VAT N. 11513540960, duly represented by Dott. Massimo Lombardo, in his capacity as General Director (“**Collaborator**”)

hereinafter, jointly or individually, referred to as “Parties” or “Party”.

WHEREAS:

A. KI is a well renowned medical university with special competence within the area of medical research and education.

B. The Collaborator is a regional body of the S.S.R. governed by Article 16 of Regional Law N. 33/2009, and subsequent amendments, tasked with ensuring intra-regional and inter-regional coordination, management, implementation, monitoring of extra-hospital emergency and urgency networks, and overseeing the NUE 112 Service. AREU also coordinates transfusion activities, blood exchange and compensation, organ and tissue collection logistics, and integrated operations centers for continuity of care;

C. KI is sponsoring a study in Sweden entitled “TANGO2” with Clinical Trials Identifier-number NCT02401633 / NCT03981107, hereinafter the “Study”, funded by the Swedish Research Council (Vetenskapsrådet) among others.

D. KI and Collaborator have a mutual interest in research regarding comparing the effect of a simplified form of Cardiopulmonary resuscitation (CPR) consisting of compressions only compared to CPR with compressions and rescue breaths.

E. The Parties wish to **collaborate as co-sponsors** to enable the conduct of the Study in Italy (hereinafter the “Project”), provided that local regulatory approvals are obtained, in accordance with the allocation of responsibilities defined in this Agreement.

F. The Parties therefore wish to set out the following terms and conditions of the collaboration pertaining to the Project.

NOW, THEREFORE, IT IS HEREBY AGREED AS FOLLOWS:

1 DEFINITIONS

Words beginning with a capital letter shall have the meaning defined herein.

“**Arising IPR**” means Rights to patents, designs, technical and commercial know-how, and any other intellectual property rights irrespective of whether such rights are or may become subject to intellectual property protection – however always in accordance with the KI guidelines on intellectual property and corporate collaborations (as amended from time to time) as well as any applicable specific byelaws at the relevant institution of KI, which are subsequently developed in the Project, for the avoidance of doubt never to include any Background IPR and/or Results such as referring but not limited to data, records, lab journals, statistics, documents, database, KI raw data or the like, as well as personal data.

"**Background IPR**" means Rights to patents, designs, technical and commercial know-how, and any other intellectual property rights, irrespective of whether such rights are or may become subject to intellectual property protection, which are held by a Party at the commencement of the Collaboration or subsequently developed independently of the Collaboration, but which shall be contributed to the Project for use by the other Party. This shall also include access rights over which a Party exercises full control without restriction. For clarity, KI's Background IPR includes the Protocol.

"**Case Report Form", "CRF" or "e-CRF**" means an auditable electronic record designed to capture information required by the Study Protocol to be reported to the Co-Sponsors on each trial subject, or a document or database designed to record all of the information to be reported to the Co-Sponsors on each Subject, as required by the Study Protocol.

"Confidential Information" shall mean information which is classified as confidential by KI pursuant to the Swedish Information and Secrecy Act (SFS 2009:400) as well as information in the hands of Collaborator relating to commercial or operational matters or intellectual property rights, irrespective of whether or not it is in documented form, which is classified as confidential and the disclosure of which may cause the holder considerable loss. It is advised to identify Confidential Information as confidential at the time of disclosure.

"Coordinating Investigator" means the KI researcher who will take primary responsibility for the coordination of the Study.

"Database" shall mean the electronic repository created by KI for the purpose of receiving and storing the Trial Data and the Swedish Trial Data.

"**Funding Authority**" is main funding authority and is the Swedish Research Council (Vetenskapsrådet)**.**

"**Grant**" means the funding provided for the Study by the Swedish Research Council decision.

"**Good Clinical Practice**" or "**GCP**" shall have the meaning defined by the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) together with such other good clinical practice requirements as are specified in Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 relating to medicinal products for human use as amended from time to time, alternatively Regulation (EU) No 536/2014 of the European parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use as amended from time to time, repealing Directive 2001/20/EC, and any guidance published by the European Commission pursuant to such Directive or Regulation.

"**Ethics Committee**" means an independent body, committee or review board, whose responsibility is to ensure the protection or rights, safety and well-being of human subjects in a clinical trial and responsible for, among other things, reviewing and approving, providing opinion on, the Protocol, the sustainability of the Investigator, facilities, subject recruitment materials, methods and informed consent.

"Individual Arising IPR" means Arising IPR which a Party can demonstrate has been generated solely by such Party or independently of any collaboration with the other Party.

"Joint Arising IPR" means Arising IPR which cannot be demonstrated to constitute an Individual Result or which has otherwise been generated in collaboration with the other Party.

"**National Coordinator"** means the researcher who will take primary responsibility for the coordination of the Project in Italy.

"**Principal Investigator**" means the researcher who will take primary responsibility for the conduct of the Trial at the Trial Site(s) on behalf of Collaborator, or any other person as may be agreed upon from time to time between each Trial Site and Collaborator as a replacement.

"**Project**" means the collaboration between the Parties to conduct the Trial in Italy as part of the Study.

"**Protocol**" means the description of the Study (a copy of which is found in **Schedule 1** to be signed by each Principal Investigator) which has been developed by KI, and all amendments thereto as the Parties

may from time to time agree in accordance with Article 14 and which will be signed by the Principal Investigators. Such amendments will be signed by the Parties and form a part of this Agreement.

"**Results**" means any generated data, including but not limited to Trial Data, raw data and personal data, records, lab journals, documents, statistics, database or other outcome of the work performed under this Agreement, arising in the Project.

"Co-Sponsor(s)" means Collaborator and Karolinska Institutet as the organizations responsible for the initiation and management of the Study in the European Union in accordance with the ICH Guideline för GCP.

"Study" means the [on-going academic driven, multicentre, prospective, open label, randomized trial of comparing the effect of a simplified form of cardiopulmonary resuscitation (CPR) consisting of Compression-only, compared to CPR with compressions and rescue breaths, referred to as "TANGO2" number NCT02401633 / NCT03981107.

"**Trial**" means the clinical trial conducted by Collaborator in country and whose Trial Data will be included in the Study pursuant to this Agreement.

"**Trial Data**" means the data collected in the Trial conducted in Italy.

"~~**Trial Site**" means any hospital or clinic in country involved by Collaborator in the conduct of the Trial under Collaborator's responsibility~~.

"**Subject**" means a person recruited to participate in the Trial.

"**Swedish Trial**" means the clinical trial conducted in Sweden.

"**Swedish Trial Data**" means the data collected in the Swedish Trial that will be included in the Study.

Any reference to a statutory provision, code or guidance shall be deemed to include reference to any statutory modification or re-enactment of it.

2 PURPOSE AND DURATION

2.1 Purpose

The purpose of this Agreement is to specify with respect to the Project the relationship among the Parties, in particular concerning the organisation of the work between the Parties, the management of the Project and the rights and obligations of the Parties concerning inter alia liability, intellectual property rights and dispute resolution.

2.2 Entry into force

This Agreement shall be deemed to have become effective as of the Effective Date.

This Agreement shall continue in full force and effect until the Project has been completed.

However, this Agreement may be terminated earlier in accordance with the terms of this Agreement and the Grant.

If Collaborator in its capacity as a Co-Sponsor does not obtain all necessary approvals for the Project from relevant authorities, this Agreement shall be terminated as soon as practicable with due consideration to patient safety and research matters.

2.3 Survival

The provisions relating to confidentiality for the time period mentioned therein, as well as for liability, applicable law and Disputes shall survive the expiration or termination of this Agreement, as shall other provisions if found to be clearly intended to survive the expiration or termination of this Agreement.

3 RESPONSIBILITIES OF THE PARTIES

3.1 General principles

3.1.1 Each Party undertakes to take part in the efficient implementation of the Project, and to cooperate, perform and fulfil all of its obligations under this Agreement, in a manner of good faith. The Collaborator acknowledges and agrees that the Project must be conducted in accordance with Funding Authority's general terms and conditions and therefore agrees to, where relevant, comply with any such terms and conditions and to abide by any decisions of the Funding Authority regarding the Grant.

3.1.2 Each Party undertakes to notify promptly to the other any significant information, fact, problem or delay likely to affect the Project. When acting as Co-Sponsors, the Parties will share all relevant information with each other and provide each other with copies of any documents required to enable them to fulfil their responsibilities under this Agreement and under applicable laws and regulations.

3.1.3 Each Party shall promptly provide all information reasonably required by any of the other Parties to carry out its tasks and shall take reasonable measures to ensure the accuracy of any information or materials it supplies to the other Party.

3.1.4 Each Party shall remain fully and directly liable for its own activities and for its compliance with applicable laws.

3.2 Involvement of third parties

A Party that enters into a subcontract or otherwise involves third parties in the Project remains solely responsible for its undertakings and obligations under this Agreement and for such third party's compliance with the provisions of this Agreement including the Protocol.
Such Party shall ensure that the involvement of third parties does not affect the rights and obligations of the other Party under this Agreement.

3.3 Specific responsibilities of co-sponsors

The Parties are **Co-Sponsors in accordance with Article 72 of the EU Clinical Trial Regulation**. In addition to the responsibilities attributed solely to one of the Parties under Sections 3.4.1 and 3.4.2 below, the Parties have further set out the division of their responsibilities as Co-Sponsors in Schedule 3 (Division of Responsibilities).

3.3.1 Responsibilities attributed solely to Karolinska Institutet (KI)

With regards to the conduct of the Study, KI shall be responsible for:

a. All obligations incumbent on it as a Co-Sponsor with regards to the Swedish Trial
b. Providing scientific support to the National Coordinator Professor Giuseppe Ristagno.
c. Analysing the Trial Data and creating a Database at KI.
d. Merging the Trial Data with all data from the Study.
e. The interpretation of findings.
f. Coordinating and drafting publications and shaping dissemination messages in collaboration with collaborators at Trial Sites.
g. Registration of the Study on clinical trials registries and publish the results in clinical results databases, as required by applicable laws and regulations.

h. Record keeping of all results and documents relating to the Project, including the Trial Data as required by applicable laws (25 years) and to make them available to competent authorities and any auditor.

With regards to the conduct of the Trial, KI shall assume, the following responsibilities incumbent on it as the Co-Sponsor, as follows:

a. Assist the Collaborator in obtaining any local regulatory approvals necessary to conduct the Trial and approvals of any amendment (agreed in writing by the Parties) to a Protocol.

b. Prepare together with Collaborator the Subject information documents and informed consent forms.

c. Implement and maintain an electronic case report form" or "CRF" designed to record all of the information to be reported to KI on each Subject, as required by the Protocol.

d. Maintain quality assurance and quality control systems with written standard operating procedures to ensure that the data is generated, documented, recorded and reported in compliance with applicable laws and Requirements, the Protocol and GCP.

e. Provide Collaborator with all current and relevant information regarding the Procedures.

3.3.2 Responsibilities attributed solely to Collaborator

Collaborator shall assume, the following obligations incumbent on it as the Co-Sponsor of the Trial:

Authorizations, documentation and insurance

a) Translation of the Synopsis and additional documentation, including Subject documents and informed consent forms into local language.

b) Entering into appropriate written agreements with the Trial Sites for the performance of the Trial, in accordance with applicable laws and the terms of this Agreement.

c) Transmitting documents and information connected with the Project between Trial Sites and KI.

d) Ensuring appropriate insurance cover or providing an indemnity satisfactory to KI in respect of its potential liability and ensure that each Trial Site maintains relevant clinical negligence insurance for the duration of the Trial.

e) Ensuring appropriate patient insurance and medicinal product insurance in accordance with applicable laws and regulations.

f) Being a contact point for receiving all questions from Subjects, Principal Investigators and national regulatory authorities regarding the Trial and providing answers to them.

g) Ensuring that the costs of treatment of Study subjects in the event of Study-related injuries in accordance with the applicable legal and regulatory requirement(s) is covered by the Trial Site(s).

Conduct of the Trial and monitoring

h) Engaging Trial Sites and any subcontractors and liaising with them to ensure that the Trial is conducted in accordance with the Protocol, GCP and applicable laws.

i) Ensuring the Trial is conducted in accordance with the terms of this Agreement, the Protocol, GCP and the opinion of the Ethics Committee.

j) Upon agreement with KI, implementing corrective measures in accordance with Article 77 of the EU Clinical Trial Regulation if considering that the requirements set out in the EU Clinical Trial Regulation are no longer met.

k) Ensuring that Trial Sites implement and maintain quality assurance and quality control systems with written standard operating procedures to ensure that the conduct of the Trial and resulting data is generated, documented, recorded and reported in compliance with applicable laws, the Protocol, CRF instructions and GCP.

Reporting

l) Ensuring that each Trial Site shall retain and store complete, current, accurate, organised and legible Trial documentation in a manner acceptable for the collection of data for submission to, or review by, a regulatory authority and in full compliance with the Protocol and all applicable laws and GCP requirements.

m) Reporting in writing to KI any serious adverse events, such as unanticipated or suspected problems that occur, which may involve risks to Subjects or others as well as any injuries, damages, losses or deaths occurring during the Project.

n) Be responsible for and handle all safety and serious adverse event reporting to Principal Investigators and SUSARs to Eudravigilance Informing KI promptly of any suspension or termination of the participation of a Trial Site.

o) Ensuring that Trial Sites keeps and maintains all medical records of all Subjects in accordance with CRF instructions.

3.4 Procedure

KI shall be responsible for informing the Collaborator of the procedures on how the trail will be conducted, regarding CO-CPR and S-CPR, as further detailed in the Protocol ("Procedures").

Collaborator shall ensure that Trial Sites handle and maintain the Procedure with the necessary degree of care, in accordance with the instructions from KI and that they maintain complete and accurate records relating to the Procedures.

3.5 Personal data

3.5.1 Each Party shall maintain the confidentiality, in accordance with the applicable laws, regulations and guidelines, of all samples and personal data (including digital and paper data) relating to the use of human subjects, which is created or used in the course of the Project and shall ensure that all local communities, hospitals and primary health facilities involved in the Project comply with said obligations and any further instructions and security measures to ensure personal data is processed as required by applicable laws.

3.5.2 Collaborator shall ensure that documentation and collection of data in the Trial is made in full compliance with the Protocol and all applicable laws and regulations, including GCP and that the collection of data is conducted in a manner which provides for the correct submission to, or review by, relevant regulatory authorities.

3.5.3 The Parties acknowledge that for the performance of their obligations under this Agreement they will share Trial Data that consists of "personal data" as such term is defined in the General Data Protection Regulation ((EU) 2016/679) (hereinafter the "GDPR Regulation"). For the purposes of this clause the terms "Controller", "Data Subject", "Personal Data", "Personal Data Breach" and "Processing" shall have the meaning set out in the GDPR Regulation.

3.5.4 The Parties acknowledge and agree that in relation to the Trial Data disclosed by Collaborator to KI in connection with the Trial the Parties are joint Controllers pursuant to

Article 26 GDPR and their respective responsibilities are agreed upon in the separate Joint Controller Agreement and included in Schedule 4.

3.5.5 In respect of Personal Data collected by Collaborator under and in connection with the Trial, Collaborator: (i) shall comply with any applicable data protection laws; (ii) shall use reasonable endeavours to ensure that KI is able to Process the Personal Data lawfully, fairly and in a transparent manner and in compliance with the data protection laws to which it is subject; (iii) enter into such other written agreements with third parties as may be required from time to time to enable the Processing of Personal Data by the Parties.

3.5.6 Both Parties acknowledge that the Raw Personal Data collected by Collaborator or Site engaged by Collaborator, will be transferred to KI using Redcap following KI's detailed instructions, for further processing and analysis.

4 MANAGEMENT

4.1 The Parties shall appoint one representative each who shall be responsible for the conduct and monitoring of the Project ("Coordinating Group"). The Coordinating Group shall be responsible for coordinating the performance of the Project in accordance with the Protocol and this Agreement.

- **For KI: Coordinating Investigator Jacob Hollenberg, MD, Professor**
- **For Collaborator: National Coordinator in Italy, Maurizio Migliari, Head of the Healthcare Department in AREU**

4.2 The Coordinating Group shall meet from time to time, but not less than once a month, to discuss the planning and progress of the Project. Where material amendments to the Agreement are deemed necessary in order for the successful completion of the Project, the Steering Group shall propose such amendments to the Parties who shall decide on amendments to this Agreement in accordance with section 8.3.

4.3 The National Coordinator shall be responsible for liaising with all Trial Sites and their Principal Investigators and for providing them all necessary information.

5 LIABILITY TOWARDS EACH OTHER

5.1 No warranties

Therefore, the recipient Party shall in all cases be entirely and solely liable for the use to which it puts such information and materials, and no Party shall be liable in case of infringement of proprietary rights of a third party resulting from any other Party (or its affiliated entities) use of said information or materials.

5.2 Limitations of contractual liability

Collaborator agrees to indemnify KI and hold KI and KI Investigator harmless in respect of and against all claims and proceedings made or brought by or on behalf of Subjects against a Trial Site, Collaborator or a Principal Investigator for personal injury to Subjects, to the extent arising out of or relating to (i) the administration of the Product in accordance with this Agreement, the applicable Protocol (and any amendments thereto) and any other written instructions of KI, or (ii) the performance of any test of procedure that is required by the applicable Protocol (and any amendments thereto) to which the Subject would not have been exposed but for their participation in the Project.

Collaborator's obligation to indemnify under Article above, will not apply to the extent that such claims or proceedings arise out of the gross negligence, or wilful misconduct of KI in performing their obligations under this Agreement.

Collaborator shall maintain liability insurance in respect of its obligations to third parties and sufficient limits to cover the indemnification obligations in this Agreement.

KI shall not be responsible for any indirect or consequential loss or similar damage such as, but not limited to, loss of profit, loss of revenue or loss of contracts, provided such damage was not caused by wilful act or gross negligence.

The terms of this Agreement shall not be construed to amend or limit any Party's statutory liability.

For the avoidance of doubt, this Agreement does not apply to the Swedish Trial, which shall be conducted according to the Protocol in Sweden, subject to separate agreements between KI and the Swedish study sites. Notwithstanding anything else in this Agreement, KI shall incur no liability in the event that, for any reason not attributable to KI, the Project will be suspended or terminated due to payments of the Grant to KI being withheld, delayed or adjusted through the fault of KI or by decision by KI or the Funding Authority.

5.3 Damage caused to third parties

Each Party shall be solely liable for any loss, damage or injury to third parties resulting from its performance under this Agreement or from its use of Results or Background IPR.

5.4 Force Majeure

No Party shall be considered to be in breach of this Collaboration Agreement if it is prevented from fulfilling its obligations under the Collaboration Agreement by "Force Majeure", i.e. any unforeseeable, exceptional situation or event which is beyond the reasonable control of a Party and which could not have been anticipated or mitigated, such as war, general strikes, general mobilisation or unforeseen military mobilisations to a similar extent, fire, flood and other natural disasters, as well as lawful decisions by local, regional, national or supranational governing bodies or other circumstances of similar importance. Each Party will notify the other Party promptly in the event of a performance, obligation or undertaking is affected by any Force Majeure event.

6 FINANCIAL PROVISIONS

6.1 General Principles

6.1.1 KI shall use the Grant to fund part of the costs incurred by Collaborator for the implementation of the Project as specified in Schedule 2. Collaborator shall be funded only for tasks carried out in accordance with this Agreement and during the Grant availability period and for eligible costs. Any additional costs incurred by Collaborator which may be needed to ensure full completion of the Trial which are not specified in Schedule 2 shall be subject to further approval by KI and the Funding Authority. KI shall not be responsible for providing any such additional funding.

6.1.2 Collaborator agrees to collaborate with KI and enable the audit of records and accounts associated with the Project by an authorised auditor appointed by the Funding Authority.

6.1.3 In the event of premature termination of the Grant by the Funding Authority due to Collaborator having been found to have breached this Agreement, Collaborator shall, within the limits specified in Section 4.2 of this Agreement, bear any reasonable and justifiable additional costs occurring to KI in order to perform the additional tasks that KI might have as a result of the breach.

6.2 Payments

6.2.1 Payments shall be made in euro according to the payment plan in Schedule 2. KI shall incur no liability to the Collaborator in the event that, for any reason not attributable to KI,

the payments of the Grant to KI shall be withheld, delayed or adjusted by the Funding Authority.

6.2.2 Invoices with amount in euro shall be sent electronically to KI.

6.2.3 Payments shall be made to the bank account provided by the Collaborator within 30 days of receipt of a valid invoice.

6.2.4 The invoices shall include a clear reference to this Agreement and information about whether partial or full payment, and amount of the invoice. The Collaborator shall upon request be able to show documentation in support of a certain invoice phase having been attained. Such documentation shall include necessary receipts and documentation concerning the costs. Invoicing charges are not acceptable.

6.2.5 KI is entitled to withhold any payments in the event of the Collaborator being found to be in breach of its obligations under this Agreement or when this is agreed with the Funding Authority. In the event that KI is obliged to repay any amount of the Grant to the Funding Authority, and this is caused by a contractual breach on the part of the Collaborator, KI shall be entitled to recover the relevant amounts from Collaborator.

6.3 Reporting

Collaborator shall collaborate to facilitate timely submission of any scientific and financial reports concerning the Project to the Funding Authority and will provide any necessary information in conjunction with the following up and evaluation of the research, either during or after termination of the Project.

7 INTELLECTUAL PROPERTY RIGHTS

7.1 Background

7.1.1 Background IPR or other background is, and shall remain, the property of the contributing Party, and may, during the term of the Agreement and without compensation, be used solely for the purpose of performing the Project. Other than expressly stated herein, this Agreement does not constitute any grant, option or license under the Background IPR or other background held by either Party.

7.2 Arising IPR and Results

7.2.1 Title to a Result shall vest in the Party who generated the Result. For the avoidance of doubt, mere financing of the Project or provision of materials does not constitute ownership or the generating of Results and/or Arising IPRs. For clarity, the Trial Data shall be a joint Result of KI and Collaborator. The Database and related data analysis shall be the sole Result of KI. Title to any Arising IPR generated under the Project shall vest in KI and/or the researchers at KI (the “KI Researchers”) as applicable, in accordance with the Swedish professor’s privilege.

7.2.2 Individual Arising IPR shall vest solely in the Party (and/or the KI Researchers) who generated the Individual IPR. Any application for, or maintenance of, intellectual property protection, such as patents or other intellectual property rights relating to an Individual

Arising IPR, shall be determined and defrayed solely by the Party (and/or the KI Researchers) who owns the Arising IPR.

7.2.3 The Parties (and/or the KI Researchers) hereby grant each other a non-exclusive, gratuitous licence, without the right to sublicense, to use Arising IPR for the purpose of performing the Project.

7.2.4 The Parties (and/or the KI Researchers) hereby grant each other a non-exclusive, gratuitous license, without the right to sublicense, to use jointly owned Results, within the scope of further research, education and dissemination. Notwithstanding the above, Collaborator shall not use or allow third parties to disclose or use any jointly owned Results until such Results have been published by KI.

7.4 Publications

Results of the Project will be first published by KI, after collecting data from the ongoing Study in Sweden and the other participating countries (according to data management plan), in scientific journals of international scope, in accordance with the terms of the Grant. Collaborator will not influence or restrict the publication of the Results.

Decisions of the timing of all publications resulting from the TANGO2 trial will be decided by the Steering Committee, Professor Giuseppe Ristagno will be part of the Steeering Committé. Separate substudies coming from TANGO2 are encouraged and could be led parties other than KI but need to be approved by Steering Committee.

The first publication of the Project will be prepared by KI promptly after the data analysis is available. Collaborator shall ensure that no publications by Collaborator nor by individual Principal Investigator at Trial Sites in Italy will be made before, unless approved in writing in advance by KI. Collaborator's contribution as the Co-Sponsor of the Study shall be acknowledged in all publications.

The Parties shall not enter into agreements with any commercial actor or other stakeholder that could limit publication of the Results of research conducted with funding from the Swedish Research Council.

Authorship on publications will be based on academic standards and custom as further specified in the Protocol. In accordance with normal academic practice, all investigators and contributors to a publication will be acknowledged, always in compliance with recognized standards concerning publication and authorship, including the most recent "Recommendations for the Conduct, Reporting, Editing and Publications of Scholarly Work in Medical Journals" developed by the International Committee of Medical Journal Editors (ICMJE).

The Parties agree that Results from the Project shall be made openly accessible (open access) within six (6) months of publications.

Publications and dissemination of the Project's Results shall include acknowledgement to the Swedish Research Council as further specified in the Grant.

During the Project and for a period of 1 year after the end of the Project, the dissemination of Results by one or several parties including but not restricted to publications and presentations, shall be governed subject to the following provisions:

Prior notice of any planned publication shall be given to the other Parties at least 45 calendar days before the publication. Any objection to the planned publication shall be made to the Party proposing the publication within 30 calendar days after receipt of the notice. If no objection is made within the time limit stated above, the publication is permitted. The objection has to include a precise request for necessary modifications.

An objection is justified if (a) the protection of the Results would be adversely affected or (b) the objecting Party's legitimate interests in relation to the Results or Background would be significantly harmed.

If an objection has been raised the Parties shall discuss how to overcome the justified grounds for the objection on a timely basis (for example by amendment to the planned publication and/or by protecting

information before publication) and the objecting Party shall not unreasonably continue the opposition if appropriate measures are taken following the discussion.

The objecting Party can request a publication delay of not more than 60 calendar days from the time it raises such an objection. A delay may, however, last a maximum of four months if the purpose is to facilitate a patent application based, in whole or in part, on the Results.

8 NON-DISCLOSURE OF INFORMATION

8.1.1 Subject to the other provisions of this Agreement, during the course of the Project and for a period of five years thereafter, the Parties shall treat all Confidential Information as confidential and shall take reasonable care to ensure that the other Party's Confidential Information is treated with at least the same degree of caution as the Party's own Confidential Information. Notwithstanding the above, Trial Data shall be kept confidential for as long as necessary in accordance with applicable laws, regulations and guidelines.

8.1.2 A Party who receives Confidential Information (the "Recipient Party") from the other Party (the "Disclosing Party") shall ensure that it is disclosed only to those individuals who need Confidential Information to perform their work, services or activities in the Project. The Recipient Party shall also ensure that these individuals are bound by confidentiality undertakings which are equivalent to those set forth in this Agreement and take such other measures as may reasonably be required to ensure that Confidential Information is not disclosed to unauthorised third parties.

8.1.3 Written information or other documentation which contains or constitutes Confidential Information shall be returned to the Disclosing Party upon request at the conclusion of the Project, subject to the provisions below concerning access rights to Background or unless otherwise provided for by law. In addition, the Parties shall always have the right to save one (1) copy of any information inter alia as required by mandatory archiving laws.

8.1.4 Notwithstanding anything else stated in this Agreement, the Recipient Party shall also be permitted to retain such additional copies of any computer records or files containing such confidential information that have been created solely by the Recipient Party's automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with the Recipient Party's standard archiving and back-up procedures, but not for any other use or purpose if not required by mandatory law.

8.1.5 Notwithstanding the above, the Recipient Party may disclose Confidential Information to a third party if:

a) the information was already demonstrably held by the Recipient Party before the commencement of the Project or had been produced by the Recipient Party independently of the Project;

b) the information was received from an independent third party without being subject to any restrictions concerning disclosure;

c) the information entered the public domain other than as a result of a breach of this Agreement;

d) the information may be disclosed to a third party according to the written consent of the Disclosing Party; or

e) there is a duty to disclose Confidential Information pursuant to law or a court or administrative order.

9 MISCELLANEOUS

9.1 No representation, partnership or agency

No Party shall be entitled to act or to make legally binding declarations on behalf of any other Party. Nothing in this Agreement shall be deemed to constitute a joint venture, agency, partnership, interest grouping or any other kind of formal business grouping or entity between the Parties.

9.2 Notices and other communication

Formal notices to be given under this Agreement shall be in writing and be delivered to the person stated below, unless the receiving Party has specifically notified the sending Party of another address for this purpose. The notice may either be served personally or sent by mail with recorded delivery (Sw. "*rekommenderat brev*")

To KI:	Jacob Hollenberg Email Jacob.Hollenberg@ki.se address Södersjukhuset, VO Kardiologi, 11883 Stockholm, Sweden
To Collaborator:	Name Maurizio Migliari Email segreteria.scientifica@areu.lombardia.it address Milano, Viale Monza n. 223, Italy

9.3 Term and Termination

This Agreement will enter into force on the Effective Date and shall remain in force until all obligations undertaken have been fulfilled and the agreed Project performed or until earlier terminated in accordance with this Article.

The Parties may terminate this Agreement with immediate effect at any time upon written notification if the other Party is

(a) in breach of any obligations under the Agreement or the Protocol and fails to remedy such breach, where it is capable of cure, within thirty (30) days of written notice from the other Party specifying the breach and requiring its cure.

(b) declared insolvent; or has an administrator or receiver appointed over all or parts of its assets or ceases or threatens to cease to carry on its business.

A Party may terminate this Agreement with immediate effect at any time upon written notification to the other Party, if it on reasonable grounds believes the Project should cease in the interest of the health, safety or well-being of the Subjects.

In addition to what is stated in this Section above, KI may terminate or suspend the Project and/or terminate this Agreement immediately for any reason upon thirty (30) days written notice to the other Party.

In the event of termination of this Agreement by either of the Parties, the Parties shall use their best efforts to minimise any inconvenience or harm to any Subjects involved in the Trial.

Upon notice of termination of this Agreement, Collaborator shall immediately cease enrolment of Subjects into the Trial and provide any necessary assistance to ensure a smooth and orderly transition of the Trial with no disruption of the Protocol.

Upon expiration or early termination of this Agreement, KI shall, upon receipt of invoices and other supporting documentation, pay all costs incurred falling due for payment up to the date of termination and all non-cancellable costs committed before receipt of notice of termination, provided that such commitments are reasonable and necessarily incurred by Collaborator for the performance of the Project prior to the date of termination.

9.4 Assignment and amendments

Except as pertains to the subcontractors of the Collaborator to implement the Trial, no rights or obligations of the Parties arising from this Agreement may be assigned or transferred, in whole or in part, to any third party without the other Parties' prior formal approval. Amendments and modifications to the text of this Agreement require a separate written agreement to be signed between all Parties.

9.5 Mandatory statutory law

Nothing in this Agreement shall be deemed to require a Party to breach any mandatory statutory law under which the Party is operating.

9.6 Applicable law and Settlement of Disputes

9.6.1 This Agreement shall be construed in accordance with and governed by the laws of Sweden excluding its conflict of law provisions.

9.6.2 The Parties shall endeavour to settle their disputes amicably. However, where a conflict cannot be resolved by persons at an operative level, a Party may request that negotiations be initiated between persons on executive management level.

10 ATTACHMENTS AND SCHEDULES

This Agreement has the following Schedules:

Schedule 1: PROTOCOL
Schedule 2: PAYMENT SPECIFICATION
Schedule 3: Division of Responsibilities
Schedule 4: Joint Controller Agreement

11 SIGNATURES

AS WITNESS:
The Parties have caused this Agreement to be duly signed by the undersigned authorised representatives in separate signature pages the day and year first above written.

Authorised to sign on behalf of Karolinska Institutet

Date:

Signature _____
Name Erik Melén
Title Head of Department
Department of Clinical Science and Education, Södersjukhuset

Read and acknowledged by:

Date:

Signature _____
Name Jacob Hollenberg
Title Principal Investigator
Department of Clinical Science and Education, Södersjukhuset

Authorised to sign on behalf of Collaborator, Regionale Emergenza Urgenza (AREU)

Date:

Stamp of the organisation

Signature _____

Name Maurizio Migliari
Title General Directo
National Coordinator
Head of Department
Healthcare Department

SCHEDULE 1 PROTOCOL

[insert protocol]

MAIN TRIAL PROTOCOL, sept 2022

TANGO2

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

Version:	2.1
Date:	2022 09 15
Clinical Trials Identifier:	NCT02401633 / NCT03981107

Table of content

List of abbreviations

AHA	American Heart Association
ACLS	Advanced Cardiac Life Support
AED	Automated External Defibrillator
CO-CPR	Compression-Only CPR
CPC	Cerebral Performance Category
CPR	Cardio-Pulmonary-Resuscitation
CRF	Clinical Report Form
DC	Dispatch Centre
DCO	Dispatch Centre Operator
DSMC	Data Safety Monitoring Committee
DNR	Do Not Resuscitate
EMS	Emergency Medical Service
ER	Emergency Room
ERC	European Resuscitation Council
FR	First Responder (fire-fighters or police)
ICD	Implantable Cardioversion Device
ITT	Intention to treat
OHCA	Out of hospital Cardiac Arrest
PAD	Public Access Defibrillator
PP	Per Protocol
PROM	Patient Reported Outcome Measures
ROSC	Return of Spontaneous Circulation
RCT	Randomized Controlled Trial
SCAR	Swedish Cardiac Arrest Register
S-CPR	Standard CPR
T-CPR	Telephone-assisted CPR
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

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 knowledge of CPR 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 bystander CPR (performed by bystanders with prior CPR-training) consisting of compressions only (CO-CPR) is non-inferior, or better, than standard CPR (S-CPR) in witnessed cases of OHCA.

Intervention: Cases of witnessed suspected OHCAs, where bystanders have previous knowledge in CPR, will be randomized at the dispatch center to instructions to perform either CO-CPR (interventional group) or S-CPR (control group) until arrival of the EMS. Upon arrival of the EMS, all patients will receive standard advanced cardiac life support (ACLS) in accordance to current guidelines.

Design: Interventional, prospective, open label, multicenter randomized trial with 1:1 allocation. Since CO-CPR is a simplified form of CPR that could lead to a higher incidence of bystander-CPR in itself, a non-inferiority design has been chosen. This will be further discussed in part 10, "statistical analysis plan".

Inclusion criteria:

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

Exclusion criteria:

- Age 18 or younger
- Collapse is not witnessed
- Bystander has never been taught CPR. *(These bystanders should be instructed to administer CO-CPR in accordance to guidelines)*
- Obvious asphyxia, *i.e.* drowning, strangulation, hanging
- Obvious intoxication or drug overdose
- Pregnancy
- Trauma

Primary outcome: 30-day survival

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

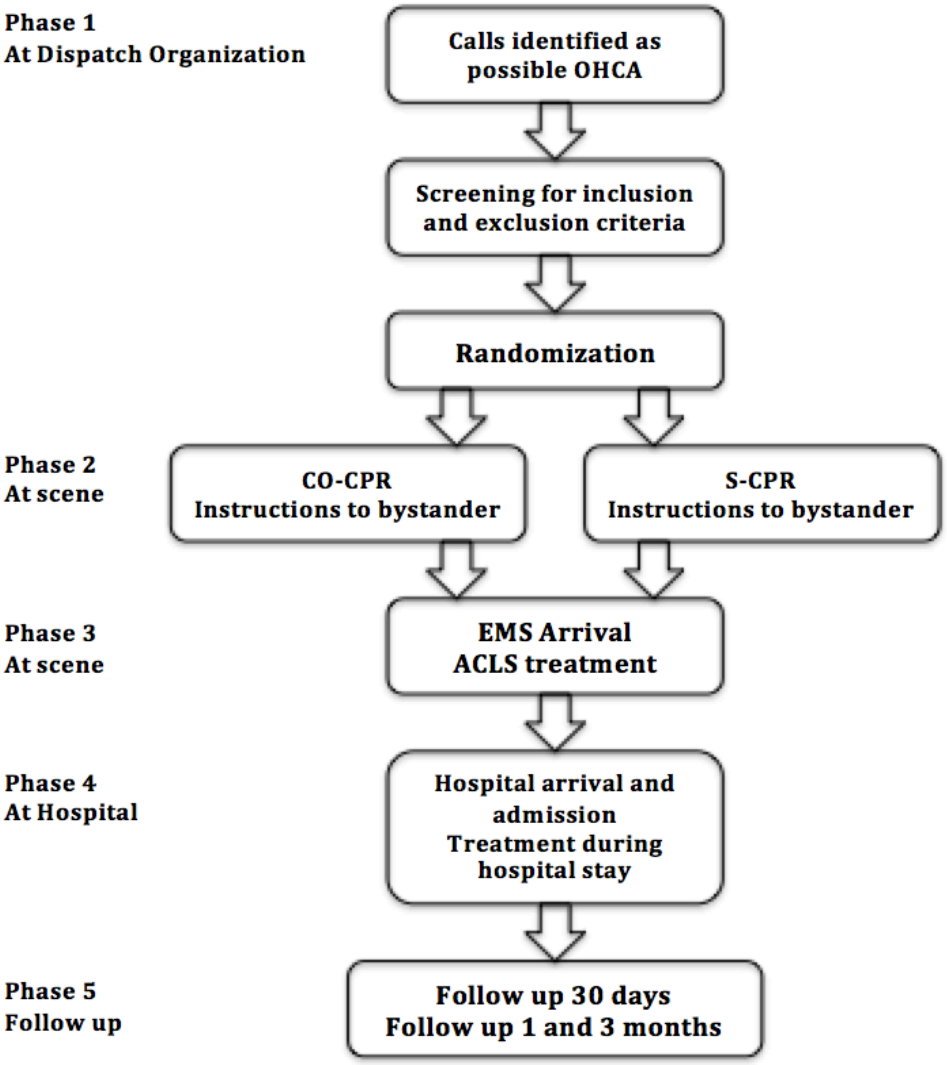
2. Trial overview

2.1. Flow chart

Trial flow-chart and the different phases are presented below in Figure 1.

For detailed description of 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 (Chest compressions and rescue breaths 30:2) EMS = Emergency Medical Services, ACLS = Advanced Cardiac Life Support

2.2 Principal investigators and sponsors

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Sankt Göransplan 1, SE-112 19 Stockholm, Sweden
Phone: + 46 70 545 20 86
Mail: Gabriel.riva@ki.se

2.3 Trial sites

This is a national dispatch study were all dispatch centrals participate. This include all SOS Alarm AB dispatch centers as well as the dispatch centers of Sjukvårdens larmcentral

SOS Alarm dispatch centers:

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

Sjukvårdens larmcentral dispatch centers:

- Uppsala
- Västerås
- Södermanland

2.4. Ethical approvals

The study has obtained ethical approval from the ethical vetting committee in Stockholm;

Dnr 2014/97-31/2. Main approval

Dnr 2015/1833-32. Amendment

Dnr 2019-0489. Amendment

3. Introduction

3.1 Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of mortality in the industrialized world. The etiology for OHCA is heterogeneous but cardiovascular disease remains the most common underlying cause. In Sweden, the yearly incidence of EMS treated OHCA is around 5,000 and overall survival has remained around 10 % 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 best form of bystander CPR has been debated.(7-9) To perform rescue breathing is a complex task and bystanders not recently trained in CPR are likely to have difficulties in deliver good rescue breaths. Chest compression only CPR (CO-CPR) has been advocated as a preferable method in situations where the bystander has no previous knowledge in CPR, both because its believed to be equally efficient but also a simplified form of CPR that could lead to increased use of bystander-CPR.(10) Furthermore, this more simplified 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 prior and after defibrillation is associated with worse outcome.(16) On the other hand, compression-only 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 to not give crucial oxygen delivery to vital organs even though the blood flow to these organs is maintained.(13)

3.3 Previous published clinical results

Several registry-studies have showed 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 telephone-guided CO-CPR for untrained rescuers and

trained bystanders unwilling unable or unwilling 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 updates 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 has been no public campaigns promoting CO-CPR.

Whether CO-CPR leads to a survival rate no worse than, equally effective, or even superior to standard CPR in situations where the bystander has previous CPR training however 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 with this research project is to investigate whether instructions to perform a simplified form of CPR consisting of compressions only (CO-CPR) to bystanders with prior CPR-training is non-inferior, or better than, standard CPR (S-CPR) in witnessed out-of-hospital cardiac arrest (OHCA).

4.1 Primary objective

To evaluate whether survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR to bystanders with prior CPR training in witnessed OHCA.

4.2 Secondary objectives

To evaluate whether there is a difference between CO-CPR and S-CPR in survival to hospital admission, neurological favorable survival, defined as survival with cerebral performance category (CPC) 1-2, neurologically intact survival defined as CPC 1 and long-term survival, defined as survival to one year. To evaluate whether there is a difference between CO-CPR and S-CPR in VT/VF as first rhythm and Return of Spontaneous Circulation (ROSC). To compare 30-day survival between CO-CPR and S-CPR in pre specified subgroups.

4.3 PICO-question

P	Among adults suffering from non-traumatic witnessed OHCA (P),
I	Does instructions to perform CO-CPR performed by trained bystanders (I)
C	Compared to instructions to perform S-CPR (C)
O	Change 30-day survival (O)

5. Eligibility

Witnessed cases of adult OHCAs with a non-asphyxic etiology 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, abnormal or agonal breathing (suspected OHCA)

- The suspected OHCA is witnessed (seen or heard)

- Any bystander at the scene has previous training in CPR

5.2 Exclusion criteria:

- Age 18 or younger

- Collapse is not witnessed

- Bystander has never been taught CPR. *(These bystanders should be instructed to administer CO-CPR in accordance to guidelines)*

- Obvious asphyxia, *i.e.* drowning, strangulation, hanging

- Obvious intoxication or drug overdose

- Pregnancy

- Trauma

5.3: Post randomization exclusion from data analysis:

- Previous decision that CPR should not be initiated i.e. terminal illness or palliative care

- No cardiac arrest, other condition (cases where EMS did not start CPR)

6. Trial design

This is an interventional, prospective, randomized, 1:1 open label, multicenter trial comparing two different methods of bystander CPR in witnessed cases of OHCA. Since CO-CPR is a simplified form of CPR that could lead to a higher incidence of bystander-CPR by itself a non-inferiority design for the primary outcome has been chosen. Superiority testing will also be performed for the purpose of demonstrating a possible increase in survival with CO-CPR.

6.1 Principal study population and intervention

Witnessed cases of OHCAs with a non-asphyxic etiology will be the principal study population. According to current guidelines an unresponsive patient with no or agonal breathing is handled as a suspected case of OHCA at the dispatch center. These cases are eligible for screening for inclusion. If the case is witnessed, any bystander at the scene has previous knowledge in CPR and no exclusion criteria are present, the case can be included and randomly assigned to instructions to perform either CO-CPR (intervention) or S-CPR (control).

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

The control arm will consist the instructions from a dispatcher at the dispatch center 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. Phase 1 and 2: The work at the dispatch center and CPR by bystander

- Identification of cases
- Screening for inclusion and exclusion
- Randomization
- Instructions according to allocation

Suspected OHCAs identified at the dispatch centre, classified as unconscious with no or agonal breathing, are eligible for screening. When a dispatcher suspects a case of OHCA, inclusion criteria and exclusion criteria will automatically pop up on their computer screen. The first inclusion criterion is if the collapse is witnessed (has been seen or heard). The second inclusion criterion is if any bystander on the scene has previous CPR-training. According to current guidelines, the dispatch operator asks whether the witness has training in bystander CPR. If not, they are offered instructions on how to perform telephone-guided CPR (T-CPR) and the case is not further screened for inclusion in the study. If any bystander at the scene has previous CPR-training (any time), or if CPR is already on going, the case can be further screened for inclusion in the study. The dispatch operator will mark this on their desktop environment. This automatically triggers the appearance of exclusion criteria on the

operator´s desktop: 1) OHCA victim aged 18 or younger? 2) Asphyxia (i.e. drowning, strangulation, hanging 3) intoxication, drug overdose? 4) trauma? or 5) pregnancy?

If any of the exclusion criteria are met, the case is not randomized (and is handled according to standard protocol). If no exclusion criteria are present, the case will undergo randomization using a Microsoft.NET Random Constructor (Int 32). This will generate a randomized allocation to either intervention (CO-CPR) or control (S-CPR). A new pop-up will then appear on the operator's desktop with detailed instructions to the caller in both groups. Simultaneously, the EMS will be dispatched.

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

The instructions from the dispatcher in INTERVENTION arm include:

- An ambulance is dispatched and is on its way to you
- Do CPR with chest compressions only
- Push hard on the chest with a pace of 100/minute without interruptions for rescue breathing.

The Instructions from the dispatcher in the CONTROL arm include:

- An ambulance is dispatched and is on its way to you
- Do 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 100/minute.

Dispatchers are furthermore instructed to encourage all callers in both groups to stay in connection with the callers until arrival of EMS or first responders, instruct callers to put the phone on loudspeaker when possible and to ask callers to count aloud while performing chest compressions. Dispatchers should try to aim for a compression rate of 100-120/minute and suggest switching CPR-provider every 2 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. EMS crew will further treat all patients with all guidelines (AHA/ERC)(24) recommended standard ACLS, including bag mask ventilation, advanced airway management with endotracheal tube or laryngeal mask, oxygen, defibrillation and i.v. drugs as well as if ROSC is not achieved (cessation of CPR).

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

If the patient is admitted to hospital, patients are treated according to local hospital protocol and practice including diagnostic coronary angiography, therapeutic hypothermia (33 or 36 degrees Celsius) and intensive care. Hospital practitioners will not know the randomized allocation.

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

Survival is evaluated for primary endpoint at day 30 through the Swedish cardiac arrest register (SCAR) through linkage with the Swedish public population register (folkbokföringsregistret). For the secondary outcome of neurologically favorable outcome CPC is obtained through SCAR. In a subset of patients (survivors treated at specifically named hospitals), a comprehensive neurological assessment using Patient Reported Outcome Measurement (PROM) related follow-up is performed between 30-90 days. This follow-up is performed by a nurse and/or behavioral therapists blinded to the intervention allocation. This comprehensive follow up will not be possible in all sites of the TANGO2 trial.

6.3. Blinding

Because of the inherent logistical problems with blinding of CPR techniques for dispatchers, the trial is considered as an "open labeled" trial. Treatment allocation will, however, be blinded in data management and at follow-up, for personnel treating the patients at the hospitals and for all responsible researchers. Allocation concealment will be preserved.

6.4. Outcome

6.4.1 Primary outcome:

- 30-day survival

6.4.2 Secondary outcomes:

- Survival to hospital admission
- 1-year survival
- Survival with good neurologic outcome at discharge, defined as cerebral performance category (CPC) 1-2
- Survival with complete neurologically outcome defined as CPC 1

6.4.3 Exploratory outcomes:

- VT/VF as first rhythm
- Return of spontaneous circulation (ROSC)
- Repeated analysis of primary endpoint and all secondary endpoints at 24 months

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

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

The overall study project is conducted in three different phases:

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

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

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

7.1.1. Objective pre study RUN-IN period

In order to test the technical inclusion procedures, logistics, feasibility and data collection a pre-study RUN-IN period started in Stockholm during 2015.

7.1.2. Objective PILOT study

The original aim of the PILOT study was to assess safety and feasibility of the TANGO2 trial, as well as intermediate clinical outcomes. The TANGO2 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 section 7.2 and 7.3 below).

7.1.2. Objective MAIN study

The aim of the MAIN study is to evaluate whether survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR bystanders in witnessed OHCA where the bystander has previous CPR training. Secondary and exploratory objectives include the evaluation of neurological favorable survival, ROSC, admission to hospital, long-term survival and other clinical outcome variables as well as evaluations of 30-day survival between CO-CPR and S-CPR in pre-specified subgroups. The MAIN study will include patients from the PILOT phase in a seamless design (for details, see section 7.2 and 7.3 below).

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

The pre-study RUN-IN period started in Stockholm County in 2015 and analysis were performed during 2016. After continuous technological adjustments, the randomization module was integrated within the computer aided dispatch system and was found to function well in the end of 2016. However, during pre-study RUN-IN period, one major obstacle was identified. Due to unexpected technological difficulties and an unanticipated new organization of the dispatch centers in Sweden only about 15% of the cardiac arrest calls for patients suffering cardiac arrest in Stockholm were

actually answered by dispatchers in Stockholm; all other calls were transferred to other dispatch centers 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. This new organization and logistics, were the call could be made in one area and answered and handled at another site and county during the pre-study RUN-IN period, resulted in a far slower inclusion rate than anticipated and made a correct follow-up of patients unmanageable and unreliable. This made it impossible to conduct a PILOT study in Stockholm 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 two years to assure sufficient inclusion of patients to assess safety in terms of survival to hospital admission.

B) That the PILOT study seamlessly will move on into the MAIN study in an inferentially seamless manner after the PILOT phase inclusion ended on Dec 31 2018. 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 (see 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 and effects of the Covid19 pandemic.

Previous changes from original protocol (February 2019):

- As described above, the start and size of the PILOT-study was modified to include all patients during 2 years (2017-18).

- 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 was modified not only to asses feasibility but also to include assessment of safety as well as intermediate clinical outcomes until hospital admission.

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

- Inclusion / Exclusion criteria and intervention/control instructions have remained unchanged since the first initial protocol throughout all parts 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 audit all calls during the PILOT study and MAIN study using a standardized template for evaluation of dispatcher assisted CPR (cardiac arrest registry to enhance survival – CARES)(25) and that all audit evaluators will be blinded to allocation.

Effects of the Covid19 pandemic:

- Due to the outbreak of the Covid19 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 chest compressions only.(26, 27) Therefore, this study was put on hold on date: 12-03-2020.

- The initial plan was to publish the Pilot-study including years 2017 and 2018. Due to the uncertainty during the Covid19-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 Covid19-pandemic an independent data monitoring committee reviewed all data up until 12-03-2020 (pre-Covid19). Their recommendation was to continue the trial without modifications, please see also "11. Interim analysis and data monitoring committee".

- When the temporary Covid-19 guidelines were removed the 1 April 2022 the main trail was relaunched, and inclusion started in August 2022.

- A decision was made to include all patients during the period pre-Covid19 in the Pilot-study and the dates of the pilot-study were changed accordingly.

- To assure follow-up all, all EMS records of all calls of suspected OHCA with no matching record in SCAR will be reviewed. Please see "8. Data Collection"

8. Data collection

From the dispatch organization (SOS-Alarm AB) the following variables will be collected:

Time of incoming call, time of dispatch of EMS, time of dispatch of first responders when applicable, time for screening for inclusion, time of randomization and time of arrival of EMS and first responders. Event times are automatically generated and stored in the dispatch organization´s computer system. The randomized assignment for each call is stored in a separate data-file generated by the random sequence constructor.

For evaluation of included calls and adherence to protocol all randomized, EMS treated OHCA dispatch calls will be audited. All audit evaluators will be blinded to allocation. A standardized template for evaluation of dispatcher assisted CPR will be used (cardiac arrest registry to enhance survival – CARES).(25) The study specific inclusion criteria will be added as auxiliary variables (supplementary app).

From the Swedish Cardiac Arrest Register the following variables will be collected:

All EMS units participating in TANGO2 report to the SCAR. For all EMS treated OHCA the following variables will be collected from the Swedish Cardiac Arrest Register:

Date of OHCA, Age, Sex, Location of OHCA, CPR prior to EMS arrival, highest medical educational level of CPR provider, first recorded rhythm, defibrillation, airway management and drug administration, Return of spontaneous circulation (ROSC) and survival to admission to hospital.

In calls where there is no matching report in SCAR, ambulance records will be reviewed; if EMS has performed CPR or the patient had been defibrillated by an AED the case will be classified as “EMS treated” and corresponding variables will be extracted from ambulance records instead.

The EMS will obtain information on what type of CPR that was provided to the patient before their arrival at the scene. This information is obtained by observing on-going CPR at their arrival and asking bystanders what type of CPR they provided. EMS crew will also ask bystanders what kind of CPR training they have according to a three-leveled division of the bystander’s medical educational level (a – off-duty professional caregiver, doctor, nurse; b – CPR-trained layman (including off-duty police and fire-fighters); or c – layman with no CPR training). This information is a part of SCAR, but there will be emphasis on obtaining this specific data in the TANGO2 trial.Survival is collected for primary endpoint at day 30 from SCAR trough linkage with the Swedish public population register (folkbokföringsregistret). For the secondary outcome of neurologically favorable outcome CPC is obtained through SCAR. In a subset of patients (survivors treated at specifically named hospitals), a comprehensive neurological assessment using Patient Reported Outcome Measurement (PROM) related follow-up is performed between 30-90 days. This follow-up is performed by a nurse and/or behavioral therapists blinded to the intervention allocation. This comprehensive follow up will not be possible in all sites of the TANGO2 trial.

8.1 Data handling and record keeping

For each call to the dispatch center a unique log number automatically is generated. This log number is stored at the dispatch center and used to match calls with EMS records, SCAR reports and hospital data. All log numbers and audio-files related to the study will be saved and kept at SOS Alarm, Stockholm. A list with all log numbers will be exported to a study specific database at the center for resuscitation science. A list of all randomized calls with the randomization allocation for each case will be generated by the random sequence constructor and will be exported separately. Finally, data from call audit evaluation, SCAR reports and EMS and hospital records will be imported. All data will be merged and stored in a specific database at center for resuscitation science. This system fulfills all criteria for handling of patient data according to the Swedish legislation on management of personal data “GDPR”. In the database, the allocation of each specific case will be blinded during the data collection to avoid any bias in reporting or collecting data. Allocation concealment will be preserved. In the central database there will be manual crosschecking and completion of missing data through EMS and hospital records.

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 incapacitated of providing informed consent. OHCA is however also a medical emergency and treatment has to 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."

This study has been approved by the ethics committee of Stockholm; Dnr 2014/97-31/2 and reasons for involving patients unable to give informed consent have been stated in the research plan.

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 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. This pain and discomfort is also relatively simple to treat. 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 to 30 days after a cardiac arrest often have good quality of life with only minor neurological disability. This contradicts the fear that an increased number of cases of successful resuscitation lead to a large number of surviving patients with severe disabilities. For the helper, however, some discomfort can arise. Potential risks with this trial are delayed start of CPR due to inclusion and randomization. These issues are separately evaluated in the TANGO2 RUN-IN and TANGO2 PILOT study. 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 respiratory causes,

i.e. drowning, strangulation, hanging or intoxication, some of these involve children. These cases are filtered out at the dispatch center and excluded from the study as described in the study protocol. We believe that a small group of unclear cases that are not identified by either the witness or by the dispatcher at the dispatch center (severe renal failure, pulmonary embolism, hemorrhagic stroke or chronic obstructive pulmonary disease) could experience a small risk with this intervention. These are very few in numbers 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 prior to randomization. CO-CPR could lead to an earlier start of CPR, no interruptions in chest-compressions and could therefore be beneficial for a majority of cases. In cases of OHCA immediate, effective chest compressions is of absolute necessity to increase the otherwise low chance of survival.

Today, Sweden has amongst 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 but has the potential to dramatically increase bystander rates throughout Europe and more.

A simplified method of CPR with shorter CO-CPR courses optimally provided by the Swedish CPR council 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, equally effective, or even superior to 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) simplified CPR might be better than traditional CPR b) simplified CPR could lead to more people performing it.

10. Data analytic and statistical analysis plan (SAP)

10.1 General statistical analysis plan

This trial is designed to investigate whether CO-CPR is no worse than S-CPR using a non-inferiority design. It has also been designed for the possible of a superiority testing. This statistical design has been chosen appropriately judged on the presumption that CO-CPR has potential clinical benefit but also is easier to perform (and therefore would lead to a higher number of patients receiving the treatment). The largest difference in 30-day survival (primary outcome) that is considered clinically relevant is 1.0 percentage point (please see also section 9.3).

Eligibility, allocation, inclusion and exclusion will be displayed in a Consort diagram. Differences in proportions between baseline characteristics and outcome will be tested by Fisher exact test. Differences in mean or medians between the treatment groups will be tested by either Student's t-test or Mann Whitney U test depending on distribution. Normality assumptions will be assessed with Kolmogorov Smirnov – test. The estimated between group differences will be presented as proportions and 95% confidence intervals (CI), which will be calculated by the asymptotic method without continuity correction. P-values below 0,05 will be considered statistically significant. Main results will be reported as proportions.

In addition, comparisons between the treatment groups (CO-CPR vs CPR) with respect to the outcomes will be adjusted for background characteristics factors through Binary logistic regression to adjust for possible imbalances due to randomization between the treatment groups. The association between treatment and primary outcome will be presented as odds ratios and corresponding 95% CI intervals. Statisticians at Karolinska Institutet will be responsible for the statistical analysis.

10.2 Statistical hypothesis for non-inferiority

10.2.1 Null hypothesis:

The percentage in 30-day survival for those on the standard treatment instruction CPR is better (higher) than the percentage for those on instruction CO-CPR by an amount of 1.0-percentage units.

10.2.2 Alternative hypothesis:

The percentage in 30-day survival for those on instruction CO-CPR is better than the standard treatment instruction CPR or only slightly worse (by no more than 1.0 percentage unit). We will call instruction of CO-CPR non-inferior to instruction of S-CPR with respect to 30-day survival if the null hypothesis is rejected.

10.3 General statistical methods

All statistical analyses will be performed using IBM SPSS version 25 and R version 3.3.0 *or higher*. Patient data listings, summary tables and graphical presentations will be provided as applicable. For continuous variables, descriptive statistics such as mean, standard deviation, median and range will be presented. For discrete variables, counts and percentages will be presented.

Unless otherwise stated, all statistical tests will be performed at the 5 % two-sided alpha significance level.

10.4 Analysis step and strategy of the whole study populations

The target study population is witnessed OHCA of medical origin where any bystander at the scene has previous CPR training. All randomized calls of suspected OHCA will be included.

Patient with previous decision that CPR should not be initiated i.e. terminal illness or palliative care and cases where EMS did not start CPR for other reasons (sure signs of death, not true OHCA) will be excluded from data analysis. The remaining patients will be analyzed in the ITT population.
Blinded call audit will be used to define type of CPR instructions provided. All randomized EMS treated OHCA receiving instructions in accordance with randomized allocation will be treated as the target study population treated per protocol (PP1).

Finally, patients who are randomized but later judged as not fulfilling all criteria for inclusion before randomization, as evaluated by call audit (not witnessed, asphyxic, bystanders with no previous CPR training), will be removed and remaining patients will be analyzed as PP2.

Thus, we perform ITT analysis, PP1 and PP2 analysis based on the following patients:

Intention to treat (ITT) analysis: We define the ITT population as all included and randomized EMS treated OHCA patients that not fulfilled any exclusion criteria's.

Per protocol 1 (PP1): We define the PP population as the subset of the ITT population where the bystanders received the allocated instructions by the dispatch operator, as defined by the call audit.

Per protocol 2 (PP2): We define the PP2 population as the subset of the PP1 population where the patients fulfilled all inclusion criteria, as defined by call audit.

Please see also Consort Diagram in section 10.5.

The reasoning behind excluding patients after randomization is two-folded:

First: Dispatchers suspecting OHCA based on initial information in a phone-call do patient inclusion and randomization. In this situation there is very limited information and dispatchers are encouraged to treat all calls were the patients is not conscious and not breathing normally as suspected OHCA

and start CPR instructions. Therefore, patients who do not have a treatable OHCA might be included and randomized. These patients can be divided in two categories, either it´s not a true OHCA (the patient never suffered an OHCA, for example fainted and thus has a pulse at EMS arrival) or the patients is already dead or had a previous decision that CPR should not be initiated. Therefore, EMS treated OHCA will serve as the best possible evaluation of treatable OHCA.

Second: The reason for including all randomized EMS treated OHCA is because at the time of randomization the dispatch operator judges the call as meeting all inclusion criteria and no exclusion criteria. If call audit or EMS record later reveal that the OHCA was not witnessed, traumatic, caused by asphyxia or bystanders without previous CPR training, the initial selection still relied on the dispatcher. Therefore, further removal of patients in the PP1 analysis might interfere with the interpretation of the study intervention in a real-life setting. A secondary analysis will be performed in all patient fulfilling all inclusion (PP2).

10.5 Power and sample size estimation

We estimated that 3260 patients (1630 in each group) would be needed in the primary analysis PP1 to have 80% power to show that CO-CPR is non-inferior to standard CPR. This calculation is based on the assumptions that the true survival rates after 30 days (primary outcome) in the population for standard CPR is 11% compared with 13.1% for CO-CPR, and that alpha (1 tailed) is set at 2.5%.

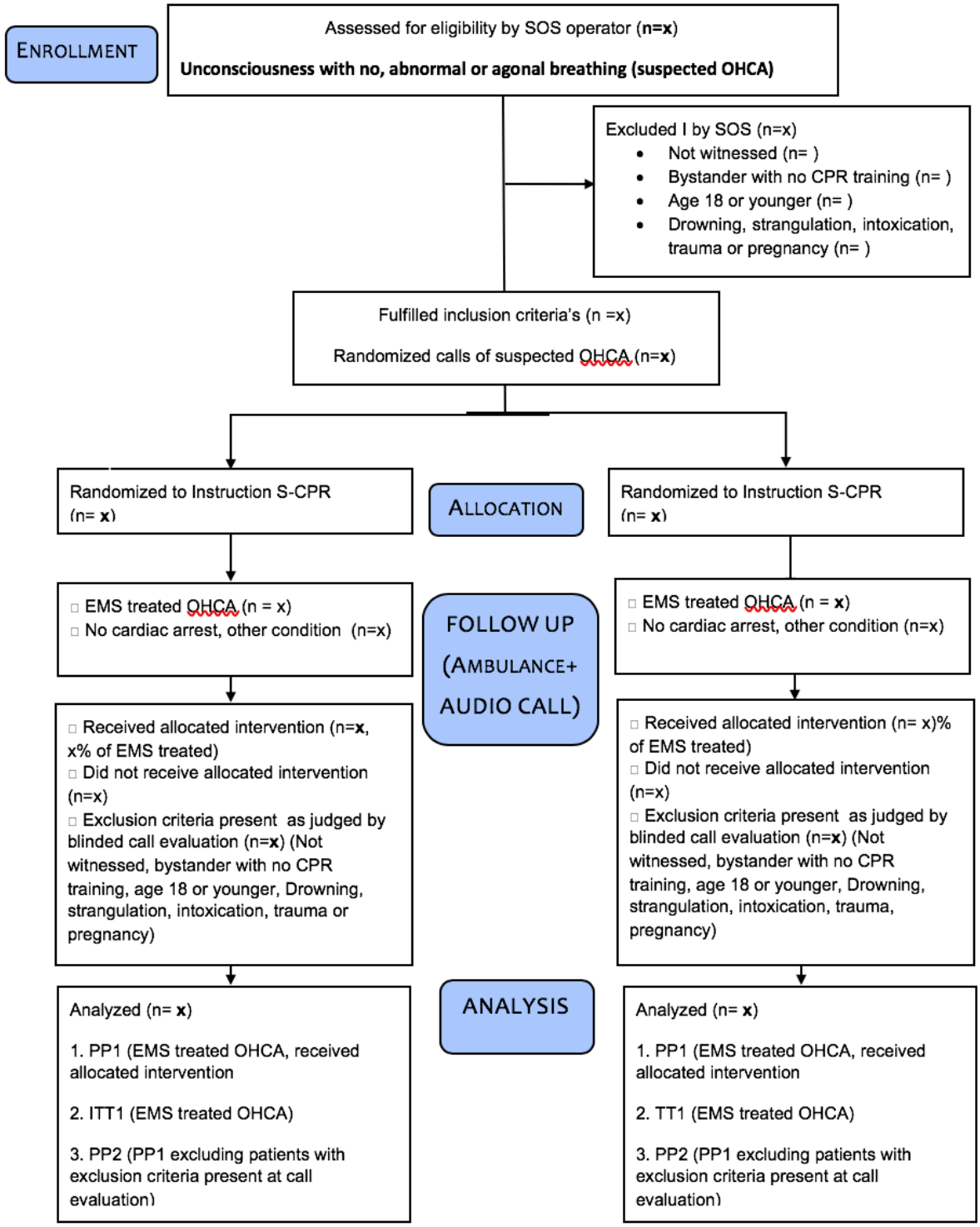
We defined 1.0 percentage point or less as the largest difference in survival that is clinically acceptable (i.e. the non-inferiority level which imply that a difference bigger than this would matter in practise). This difference is equivalent to an NNT of 100 (one person of 100 will die among those recommended CO-CPR, due to this recommendation). The reason for accepting this difference relies on the assumption that CO-CPR is easier to teach and perform, and therefore the treatment can be offered to more victims (please see also section 9.3).

In addition, we assumed that 20% will not receive the allocated intervention (e.g. randomized to CO-CPR but received S-CPR instructions or vice versa). We also assumed that 40% of the included patients will be excluded because of exclusion criteria's not possible to detect at the randomization (not OHCA, see section 5.3). Therefore, the recruitment goal was set to 6792 (3260 / (0.8*0.6)) randomized cases of suspected out-of-hospital cardiac arrest in order to receive 3260 in the primary PP1 analysis. (Please see also Consort Flow Diagram below)

Karolinska Institutet

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



10.6 Non-Inferiority and Superiority testing

First, the primary analysis will be performed for non-inferiority in the PP1 population. If the primary analysis rejects the null hypothesis (i.e. CO-CPR is non-inferior to CPR with respect to the primary or some secondary outcomes), the comparisons between the treatment groups will also be done for superiority using 95% two sided confidence interval.(28) Second, the same analysis (first non-inferiority and then superiority) as above will be done for the ITT and PP2 population. The non-inferiority limit 1% will be used for both primary and secondary outcomes.

10.7 Subgroup analyses

Subgroup analyses will be performed for the primary outcome variable using logistic regression models with test of treatment-subgroup interaction for each of the predefined subgroup variables. The results will be presented as the odds ratio with 95 % confidence interval for each subgroup and the corresponding p-value for interaction between treatment and each subgroup variable.

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

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

10.8 Randomization

Randomization will be performed by a computerized random generator (Microsoft.NET Random Constructor (Int 32)) in a 1:1 allocation ratio. The random generator is integrated in the dispatcher's software and there is no possibility for a dispatcher to see or guess randomization results before randomizing, therefore allocation concealment is preserved before randomization. For implementation the random generator is programmed so one dispatcher can only randomize a specific call one time. The computerized random generator is implemented by SOS-alarm into their software "Cord-comp".

11. Interim analysis and data monitoring committee

The trial will be monitored by an independent Data Safety Monitoring Committee (DSMC) that will receive unblinded summaries of data at the two interim analyses scheduled at 750 and 1500 patients. The DSMC will have 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 is continued until 3260 patients have been enrolled. Early stopping for efficacy reasons will only be considered if primary outcome differences are seen between the groups according to the Pato-Haybittle rule with a p-value ≤0,001. The DSMC will be able to request unblinding of data if they find it necessary. The DSMC can initiate analysis at any time they request.

A Interim analysis was performed by an independent data monitoring committee in early 2022, reviewing all data including 30-day survival, after a total of 1250 patients (out of which 696 patients were included in the main PP1 population). The recommendation by the data monitoring committee was to continue the trial without modification.

12. Publication plan and author policy

The trial will be analyzed by an independent statistician and the results interpreted by the steering group. The principal investigator will prepare the manuscript before the allocation code is broken. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The author list will start with Gabriel Riva and the last name will be Jacob Hollenberg. A separate publication list for all authors including the main study, as well as sub studies, has been created.

13. Enrolment and timeline

Q1-2 2014	Application to ethics committee
Q3-4 2014	Preparation
2015-2016	RUN-IN study
2017-2020	PILOT study
2022-2026	MAIN STUDY

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SCHEDULE 2: BUDGET AND PAYMENT SPECIFICATION

FINANCIAL CONTRIBUTION:

KI will financially contribute to the Collaborator according to the following:

* 100 euro per randomized and included patient with complete submitted data (according to all relevant study variables in RedCap)

* A Starting grant of 25000 Euro

* Details regarding financial provisions and payments can be found in the section 6 (*FINANCIAL PROVISIONS*) of this agreement.

* Financial contribution is valid to a maxium number of 1000 patients.

SCHEDULE 3: DRUGS AND PLACEBO

NOT APPLICABLE

SCHEDULE 3

DIVISION OF RESPONSIBILITIES

Trial preparation	Ensure that suitable clinical trial insurance is in place to cover liabilities [patient insurance, medicinal product insurance]	Both sponsors	
	Ensure that Collaborator has sufficient insurance to cover its responsibilities as Sponsor for the Trial to support indemnities given under Agreement.	KI	
	Secure and administer funding for the Trial.	KI	
	Provide for the Trial to be carried out within Trial Site(s), and for Trial Site(s) staff to work in collaboration with the Coordinating Investigator, Italian National Coordinator, and their teams.	Both sponsors	
	Secure and contract for supplies and services required for the Trial.	Both sponsors	
	Provide suitable Trial Site(s) for Trial activities involving dosing Subjects with the Product, including suitably equipped consulting room, storage and preparation areas.	KI	
	Make suitable arrangements for access to emergency medical facilities if required for Subjects.	Both sponsors	
	Provide those responsible for emergency medical facilities with Trial-specific information and Subject dosing details.	Both sponsors	
Applications and Registration	Ensure that the Protocol has undergone independent scientific and statistical review and is compliant with the relevant regulations/ guidelines.	KI	
	Prepare Subject information sheet, consent form, and synopsis	KI	
	Prepare and submit an application dossier through the CTIS in order to receive authorisation in accordance with the EU Clinical Trial Regulation 536/2014	Not applicable	
	When requested, provide comments or complete the application dossier in the CTIS.	Not applicable	

	Ensure that all communication in CTIS is made within the period set by the applicable law.	Not applicable	
Protocol Amendments	When necessary, prepare and submit proposed substantial amendments of the Protocol through the CTIS.	Not applicable	
	Ensure the Principal Investigators are informed of all amendments requiring implementation at the Trial Site(s), including the date on which the amendment should be implemented	Both sponsors	
	Ensure all amendments of which the Trial Site(s) is notified and that require local implementation are implemented at Trial Site(s), or that the Co-Sponsors are promptly notified that the amendment cannot be implemented and given the reason for this.	Both sponsors	
Trial Conduct	Ensure that no Subject is recruited to the Trial until approval in CTIS.	Not applicable	
	Ensure that the Trial is regularly monitored to ensure GCP compliance.	KI	
	Receive monitoring reports on behalf of the Co-Sponsors and ensure any necessary preventive or corrective actions are taken.	KI	
	Ensure that the rights of Subjects are protected and that they receive appropriate medical care whilst participating in the Trial.	Both sponsors	
	Assess capability of Subjects to give informed consent.	Both sponsors	
	Ensure no Trial procedure is carried out on a Subject until consent (where required) is obtained in accordance with the Protocol.	Both sponsors	
	Maintain and archive Trial documentation, including trial master files, always ensuring compliance with requirement under the Protocol and applicable laws.	KI	

	Ensure that all data and documentation are available for the purposes of monitoring, inspection or audit by the Co-Sponsors and any third-party authority.	KI	
	Ensure adequate facilities, resources and support are available to conduct the Trial.	KI	
	Notify the end of the Trial through CTIS	Not applicable	
	Notify the early termination of the Trial through CTIS.	Not applicable	
Adverse events	Maintain detailed records of all adverse events as specified in the Protocol.	KI	
	Report serious adverse events and incidents in accordance with the Protocol and the applicable laws and regulations.	Both sponsors	
	Promptly inform through the CTIS of any urgent safety measures taken to protect Subjects in the Trial.	Not applicable	
	Submit any necessary safety reports through the CTIS.	Not applicable	
	Ensure that all investigators are, at all times, in possession of the current relevant safety information for the Trial.	KI	
Laboratory Work	Ensure that laboratory work for the Trial carried out within Trial Site(s) is done in accordance with GCLP	Not applicable	
Data Management	Design of case report forms	KI	
	Design and maintenance of database	KI	
	Data entry	Both sponsors	
	Ensure appropriate data analysis.	KI	
Publication	Initiate and coordinate review and submission of abstracts, posters and publications.	KI	
Archiving	Ensure that all Trial records are archived appropriately on conclusion of the Trial and retained in accordance with applicable laws and regulations.	KI	

Product	Ensure that Product is manufactured, packaged, labelled and shipped in accordance with GMP and applicable laws and regulations.	Not applicable	
	Provide GCP compliant means of handling and storing Product at the Trial Site(s).	Not applicable	
	Ensure that IMP is not used for any purposes other than conduct of the Trial and in strict accordance with the Protocol.	Not applicable	
	Ensure that Product is stored in appropriate and secure conditions and that detailed records are maintained regarding its movement from delivery to return/destruction.	KI	
Contracts	Negotiation and finalization of the contracts with the Trial Sites	KI	
	Operative Trial coordination in Italy	Prof Giuseppe Risagno	

SCHEDULE 4 – JOINT CONTROLLER AGREEMENT

NOT APPLICABLE