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## Clinical paper

# Vasopressin and methylprednisolone for in-hospital cardiac arrest — Protocol for a randomized, double-blind, placebo-controlled trial



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## Abstract

**Objective:** To describe the clinical trial “Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest” (VAM-IHCA).

**Methods:** The VAM-IHCA trial is an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest. The study drugs consist of 40 mg methylprednisolone and 20 IU of vasopressin given as soon as possible after the first dose of adrenaline. Additional doses of vasopressin (20 IU) will be administered after each adrenaline dose for a maximum of four doses (80 IU).

The primary outcome is return of spontaneous circulation and key secondary outcomes include survival and survival with a favorable neurological outcome at 30 days. 492 patients will be enrolled. The trial was registered at the EU Clinical Trials Register (EudraCT Number: 2017-004773-13) on Jan. 25, 2018 and ClinicalTrials.gov (Identifier: NCT03640949) on Aug. 21, 2018.

**Results:** The trial started in October 2018 and the last patient is anticipated to be included in January 2021. The primary results will be reported after 3-months follow-up and are, therefore, anticipated in mid-2021.

**Conclusion:** The current article describes the design of the VAM-IHCA trial. The results from this trial will help clarify whether the combination of vasopressin and methylprednisolone when administered during in-hospital cardiac arrest improves outcomes.

**Keywords:** In-hospital cardiac arrest, Vasopressin, Methylprednisolone, Randomized trial

## Introduction

In-hospital cardiac arrest is a relatively common condition with high mortality.<sup>1–3</sup> Although outcomes have improved over the last decades, in-hospital survival has plateaued in the last 10 years at approximately 26% in the United States.<sup>1</sup> Although survival varies among different studies and countries, it is generally low.<sup>4</sup> In Denmark, 28% are alive after 30 days while 20% are alive after 1 year.<sup>3</sup>

Despite these dismal outcomes, clinical trials are sparse in in-hospital cardiac arrest<sup>5</sup> and there is a scarcity of evidence-based pharmacological interventions.<sup>6–8</sup> Thus, there is an need for additional randomized clinical trials in in-hospital cardiac arrest in order to advance the science and improve patient outcomes.

In two trials, published in 2009 and 2013, Mentzelopoulos et al. examined the effect of adding vasopressin and glucocorticoids to standard treatment in in-hospital cardiac arrest.<sup>9,10</sup> In these two randomized, double-blind trials, the investigators compared the addition of vasopressin (20 IU for each dose of adrenaline) and glucocorticoids (40 mg methylprednisolone) during cardiac arrest to placebo. After the cardiac arrest, patients in the intervention arm furthermore received glucocorticoids (300 mg hydrocortisone) if they had vasopressor-dependent shock. In both trials, the authors found improved outcomes, including survival, in the vasopressin and methylprednisolone group.<sup>9,10</sup> However, the American and European guidelines from 2015 do not recommend the routine use of vasopressin and glucocorticoids in in-hospital cardiac arrest primarily due to lack of studies externally validating the findings from the two previous trials.<sup>7,8</sup>

To further understand whether vasopressin and methylprednisolone improves outcomes for patients with in-hospital cardiac arrest, we designed the “Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest trial” (VAM-IHCA). We hypothesized that the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest would improve outcomes.

## Methods

### Protocol

The full protocol is provided in the Supplemental material and all previous versions are available on the trial website.<sup>11</sup> The protocol

was developed in accordance with the International Conference on Harmonization (ICH) guidelines<sup>12–14</sup> and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.<sup>15,16</sup> The trial was registered at the EU Clinical Trials Register (EudraCT Number: 2017-004773-13) on Jan. 25, 2018 and ClinicalTrials.gov (Identifier: NCT03640949) on Aug. 21, 2018.

### Design

The VAM-IHCA trial is an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest.

### Setting

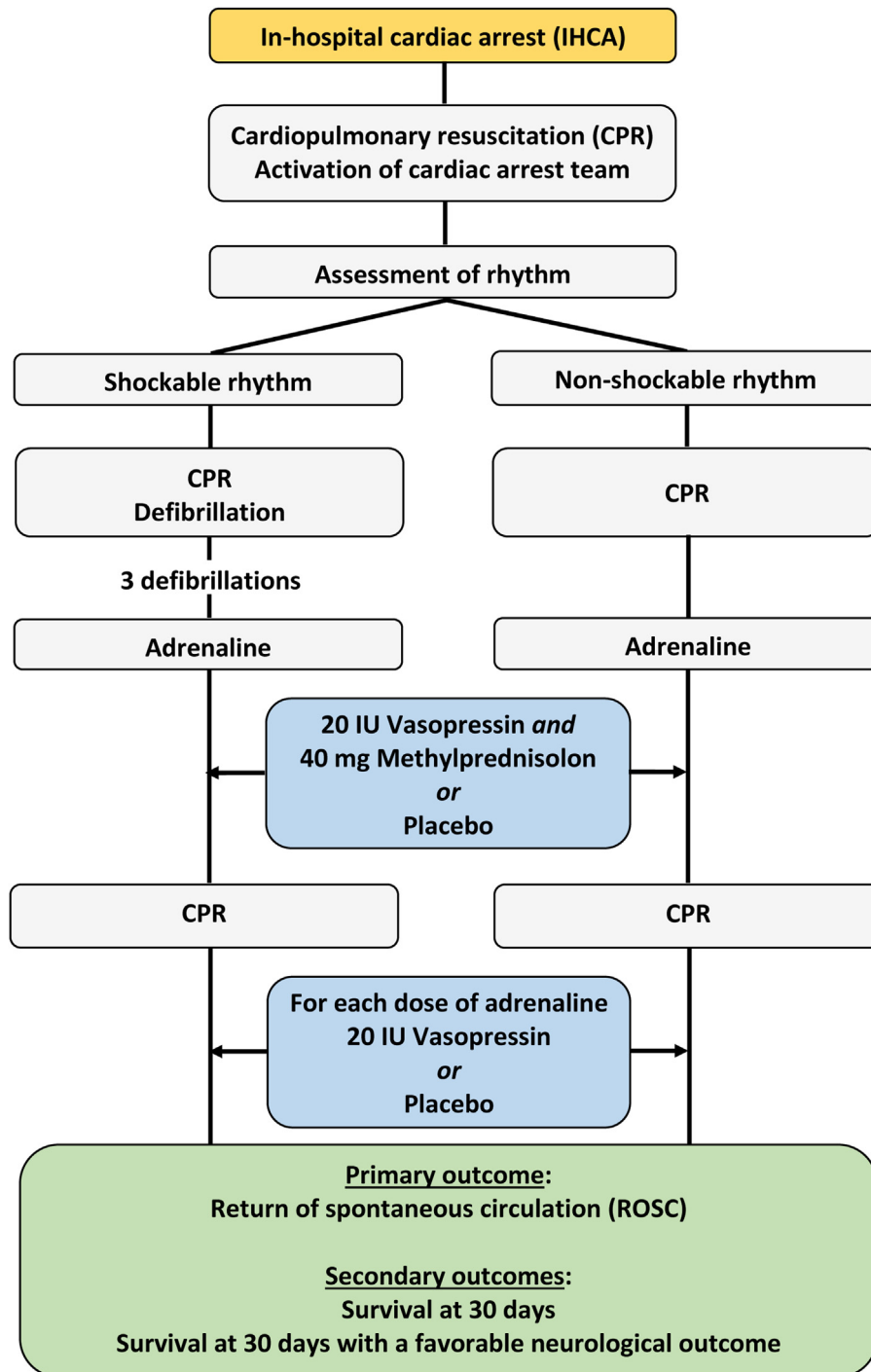
The trial is conducted at 10 hospitals in Denmark including four large university hospitals. A full list of participating centers is provided in the full protocol in the Supplemental material.

### Eligibility criteria

Patients will be included based on the following criteria: In-hospital cardiac arrest, age  $\geq 18$  years, and receipt of at least one dose of adrenaline during the cardiac arrest. Exclusion criteria are: Clearly documented “do-not-resuscitate” order prior to the cardiac arrest, prior enrollment in the trial, invasive mechanical circulatory support at the time of the cardiac arrest, and known or suspected pregnancy at the time of the cardiac arrest.

### Intervention

The study drugs consist of 40 mg methylprednisolone (Solu-medrol<sup>®</sup>, Pfizer) and 20 IU of vasopressin (Empressin<sup>®</sup>, Amomed Pharma GmbH) given as soon as possible after the first dose of adrenaline which is part of standard care. Additional doses of vasopressin (20 IU) will be administered after each adrenaline dose for a maximum of four doses (80 IU) (see Fig. 1). These drugs and doses are similar to the original trials by Mentzelopoulos et al.<sup>9,10</sup> However, for practical reasons (i.e., that one ampule of vasopressin contain two doses) this



**Fig. 1 – Overview of the trial interventions.**

trial will include a maximum of four doses of vasopressin as compared to a maximum of five doses in the original trials.<sup>9,10</sup>

The placebo for vasopressin will consist of 1 mL of 9 mg/mL NaCl (“normal saline”) from 2 mL ampules identical to the vasopressin ampules. The placebo for methylprednisolone will also consist of 1 mL of 9 mg/mL NaCl.

The study drugs are placed in a blinded study kit (a small box, see Appendix 2 in the full protocol) containing one 40 mg dose of

methylprednisolone (or placebo) and two 40 IU ampules (i.e., four 20 IU doses) of vasopressin (or placebo).

### **Blinding**

The trial is double-blind; patients, investigators, and the clinical team are blinded to the allocated treatment. In the blinded study kit, a sealed opaque envelope contains the allocation assignment which will allow

for emergency unblinding. The decision to unblind will be at the discretion of the treating physician and clinical team.

### **Allocation**

Patients are randomized in a 1:1 ratio to either vasopressin and methylprednisolone or placebo in blocks with random sizes of 2, 4, or 6. The randomization is stratified according to site.<sup>17</sup>

### **Outcomes**

The primary outcome is return of spontaneous circulation (ROSC). ROSC is defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 min.

The key secondary outcomes are survival at 30 days and survival at 30 days with a favorable neurological outcome. A favorable neurological outcome will be defined as a cerebral performance category (CPC) score of 1 or 2. The CPC score is a 5-point scale assessing neurological/functional outcomes after brain damage.<sup>18</sup> Patients not alive at 30 days will be categorized as a poor neurological outcome.

A number of additional outcomes are also collected, and a full list is provided in the protocol in the Supplemental material. These outcomes include survival, neurological outcome, and quality of life at 90 days, 180 days, and 1 year after the cardiac arrest.

Specific adverse events are also collected.

The outcomes adhere to the “Core Outcome Set for Cardiac Arrest” (COSCA) guidelines.<sup>19</sup>

### **Sample size**

The trial is powered to the primary outcome of ROSC. Combining the original trials by Mentzelopoulos et al., the proportion of patients with ROSC was 148/178 (83% [95% CI: 77%, 88%]) in the intervention group and 118/190 (62% [95% CI: 55%, 69%]) in the placebo group yielding an absolute risk difference of 21% and a relative risk of 1.34.<sup>9,10</sup> For this trial, we assumed a ROSC rate of 45% in the control group (based on unpublished preliminary data from some of the participating sites). We assumed an absolute difference of 13% between the control and intervention group corresponding to a ROSC rate of 58% in the intervention group and a relative risk of 1.29. With these estimates, an alpha of 0.05, and the use of the chi-squared test, we will need a total of 492 patients (i.e., 246 in each group) to have 80% power to detect a statistically significant difference between groups.

### **Statistical analysis plan**

A detailed statistical analysis plan is provided in the protocol in the Supplemental material. The statistical analyses and reporting will adhere to the CONSORT guidelines.<sup>20,21</sup>

All analyses will be conducted on a modified intention-to-treat basis only including patients receiving the first dose of the study drug and meeting all inclusion criteria and no exclusion criteria (except pregnancy). In a double-blind trial, this approach is unbiased while increasing precision.<sup>22</sup>

The primary and key secondary outcomes (binary variables) will be presented as counts and proportions in each group. Results will be reported as both risk ratios and risk differences. P values will be obtained from Fisher's Exact test. As a sensitivity analysis, we will estimate the risk ratio with 95% confidence intervals for the primary

outcome while adjusting for center and strong prognostic factors, specifically age, whether the cardiac arrest was witnessed, and the initial rhythm, as covariates.<sup>23–26</sup>

Subgroup analyses will be performed on both the absolute and relative scale. The analyses will include five pre-defined subgroup analyses for the primary and key secondary outcomes according to 1) first documented rhythm (shockable vs. non-shockable), 2) whether the cardiac arrest was witnessed, 3) patient age (dichotomized by the median), 4) time from cardiac arrest to first study drug (dichotomized by the median), and 5) time from adrenaline administration to first study drug (dichotomized by the median).

Blinded interim analyses are conducted by an independent data-monitoring committee approximately every 6 months. There are no formal stopping criteria.

### **Data collection and follow-up**

Data on drug administration and the primary outcome ROSC will be obtained from the clinical cardiac arrest team in real-time on a numbered case report form that accompanies the study kit. Additional data will be manually obtained from the electronic medical records by trained research staff and entered into a REDCap database. Details of the included variables and their definitions are provided on the trial website.<sup>11</sup>

### **Clinical treatment**

The clinical management of included patients will be at the discretion of the treating clinical team in order to test the interventions in a real-life clinical scenario. In general, management will adhere to the intra- and post-cardiac arrest guidelines provided by the European Resuscitation Council<sup>27</sup> and the Danish Resuscitation Council<sup>28</sup> but no specific treatments will be prohibited or mandated.

### **Ethical considerations and consent**

A detailed description of the ethical considerations is provided in the protocol in the Supplemental material. The trial was approved by the regional ethics committee (case number: 1-10-72–42-18) on Apr. 11, 2018 and the Danish Medicine Agency (EudraCT Number: 2017-004773-13) on Feb. 28, 2018.

Consent is obtained according to Danish law using a 3-step approach. First, verbal, and subsequent written, consent for enrollment is obtained from an independent physician during the cardiac arrest. Second, if the patient survives the cardiac arrest, written consent for further data collection and follow-up is obtained from a surrogate. Third, if the patient regains consciousness, written consent is obtained from the patient.

### **Data sharing**

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing.<sup>29</sup> Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data.

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## **Discussion**

The current article, along with the full protocol available in the Supplemental material, describes the design of the VAM-IHCA trial,

which is testing the combination of vasopressin and methylprednisolone in patients during in-hospital cardiac arrest.

Vasopressin (also known as antidiuretic hormone or arginine vasopressin) is a nonapeptide produced in the hypothalamus and secreted into the circulation through the posterior pituitary gland. During states of shock, levels of vasopressin are low and exogenously administered vasopressin exerts profound vasoconstrictive effects. The rationale for the use of vasopressin during cardiac arrest is based on studies demonstrating that plasma levels of vasopressin are lower in non-survivors compared to survivors,<sup>30</sup> and that vasopressin, through its potent vasoconstrictive properties, increases coronary perfusion pressure and thereby the chance of ROSC.<sup>31,32</sup> These properties lead to clinical trials where vasopressin was compared to standard treatment in patients with cardiac arrest.<sup>33–36</sup> Only one relatively small trial ( $n = 200$ ) included in-hospital cardiac arrest patients.<sup>37</sup> In a meta-analysis of six randomized clinical trials, there was no overall benefit of vasopressin administration during cardiac arrest.<sup>34</sup>

Methylprednisolone is a synthetic glucocorticoid, which is a class of corticosteroids that is part of the larger group of steroid hormones. Studies in patients with cardiac arrest have demonstrated that levels of cortisol are higher in patients that are resuscitated when compared to patients that are not resuscitated,<sup>38</sup> which may illustrate an impaired endocrine response in non-survivors. This is supported by animal studies where the administration of hydrocortisone during cardiac arrest increases ROSC.<sup>39</sup> This may relate to the cardiovascular effects of glucocorticoids, which include increases in enzymes involved in adrenaline synthesis, inhibition of catecholamine re-uptake and breakdown, and by enhancement of cardiovascular sensitivity to catecholamines by increasing the binding capacity and affinity.<sup>40,41</sup> Data on glucocorticoid administration during human cardiac arrest is limited and small studies have shown conflicting results.<sup>42</sup>

Although the benefit of vasopressin and glucocorticoid administration as individual drugs is unclear, Mentzelopoulos et al. tested the combination of the drugs in two trials.<sup>9,10</sup> These trials, which were relatively small (100 and 268 patients) had remarkable results with very large treatment effects. In the first trial, survival to hospital discharge was higher in the intervention group as compared to the placebo group (9/48 [19%] vs. 2/52 [4%],  $p = 0.02$ ).<sup>9</sup> In the second trial, the primary outcome of survival to hospital discharge with a favorable neurological outcome (CPC score of 1 or 2) was higher in the intervention group as compared to the placebo group (18/130 [14%] vs. 7/138 [5%],  $p = 0.02$ ).<sup>10</sup> The authors also showed beneficial effects on post-cardiac arrest hemodynamics, organ failure, and inflammation.<sup>9,10</sup> Despite these remarkable results, the interventions have not been implemented into guidelines and clinical practice. The trials have received a great deal of attention in the literature with most commentaries arguing for external validation studies before clinical implementation.<sup>43–46</sup> The International Liaison Committee on Resuscitation (ILCOR) reached the same conclusion: “Confidence in the treatment effects from bundled treatments [i.e., vasopressin and glucocorticoids] will increase if confirmed in further studies”.<sup>6</sup> Hopefully, the results of the current trial, along with those from Mentzelopoulos et al., will provide a clearer picture about the benefit of vasopressin and methylprednisolone.

The intervention in the Mentzelopoulos et al. trials included hydrocortisone for patients with vasopressor dependent shock four hours after the cardiac arrest. A dose of 300 mg of hydrocortisone was administered per day until shock reversal or for a maximum of

7 days.<sup>9,10</sup> For several reasons, this part of the intervention is not included in the current trial. First, considerable beneficial effects were seen in the original trials before the hydrocortisone was administered. This includes a substantial increase in ROSC, improvements in early hemodynamics, and an increase in 4-h survival.<sup>9,10</sup> Second, a separate randomized clinical trial, not including the intra-cardiac arrest interventions, found no benefit of hydrocortisone for post-cardiac arrest patients with vasopressor dependent shock.<sup>47</sup> Third, assessing both intra- and post-cardiac arrest interventions combined does not allow for assessment of the individual effects of each intervention. If the current trial is positive, future trials are needed to then assess the post-cardiac arrest aspect of the Mentzelopoulos et al. trials. Lastly, the primary outcome of the current trial is ROSC, which will not be influenced by post-cardiac arrest treatment.

The primary outcome of the current trial is ROSC. Ideally, the trial should be powered for a more patient-centered outcome, such as 90-day survival with a good neurological and functional outcome. As such outcomes, especially in those patients eligible for the trial (i.e., receiving adrenaline), are relatively rare (approximate 5–10%), powering a trial for a clinically relevant difference is challenging. For example, if the outcome occurred in 10% and 12% of the patients in the control and intervention groups respectively, more than 7000 patients would need to be included. This was not considered feasible at the time of the design of the current trial. However, if the treatment effect on survival is as large as seen in the Mentzelopoulos et al. trials, the trial is well-powered to detect such a difference (see protocol available in the Supplemental material for additional details).

The conduct of trials during cardiac arrest provides a number of ethical and logistical challenges.<sup>48</sup> Although international guidelines, such as the revised Declaration of Helsinki,<sup>49</sup> European regulations,<sup>50</sup> and the Good Clinical Practice guidelines,<sup>12</sup> supports research in acute settings where patients are not able to provide consent, great international variability exists in the rules and regulations for such research.<sup>51,52</sup> In Denmark, it is currently a requirement to obtain consent from an independent physician (i.e., someone not involved in the research) before a patient can be enrolled and medication administered. While this approach provides an opportunity to conduct such research, it introduces important logistical challenges that can result in missed enrollments or delays in administration of the study drug.

The trial started in October 2018 and the last patient is anticipated to be included in January 2021. The primary results will be reported after 3-months follow-up and are, therefore, anticipated in mid-2021. These results will help clarify whether the combination of vasopressin and methylprednisolone when administered during cardiac arrest improves outcomes.

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## Conflicts of interest

None of the authors have any conflicts related to the current trial or manuscript.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resplu.2021.100081>.

## REFERENCES

- Holmberg MJ, Granfeldt A, Girotra S, Donnino MW, Andersen LW. Trends in survival and introduction of the 2010 and 2015 guidelines for adult in-hospital cardiac arrest. *Resuscitation* 2020;157:112–20.
- Holmberg MJ, Ross CE, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, et al. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes* 2019;12:e005580.
- Andersen LW, Holmberg MJ, Lofgren B, Kirkegaard H, Granfeldt A. Adult in-hospital cardiac arrest in Denmark. *Resuscitation* 2019;140:31–6.
- Schluep M, Gravesteyn BY, Stolker RJ, Endeman H, Hoeks SE. One-year survival after in-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation* 2018;132:90–100.
- Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA* 2019;321:1200–10.
- Callaway CW, Soar J, Aibiki M, Bottiger BW, Brooks SC, Deakin CD, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2015;132:S84–145.
- Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European resuscitation council guidelines for resuscitation 2015: section 3. Adult advanced life support. *Resuscitation* 2015;95:100–47.
- Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S444–64.
- Mentzelopoulos SD, Zakyntinos SG, Tzoufi M, Katsios N, Papastilianou A, Gkisioti S, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009;169:15–24.
- Mentzelopoulos SD, Malachias S, Chamos C, Konstantopoulos D, Ntaidou T, Papastilianou A, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2013;310:270–9.
- Website for the VAM-IHCA trial. 2020 Available from: <https://www.vam-ihca.com/>. [cited 5 December 2020].
- ICH Harmonised Tripartite Guideline. Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2). 2016 Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R2\\_Step\\_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4.pdf). [cited 30 June 2017].
- ICH Harmonised Tripartite Guideline. General Considerations for Clinical Trials E8. 1997 Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E8/Step4/E8\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf). [cited 30 June 2017].
- ICH Harmonised Tripartite Guidelines. Statistical Principles for Clinical Trials. 1998 Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E9/Step4/E9\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf). [cited 30 June 2017].
- Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. *J Clin Epidemiol* 1999;52:19–26.
- Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480–4.
- Haywood K, et al. COSCA (core outcome set for cardiac arrest) in adults: an advisory statement from the international liaison committee on resuscitation. *Resuscitation* 2018;127:147–63.
- Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
- Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4.
- Fernando SM, Tran A, Cheng W, Rochweg B, Taljaard M, Vaillancourt C, et al. Pre-arrest and intra-arrest prognostic factors associated with survival after in-hospital cardiac arrest: systematic review and meta-analysis. *BMJ* 2019;367:l6373.
- Hernandez AV, Steyerberg EW, Habbema JD. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. *J Clin Epidemiol* 2004;57:454–60.
- Kahan BC, Jairath V, Dore CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* 2014;15:139.
- Kahan BC. Accounting for centre-effects in multicentre trials with a binary outcome - when, why, and how? *BMC Med Res Methodol* 2014;14:20.
- Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European resuscitation council guidelines for resuscitation 2015: section 1. Executive summary. *Resuscitation* 2015;95:1–80.
- Danish Resuscitation Council. Advanced Resuscitation [Danish]. Available from: <http://genoplivning.dk/avanceret-genoplivning/>.
- Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials - a requirement of the international committee of medical journal editors. *N Engl J Med* 2017;376:2277–9.
- Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart* 1996;75:145–50.
- Miano TA, Crouch MA. Evolving role of vasopressin in the treatment of cardiac arrest. *Pharmacotherapy* 2006;26:828–39.
- Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990;263:1106–13.
- Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105–13.
- Mentzelopoulos SD, Zakyntinos SG, Siempos I, Malachias S, Ulmer H, Wenzel V. Vasopressin for cardiac arrest: meta-analysis of randomized controlled trials. *Resuscitation* 2012;83:32–9.

35. Gueugniaud PY, David JS, Chanzy E, Hubert H, Dubien PY, Mauriaucourt P, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008;359:21–30.
36. Layek A, Maitra S, Pal S, Bhattacharjee S, Baidya DK, et al. Efficacy of vasopressin during cardio-pulmonary resuscitation in adult patients: a meta-analysis. *Resuscitation* 2014;85:855–63.
37. Stiell IG, Hebert PC, Wells GA, Vandemheen KL, Tang AS, Higginson LA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet* 2001;358:105–9.
38. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992;77:662–8.
39. Smithline H, Rivers E, Appleton T, Nowak R. Corticosteroid supplementation during cardiac arrest in rats. *Resuscitation* 1993;25:257–64.
40. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 2000;21:55–89.
41. Shi WL, Zhang T, Zhou JR, Huang YH, Jiang CL. Rapid permissive action of dexamethasone on the regulation of blood pressure in a rat model of septic shock. *Biomed Pharmacother* 2016;84:1119–25.
42. Varvarousi G, Stefanidou A, Varvaroussi D, Xanthos T. Glucocorticoids as an emerging pharmacologic agent for cardiopulmonary resuscitation. *Cardiovasc Drugs Ther* 2014;28:477–88.
43. Botnaru T, Altherwi T, Dankoff J. Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone. *CJEM* 2015;17:202–5.
44. Ballew KA. ACP Journal Club. Combined vasopressin, steroids, and epinephrine improved survival in in-hospital cardiac arrest. *Ann Intern Med* 2013;159:JC4.
45. Buddineni JP, Callaway C, Huang DT. Epinephrine, vasopressin and steroids for in-hospital cardiac arrest: the right cocktail therapy? *Crit Care* 2014;18:308.
46. Hwang JY, Arredondo AF, Paul TK. Lung cancer screening, targeted temperature after cardiac arrest, and vasopressin and steroids in cardiac arrest. *Am J Respir Crit Care Med* 2014;189:994–5.
47. Donnino MW, Andersen LW, Berg KM, Chase M, Sherwin R, Smithline H, et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. *Crit Care* 2016;20:82.
48. Mentzelopoulos SD, Slowther AM, Fritz Z, Sandroni C, Xanthos T, Callaway C, et al. Ethical challenges in resuscitation. *Intensive Care Med* 2018;44:703–16.
49. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
50. The European Parliament and the Council of the European Union. Clinical Trials Regulation (CTR) EU No 536/2014. 2014 Available from: [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg\\_2014\\_536/reg\\_2014\\_536\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf). [cited 18 July 2017].
51. van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G, et al. International variation in policies and practices related to informed consent in acute cardiovascular research: results from a 44 country survey. *Resuscitation* 2015;91:76–83.
52. Mentzelopoulos D, Bossaert L, Raffay V, Askitopoulou H, Perkins GD, Greif R, et al. A survey of key opinion leaders on ethical resuscitation practices in 31 European Countries. *Resuscitation* 2016;100:11–7.