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## Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study

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**Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study**

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**Abstract**

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**Introduction**

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France. Their management is performed by a particular prehospital system based on medicalisation of both ambulance dispatch and mobile intensive care units. It follows the European recommendations which advocate for the use of early point-of-care focused echocardiography (EPOCE) in particular to identify reversible causes of OHCA. Another ability of EPOCE is to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion.

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**Methods**

The ACE trial aims to assess the positive predictive value of absence of cardiac motion viewed with early EPOCE on the absence of ROSC. It is a prospective multicentre (n=8) prognosis study which will recruit a large sample of patients (n=624). Briefly, once the diagnosis of OHCA done and advanced life-support (ALS) initiated, an EPOCE will be performed during the defibrillator's analysis period. The physician will notice cardiac motion or lack and will look for a curable etiology. ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. ROSC will be assessed after ALS termination.

## Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion on the absence of ROSC. Secondary endpoints are predictive characteristics of EPOCE on morbimortality 30 days after OHCA, description of curable etiologies, analysis of EPOCE technique.

## Ethic

ACE was approved by an ethical committee (2018-AO1491-54)

## Dissemination

While ACE is adapted to the French prehospital system, its results will be translatable to other organisations. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE on absence of ROSC will be the same.

## Trial status

ACE has received a grant from the French Minister for Health, was registered in clinicaltrials.gov (RC17\_0464) on April 11, 2018

## Keywords :

Cardiac arrest, prognosis, cardiac ultrasound

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## Strength and limitations of the study

- First prospective multicentre prognosis study of Point-of-care Ultrasound in out-of-hospital cardiac arrest
- positive predictive value of early Point-of-care ultrasound absence of cardiac motion on absence of return of spontaneous circulation
- if positive, might allow for shorter delays before extracorporeal membrane oxygenation or organ donation processes

## Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5 to 6% of patients will leave the hospital alive with satisfying neurological condition [2, 3, 4]. Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drugs administration, and defibrillation if needed) [4, 5]. Based on published studies [5, 6, 7], 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in emergency medicine, in particular to identify reversible causes of OHCA [4, 5]. Indeed, POCE can reveal various curable aetiologies such as tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax [5, 6]. Their identification allows the clinician to better adjust his therapeutic strategy and, accordingly, might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion. Several studies found a strong correlation between absence of cardiac motion and absence of ROSC [6] [7], [8], [9], [10], [11]. This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delays, management, and



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2 86 environment. In this context, the European Resuscitation Council (ERC) stated in 2015 that,  
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4 87 while the absence of cardiac motion is highly predictive of death, sensitivity and specificity  
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6 88 have not been reported. Thus, usage of this ascertainment for determination of premature  
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9 89 termination of resuscitation is currently not recommended until publication of a pivotal study.  
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## 11 12 90 **Methods and analysis**

### 13 14 15 16 91 **Objectives**

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20 92 The ACE French national trial fits precisely into this bibliographic gap. Our objectives are  
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22 93 multiple:

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24 94 • The main objective is to assess the positive predictive value of early POCE (EPOCE;  
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27 95 i.e. < 12 min after initiation of advanced life support (ALS)) on the absence of ROSC  
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- 29 96 • Secondary objectives are:  
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31 97 1. assess the prognostic value of early POCE on survival at hospital admission and  
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33 98 on morbi-mortality at Day 30 after the OHCA (D30),  
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35 99 2. assess prognostic performances of early POCE on the absence of ROSC,  
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37 100 3. assess prognostic values of EPOCE according to timing of realisation,  
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39 101 4. assess the relationship between EPOCE findings and ECG rhythms,  
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41 102 5. describe frequency and typology of curable aetiologies in the context of OHCA,  
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43 103 6. describe EPOCE characteristics: timing, quality assessed by the operator, and  
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45 104 by an expert committee,  
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48 105 7. assess prognostic performances of EPOCE in patients with ventricular  
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8. creation of a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age on the absence of ROSC, and
9. measurement of the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

## Design

ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous methodology, has a high proof-level design, and will recruit a large sample of patients ( $n = 624$ ). Recruiting centres include both rural and urban community and university hospitals. This pragmatic approach intends to validate the performance of EPOCE for the prediction of absence of ROSC in cases of absence of cardiac motion in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays before extracorporeal membrane oxygenation (ECMO) or organ donation processes. Echographic asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements.

## Methods

### *Patients*

Inclusion criteria: patients > 18 years old presenting with an OHCA for whom an EPOCE was performed.

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2 128 Non-inclusion criteria: do not resuscitate order, ALS not performed by the prehospital team,  
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4 129 pregnancy, breastfeeding women, and inmates.  
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7 130 **Procedure**  
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10 131 After verification of inclusion and exclusion criteria, advanced life support intervention will  
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12 132 replace basic life support with an overlap period, as usual. ALS will be performed according to  
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15 133 the latest ERC regulations. Once standard ALS interventions are done, according to the  
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17 134 focused echocardiographic evaluation in life support (FEEL) protocol and ERC  
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19 135 recommendations [4, 5], the physician will perform a POCE during the defibrillator's analysis  
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22 136 period, thus in less than 10 seconds. It will be done using a phased array probe with a  
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24 137 subcostal view. It has to be done as early as possible and always before 12 min after ALS  
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26 138 initiation. The physician will notice cardiac motion or lack thereof and will look for curable  
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29 139 aetiologies. Video clips will be stored in the echographic device and secondarily uploaded in  
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31 140 the electronic case report file (eCRF) for random reviewing by an expert committee. The  
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33 141 whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic  
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35 142 delays. ALS will be terminated following ERC rules, the POCE results will not be used for that  
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38 143 purpose. Presence or absence of ROCS will be assessed after ALS termination. In the case  
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40 144 of ROCS, the hospital pathway will be described. At D30, vital status of all patients will be  
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42 145 assessed by either hospital file consult or phone call if the patient is still alive. For them,  
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45 146 autonomy will be assessed using the Glasgow Outcome Scale.  
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47 147 **Endpoints**  
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51 148 **Primary endpoint**  
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- Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the predictive positive value (PPV) as the primary endpoint because we wish to limit the number of false positives as much as possible in order to isolate a population without ROCS with POCE asystole.

### **Secondary endpoints**

1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on hospital admission and on morbimortality evaluated at 30 days.
2. Sensitivity, specificity, and positive (PPV) and negative predictive (NPV) values of EPOCE asystole on absence of ROSC.
3. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole on absence of ROSC according to their timing of realisation after ALS initiation on the absence of ROSC (by 2 min).
4. Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram electrical activity (pulseless activity, asystole, ventricular fibrillation, and ventricular tachycardia).
5. Description of curable aetiologies, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies on ROCS and 30 day morbimortality.
6. Analysis of EPOCE technique during OHCA resuscitation: duration, quality of the video clips assessed by the operator (from 0 = impossible to 10 = excellent), and an expert committee reviewing a 10% random sample.
7. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in patients with ventricular fibrillation.

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2 172 8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow  
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4 173 duration, initial treatment, electrical activity, and cardiac motion) associated with the  
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6 174 absence of ROSC in order to determine a score with a 100% PPV.  
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9 175 9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using  
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11 176 a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).  
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14 177 **Recruiting centres**

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17 178 Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny)  
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19 179 and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).  
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22 180 **Sample size calculation**

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25 181 The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of  
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27 182 ROSC. For a PPV of  $95 \pm 3\%$ , 203 patients without cardiac motion are required. Based on  
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29 183 37.5% asystole rate [10], 542 total patients are required. Taking into account a 15% attrition  
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31 184 rate, the required population will, finally, be 624 patients.  
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35 185 **Recruitment**

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38 186 Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound  
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40 187 and already use this technique in their emergency department. A monthly newsletter will be  
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42 188 published with individual and global recruitment trends. Patients will be followed-up until day  
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44 189 30 and defined gradually as: survival without neurological deficit, survival with neurological  
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46 190 deficit, or death.  
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## **Data management**

Electronic case report files will be used via a web-based interface and video clips will be uploaded. All data will be stored in the Nantes University Hospital secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be only available to the steering committee.

## **Monitoring**

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

## **Statistical analysis**

Sensitivity, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will be estimated to analyse the time of EPOCE realisation that allows the best prognostic performances on the absence of ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. Curable aetiologies, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score

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2 213 associated with the absence of ROSC will be constructed with a logistic regression model.  
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4 214 Parameters that will be taken into account will be: myocardial and/or electrical activity,  
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6 215 capnography, no/low flow duration, and clinical profile including sex and age. Measure of  
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9 216 mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values  
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11 217 less than 0.05 will be considered statistically significant. All analyses will be performed using  
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13 218 SAS version 9.4 ®.

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16 219 **Ethics**

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19 220 The ACE trial has been approved by the ethics committee (Comité de Protection des  
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21 221 Personnes “Ile de France II” France, 2018-AO1491-54). In accordance with their  
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23 222 recommendations, patient and/or legal authority consent will be requested only for survivors.  
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25 223 Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives’  
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27 224 consent. Regarding the very low survival rate of patients with OHCR (5%), anonymised  
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29 225 database, and family induced traumatism, we have asked for a derogation to surrogates  
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31 226 information for deceased patients. A consent will be requested for surviving patients.  
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36 227 **Dissemination**

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39 228 We intend to publish ACE results in a major journal of Emergency Medicine, raw data will be  
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48 231 **Discussion**

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51 232 There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA.  
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53 233 Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures  
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without waiting for a median time of 30 min after ALS onset. Conversely, in cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for curative aetiologies.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols [6] [7] [8] [9] [10] [11]. This was stated by the European Resuscitation Council in its 2015 recommendations [5].

ACE is adapted to the particularities of the French prehospital system but its results will be translatable to other organisations such as European or American ones. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE on absence of ROSC will be the same.

ACE has the potential to provide a definitive response to this question. It is a multicentre, prospective trial with a rigorous methodology and a large sample of patients. Furthermore, it will answer the question of frequency of curable aetiologies and their management. This question also needs hard evidence, ACE has the potential to provide this since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions [12] that would alter the prognosis. However, the training of physicians in POCE in this study was not reported [13] and might be low, regarding the number of included patients. Anyway, this potential flaw has to be addressed: in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

## Availability of data and material

Data will be available upon reasonable request.



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## References

1. Luc G, Baert V, Escutnaire J, Genin M, Vilhelm C, Di Pompéo C, et al. Epidemiology of out-of-hospital cardiac arrest: A French national incidence and mid-term survival rate study. *Anaesth Crit Care Pain Med*. 2018; doi:10.1016/j.accpm.2018.04.006
2. Nicolas G, Lecomte D. [Sudden cardiac death in adults. Epidemiology]. *Bull Acad Natl Med*. 1999;183:1573–9; discussion 1579–80.
3. Stiell IG, Nichol G, Leroux BG, Rea TD, Ornato JP, Powell J, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365(9):787–97.
4. Les statistiques publiques | RéAC [Internet]. 2018. [http://registreac.org/?page\\_id=2822](http://registreac.org/?page_id=2822) Accessed 15 Sep 2018
5. Soar J, Nolan JP, Böttiger 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.
6. Breitzkreutz R, Price S, Steiger HV, Seeger FH, Ilper H, Ackermann H, et al. Focused echocardiographic evaluation in life support and peri-resuscitation of emergency patients: a prospective trial. *Resuscitation*. 2010;81:1527–33.
7. Blyth L, Atkinson P, Gadd K, Lang E. Bedside focused echocardiography as predictor of survival in cardiac arrest patients: a systematic review. *Acad Emerg Med*. 2012;19:1119–26.
8. Tsou P-Y, Kurbedin J, Chen Y-S, Chou EH, Lee M-TG, Lee MC-H, et al. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. *Resuscitation*. 2017;114:92–9.
9. Aichinger G, Zechner PM, Prause G, Sacherer F, Wildner G, Anderson CL, et al. Cardiac movement identified on prehospital echocardiography predicts outcome in cardiac arrest patients. *Prehosp Emerg Care*. 2012;16:251–5.
10. Kim HB, Suh JY, Choi JH, Cho YS. Can serial focussed echocardiographic evaluation in life support (FEEL) predict resuscitation outcome or termination of resuscitation (TOR)? A pilot study. *Resuscitation*. 2016;101:21–6.
11. Gaspari R, Weekes A, Adhikari S, Noble VE, Nomura JT, Theodoro D, et al. Emergency department point-of-care ultrasound in out-of-hospital and in-hospital cardiac arrest. *Resuscitation*. 2016;109:33–9.
12. Huis In 't Veld MA, Allison MG, Bostick DS, Fisher KR, Golubeva OG, Witting MD, et al. Ultrasound use during cardiopulmonary resuscitation is associated with delays in chest compressions. *Resuscitation*. 2017;119:95–8.

1  
2 1 Luc G, Baert V, Escutnaire J, *et al.* Epidemiology of out-of-hospital cardiac arrest: A  
3 French national incidence and mid-term survival rate study. *Anaesth Crit Care Pain Med*  
4 Published Online First: 21 April 2018. doi:10.1016/j.accpm.2018.04.006  
5  
6 2 Nicolas G, Lecomte D. [Sudden cardiac death in adults. Epidemiology]. *Bull Acad Natl*  
7 *Med* 1999;**183**:1573–9; discussion 1579-1580.  
8  
9 3 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients with  
10 Out-of-Hospital Cardiac Arrest. <http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1010076>.  
11 2011. doi:10.1056/NEJMoa1010076  
12  
13 4 Les statistiques publiques | RéAC. [http://registreac.org/?page\\_id=2822](http://registreac.org/?page_id=2822)  
14  
15 5 Soar J, Nolan JP, Böttiger BW, *et al.* European Resuscitation Council Guidelines for  
16 Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;**95**:100–  
17 47. doi:10.1016/j.resuscitation.2015.07.016  
18  
19 6 Breitzkreutz R, Price S, Steiger HV, *et al.* Focused echocardiographic evaluation in life  
20 support and peri-resuscitation of emergency patients: a prospective trial. *Resuscitation*  
21 2010;**81**:1527–33. doi:10.1016/j.resuscitation.2010.07.013  
22  
23 7 Blyth L, Atkinson P, Gadd K, *et al.* Bedside Focused Echocardiography as Predictor of  
24 Survival in Cardiac Arrest Patients: A Systematic Review. *Academic Emergency Medicine*  
25 2012;**19**:1119–26. doi:10.1111/j.1553-2712.2012.01456.x  
26  
27 8 Tsou P-Y, Kurbedin J, Chen Y-S, *et al.* Accuracy of point-of-care focused  
28 echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A  
29 systematic review and meta-analysis. *Resuscitation* 2017;**114**:92–9.  
30 doi:10.1016/j.resuscitation.2017.02.021  
31  
32 9 Aichinger G, Zechner PM, Prause G, *et al.* Cardiac movement identified on prehospital  
33 echocardiography predicts outcome in cardiac arrest patients. *Prehosp Emerg Care*  
34 2012;**16**:251–5. doi:10.3109/10903127.2011.640414  
35  
36 10 Kim HB, Suh JY, Choi JH, *et al.* Can serial focussed echocardiographic evaluation in life  
37 support (FEEL) predict resuscitation outcome or termination of resuscitation (TOR)? A  
38 pilot study. *Resuscitation* 2016;**101**:21–6. doi:10.1016/j.resuscitation.2016.01.013  
39  
40 11 Gaspari R, Weekes A, Adhikari S, *et al.* Emergency Department Point-of-care Ultrasound  
41 in Out-of-Hospital and in-ED Cardiac Arrest. *Resuscitation* Published Online First: 27  
42 September 2016. doi:10.1016/j.resuscitation.2016.09.018  
43  
44 12 Huis In 't Veld MA, Allison MG, Bostick DS, *et al.* Ultrasound use during cardiopulmonary  
45 resuscitation is associated with delays in chest compressions. *Resuscitation*  
46 2017;**119**:95–8. doi:10.1016/j.resuscitation.2017.07.021  
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2 13 Lapostolle F, Le Conte P P, Arnaudet I, *et al.* Point-of-care ultrasound during advanced  
3 cardiopulmonary resuscitation: rule of art has to be respected! *Resuscitation* Published  
4 Online First: 28 October 2017. doi:10.1016/j.resuscitation.2017.10.022  
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**Authors' contributions**

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

**Funding**

ACE is supported by a €193,000 grant from the French Ministry for Health (PHRC-IR 2017), grant number API17/N/035. ACE is currently supported by the French Society of Emergency Medicine (Société Française de Médecine d'Urgence) and by Winfocus France without funding. There is ongoing discussions with Philips and Sonosite for the loan of echographic devices in order to increase the number of available devices for prehospital teams. Funders have no role in the ACE study.

**Competing interests statement**

There was no conflict of interest for all contributors

**Word count**

3009 words

**Potentially eligible patients**

OHCA BMJ Open  
> 18 years old  
ALS started

**Exclusion criteria**

DNR order  
Pregnancy, breastfeeding  
Inmaters  
No ALS

Eligible patients

EPOCE

Asystole present

Asystole absent

ROSC absent

ROSC present

ROSC absent

ROSC present

True positive

False positive

False negative

True negative



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
<b>Methods: Assignment of interventions (for controlled trials)</b>			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA



Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
<b>Methods: Data collection, management, and analysis</b>			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND
<b>Ethics and dissemination</b>			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study: study protocol

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<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

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**Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests, prospective multicenter observational study: study protocol**

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## Abstract

## Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France. Their management is performed by a particular prehospital system based on medicalisation of both ambulance dispatch and mobile intensive care units composed by an emergency physician and an emergency nurse with all the required devices for advanced care. It follows the European recommendations [1] which advocate for the use of early point-of-care focused echocardiography (EPOCE) in the pre-hospital setting, in particular to identify reversible causes of OHCA. Another ability of EPOCE may be to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion.

## Methods

Our trial, The ACE trial, aims to assess the positive predictive value of absence of cardiac motion viewed with EPOCE for the absence of final ROSC. It is a prospective multicentre (n=8) prognosis study which will recruit a large sample of patients (n=624). Briefly, once the diagnosis of OHCA done and advanced life-support (ALS) initiated, an EPOCE will be performed during the defibrillator's analysis period. The physician will notice presence or not of cardiac motion and will look for a reversible cause. Since the prognosis value of absence of cardiac motion is not currently validated, the EPOCE results will not be used for ALS termination. It will be done following European Resuscitation Council rules. ROSC will be assessed for the study purpose at this moment.

## Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion for the absence of final ROSC. Secondary endpoints are predictive characteristics of EPOCE on

morbimortality 30 days after OHCA, description of reversible cause, analysis of EPOCE technique.

**Ethic**

ACE was approved by an ethical committee (2018-AO1491-54)

**Dissemination**

While ACE is adapted to the French prehospital system, its results will be translatable to other organisations if inter-rater variability is not found. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE for the absence of final ROSC will be the same.

**Trial status**

ACE has received a grant from the French Minister for Health, was registered in clinicaltrials.gov (NCT03494153) in 2018

**Keywords :**

Cardiac arrest, prognosis, cardiac ultrasound

## Strength and limitations of the study

- Strengths
  - Broad inclusion criteria that would allow an extrapolation to rather all OHCA
  - High planned number of patients
  - Previous pilot study demonstrated the feasibility of this protocol
  - Verification of protocol's respect by the video recording
- Limitations
  - Cardiac massage interruption will be monitored in 3 centers out of 8
  - Planned missed patients rate of 15%: what characteristics for these patients? What consequences on results?
  - Observational not interventional study

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Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5 to 6% of patients will leave the hospital alive with satisfying neurological condition [2] [3] [4]. Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drugs administration, and defibrillation if needed) [1] [5] Based on published studies [6] [7] [8], 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in in the pre-hospital setting, in particular to identify reversible causes of OHCA [1] [6]. Indeed, POCE can reveal various reversible causes such as tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax [6] [7]. Their identification allows the clinician to better adjust his therapeutic strategy and, accordingly, might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) at the end of advanced life support (ALS) procedure in cases of absence of cardiac motion. ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse in the Utstein registries recommendation [9]. Several studies found a strong correlation between absence of cardiac motion and absence of ROSC [6] [7] [8] [10] [11]. This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delays, management, and environment. In this context, the European Resuscitation Council (ERC) stated in 2015



that, while the absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment for determination of premature termination of resuscitation is currently not recommended until publication of a pivotal study.

## Methods and analysis

### Objectives

The ACE French national trial fits precisely into this bibliographic gap, uncertainty on diagnosis value of absence of cardiac motion for absence of final ROSC. Our objectives are multiple:

- The main objective is to assess the positive predictive value of EPOCE (EPOCE; i.e. < 12 min after initiation of ALS) for the absence of final ROSC
- Secondary objectives are:
  1. assess the prognostic value of EPOCE on survival at hospital admission and on morbidity at Day 30 after the OHCA (D30),
  2. assess prognostic performances of EPOCE for the absence of final ROSC,
  3. assess prognostic values of EPOCE according to timing of initiation,
  4. assess the relationship between EPOCE findings and ECG rhythms,
  5. describe frequency and typology of reversible causes in the context of OHCA,
  6. describe EPOCE characteristics: timing, quality assessed by the operator, and by an expert committee,
  7. assess prognostic performances of EPOCE in patients with ventricular tachycardia,
  8. creation of a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography,

1 no/low flow duration, and clinical profile including sex and age for the absence of final  
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4 ROSC, and  
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7 9. measurement of the cardiac massage interruption associated with EPOCE realisation  
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9 by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

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11 Design

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13 ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous  
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15 methodology (prospective observational study with a unique protocol), has a high proof-  
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17 level design, and will recruit a large sample of patients ( $n = 624$ ). The SPIRIT check-list is  
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19 in Supplementary files. Recruiting centres include both rural and urban community and  
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21 university hospitals. This pragmatic approach intends to validate the performance of  
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23 EPOCE for the prediction of absence of final ROSC in cases of absence of cardiac motion  
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25 in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays  
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27 before extracorporeal membrane oxygenation (ECMO) or organ donation processes.

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29 Echographic asystole is defined by the complete absence of cardiac motion (coordinated  
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31 or fibrillation) and the absence of valve movements.

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36 Methods

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38 Patients

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40 Inclusion criteria: all patients > 18 years old presenting with an OHCA for whom an  
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42 EPOCE could be initiated in less than 12 min after ALS initiation

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44 Non-inclusion criteria: do not resuscitate order, ROSC prior EPOCE, ALS not performed  
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46 by the prehospital team, pregnancy, breastfeeding women, and inmates.

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49 Procedure

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51 After verification of inclusion and exclusion criteria, advanced life support intervention will  
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53 replace basic life support with an overlap period, as usual (Figure 1). ALS will be  
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55 performed according to the latest ERC regulations. Once standard ALS interventions are  
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done, according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations [4, 5], FEEL protocol was designed and evaluated in a prospective observational study using an ALS compliant focused echocardiography. Briefly, once arrived on scene, CPR was started, ECG performed and a clinical diagnosis established. A focused echocardiography was then realized. Outcome defined as survival to admission was better regardless of initial rhythm when cardiac motion was present. the physician will perform a POCE during the defibrillator's analysis period, thus in less than 10 seconds. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will notice cardiac motion or lack thereof and will look for reversible causes. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random reviewing by an expert committee. The whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic delays (defined as the interval between arrival time on scene and therapeutic initiations). ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. For the study purpose, presence or absence of ROCS will be assessed after ALS termination. In the case of ROCS, the hospital course will be described. At D30, vital status of all patients will be assessed by either hospital file consult or phone call if the patient is still alive. For them, autonomy will be assessed using the Glasgow Outcome Scale. These two events (dead or alive and Glasgow Outcome Scale) define the morbimortality. They will be assessed by the research team of Nantes Hospital.

## **Endpoints**

### **Primary endpoint**

- Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the

1  
2 predictive positive value (PPV) as the primary endpoint because we wish to limit the  
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4 number of false positives as much as possible in order to isolate a population  
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6 without ROCS with EPOCE asystole.  
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9 **Secondary endpoints**

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11 1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS  
12 initiation) on hospital admission and on morbi-mortality (defined as dead or alive  
13 and Glasgow Outcome Scale) evaluated at 30 days.  
14  
15 2. Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for  
16 the absence of final ROSC.  
17  
18 3. Sensitivity, specificity, and positive and negative predictive values of EPOCE  
19 asystole for the absence of final ROSC according to their timing of initiation after  
20 ALS initiation (by 2 min).  
21  
22 4. Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram  
23 electrical activity (pulse less activity, asystole, ventricular fibrillation, and ventricular  
24 tachycardia).  
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26 5. Description of reversible causes (tamponade, massive pulmonary embolism, deep  
27 hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset  
28 and diagnosis) and therapeutic delays (time between ALS onset and specific  
29 therapeutic intervention), and the effectiveness of implemented curative strategies  
30 defined by association with ROCS and 30 day morbimortality.  
31  
32 6. Analysis of EPOCE technique during OHCA resuscitation: duration, quality of the  
33 video clips assessed by the operator (from 0 = impossible to 10 = excellent), and an  
34 expert committee reviewing a 10% random sample.  
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36 7. Sensitivity, specificity, and positive and negative predictive values of EPOCE  
37 asystole to predict ROSC absence in patients with ventricular fibrillation.  
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8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity, and cardiac motion) associated with the absence of ROSC in order to determine a score with a 100% PPV.
9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).

### ***Recruiting centres***

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

### ***Sample size calculation***

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of final ROSC. For a PPV of  $95 \pm 3\%$ , 203 patients without cardiac motion are required. Based on 37.5% asystole rate [10], 542 total patients are required. Taking into account that EPOCE could not be performed in 15% of OHCA, the required population will, finally, be 624 patients.

### ***Recruitment***

Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound and already use this technique in their emergency department. A monthly newsletter will be published with individual and global recruitment trends. Patients will be followed-up until day 30 and defined gradually as: survival without neurological deficit, survival with neurological deficit, or death.

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**Data management**

Electronic case report files will be used via a web-based interface and video clips will be uploaded. All data will be stored in the Nantes University Hospital secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be only available to the steering committee.

**Monitoring**

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

**Statistical analysis**

Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will be estimated to analyse the time of EPOCE initiation that allows the best prognostic performances for the absence of final ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. reversible causes, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be: myocardial and/or electrical

activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS version 9.4 ®.

## **Ethics**

The ACE trial has been approved by the ethics committee (Comité de Protection des Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their recommendations, patient and/or legal authority consent will be requested only for survivors. Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' consent. Regarding the very low survival rate of patients with OHCA (5%), anonymised database, and family induced traumatism, we have asked for a derogation to surrogates information for deceased patients. A consent will be requested for surviving patients.

## **Dissemination**

We intend to publish ACE results in a major journal of Emergency Medicine, raw data will be available on reasonable request

## **Patient and Public Involvement**

The patient's involvement will be to participate to the study when included after an OHCA. There will no public involvement for this study.

## **Discussion**

There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA. Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures without waiting for a median time of 30 min after ALS onset. Conversely, in



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cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for reversible causes.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols [6] [7] [8] [10]. A multicentre study was performed but EPOCE was performed in the ED even the cardiac arrest occurred out-of-hospital [12] This was stated by the European Resuscitation Council in its 2015 recommendations [1]. ACE is adapted to the particularities of the French prehospital system but its results will be translatable to other organisations such as European or American ones.

ACE has the potential to provide a definitive response to this question. Furthermore, it will answer the question of frequency of reversible causes and their management. This question also needs hard evidence, ACE has the potential to provide this since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions [13] that would alter the prognosis. However, the training of physicians in POCE in this study was not reported [13] [14]. This study was performed in the United States and it might be assumed that the training was in line with established residency training requirement. Anyway, this potential flaw has to be addressed; in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

**Availability of data and material**

Data will be available upon reasonable request.



## References

- 1 Soar J, Nolan JP, Böttiger BW, *et al.* European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;**95**:100–47. doi:10.1016/j.resuscitation.2015.07.016
- 2 Luc G, Baert V, Escutnaire J, *et al.* Epidemiology of out-of-hospital cardiac arrest: A French national incidence and mid-term survival rate study. *Anaesth Crit Care Pain Med* Published Online First: 21 April 2018. doi:10.1016/j.accpm.2018.04.006
- 3 Nicolas G, Lecomte D. [Sudden cardiac death in adults. Epidemiology]. *Bull Acad Natl Med* 1999;**183**:1573–9; discussion 1579-1580.
- 4 Les statistiques publiques | RéAC. [http://registreac.org/?page\\_id=2822](http://registreac.org/?page_id=2822)
- 5 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest. *Resuscitation* 2011. doi:10.1056/NEJMoa1010076
- 6 Breitzkreutz R, Price S, Steiger HV, *et al.* Focused echocardiographic evaluation in life support and peri-resuscitation of emergency patients: a prospective trial. *Resuscitation* 2010;**81**:1527–33. doi:10.1016/j.resuscitation.2010.07.013
- 7 Blyth L, Atkinson P, Gadd K, *et al.* Bedside Focused Echocardiography as Predictor of Survival in Cardiac Arrest Patients: A Systematic Review. *Academic Emergency Medicine* 2012;**19**:1119–26. doi:10.1111/j.1553-2712.2012.01456.x
- 8 Tsou P-Y, Kurbedin J, Chen Y-S, *et al.* Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A systematic review and meta-analysis. *Resuscitation* 2017;**114**:92–9. doi:10.1016/j.resuscitation.2017.02.021
- 9 Jacobs Ian, Nadkarni Vinay, null null, *et al.* Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports. *Circulation* 2004;**110**:3385–97. doi:10.1161/01.CIR.0000147236.85306.15
- 10 Aichinger G, Zechner PM, Prause G, *et al.* Cardiac movement identified on prehospital echocardiography predicts outcome in cardiac arrest patients. *Prehosp Emerg Care* 2012;**16**:251–5. doi:10.3109/10903127.2011.640414
- 11 Kim HB, Suh JY, Choi JH, *et al.* Can serial focussed echocardiographic evaluation in life support (FEEL) predict resuscitation outcome or termination of resuscitation (TOR)? A pilot study. *Resuscitation* 2016;**101**:21–6. doi:10.1016/j.resuscitation.2016.01.013
- 12 Gaspari R, Weekes A, Adhikari S, *et al.* Emergency Department Point-of-care Ultrasound in Out-of-Hospital and in-ED Cardiac Arrest. *Resuscitation* Published Online First: 27 September 2016. doi:10.1016/j.resuscitation.2016.09.018

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13 Huis In 't Veld MA, Allison MG, Bostick DS, *et al.* Ultrasound use during cardiopulmonary resuscitation is associated with delays in chest compressions. *Resuscitation* 2017;**119**:95–8. doi:10.1016/j.resuscitation.2017.07.021

14 Lapostolle F, Le Conte P P, Arnaudet I, *et al.* Point-of-care ultrasound during advanced cardiopulmonary resuscitation: rule of art has to be respected! *Resuscitation* Published Online First: 28 October 2017. doi:10.1016/j.resuscitation.2017.10.022

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Enseignement Supérieur (ABES).

## Authors' contributions

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

## Funding

ACE is supported by a €193,000 grant from the French Ministry for Health (PHRC-IR 2017), grant number API17/N/035. ACE is currently supported by the French Society of Emergency Medicine (Société Française de Médecine d'Urgence) and by Winfocus France without funding. There is ongoing discussions with Philips and Sonosite for the loan of echographic devices in order to increase the number of available devices for prehospital teams. Funders have no role in the ACE study.

## Competing interests statement

There was no conflict of interest for all contributors

## Word count

3267 words

Figure 1 legend : patient's flow chart of ACE trial

# Potentially eligible patients

OHCA BMJ Open  
> 18 years old  
ALS started

## Exclusion criteria

DNR order  
Pregnancy, breastfeeding  
Inmaters  
No ALS

Eligible patients

EPOCE

Asystole present

Asystole absent

ROSC absent

ROSC present

ROSC absent

ROSC present

True positive

False positive

False negative

True negative



## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

1	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
2				
3	<b>Methods: Participants, interventions, and outcomes</b>			
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
5	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for sites/centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
6	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
7		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
8		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
9		11d	Relevant concomitant care and interventions that are permitted or prohibited during trial	NA
10	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
12	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
14	<b>Methods: Assignment of interventions (for controlled trials)</b>			
15	Allocation:			
16	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
<b>Methods: Data collection, management, and analysis</b>			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors), and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND

<b>Ethics and dissemination</b>				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval		7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)		7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, shared, and maintained in order to protect confidentiality before, during, and after the trial		6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site		7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators		6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		
	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code		NA
<b>Appendices</b>				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates		NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable		NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.



# BMJ Open

## Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study: study protocol

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<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

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**Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests, prospective multicenter observational study: study protocol**

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## Abstract

## Introduction

Management of Out-of-hospital cardiac arrests (OHCA) in France is performed by a particular prehospital system based on medicalisation of mobile intensive care units composed by emergency physician and nurse with all the required devices for advanced care. It follows the European recommendations which advocate for the use of early point-of-care focused echocardiography (EPOCE) in the pre-hospital setting. An ability of EPOCE may be to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion. We thus intended to investigate this predicting value with a prospective multicenter study. This paper describes the study protocol while the first patients were included in December 2018.

## Methods

ACE is a prospective multicentre (n=8) prognosis study. Briefly, as soon as the OHCA is diagnosed and advanced life-support (ALS) initiated, EPOCE will be performed during an analysis period of the automated external defibrillator. The physician will assess detectable motion within the heart and reversible causes of OHCA. However, as the prognosis value of absence of cardiac motion is not currently validated, the EPOCE results will not be used to withdraw ALS, and decision to withdraw life support will be done following European Resuscitation Council recommendations during our study.

## Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion for the absence of final ROSC. Secondary endpoints are predictive characteristics of EPOCE asystole on morbimortality 30 days after OHCA, description of reversible cause, analysis of EPOCE technique.

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246Ethic

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547ACE was approved by an ethical committee (2018-AO1491-54)

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848Dissemination

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1149While ACE is adapted to the French prehospital system, its results will be translatable to

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1350other organisations if inter-rater variability is not found.

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1651Trial status

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1952ACE has received a grant from the French Minister for Health, was registered in

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2153clinicaltrials.gov (NCT03494153) in 2018

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2454Keywords :

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2755Cardiac arrest, prognosis, cardiac ultrasound

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## Strength and limitations of the study

- Strengths

- Broad inclusion criteria that would allow an extrapolation to rather all OHCA
- High planned number of patients
- Previous pilot study demonstrated the feasibility of this protocol

- Limitations

- Cardiac massage interruption will be monitored in 3 centers out of 8
- Observational not interventional study

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2 65 **Introduction**  
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5 66 Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between  
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7 67 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5  
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9 68 to 6% of patients will leave the hospital alive with satisfying neurological condition [2] [3]  
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11 69 [4]. Their management in France is performed by a particular prehospital system based on  
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14 70 medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units  
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16 71 (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac  
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18 72 rhythm analysis, drugs administration, and defibrillation if needed) [1] [5] Based on  
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21 73 published studies [6] [7] [8], 2015 European recommendations advocate for the use of  
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23 74 point-of-care focused echocardiography (POCE) in in the pre-hospital setting, in particular  
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25 75 to identify reversible causes of OHCA [1] [6]. Indeed, POCE can reveal various reversible  
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28 76 causes such as tamponade, massive pulmonary embolism, deep hypovolaemia, or  
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30 77 suffocating pneumothorax [6] [7]. Their identification allows the clinician to better adjust his  
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32 78 therapeutic strategy and, accordingly, might improve the patient's prognosis.  
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35 79 Another ability of POCE is to predict the absence of return of spontaneous circulation  
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37 80 (ROSC) at the end of advanced life support (ALS) procedure in cases of absence of  
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39 81 cardiac motion. ROSC was defined as a spontaneous cardiac rhythm accompanied by  
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41 82 breathing, coughing, movements or fleeting palpated pulse in the Utstein registries  
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44 83 recommendation [9]. Several studies found a strong correlation between absence of  
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46 84 cardiac motion and absence of ROSC [6] [7] [8] [10] [11]. This fact deeply impacts  
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48 85 extracorporeal circulation indications and organ donation procedures. However, these  
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51 86 studies, mainly performed in a hospital setting, included rather small populations and used  
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53 87 different cardiac motion definitions and procedures. Furthermore, they cannot be  
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55 88 extrapolated to OHCA because of differences in terms of delays, management, and  
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58 89 environment. In this context, the European Resuscitation Council (ERC) stated in 2015  
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that, while the absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment for determination of premature termination of resuscitation is currently not recommended until publication of a pivotal study.

## Methods and analysis

### Objectives

The ACE French national trial fits precisely into this bibliographic gap, uncertainty on diagnosis value of absence of cardiac motion for absence of final ROSC. Our objectives are multiple:

- The main objective is to assess the positive predictive value of EPOCE asystole for the absence of final ROSC
- Secondary objectives are:
  1. assess the prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on survival at hospital admission and on morbi-mortality at Day 30 after the OHCA (D30),
  2. assess prognostic performances of EPOCE asystole for the absence of final ROSC,
  3. assess prognostic values of EPOCE asystole according to timing of initiation after ALS initiation (by 2 min increment).
  4. assess the relationship between EPOCE findings and ECG rhythms,
  5. describe frequency and typology of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax) in the context of OHCA,
  6. describe EPOCE characteristics: timing, quality assessed by the operator, and by an expert committee,
  7. assess prognostic performances of EPOCE in patients with ventricular tachycardia,





After verification of inclusion and exclusion criteria, advanced life support intervention will replace basic life support with an overlap period, as usual (Figure 1). ALS will be performed according to the latest ERC regulations including realisation of an ECG. Once standard ALS interventions are done according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations [4, 5]. FEEL protocol was designed and evaluated in a prospective observational study using an ALS compliant focused echocardiography. Briefly, once arrived on scene, if the patient was in cardiac arrest, CPR was started, ECG performed and a clinical diagnosis established. A focused echocardiography was then realized. Outcome defined as survival to admission was better regardless of initial rhythm when cardiac motion was present. In our study, the physician will perform a EPOCE during the defibrillator's analysis period, thus in less than 10 seconds. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will notice cardiac motion or lack thereof and will look for reversible causes. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random reviewing by an expert committee. The whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic delays (defined as the interval between arrival time on scene and therapeutic initiations). ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. For the study purpose, presence or absence of ROCS will be assessed after ALS termination. In the case of ROCS, the hospital course (Intensive care unit, medicine ward..) will be described. At D30, vital status of all patients will be assessed by either hospital file consult or phone call if the patient is still alive. For them, autonomy will be assessed using the Glasgow Outcome Scale. These two events (dead or alive and Glasgow Outcome Scale) define the morbimortality. They will be assessed by the research team of Nantes Hospital. In three

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2 163 centres, the whole resuscitation procedure will be monitored via a mobile video recorder.  
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4 164 Video clips will be uploaded and analysed in order to measure the duration of cardiac  
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6 165 massage interruptions.  
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10 166 **Endpoints**

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12 167 **Primary endpoint**

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  - Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of
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  - 17 169 ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the
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  - 19 170 predictive positive value (PPV) as the primary endpoint because we want to isolate a
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  - 21 171 population without ROCS with EPOCE asystole.
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24 172 **Secondary endpoints**

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  1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS
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  - 28 174 initiation) on hospital admission and on morbi-mortality (defined as dead or alive
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  - 30 and Glasgow Outcome Scale) evaluated at 30 days.
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  - 33 176 2. Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for
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  - 35 177 the absence of final ROSC.
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  - 37
  - 38 178 3. Sensitivity, specificity, and positive and negative predictive values of EPOCE
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  - 40 179 asystole for the absence of final ROSC according to their timing of initiation after
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  - 42 180 ALS initiation (by 2 min).
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  - 45 181 4. Association between the ultrasound asystole rate according to the cardiac electrical
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  - 47 182 activity (pulse less activity, asystole, ventricular fibrillation, and ventricular
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  - 49 183 tachycardia)
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  - 51 184 5. Description of reversible causes (tamponade, massive pulmonary embolism, deep
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  - 53 hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset
  - 54 185 and diagnosis) and therapeutic delays (time between ALS onset and specific
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therapeutic intervention), and the effectiveness of implemented curative strategies defined by association with ROCS and 30 day morbimortality.

6. Analysis of EPOCE technique during OHCA resuscitation: duration, whole quality of the video clips assessed by the operator on a predetermined scale (from 0 = impossible to 10 = excellent), and an expert committee reviewing a 10% random sample.
7. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in the sub-group of patients with ventricular fibrillation on the ECG.
8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity, and cardiac motion) associated with the absence of ROSC in order to determine a score with a 100% PPV.
9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).

### ***Recruiting centres***

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

### ***Sample size calculation***

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of final ROSC. To specify the width of the confidence interval at  $\pm 3\%$  with a 95% PPV, 203 patients without cardiac motion are required. Based on 37.5% ultrasound asystole rate [10], 542 total patients are required. Taking into account a +15% attrition rate (incomplete

1  
2 210 data, too poor quality of the ultrasound for interpretation, etc...), the required population  
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4 211 will, finally, be 624 patients.  
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7 212 **Recruitment**  
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10 213 Chosen prehospital teams were recruited because they are highly skilled in clinical  
11  
12 214 ultrasound and already use this technique in their emergency department. A monthly  
13  
14 215 newsletter will be published with individual and global recruitment trends. Patients will be  
15  
16  
17 216 followed-up until day 30 and defined gradually as: survival without neurological deficit,  
18  
19 217 survival with neurological deficit, or death.  
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21

22 218 **Data management**  
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25 219 Electronic case report files will be used via a web-based interface and video clips will be  
26  
27 220 uploaded. All data will be stored in the Nantes University Hospital secured databases. The  
28  
29 221 data management team will be responsible for the entire process. Data will be anonymised  
30  
31  
32 222 with an incremental number assigned to each patient. The final database will be only  
33  
34 223 available to the steering committee. Subjects with missing data for the primary endpoint  
35  
36 224 will not be analyzed (+15% subjects in sample size calculation)  
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38

39 225 **Monitoring**  
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42 226 Monitoring will be performed both by electronic surveillance of recruitment and data  
43  
44 227 quality. It will be done by the Clinical Research Department of Nantes University Hospital.  
45  
46

47 228 **Statistical analysis**  
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50 229 Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation  
51  
52 230 failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence  
53  
54 231 interval. Logistic model regression and receiver operating characteristic (ROC) curve will  
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57 232 be estimated to analyse the time of EPOCE initiation that allows the best prognostic  
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performances for the absence of final ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. reversible causes, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be: myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS version 9.4 ®.

### **Ethics**

The ACE trial has been approved by the ethics committee (Comité de Protection des Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their recommendations, patient and/or legal authority consent will be requested only for survivors. Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' consent. Regarding the very low survival rate of patients with OHCA (5%), anonymised database, and family induced traumatism, we have asked for a derogation to surrogates information for deceased patients. A consent will be requested for surviving patients.

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2 256 **Dissemination**  
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5 257 We intend to publish ACE results in a major journal of Emergency Medicine, raw data will  
6  
7 258 be available on reasonable request  
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10 259 **Patient and Public Involvement**  
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12  
13 260 Patients and public had no involvement in the design or the planning of the study  
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16 261 **Discussion**  
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18  
19 262 There is a strong rationale for the interest of early diagnosis of absence of ROSC in  
20  
21 263 OHCA. Actually, it might allow to prematurely initiate ECMO indications or organ donation  
22  
23 264 procedures without waiting for a median time of 30 min after ALS onset. Conversely, in  
24  
25 265 cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams  
26  
27 266 might search for reversible causes.  
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30 267 Hard evidence is currently missing in the literature since the majority of published studies  
31  
32 268 included small series of patients, in the hospital, and used different protocols [6] [7] [8]  
33  
34 269 [10]. A multicentre study was performed but EPOCE was performed in the ED even the  
35  
36 270 cardiac arrest occurred out-of-hospital [12] This was stated by the European Resuscitation  
37  
38 271 Council in its 2015 recommendations [1]. ACE is adapted to the particularities of the  
39  
40 272 French prehospital system but its results will be translatable to other organisations such as  
41  
42 273 European or American ones.  
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45  
46 274 ACE has the potential to provide a definitive response to this question. Furthermore, it will  
47  
48 275 answer the question of frequency of reversible causes and their management. This  
49  
50 276 question also needs hard evidence, ACE has the potential to provide this since it will  
51  
52 277 include 624 non-selected patients with OHCA.  
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56 278 POCE has been associated with delays in chest compressions [13] that would alter the  
57  
58 279 prognosis. However, the training of physicians in POCE in this study was not reported [13]  
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60

[14]. This study was performed in the United States and it might be assumed that the training was in line with established residency training requirement. Anyway, this potential flaw has to be addressed; in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

#### **Availability of data and material**

Data will be available upon reasonable request.

For peer review only



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2 286 **References**

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4  
5 1 Soar J, Nolan JP, Böttiger BW, *et al.* European Resuscitation Council Guidelines for  
6 Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation*  
7 2015;**95**:100–47. doi:10.1016/j.resuscitation.2015.07.016  
8  
9 2 Luc G, Baert V, Escutnaire J, *et al.* Epidemiology of out-of-hospital cardiac arrest: A  
10 French national incidence and mid-term survival rate study. *Anaesth Crit Care Pain*  
11 *Med* Published Online First: 21 April 2018. doi:10.1016/j.accpm.2018.04.006  
12  
13 3 Nicolas G, Lecomte D. [Sudden cardiac death in adults. Epidemiology]. *Bull Acad Natl*  
14 *Med* 1999;**183**:1573–9; discussion 1579-1580.  
15  
16 4 Les statistiques publiques | RéAC. [http://registreac.org/?page\\_id=2822](http://registreac.org/?page_id=2822)  
17  
18 5 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients  
19 with Out-of-Hospital Cardiac Arrest. 2011.  
20 <http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1010076>.  
21 doi:10.1056/NEJMoa1010076  
22  
23 6 Breitzkreutz R, Price S, Steiger HV, *et al.* Focused echocardiographic evaluation in life  
24 support and peri-resuscitation of emergency patients: a prospective trial. *Resuscitation*  
25 2010;**81**:1527–33. doi:10.1016/j.resuscitation.2010.07.013  
26  
27 7 Blyth L, Atkinson P, Gadd K, *et al.* Bedside Focused Echocardiography as Predictor of  
28 Survival in Cardiac Arrest Patients: A Systematic Review. *Academic Emergency*  
29 *Medicine* 2012;**19**:1119–26. doi:10.1111/j.1553-2712.2012.01456.x  
30  
31 8 Tsou P-Y, Kurbedin J, Chen Y-S, *et al.* Accuracy of point-of-care focused  
32 echocardiography in predicting outcome of resuscitation in cardiac arrest patients: A  
33 systematic review and meta-analysis. *Resuscitation* 2017;**114**:92–9.  
34 doi:10.1016/j.resuscitation.2017.02.021  
35  
36 9 Jacobs Ian, Nadkarni Vinay, null null, *et al.* Cardiac Arrest and Cardiopulmonary  
37 Resuscitation Outcome Reports. *Circulation* 2004;**110**:3385–97.  
38 doi:10.1161/01.CIR.0000147236.85306.15  
39  
40 10 Aichinger G, Zechner PM, Prause G, *et al.* Cardiac movement identified on prehospital  
41 echocardiography predicts outcome in cardiac arrest patients. *Prehosp Emerg Care*  
42 2012;**16**:251–5. doi:10.3109/10903127.2011.640414  
43  
44 11 Kim HB, Suh JY, Choi JH, *et al.* Can serial focussed echocardiographic evaluation in  
45 life support (FEEL) predict resuscitation outcome or termination of resuscitation  
46 (TOR)? A pilot study. *Resuscitation* 2016;**101**:21–6.  
47 doi:10.1016/j.resuscitation.2016.01.013  
48  
49 12 Gaspari R, Weekes A, Adhikari S, *et al.* Emergency Department Point-of-care  
50 Ultrasound in Out-of-Hospital and in-ED Cardiac Arrest. *Resuscitation* Published  
51 Online First: 27 September 2016. doi:10.1016/j.resuscitation.2016.09.018  
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- 1  
2 13 Huis In 't Veld MA, Allison MG, Bostick DS, *et al.* Ultrasound use during  
3 cardiopulmonary resuscitation is associated with delays in chest compressions.  
4 *Resuscitation* 2017;**119**:95–8. doi:10.1016/j.resuscitation.2017.07.021  
5  
6 14 Lapostolle F, Le Conte P P, Arnaudet I, *et al.* Point-of-care ultrasound during advanced  
7 cardiopulmonary resuscitation: rule of art has to be respected! *Resuscitation* Published  
8 Online First: 28 October 2017. doi:10.1016/j.resuscitation.2017.10.022  
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**Authors' contributions**

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

**Funding**

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**Competing interests statement**

There was no conflict of interest for all contributors

**Word count**

3435 words

Figure 1 legend : patient's flow chart of ACE trial

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**Potentially eligible patients**  
OHCA BMJ Open  
> 18 years old  
ALS started

**Exclusion criteria**  
DNR order  
Pregnancy, breastfeeding  
Inmaters  
No ALS

Eligible patients

EPOCE

Asystole present

Asystole absent

ROSC absent

ROSC present

ROSC absent

ROSC present

True positive

False positive

False negative

True negative



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for sites/centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
<b>Methods: Assignment of interventions (for controlled trials)</b>			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
<b>Methods: Data collection, management, and analysis</b>			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors), and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND

## Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.