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# **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

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Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY
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	4	рі	ospective multicenter observational study				
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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. lt follows the European for recommendations which advocate 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.

# 31 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.

# 40 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.

# 45 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.

# 51 Trial status

52 ACE has received a grant from the French Minister for Health, was registered in 53 clinicaltrials.gov (RC17\_0464) on April 11, 2018

# 54 Keywords :

55 Cardiac arrest, prognosis, cardiac ultrasound

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Strength and limitations of the study

gth and limitations of the study
irst prospective multicentre prognosis study of Point-of-care Ultrasound in out-of-
nospital cardiac arrest
positive predictive value of early Point-of-care ultrasound absence of cardiac motion on
absence of return of spontaneous circulation
f positive, might allow for shorter delays before extracorporeal membrane oxygenation
or organ donation processes
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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) [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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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. Our objectives are multiple: The main objective is to assess the positive predictive value of early POCE (EPOCE; i.e. < 12 min after initiation of advanced life support (ALS)) on the absence of ROSC Secondary objectives are: 1. assess the prognostic value of early POCE on survival at hospital admission and 34 98 on morbi-mortality at Day 30 after the OHCA (D30), 2. assess prognostic performances of early POCE on the absence of ROSC, 3. assess prognostic values of EPOCE according to timing of realisation, assess the relationship between EPOCE findings and ECG rhythms, <sup>43</sup>102 5. describe frequency and typology of curable aetiologies 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 <sup>52</sup>106 tachycardia, 

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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 

<sup>11</sup>111 9. measurement of the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

#### Design <sup>19</sup>114

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 <sub>32</sub>119 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 <sup>36</sup>121 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. 

#### <sup>44</sup>124 **Methods**

Patients

performed.

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

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8 9 Non-inclusion criteria: do not resuscitate order, ALS not performed by the prehospital team,pregnancy, breastfeeding women, and inmates.

# 130 **Procedure**

<sup>10</sup>131 After verification of inclusion and exclusion criteria, advanced life support intervention will 11 12 1<sub>3</sub>132 replace basic life support with an overlap period, as usual. ALS will be performed according to 14 15133 the latest ERC regulations. Once standard ALS interventions are done, according to the 16 <sup>17</sup>134 echocardiographic evaluation in life support (FEEL) protocol and focused ERC 18 19 20<sup>135</sup> recommendations [4, 5], the physician will perform a POCE during the defibrillator's analysis 21 22136 period, thus in less than 10 seconds. It will be done using a phased array probe with a 23 <sup>24</sup>137 subcostal view. It has to be done as early as possible and always before 12 min after ALS 25 <sup>26</sup>138 initiation. The physician will notice cardiac motion or lack thereof and will look for curable 27 28 <sub>29</sub>139 aetiologies. Video clips will be stored in the echographic device and secondarily uploaded in 30 31140 the electronic case report file (eCRF) for random reviewing by an expert committee. The 32 <sup>33</sup>141 whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic 34 35 <sub>36</sub>142 delays. ALS will be terminated following ERC rules, the POCE results will not be used for that 37 38143 purpose. Presence or absence of ROCS will be assessed after ALS termination. In the case 39 <sup>40</sup>144 of ROCS, the hospital pathway will be described. At D30, vital status of all patients will be 41 42 145 assessed by either hospital file consult or phone call if the patient is still alive. For them, 43 44 45146 autonomy will be assessed using the Glasgow Outcome Scale. 46

# 48147 Endpoints

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51148 Primary endpoint

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1 2 <b>149</b>	•	Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of
3 4 150		ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the
5 7 7 151		predictive positive value (PPV) as the primary endpoint because we wish to limit the
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9 <b>152</b> 10		number of false positives as much as possible in order to isolate a population without
<sup>11</sup> 153 12		ROCS with POCE asystole.
<sup>13</sup> <sub>14</sub> 154	Seco	ndary endpoints
15 16 <b>155</b> 17	1.	Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS
<sup>18</sup> 156 19		initiation) on hospital admission and on morbimortality evaluated at 30 days.
<sup>20</sup> <sub>21</sub> 157	2.	Sensitivity, specificity, and positive (PPV) and negative predictive (NPV) values of
22 23 <b>158</b>		EPOCE asystole on absence of ROSC.
24 25 <b>159</b> 26	3.	Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole
<sup>27</sup> <sub>28</sub> 160		on absence of ROSC according to their timing of realisation after ALS initiation on the
<sup>29</sup> 30161		absence of ROSC (by 2 min).
31 32 <b>162</b> 33	4.	Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram
<sup>34</sup> 163		electrical activity (pulseless activity, asystole, ventricular fibrillation, and ventricular
<sup>36</sup> 37164		tachycardia).
38 39 <b>165</b>	5.	Description of curable aetiologies, diagnostic and therapeutic delays, and the
40 41 <b>166</b> 42		effectiveness of implemented curative strategies on ROCS and 30 day morbimortality.
<sup>43</sup> <sub>44</sub> 167	6.	Analysis of EPOCE technique during OHCA resuscitation: duration, quality of the video
45 46 <b>168</b>		clips assessed by the operator (from 0 = impossible to 10 = excellent), and an expert
47 48 <b>169</b> 49		committee reviewing a 10% random sample.
<sup>50</sup> 51 51	7.	Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole
<sup>52</sup> 53171		to predict ROSC absence in patients with ventricular fibrillation.
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1 2 <b>172</b> 3	8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow
4 173 5	duration, initial treatment, electrical activity, and cardiac motion) associated with the
6 7 174	absence of ROSC in order to determine a score with a 100% PPV.
8 9 <b>175</b> 10	9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using
<sup>11</sup> 176 <sub>12</sub>	a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).
13 <sup>14</sup> 177 15	Recruiting centres
<sup>16</sup> <sup>17</sup> 178 <sup>18</sup>	Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny)
<sup>19</sup> 20 21	and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).
<sup>22</sup> 23 28	Sample size calculation
<sup>25</sup> 26181	The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of
27 28 <b>182</b> 29	ROSC. For a PPV of 95 ± 3%, 203 patients without cardiac motion are required. Based on
<sup>30</sup> 183 <sub>31</sub>	37.5% asystole rate [10], 542 total patients are required. Taking into account a 15% attrition
<sup>32</sup> 33184 34	rate, the required population will, finally, be 624 patients.
<sup>35</sup> 36 37	Recruitment
<sup>38</sup> 39186	Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound
40 41 <b>187</b> 42	and already use this technique in their emergency department. A monthly newsletter will be
<sup>43</sup> 188 44	published with individual and global recruitment trends. Patients will be followed-up until day
<sup>45</sup> 46189	30 and defined gradually as: survival without neurological deficit, survival with neurological
47 48 <b>190</b> 49 50 51 52 53 54	deficit, or death.
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# Data management

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192 Electronic case report files will be used via a web-based interface and video clips will be 193 uploaded. All data will be stored in the Nantes University Hospital secured databases. The 10194 data management team will be responsible for the entire process. Data will be anonymised 12195 with an incremental number assigned to each patient. The final database will be only <sup>14</sup>196 available to the steering committee.

#### <sup>17</sup>197 Monitoring

<sup>20</sup>198 Monitoring will be performed both by electronic surveillance of recruitment and data quality. It <sub>23</sub>199 will be done by the Clinical Research Department of Nantes University Hospital.

# Statistical analysis

29**201** Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation 31202 failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence <sup>33</sup>.203 interval. Logistic model regression and receiver operating characteristic (ROC) curve will be <sub>36</sub>204 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 38205 <sup>40</sup>206 the association between ultrasound diagnosis and electrocardiogram electrical patterns. <sup>42</sup> 43</sub>207 Curable aetiologies, diagnostic and therapeutic delays, and the effectiveness of implemented 45208 curative strategies will be described. EPOCE technique during the OHCA resuscitation: 47209 duration and quality of the video clips will be described. Chi-squared and Student's tests will <sub>50</sub>210 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 52**211** 54212 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. 214 Parameters that will be taken into account will be: myocardial and/or electrical activity. 215 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 9 216 10 <sup>11</sup>217 less than 0.05 will be considered statistically significant. All analyses will be performed using 12 13 218 SAS version 9.4 ®. 14

#### Ethics 219

19 .) 20<sup>220</sup> The ACE trial has been approved by the ethics committee (Comité de Protection des 21 22**221** Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their 23 <sup>24</sup>222 recommendations, patient and/or legal authority consent will be requested only for survivors. 25 <sup>26</sup>223 Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' 27 28 29**224** consent. Regarding the very low survival rate of patients with OHCR (5%), anonymised 30 31225 database, and family induced traumatism, we have asked for a derogation to surrogates 32 <sup>33</sup>226 information for deceased patients. A consent will be requested for surviving patients. 34

#### <sup>36</sup>227 Dissemination

<sup>39</sup>228 We intend to publish ACE results in a major journal of Emergency Medicine, raw date will be 42229 available on reasonable request

#### Discussion 48231

<sup>51</sup>232 There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA. <sub>54</sub>233 Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures

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1 without waiting for a median time of 30 min after ALS onset. Conversely, in cases of cardiac 2 234 3 4 235 motion visualisation, a far better prognosis is likely and prehospital teams might search for 5 6 236 curative aetiologies. 7

8 9 237 Hard evidence is currently missing in the literature since the majority of published studies 10 <sup>11</sup>238 included small series of patients, in the hospital, and used different protocols [6] [7] [8] [9] [10] 12 <sup>13</sup><sub>14</sub>239 [11]. This was stated by the European Resuscitation Council in its 2015 recommendations [5]. 15 16240 ACE is adapted to the particularities of the French prehospital system but its results will be 17 18241 translatable to other organisations such as European or American ones. Actually, where ever 19 <sup>20</sup>242 the place where cardiac arrest is managed, the prognostic value of EPOCE on absence of 21 22 <sub>23</sub>243 ROSC will be the same.

25244 ACE has the potential to provide a definitive response to this question. It is a multicentre, 26 <sup>27</sup>245 prospective trial with a rigorous methodology and a large sample of patients. Furthermore, it 28 29 <sup>2</sup><sub>30</sub>246 will answer the question of frequency of curable aetiologies and their management. This 31 32**247** question also needs hard evidence, ACE has the potential to provide this since it will include 33 <sup>34</sup>248 624 non-selected patients with OHCA. 35

<sup>36</sup><sub>37</sub>249 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] 39250 40 41251 and might be low, regarding the number of included patients. Anyway, this potential flaw has <sup>43</sup>.252 to be addressed: in ACE, physicians will be trained before the trial's onset and cardiac <sub>46</sub>253 massage interruption will be recorded and measured in a subgroup of patients.

Availability of data and material <sup>49</sup>254

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Data will be available upon reasonable request.

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59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# References

- 1. Luc G, Baert V, Escutnaire J, Genin M, Vilhelm C, Di Pompéo C, et al. Epidemiology of outof-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. <u>http://registreac.org/?page\_id=2822</u> 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. Breitkreutz 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.
- 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 pointof-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.
- 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-ed cardiac arrest. Resuscitation. 2016;109:33–9.
- 12. Huis In 't Veld MA, Allison MG, Bostick DS, Fisher KR, Goloubeva OG, Witting MD, et al. Ultrasound use during cardiopulmonary resuscitation is associated with delays in chest compressions. Resuscitation. 2017;119:95–8.

- 1 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
  - 2 Nicolas G, Lecomte D. [Sudden cardiac death in adults. Epidemiology]. *Bull Acad Natl Med* 1999;**183**:1573–9; discussion 1579-1580.
  - 3 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest. http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1010076. 2011. doi:10.1056/NEJMoa1010076
- 4 Les statistiques publiques | RéAC. http://registreac.org/?page\_id=2822
- 5 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
- 6 Breitkreutz 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 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
- 10 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
- 11 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
- 12 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

13 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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# 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.

# 7 Funding

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# Competing interests statement

There was no conflict of interest for all contributors

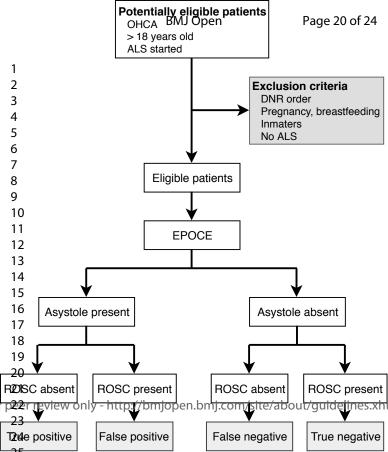
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1 2 3 4 5 6 7			Standard Protocol Items: Recommendations for Interventional Trials	
8 9	SPIRIT 2013 Chec	cklist: Re	ecommended items to address in a clinical trial protocol and related documents*	
9 10 11	Section/item	ltem No	Description	Addressed on page number
12 13	Administrative inf	formatio	an en	• •
14 15	Title	1	Descriptive title identifying the study design, population, interventions, and, if application	1
16 17	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
17	0	2b	All items from the World Health Organization Trial Registration Data Set	NA
19	Protocol version	3	Date and version identifier	6
20	Funding	4	Sources and types of financial, material, and other support	6
21 22	Roles and	5a	Names, affiliations, and roles of protocol contributors	6
23	responsibilities	5b	Name and contact information for the trial sponsor	NA
24 25 26 27		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
28 29 30 31 32 33 34		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, and point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
35 36	Introduction		A g	
37 38 39	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 int	2
39 40		6b	Explanation for choice of comparators	NA
41	Objectives	7	Specific objectives or hypotheses	3
42 43 44 45 46 47			Specific objectives or hypotheses     Bit       For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml     E	1

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factor in straight	
		allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratary)	3-4
Methods: Participa	ants, ir	nterventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of coentries 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 stuৰ្dy centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ឆ្គំ ញូជ្ន៍	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 participart (eg., drug dose change in response to harms, participant request, or improving/worsening discases	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for not be adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variaber and be blood pressure), analysis metric (eg, change from baseline, final value, time to even b, 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
Methods: Assignm	nent of	interventions (for controlled trials)	
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random number), 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 those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequential) umbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
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Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will ession participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care provides, 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
Methods: Data col	lection	i, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, inclusing any related processes to promote data quality (eg, duplicate measurements, training of assessore and a description of study instruments (eg, questionnaires, laboratory tests) along with their evaluation and validity, if known. Reference to where data collection forms can be found, if not in the protection of the processes of the proceses of the processes o	4
	18b	Plans to promote participant retention and complete follow-up, including list of any on the 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 by mote data quality (eg, double data entry; range checks for data values). Reference to where dealed 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 the 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
Methods: Monitori	ng	simila on	
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 reterence to where further details about its charter can be found, if not in the protocol. Alternative y, 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	ND
Ethics and dissem	inatior		
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1 2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) agoro al 7
3 4 5	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria,, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participanes, trial par
6 7 8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or author educrogates, 7 and how (see Item 32)
9 10 11		26b	Additional consent provisions for collection and use of participant data and biologica specimens in NA ancillary studies, if applicable
12 13	Confidentiality	27	How personal information about potential and enrolled participants will be collected, and 6 maintained in order to protect confidentiality before, during, and after the trial 6
14 15 16	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial be detected by 7 site
17 18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contradia agreements 6 that limit such access for investigators
19 20 21	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those where the second secon
22 23 24	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, heal care professionals, the public, and other relevant groups (eg, via publication, reporting in second statements), including any publication restrictions
25 26		31b	Authorship eligibility guidelines and any intended use of professional writers
27 28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical NA
29 30	Appendices		
31 32 33	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates NA
34 35 36	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or NA molecular analysis in the current trial and for future use in ancillary studies, if applicable
37 38 39 40 41 42 43	the items. Amendr	nents to	ed that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboratian for important clarification on the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPLRIT Group under the Creative <u>nCommercial-NoDerivs 3.0 Unported</u> " license.
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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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Secondary Subject Heading:	Cardiovascular medicine
Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

# SCHOLARONE<sup>™</sup> Manuscripts

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

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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
  - Verification of protocol's respect by the video recording
- Limitations
  - Cardiac massage interruption will be monitored in 3 centers out of 8
  - , interventional L Planned missed patients rate of 15%: what characteristics for these patients? What consequences on results?
  - Observational not interventional study

### 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</li>
- Secondary objectives are:

1. assess the prognostic value of EPOCE on survival at hospital admission and on morbimortality 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,

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no/low flow duration, and clinical profile including sex and age for the absence of final 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 (prospective observational study with a unique protocol), has a high prooflevel design, and will recruit a large sample of patients (n = 624). The SPIRIT check-list is in Supplementary files. 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 final 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: all patients > 18 years old presenting with an OHCA for whom an EPOCE could be initiated in less than 12 min after ALS initiation

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

#### Procedure

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. 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

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 EPOCE asystole.

### Secondary endpoints

- Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on hospital admission and on morbi-mortality (defined as dead or alive and Glasgow Outcome Scale) evaluated at 30 days.
- 2. Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for the absence of final ROSC.
- 3. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole for the absence of final ROSC according to their timing of initiation after ALS initiation (by 2 min).
- 4. Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram electrical activity (pulse less activity, asystole, ventricular fibrillation, and ventricular tachycardia).
- 5. Description of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset and diagnosis) and therapeutic delays (time between ALS onset and specific therapeutic intervention), and the effectiveness of implemented curative strategies defined by association with ROCS and 30 day morbimortality.
- 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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- 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.
- 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.

#### 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
- 5 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest. http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1010076. 2011. doi:10.1056/NEJMoa1010076
- 6 Breitkreutz 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

- 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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### **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.

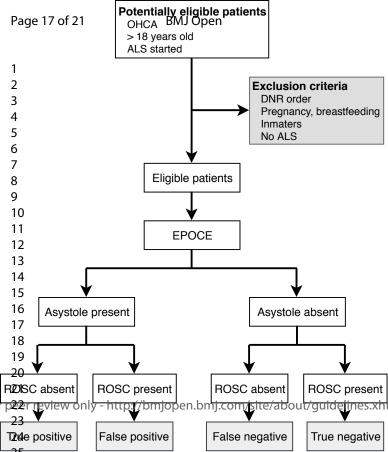
#### **Competing interests statement**

There was no conflict of interest for all contributors

## Word count

3267 words

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



		BMJ Open STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS BMJ Open TOPOP-2018-02748 on 30 Trials Trials Trials	Page
		Standard Protocol Items: Recommendations for Interventional Trials	
		n 30 , for	
SPIRIT 2013 Checl	klist: Reco	ommended items to address in a clinical trial protocol and related documents*	
Section/item	ltem No	Description	Addressed on page number
Administrative inf			
Title	1	Descriptive title identifying the study design, population, interventions, and, if apple 202, 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	5a	Names, affiliations, and roles of protocol contributors	6
responsibilities	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, managemera, adalysis, and	
		interpretation of data; writing of the report; and the decision to submit the report for publication, including	6
		whether they will have ultimate authority over any of these activities	
	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
Introduction		Agen	
Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	2
rationale		studies (published and unpublished) examining benefits and harms for each intervent	
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

Page	19 of 21		BMJ Open Gran	
1 2	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, facterial single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploration	3-4
3 4	Methods: Participa	nts, inte	erventions, and outcomes $\frac{5}{5}$	
5 6	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of aburries where data will be collected. Reference to where list of study sites can be obtained	4
7 8 9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for starting centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
10 11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
12 13 14		11b	Criteria for discontinuing or modifying allocated interventions for a given trial partic participate (eg, drug dose change in response to harms, participant request, or improving/worsening diseas ରି ହିଁ ଛି	NA
15 16		11c	Strategies to improve adherence to intervention protocols, and any procedures for the distoring adherence (eg, drug tablet return, laboratory tests)	NA
17 18		11d	Relevant concomitant care and interventions that are permitted or prohibited during to trial	NA
19 20 21 22	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 elevance of chosen	5
23 24 25	Participant timeline	13	efficacy and harm outcomes is strongly recommended 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
26 27 28	Sample size	14	Estimated number of participants needed to achieve study objectives and how it vestigation of the study objective of the stu	6
29	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
30 31	Methods: Assignme	ent of ir	nterventions (for controlled trials)	
32 33	Allocation:		jies	
34 35 36 37	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
38 39 40 41 42	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
43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2

		BMJ Open by cj.		Page 2
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will a sign 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 $receive aling a participant's allocated intervention during the trial$	NA	
Methods: Data coll	ection,	management, and analysis		
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 asses and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and salidity, 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 an 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 by promote data quality (eg, double data entry; range checks for data values). Reference to where details is to ata 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 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 randor is a analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA	
Methods: Monitorir	ng	lar te		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting surface to 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 ported 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	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		;

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Ethics and disseming Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
approval			
Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibilitize creeria, outcomes,	
amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial reថ្នាំនទ្រីies, journals, regulators) ឆ្នាំ ញ្ច	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authប៉ុរ៉ែធ្វើឆ្នាំd surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biologi as pecimens in ancillary l studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected in State 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 transford each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of cont	6
Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who be uffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healtheare professionals,	
		the public, and other relevant groups (eg, via publication, reporting in results data as s, or other data	
		sharing arrangements), including any publication restrictions	
	31b 31c	Authorship eligibility guidelines and any intended use of professional writers e ? Plans, if any, for granting public access to the full protocol, participant-level datase, as d statistical code	 NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and augorized 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
Amendments to the p	protocol	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboratien for important clarifical should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Co-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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-027448.R3
Article Type:	Protocol
Date Submitted by the Author:	10-Jul-2019
Complete List of Authors:	Javaudin, François; Centre Hospitalier Universitaire de Nantes; Universite de Nantes - Faculte de Medicine, Emergency Medicine Pes, Philippe; Centre Hospitalier Universitaire de Nantes, Emergency department Montassier, Emmanuel; Centre Hospitalier Universitaire de Nantes Legrand, Arnaud; Centre Hospitalier Universitaire de Nantes Ordureau, Aline; Centre Hospitalier Universitaire de Nantes Volteau, Christelle; Centre Hospitalier Universitaire de Nantes Arnaudet, Idriss; Centre Hospitalier Universitaire de Nantes Le Conte, Philippe; Universite de Nantes - Faculte de Medicine, Emergency Medicine
<b>Primary Subject Heading</b> :	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

## SCHOLARONE<sup>™</sup> Manuscripts

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7 8	3	absence of return of s	pontaneous circulatory in out-of-hospital cardiac arrests,			
9 10 11	4	prospective i	multicenter observational study: study protocol			
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15 16 17	6	François Javaudin <sup>1,3</sup> , Phil	ippe Pes <sup>1</sup> , Emmanuel Montassier <sup>1,3</sup> , Arnaud Legrand <sup>2</sup> , Aline			
17 18 19	7	Ordureau <sup>2</sup> , Christelle Volte	au <sup>2</sup> , Idriss Arnaudet <sup>1</sup> , Philippe Le Conte <sup>1,3</sup>			
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## 23 Introduction

Abstract

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 pointof-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.

### 3 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.

#### 41 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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1 2 3	46	Ethic
4 5 6	47	ACE was approved by an ethical committee (2018-AO1491-54)
7 8 9	48	Dissemination
10 11 12	49	While ACE is adapted to the French prehospital system, its results will be translatable to
13 14	50	other organisations if inter-rater variability is not found.
15 16 17	51	Trial status
18 19 20	52	ACE has received a grant from the French Minister for Health, was registered in
21 22 23	53	clinicaltrials.gov (NCT03494153) in 2018
24 25	54	Keywords :
26 27 28	55	Cardiac arrest, prognosis, cardiac ultrasound
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1 2 3	56	Strength and limitations of the study
4 5 6	57	Strengths
7 8 9 10 11 12	58 59 60 61	<ul> <li>Broad inclusion criteria that would allow an extrapolation to rather all OHCA</li> <li>High planned number of patients</li> <li>Previous pilot study demonstrated the feasibility of this protocol</li> <li>Limitations</li> </ul>
12 13 14 15 16 17 18 19 20 21 22 32 42 52 27 28 93 132 33 435 36 37 839 40 41 42 43 44 56 57 58 56 57 58 50 60	62 63 64	<list-item></list-item>

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 

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90 that, while the absence of cardiac motion is highly predictive of death, sensitivity and 91 specificity have not been reported. Thus, usage of this ascertainment for determination of 92 premature termination of resuscitation is currently not recommended until publication of a 93 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

 $\frac{5}{4}$  107 initiation (by 2 min increment).

4. assess the relationship between EPOCE findings and ECG rhythms,

 $\frac{3}{9}$  109 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,

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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 for the absence of final 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 16 120 18 121 ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous methodology (prospective observational study with a unique protocol), has a high proof-level design, and will recruit a large sample of patients (n = 624). The SPIRIT check-list is 25 124 in Supplementary files. 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 final 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 32 127 before extracorporeal membrane oxygenation (ECMO) or organ donation processes. Echographic or EPOCE asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements. 39 130 41 131 Methods Patients Inclusion criteria: all patients > 18 years old presenting with an OHCA for whom an 48 134 EPOCE has been initiated in less than 12 min after ALS initiation Non-inclusion criteria: do not resuscitate order, ROSC prior EPOCE, ALS not performed by the prehospital team, pregnancy, breastfeeding women, and inmates. 55 137 Procedure 

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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 32 151 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 48 158 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 55 161 morbimortality. They will be assessed by the research team of Nantes Hospital. In three 

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1 2 3	163	centre	es, the whole resuscitation procedure will be monitored via a mobile video recorder.	
4 5	164	Video	clips will be uploaded and analysed in order to measure the duration of cardiac	
6 7	165	massa	age interruptions.	
8 9 10	166	Endp	oints	
11 12 13	167	Prima	ary endpoint	
	168	•	Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of	
16 17 18	169		ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the	
19 20	170		predictive positive value (PPV) as the primary endpoint because we want to isolate a	
21 22	171		population without ROCS with EPOCE asystole.	
23 24 25	172	Seco	ndary endpoints	
25 26 27	173	1.	Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS	
28 29	174		initiation) on hospital admission and on morbi-mortality (defined as dead or alive	
	175		and Glasgow Outcome Scale) evaluated at 30 days.	
32 33 34	176	2.	Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for	
35 36	177		the absence of final ROSC.	
	178	3.	Sensitivity, specificity, and positive and negative predictive values of EPOCE	
39 40 41	179		asystole for the absence of final ROSC according to their timing of initiation after	
42 43	180		ALS initiation (by 2 min).	
75	181	4.	Association between the ultrasound asystole rate according to the cardiac electrical	
	182		activity (pulse less activity, asystole, ventricular fibrillation, and ventricular	
48 49 50	183		tachycardia)	
51 52	184	5.	Description of reversible causes (tamponade, massive pulmonary embolism, deep	
	185		hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset	
55 56 57	186		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 18 194 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 25 197 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 32 200 Bobigny).

#### 37 202 **Recruiting centres**

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) 40 203 <sup>42</sup> 204 and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

#### 45 205 Sample size calculation

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence 48 206 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 55 209

data, too poor quality of the ultrasound for interpretation, etc...), 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, 17 216 survival with neurological deficit, or death.

#### 22 218 Data management

Electronic case report files will be used via a web-based interface and video clips will be 25 219 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 32 222 available to the steering committee. Subjects with missing data for the primary endpoint will not be analyzed (+15% subjects in sample size calculation)

#### Monitoring

Monitoring will be performed both by electronic surveillance of recruitment and data 42 226 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 50 229 failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will 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 ®.

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

#### 59 Patient and Public Involvement

Dissemination

Patients and public had no involvement in the design or the planning of the study

#### 51 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 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]

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[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.

### 84 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
- 5 Stiell IG, Nichol G, Leroux BG, *et al.* Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest. http://dx.doi.org.gate2.inist.fr/10.1056/NEJMoa1010076. 2011. doi:10.1056/NEJMoa1010076
- 6 Breitkreutz 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

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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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## **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.

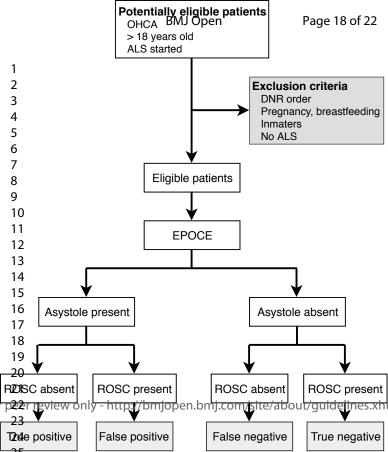
#### **Competing interests statement**

There was no conflict of interest for all contributors

#### Word count

3435 words

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



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12	Administrative info	ormation		
13 14	Title	1	· · · · · · · · · · · · · · · · · · ·	1
15	Trial registration	 2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
16 17		2b	All items from the World Health Organization Trial Registration Data Set	NA
17	Protocol version	3	Date and version identifier	6
19	Funding	4	Sources and types of financial, material, and other support	6
20	Roles and	5a	Names, affiliations, and roles of protocol contributors	6
21 22	responsibilities	5b	Name and contact information for the trial sponsor	NA
23 24 25 26		5c	Role of study sponsor and funders, if any, in study design; collection, managemeration, 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
27 28 29 30 31 32 33		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
34 35	Introduction		Age	
36	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	2
37	rationale		studies (published and unpublished) examining benefits and harms for each intervent	
38 39		6b	Explanation for choice of comparators	NA
40	Objectives	7	Specific objectives or hypotheses	3
41 42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	1

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		BMJ Open S S	Page 2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, facter single group),	
		allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explor	3-4
Methods: Participa	nts, inte	erventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of aburries 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 starts 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 partion of the construction of the construct	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for a litoring 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 elevance of chosen	5
Participant timeline	13	efficacy and harm outcomes is strongly recommended 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 versions getermined, 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
Methods: Assignm	ent of i	nterventions (for controlled trials)	
Allocation:		jies 5 a	
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 intervertions are assigned	NA
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Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will a sign 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
Methods: Data coll	ection,	management, and analysis	
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 assesses and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and salidity, 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 and 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 for 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 the 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
Methods: Monitorii	ng	ar hur te ur	
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 way 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 ported 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
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Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) populational	7
approval		Diana far communicating important protocol modifications (og. changes to cligibilite organic, outcomes	
Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibilit; creeria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals,	
amendments		regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authories d surrogates, and	7
	204	how (see Item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	NA
		studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected stated, and	6
-		maintained in order to protect confidentiality before, during, and after the trial	
Declaration of	28	Financial and other competing interests for principal investigators for the overall track and each study site	7
interests			
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of cont	6
		limit such access for investigators	
Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those with the provision of the second sec	NA
trial care		participation	
Dissemination policy	/ 31a	Plans for investigators and sponsor to communicate trial results to participants, healtheare professionals,	
		the public, and other relevant groups (eg, via publication, reporting in results datalies as 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 datas	NA
Annondiooc			
Appendices	32	Model consent form and other related documentation given to participants and augorged surrogates	NA
Informed consent			
Informed consent materials Biological	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