

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	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
<b>AUTHORS</b>	Javaudin, François; Pes, Philippe; Montassier, Emmanuel; Legrand, Arnaud; Ordureau, Aline; Volteau, Christelle; Arnaudet, Idriss; Le Conte, Philippe

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Romolo Gaspari UMASS Memorial Medical Center
<b>REVIEW RETURNED</b>	09-Nov-2018

<b>GENERAL COMMENTS</b>	<p>Thank you for allowing me to review this interesting article. I think it is very interesting and look forward to seeing the results. I have never reviewed a published protocol before, so please feel free to request additional information or a change in the format of my review if needed. I have reviewed many unpublished protocols in the past, so feel confident my comments can help with the proposed research. In addition, I practice in the United States and some of the terminology or abbreviations were unfamiliar to me. If these are commonly used in Europe or other areas of the world, please feel free to ignore my comments.</p> <p><b>Major Comments</b></p> <p>It is not clear to me if the ultrasounds that will be performed will occur in the pre-hospital setting or upon arrival to the hospital. This should be clarified.</p> <p>Definitions of events and populations should be clearly defined in the proposal. Examples of definitions that need more detail are Ecographic Asystole, and XXX. Examples of definitions that are missing include “absence of ROSC”, “curable aetiologies” and “therapeutic delays”. See specific comments for details.</p> <p>Your inclusion criteria introduce selection bias. There is not description of who have EPOCE performed. If all patients have this performed, then state this in the methods. If a subset of patients presenting in OHCA undergo EPOCE then this needs to be described in detail. This is a major flaw of the study.</p> <p><b>Specific Comments</b></p> <p><b>ABSTRACT</b></p> <p>Introduction – Page 3 Line 27. If there are European recommendation that advocate for early point of care focused echocardiography, please supply a reference.</p>
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	<p>Methods – Page 3, Line 32 – I may have missed it, but the abbreviation ACE in “ACE trial” is unfamiliar to me. Please spell out the first time it is used.</p> <p>Methods – Page 3, Line 37 – Similarly, the abbreviation ERC is used for the first time here. Please spell out the first time it is used.</p> <p>Page 5, line 57 – You state that this is the first prospective multicenter trial of Point of Care Ultrasound in out-of-hospital cardiac arrest. This is not true. Your reference 11 is a prospective multicenter trial in out-of-hospital cardiac arrest.</p> <p>MANUSCRIPT</p> <p>Methods – If you want to use the abbreviation EPOCE then be consistent when you refer to early POCE later in the manuscript</p> <p>Methods- Your objectives are redundant in placed and are vaguely described in general. During your description of your objectives you mix in the statistical methods. Specifically, your main objective and secondary objective 2 seem identical to me. Both are exploring the association between your intervention (EPOCE) and your primary outcome (ROSC). The statistical methodology to evaluate this assessment is handled in the statistics section. Objective 4 is vague, but I assume you are looking at descriptive statistics. Objective 6 is vague. What EPOCE characteristics are you referring to? Sonographic findings, image quality? Objective 7 is vague. Are you referring to similar endpoints such as ROSC or survival to hospital discharge? If so, why do you not say this? Objective 8 description of a multifactorial score is confusing to me. What is the purpose of the score, is it related to your outcomes? If so, it is redundant to objective 2, or at a minimum a statistical assessment and not a separate objective.</p> <p>Page 8, Line 122 – Your definition of Ecographic Asystole is incomplete. Valvular movement is commonly seen with bag-valve ventilation. By your protocol these would be excluded. If you are characterizing “cardiac twitching where movement is visible but no visible change in ventricular chamber size is detectable” as no cardiac movement, this should be explicitly stated. If your ultrasound views are shortened due to imaging acquisition problems (i.e. for example you get a clip of 4 seconds) what do you do if the cardiac activity is bradycardic and you have no electrical activity during the time of the ultrasound image. This would happen if the patient’s rate was 20 BPM but you happened to only get a 4 second clip.</p> <p>Page 9, Line 128 – Exclusion criteria does not include trauma. Is this intended? Do you intend to include penetrating trauma to the chest? You do not state exclusion of patients with limitations of care directives (Do Not Resuscitate) but this will affect your survival outcome. You state ALS not performed by the pre-hospital team. Do you mean if bystander CPR is performed, the patient is excluded? What if ROSC occurs prior to EPOCE being performed? What if the patient gets ROSC prior to EPOCE but then arrests again during transport? What if the EPOCE images are not recorded? What if you can’t get EPOCE images in the requisite time?</p>
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	<p>Page 9, Line 134 – Describe the FEEL protocol in detail. Include timing issues with CPR.</p> <p>Page 9, Line 137 – What if the subcostal view is not available or unobtainable?</p> <p>Page 9, line 146 – You state you will use the Glasgow Coma Score. Will this be determined from a documented GCS in the chart, abstracted from the chart, or obtained from surviving patients by research staff? What will you do if it is not recorded or available? Why are you using GCS? There are other metrics that have more validity. Mini-Mental Status Exam is one but there are more.</p> <p>Page 10, line 149 – Define absence of ROSC. How long of a return of circulation is required to define ROSC? If they get a pulse for 2 min, 5 min... Do they have to have measurable blood pressure? What level and how long?</p> <p>Page 10, Line 155 – How do you define hospital admission? Is it the decision to admit or actually transferring to the hospital team? How is morbimortality evaluated at 30 days? Specifically who will do what and when?</p> <p>Page 10, Line 155 on – As I mentioned before, secondary endpoints and statistical analysis are mixed and should be separated.</p> <p>Page 10, Line 164- How is electrical activity confirmed or recorded? What about patients with varying electrical activity (PEA to Vfib to Asystole)?</p> <p>Page 10, Line 165 – Define “curable aetiologies” fully. I would suggest making a list of those that meet this definition. Similarly, define “diagnostic and therapeutic delays” fully. Define what you mean by effectiveness of interventions. Do mean association with ROSC or hospital admission?</p> <p>Page 11, Line 175 – You discuss pauses in CPR related to ultrasound. How will you handle other events that are simultaneous with the ultrasound but may contribute to pauses? Endotracheal intubation, equipment malfunction, interventions stimulated by US (i.e. pericardiocentesis), rhythm checks, pulse checks... How to you handle pauses that lead to ROSC? (i.e. CPR never resumes because of ROSC)? Definitions for all events should occur prior to analysis.</p> <p>Page 11, Line 182 – Why did you choose PPV 95 +/-3? Enrollment is a balance between accuracy of findings and feasibility of enrolling patients. What if you chose PPV 92? What about PPV 98%?</p> <p>Page 11, Line 183 – 15% attrition seems optimistically low. Do you have data to support this assumption?</p> <p>Page 11, Line 190 – You do not include a communication plan for the study. This should be included.</p> <p>Page 12, Line 204 – Your statement on the analysis of time of EPOCE and best prognostic performance confused me. Do you mean the time of CPR delay? Do you mean the time when it was</p>
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	<p>performed (time after starting ALS)? How is your study organized to address this question?</p> <p>Page 14, line 237 – You state that published studies include small series of patients, but reference 11 included a larger number of patients that you propose to include in your study. This should be noted. It is not a problem to perform your study, as you plan to look at different endpoints, but it should be noted.</p> <p>Page 14, line 250. Your reference 13 is a letter regarding the study in reference 12. You should include reference 12 here as well as it is the actual study.</p> <p>Page 14, line 250 - You mention training in prior studies, but you do not describe the training for your research staff, pre-hospital staff.. The training for the referenced article (ref 12) is that of a residency in the united states, which has established training guidelines. You are correct in noting this deficiency in the study description, but it can be assumed that the training for those involved in the study was in line with established residency training requirements. At a minimum this should be discussed in detail. You could also simply email the author and ask them what the training is at that site. This would be reported under “persona</p>
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<b>REVIEWER</b>	Helle Søholm Zealand University Hospital, Roskilde, Denmark.
<b>REVIEW RETURNED</b>	12-Nov-2018

<b>GENERAL COMMENTS</b>	<p>Review 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</p> <p>General comments Thank you for an interesting study protocol covering a both interesting and important subject of early focused assessment of cardiac standstill by ultrasound in order to predict ROSC in OHCA-patients.</p> <p>The protocol is in general well-written, however a thorough language editing would markedly improve the readability.</p> <p>The endpoints seems to be well-chosen and reasonable.</p> <p>Is the recruitment consecutive? If not please define how you would make sure no selection in included patients will take place.</p> <p>I do not quite understand the concept “recruiting centers” as the study is examining pre-hospital ultrasound and as the in-hospital treatment (post-resuscitation care) is not mentioned?</p> <p>Specific/minor comments</p> <p>What is morbimortality? Please change “curable ethiologies” to “reversible causes” Shouldn’t “on the absence of ROSC” be “in the absence of ROSC”?</p> <p>Abstract:</p>
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	<p>Please be more precise / explain the sentence "...particular prehospital system based on medicalisation of both ambulance dispatch and mobile intensive care units." what does mobile ICU cover?</p> <p>Please add a "may" to the following sentence, as you are examining whether EPOCE may help predict ROSC... "Another ability of EPOCE is to predict the absence of return of spontaneous circulation (ROSC) ..."</p> <p>Please explain the acronym "ACE-trial"</p> <p>The language in the "methods" section of the abstract must be improved.</p> <p>Is the ambulance personal blinded for the EPOCE results? Please be more precise "the EPOCE results will not be used for that purpose."</p> <p>I do not understand the sentence "ROSC will be assessed after ALS termination." ?</p> <p>I guess some EPOCE inter-rater variability must be present affecting the prognostic value??? "the prognostic value of EPOCE on absence of ROSC will be the same."</p> <p>Introduction Ref. 2 is very old (1999)</p> <p>The OHCA-prognosis in most western countries is around 10%. Are you sure to comment on updated French numbers?</p> <p>Methods: Please define "into this bibliographic gap"</p> <p>Please be more precise "It is based on rigorous methodology"</p> <p>I do not understand "Presence or absence of ROCS will be assessed after ALS termination."</p> <p>What is the "hospital pathway" ?</p> <p>The word "attrition" seems out of place?</p> <p>Please define "time of EPOCE realisation" – is it time of finishing EPOCE?</p> <p>Discussion: A general language editing is needed. Quite a few repetitions are present in this section. Please shorten the whole manuscript or rewrite / change some of the sequences.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Romolo Gaspari

Institution and Country: UMASS Memorial Medical Center

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

Thank you for allowing me to review this interesting article. I think it is very interesting and look forward to seeing the results. I have never reviewed a published protocol before, so please feel free to request additional information or a change in the format of my review if needed. I have reviewed many unpublished protocols in the past, so feel confident my comments can help with the proposed research. In addition, I practice in the United States and some of the terminology or abbreviations were unfamiliar to me. If these are commonly used in Europe or other areas of the world, please feel free to ignore my comments.

#### Major Comments

It is not clear to me if the ultrasounds that will be performed will occur in the pre-hospital setting or upon arrival to the hospital. This should be clarified.

"in the pre-hospital setting" added both in abstract and introduction

Definitions of events and populations should be clearly defined in the proposal. Examples of definitions that need more detail are Ecographic Asystole, and XXX. Examples of definitions that are missing include "absence of ROSC", "curable aetiologies" and "therapeutic delays". See specific comments for details.

Curable etiologies defined p6 lines 75-76

Echographic asystole defined lines p8 122-23

ROSC define as "ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse in the Utstein registries recommendation". Sentence added p6 183-86

absence of ROSC defined lines p6 180-81, " at the end of advanced life support (ALS) procedure" added

Therapeutic delays defined lines 148-49, " defined as the interval between arrival time on scene and therapeutic initiations" added

Your inclusion criteria introduce selection bias. There is not description of who have EPOCE performed. If all patients have this performed, then state this in the methods. If a subset of patients presenting in OHCA undergo EPOCE then this needs to be described in detail. This is a major flaw of the study.

You are perfectly right, the inclusion criteria were not fully described : all patients for whom an EPOCE could be performed in less than 12 min after ALS initiation will be included. The sentence was modified in "Inclusion criteria: all patients > 18 years old presenting with an OHCA for whom an EPOCE could be performed in less than 12 min after ALS initiation "

#### Specific Comments

##### ABSTRACT

Introduction – Page 3 Line 27. If there are European recommendation that advocate for early point of care focused echocardiography, please supply a reference.

Done

Methods – Page 3, Line 32 – I may have missed it, but the abbreviation ACE in “ACE trial” is unfamiliar to me. Please spell out the first time it is used.

ACE is the acronym of our study, beginning of the sentence modified in “Our trial, The ACE trial...”

Methods – Page 3, Line 37 – Similarly, the abbreviation ERC is used for the first time here. Please spell out the first time it is used.

European Resuscitation Council added

Page 5, line 57 – You state that this is the first prospective multicenter trial of Point of Care Ultrasound in out-of-hospital cardiac arrest. This is not true. Your reference 11 is a prospective multicenter trial in out-of-hospital cardiac arrest.

In the study performed by Gaspari, patients with out or in-hospital cardiac arrest were included but the Ultrasound was performed in the ED, not by pre-hospital teams

# MANUSCRIPT

Methods – If you want to use the abbreviation EPOCE then be consistent when you refer to early POCE later in the manuscript  
 correction made

Methods- Your objectives are redundant in placed and are vaguely described in general. During your description of your objectives you mix in the statistical methods.

Specifically, your main objective and secondary objective 2 seem identical to me. Both are exploring the association between your intervention (EPOCE) and your primary outcome (ROSC).

The main objective is the positive predictive value while the secondary objective 2 is constituted by Sensitivity, specificity, and positive (PPV) and negative predictive (NPV) values as explain in the methodological section. By error, we kept PPV in this objective, it was released.

The statistical methodology to evaluate this assessment is handled in the statistics section.

Objective 4 is vague, but I assume you are looking at descriptive statistics.

You are right, we have planned to test associations between cardiac standstill and electrical activity (ventricular fibrillation, PEA, ventricular tachycardia) with Chi-squared or Fisher tests.

Objective 6 is vague. What EPOCE characteristics are you referring to? Sonographic findings, image quality?

The characteristics are described in the secondary endpoints section : 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.



Objective 7 is vague. Are you referring to similar endpoints such as ROSC or survival to hospital discharge? If so, why do you not say this?

We are referring to ROSC as explained in the secondary endpoints section : Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in patients with ventricular fibrillation.

Objective 8 description of a multifactorial score is confusing to me. What is the purpose of the score, is it related to your outcomes? If so, it is redundant to objective 2, or at a minimum a statistical assessment and not a separate objective.

The objective of objective 8 is to construct a multi-factorial prognosis composite score associated with absence of ROSC. It will be based on factors available at the time of cardiac arrest; It was described in the statistical analysis paragraph (p13 lines 213-15).

Page 8, Line 122 – Your definition of Ecographic Asystole is incomplete. Valvular movement is commonly seen with bag-valve ventilation. By your protocol these would be excluded. If you are characterizing “cardiac twitching where movement is visible but no visible change in ventricular chamber size is detectable” as no cardiac movement, this should be explicitly stated.

Bag-valve ventilation will be avoided during the POCUQ acquisition

If your ultrasound views are shortened due to imaging acquisition problems (i.e. for example you get a clip of 4 seconds) what do you do if the cardiac activity is bradycardic and you have no electrical activity during the time of the ultrasound image. This would happen if the patient's rate was 20 BPM but you happened to only get a 4 second clip.

You actually point on a limit of POCUS in cardiac arrest because the acquisition period should not exceed 10 seconds; We agree than an extreme bradycardia could be missed in case of technical difficulties in patients without electrical activity. However, this situation might be rare. A sentence could be added in the limit section.

Page 9, Line 128 – Exclusion criteria does not include trauma. Is this intended?

Yes, it was intended

Do you intend to include penetrating trauma to the chest?

No, we will not exclude penetrating trauma to the chest but actually, these situations are very rare in France.

You do not state exclusion of patients with limitations of care directives (Do Not Resuscitate) but this will affect your survival outcome.

Do Not Resuscitate order is listed as non-inclusion criteria (p9 line 128)

You state ALS not performed by the pre-hospital team. Do you mean if bystander CPR is performed, the patient is excluded?



If the pre-hospital medical team doesn't initiate ALS because of medical reason such as obvious death, the patient is excluded.

What if ROSC occurs prior to EPOCE being performed?

The patient will not be included, a line will be added in non-inclusion criteria

What if the patient gets ROSC prior to EPOCE but then arrests again during transport?

the patient will not be included

What if the EPOCE images are not recorded?

The patient will remain included

What if you can't get EPOCE images in the requisite time?

The patient will not be included (mentioned in the inclusion criteria)

Page 9, Line 134 – Describe the FEEL protocol in detail. Include timing issues with CPR.

The following sentences were added : "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." unfortunately, no timing was presented in the article.

Page 9, Line 137 – What if the subcostal view is not available or unobtainable?

In this particular case, the physician could use another view, parasternal or apical

Page 9, line 146 – You state you will use the Glasgow Coma Score. Will this be determine from a documented GCS in the chart, abstracted from the chart, or obtained from surviving patients by research staff? What will you do if it is not recorded or available? Why are you using GCS? There are other metrics that have more validity. Mini-Mental Status Exam is one but there are more.

We didn't intended to use Glasgow Coma Score but Glasgow Outcome Score which is a validated score in post-neurological injury. It will documented in the chart.

Page 10, line 149 – Define absence of ROSC. How long of a return of circulation is required to define ROSC? If they get a pulse for 2 min, 5 min... Do they have to have measurable blood pressure? What level and how long?

ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse in the Utstein registries recommendation. Definition and reference added in the text. (lines 83-85)

Page 10, Line 155 – How do you define hospital admission? Is it the decision to admit or actually transferring to the hospital team? How is morbimortality evaluated at 30days? Specifically who will do what and when?

Hospital admission is defined as a patient alive at the arrival at the hospital. Two events (dead or alive and Glasgow Outcome Scale) define the morbimortality. They will be assessed by the research team of Nantes Hospital.

Page 10, Line 155 on – As I mentioned before, secondary endpoints and statistical analysis are mixed and should be separated.

We intended to cite the secondary endpoints in this section without describing them, the statistical analysis is described in the mentioned section.

Page 10, Line 164- How is electrical activity confirmed or recorded? What about patients with varying electrical activity (PEA to Vfib to Asystole)?

Electrical activity is visualized on the multi-parameter monitor without recording. For this analysis, patients with varying rhythms will be excluded

Page 10, Line 165 – Define “curable aetiologies” fully. I would suggest making a list of those that meet this definition. Similarly, define “diagnostic and therapeutic delays” fully. Define what you mean by effectiveness of interventions. Do mean association with ROSC or hospital admission?

Curable aetiologies were defined page 6, lines 74-76, the list was added line 173-74. Diagnostic and therapeutic delays were defined as follow : time between ALS onset and diagnosis and time between ALS onset and specific therapeutic intervention. The sentence was modified as follows : “effectiveness of implemented curative strategies defined by association with ROCS and 30 day morbimortality”

Page 11, Line 175 – You discuss pauses in CPR related to ultrasound. How will you handle other events that are simultaneous with the ultrasound but may contribute to pauses? Endotracheal intubation, equipment malfunction, interventions stimulated by US (i.e. pericardiocentesis), rhythm checks, pulse checks... How to you handle pauses that lead to ROSC? (i.e. CPR never resumes because of ROSC)? Definitions for all events should occur prior to analysis.

We aim to investigate pauses in CPR related to ultrasound because in an article, ultrasound was responsible for lack of CPR. Other interventions that might contribute to pauses such as endotracheal intubation are not specific to our protocol.

Page 11, Line 182 – Why did you choose PPV 95 +/-3? Enrollment is a balance between accuracy of findings and feasibility of enrolling patients. What if you chose PPV 92? What about PPV 98%?

We chose a PPV 95% based on results from a pilot study performed by our prehospital teams which included 35 patients. The observed PPV was 95%. We intended to obtain a 5% CI but with the considered recruitment, a 3% CI should be possible.

Page 11, Line 183 – 15% attrition seems optimistically low. Do you have data to support this assumption?

In the same pilot study, the attrition rate was 10%, thus 15% seems accurate for ACE trial.

Page 11, Line 190 – You do not include a communication plan for the study. This should be included.

We included a communication plan: A monthly newsletter will be published with individual and global recruitment trends.

Page 12, Line 204 – Your statement on the analysis of time of EPOCE and best prognostic performance confused me. Do you mean the time of CPR delay? Do you mean the time when it was performed (time after starting ALS)? How is your study organized to address this question?

In literature, EPOCE performances are better when the delay between cardiac arrest and ultrasound is shorter. Since the exact timing of CPR is frequently imprecise, we chose delay between ALS initiation and first ultrasound. We will analyze diagnosis performances by 2min-increment.

Page 14, line 237 – You state that published studies include small series of patients, but reference 11 included a larger number of patients that you propose to include in your study. This should be noted. It is not a problem to perform your study, as you plan to look at different endpoints, but it should be noted.

You are right, there is actually more patients in this study but EPOCE was performed in the ED even the cardiac arrest occurred out-of-hospital. The following sentence was added : “A multicentre study was performed but EPOCE was performed in the ED even the cardiac arrest occurred out-of-hospital”

Page 14, line 250. Your reference 13 is a letter regarding the study in reference 12. You should include reference 12 here as well as it is the actual study.

Page 14, line 250 - You mention training in prior studies, but you do not describe the training for your research staff, pre-hospital staff.. The training for the referenced article (ref 12) is that of a residency in the united states, which has established training guidelines. You are correct in noting this deficiency in the study description, but it can be assumed that the training for those involved in the study was in line with established residency training requirements. At a minimum this should be discussed in detail. You could also simply email the author and ask them what the training is at that site. This would be reported under “persona

You are right, I have replaced the sentence by “This study was performed in the United States and it might be assumed that the training was in line with established residency training requirement.”

Reviewer: 2

Reviewer Name: Helle Søholm

Institution and Country: Zealand University Hospital, Roskilde, Denmark.

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

Please see attached file.

## Reviewer 2

We are very grateful to the reviewer' comments that pointed out a number of features needing to be addressed before publication. You will find the point-by-point responses to the items:

### General comments

... a thorough language editing would markedly improve the readability.

The whole manuscript was thoroughly reviewed by a specialized English society before submission

Is the recruitment consecutive?

Yes, the recruitment is consecutive

I do not quite understand the concept “recruiting centers” as the study is examining pre-hospital ultrasound

and as the in-hospital treatment (post-resuscitation care) is not mentioned?

The recruiting centers design the pre-hospital teams that belong to hospitals (university or not). You are right, the post-resuscitation care are not mentioned since the objectives are mainly intended to assess the diagnosis value of EPOCE for ROSC at the end of the ALS procedure.

#### specific/minor comments

What is morbimortality?

morbi-mortality was defined p8l158-9 as “These two events (dead or alive and Glasgow Outcome Scale) define the morbimortality”. It has been added p9l170 in the secondary endpoints section

Please change “curable etiologies” to “reversible causes”

It was done in the whole text

Shouldn’t “on the absence of ROSC” be “in the absence of ROSC”?

“on the absence of ROSC” has been replaced by “for the absence of final ROSC...” in the whole text

#### **Abstract**

Please be more precise / explain the sentence “...particular prehospital system based on medicalisation of

both ambulance dispatch and mobile intensive care units.”

what does mobile ICU cover?

The sentence has been added: “composed by an emergency physician and an emergency nurse with all the required devices for advanced care”

Please add a “may” to the following sentence, as you are examining whether EPOCE may help predict

ROSC...

“Another ability of EPOCE is to predict the absence of return of spontaneous circulation (ROSC) ...”  
 the sentence was modified in “Another ability of EPOCE may be to predict the...”

Please explain the acronym “ACE-trial”

ACE is actually not an acronym and has no particular meaning

Is the ambulance personal blinded for the EPOCE results? Please be more precise “the EPOCE results will

not be used for that purpose.”

The ambulance personal is not blind for the EPOCE results

The language in the “methods” section of the abstract must be improved.

I do not understand the sentence “ROSC will be assessed after ALS termination.” ?

The paragraph has been modified by “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. “

I guess some EPOCE inter-rater variability must be present affecting the prognostic value??? “the prognostic

value of EPOCE on absence of ROSC will be the same.

You are right, the following sentence has been added “if inter-rater variability is not found”

## Introduction

Ref. 2 is very old (1999)

You are right, however, references 2 and 4 show similar results in term of survival. We kept reference 3 to demonstrate that there is no actual improvement since 20 years.

The OHCA-prognosis in most western countries is around 10%. Are you sure to comment on updated French numbers?

Yes, we are sure of these results as demonstrated by reference 4 which show a 30-days 6% survival rate in OHCA since 2011

## Methods

Please define “into this bibliographic gap”

the following sentence has been added; “uncertainty on diagnosis value of absence of cardiac motion for absence of ROSC”

Please be more precise “It is based on rigorous methodology”

the following sentence has been added: “prospective observational study with a unique protocol”

I do not understand “Presence or absence of ROCS will be assessed after ALS termination.”

the sentence was modified in “For the study purpose, presence or absence of ROCS will be assessed after ALS termination”

What is the “hospital pathway”?

Hospital pathway was replaced by ‘hospital course’ intended to describe the different units in which the patients is hospitalized.

The word “attrition” seems out of place?

The sentence was modified in “Taking into account that EPOCE could not be performed in 15% of OHCA...”

Please define “time of EPOCE realisation” – is it time of finishing EPOCE?

Realisation was replaced by initiation

## Discussion

A general language editing is needed. Quite a few repetitions are present in this section. Please shorten the

whole manuscript or rewrite / change some of the sequences.

The discussion section has been shortened and a number of repetitions deleted

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Romolo Gaspari UMASS Memorial Medical Center
<b>REVIEW RETURNED</b>	30-Apr-2019

<b>GENERAL COMMENTS</b>	<p>I applaud you for attempting to address an issue that needs attention.</p> <p>This study is difficult to review for a number of reasons. The grammar is difficult to follow and unclear in many places. Each aspect of this manuscript requires significant revisions prior to publication. A few general comments. This article is describing the methods of a potential study but it is not explicitly states so in the introduction. Please include this.</p> <p>Many of the terms are vague. When describing aspects of EPOCE it is not clear to me that you know what you are looking for. Without defining this it is extremely difficult for me to see how you can complete this study.</p> <p>Your objectives are not supported by your methods. You introduce concepts in the objectives but you never describe how this will be performed in your methods.</p> <p>Your objectives are slightly different in three different places in the manuscript.</p> <p>Many of your objectives lack definitions and are too vague.</p> <p>You have too many objectives for a study of this type.</p> <p>Some of your definitions in this manuscript do not match prior publications.</p> <p>Your discussion is a continuation of your introduction. You do not discuss how your study will change practice.</p>
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<b>REVIEWER</b>	Helle Søholm Zealand University Hospital, Roskilde Department of Cardiology Denmark
<b>REVIEW RETURNED</b>	08-Apr-2019

<b>GENERAL COMMENTS</b>	The authors have performed a detailed and thorough response to the reviewer comments. I have no further comments.
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## VERSION 2 – AUTHOR RESPONSE

Responses to the second reviewer

Comment 1: the following sentence was added in introduction of both abstract and article: “We thus intended to investigate this predicting value of absence of cardiac motion on absence of ROSC with a prospective multicenter study. This paper describes the study protocol while the first patients were included in December 2018.”

Comment 2: the paragraph was rewritten by a native English speaker

Comment 3: EPOCE replaced by EPOCE asystole

Comment 4: cardiac arrest replaced by out-of-hospital cardiac arrest



Comment 5: this sentence was actually not clear, it was replaced by "Observational not interventional study"

Comment 6: we understand this remark but with all due respect, the interventions are standardized. The management of OHCA strictly follows the ERC rules and decision of resuscitation's termination doesn't take into account the results of EPOCE.

Comment 7: you are right, that was unclear, EPOCE replaced by EPOCE asystole in secondary objectives 1 to 3

Comment 8: timing of initiation completed by after ALS initiation (by 2 min increment).

Comment 9: curable etiologies replaced by reversible causes (tamponnade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax)

Comment 10: characteristics are displayed at the end of the sentence (timing, quality...)

Comment 11: with all due respect, all these secondarily objectives are analysis of data entered by the physician and his team during the resuscitation phase plus hospital data for survivors. When the database will eventually be frozen, multiple analysis could be performed, that's why there is a lot of secondarily objectives.

Comment 12: you are right, we added out-of-hospital cardiac arrest as kindly requested in comment 4.

Comment 13: there is slight differences in cardiac motion definitions between prior studies. They are all focused on presence/absence of cardiac motion We chose this one, very closed from this used in Salen et al study (2004) because it was the simplest.

Comment 14: you are right, could be replaced by has been

Comment 15: A cardiac ultrasound will be performed once the ALS in place without waiting a period of time. This is described in the following paragraph. We hope that the slight modification which was done might improve the understanding.

Comment 16: with all due respect, we believe that the brief description of the FEEL protocol actually reflects the study. However, we add "if the patient was in cardiac arrest" because this study addressed patients in cardiac arrest or in profound shock state.

Comment 17: you are right, a delay between ALS initiation and ultrasound > 12 min is an exclusion criteria. We have stated in inclusion criteria "... EPOCE has been initiated in less than 12 min after ALS initiation"

Comment 18: the patient's chart includes timing intervals.

Comment 19: you are right, there is no blinding. Actually, blinding is impossible with the actual study design.

Comment 20: It is intended to describe the hospital course (ICU, medical ward...) of the patient. Pathway replaced by course (ICU, medical ward...)

Comment 21: you are right, we added line 134 or EPOCE before the definition of asystole

Comment 22: you are right the sentence was replaced by "We have chosen the predictive positive value (PPV) as the primary endpoint because we want to isolate a population without ROCS with EPOCE asystole"

Comment 23: With all due respect, we described earlier the objectives. The endpoints are displayed in the current paragraph.

Comment 24: The 30 day assessment is described earlier, lines 164-66

Comment 25: we aim to explore the variation of EPOCE diagnostic performance according to timing of realisation. For that purpose, we will explore the possible variations by 2-min increments.

Comment 26: You are right, the sentence was replaced by "Association between the ultrasound asystole rate according to the cardiac electrical activity (pulse less activity, asystole, ventricular fibrillation, and ventricular tachycardia)"

Comment 27: a member of the resuscitation team will prospectively records timing of intervention. This methodology is currently used by the prehospital teams and is a part of the resuscitation process.

Comment 28: you are right, we didn't described the quality-rating in this article. However, it is described in the protocol as a whole quality assessment on a predetermined scale ranging from 0 (impossible) to 10 (perfect). The sentence was replaced by "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."

Comment 29: You are right but in the ERC regulation, an ECG is warranted. "...including realisation of an ECG" was added line 146

Comment 30: with all due respect, all these data are actually included in the eCRF

Comment 31: you are right, the sentences were added lines 168-70: "In three centres, the whole resuscitation procedure will be monitored via a mobile video recorder. Video clips will be uploaded and analysed in order to measure the duration of cardiac massage interruptions."

Comment 32: You are right, the sentences were modified by **"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 data, too poor quality of the ultrasound for interpretation, etc...), the required population will, finally, be 624 patients."**

Comment 33: sentence added: Subjects with missing data for the primary endpoint will not be analyzed (+15% subjects in sample size calculation)"

Comment 34: We understand the reviewer's concern. However, in the discussion section, we recalled the major points of our study protocol and discussed the delays in chest compressions.