

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

TITLE (PROVISIONAL)	Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol
AUTHORS	Wagner, Mette; Berg, Selina; Hassager, Christian; Armand, Sophia; Møller, Jacob; Ekholm, Ola; Rasmussen, Trine; Fisher, Patrick; Knudsen, Gitte; Stenbæk, Dea

VERSION 1 - REVIEW

REVIEWER	WIOLETTA Medical University of Gdansk
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	Thank you for inviting me to review the submitted article. It raises a very important issue which is cognitive decline after cardiac arrest. The work is well prepared in terms of content, but I lacked support in such publications as: Czyż-Szypenbejl, K., Neurocognitive Testing-Do We Lack in Expertise? Critical care medicine 2019. At work, I lacked a clear discussion and conclusions, as well as another important publication by Mędrzycka-Dąbrowska W. Prediction of cognitive dysfunction after resuscitation-a systematic review. Postępy w Kardiologii Interwencyjnej 2018.
-------------------------	--

REVIEWER	Jonathan Elmer University of Pittsburgh
REVIEW RETURNED	16-Jul-2020

GENERAL COMMENTS	<p>Thank you for an opportunity to review this manuscript. Overall, it is very well written. The trial that is proposed is immensely important and is well designed. The authors should be commended for this undertaking.</p> <p>I do have some minor comments that I hope the authors can address to clarify some of the decisions they've made developing this trial protocol.</p> <p>- Suggest you include a justification of why you are only including patients with cardiac etiologies of arrest. Also, be precise in language here ("presumed" cardiac, as defined by Utstein template), or confirmed cardiac based on inpatient diagnostic testing. Based on the putative mechanisms described in the introduction, I'm not sure I</p>
-------------------------	---

	<p>understand why arrest due to respiratory failure (for example) would be excluded.</p> <p>- Page 8, line 31-32 “The survivors from the coronary care units...”. I’m not sure I understand the wording here, no can I find in Figure 1 what this refers to. Please clarify what this subgroup refers. It appears that these are patients who underwent percutaneous coronary intervention, had a brief arrest, and do not require ICU admission? Please be explicit.</p> <p>- Prior literature demonstrates neuropsychiatric and cognitive sequelae of OHCA survivors may be comparable to controls with general critical illness (e.g. as shown in substudies from the ABC Trial), STEMI (as shown in work by Lilja), etc. The authors should justify in this manuscript why they’ve not chosen to include any comparator arm (critical illness or major cardiac event, without cardiac arrest) to try to disentangle unique sequelae of anoxic brain injury from post-ICU syndrome.</p> <p>- Differential loss to follow-up is correctly identified by the authors as a potential major limitation. Given the feasibility aim of the study (The overall aim described at the top of Page 5), it may be more appropriate for the primary outcome for patients to be: “Able to acquire the full battery of diagnostic testing at all timepoints” or something similar. The authors should briefly report their plans to look for missingness not at random. Based on what a priori thresholds will the authors conclude that their “novel screening procedure during hospitalization...is feasible”?</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
Author response	
<p>Thank you for inviting me to review the submitted article. It raises a very important issue which is cognitive decline after cardiac arrest.</p> <p>The work is well prepared in terms of content, but I lacked support in such publications as: Czyż-Szypenbejl, K., Neurocognitive Testing-Do We Lack in Expertise? Critical care medicine 2019.</p> <p>At work, I lacked a clear discussion and conclusions, as well as another important publication by Mędrzycka-Dąbrowska W. Prediction of cognitive dysfunction after resuscitation-a systematic review. Postepy w Kardiologii Interwencyjnej 2018.</p>	<p>Thank you for pointing this out. The publication has been added to the manuscript.</p> <p>A discussion has been added at page 14.</p> <p>Please note comment from the Editorial office. A conclusion is not a part of the protocol format.</p> <p>The publication has been added to the manuscript page 5</p>
Reviewer 2	
Author response	

<p>Thank you for an opportunity to review this manuscript. Overall, it is very well written. The trial that is proposed is immensely important and is well designed. The authors should be commended for this undertaking.</p> <p>I do have some minor comments that I hope the authors can address to clarify some of the decisions they've made developing this trial protocol.</p> <p>Suggest you include a justification of why you are only including patients with cardiac etiologies of arrest. Also, be precise in language here ("presumed" cardiac, as defined by Utstein template), or confirmed cardiac based on inpatient diagnostic testing.</p> <p>Based on the putative mechanisms described in the introduction, I'm not sure I understand why arrest due to respiratory failure (for example) would be excluded.</p>	<p>Thank you for addressing this important issue. The included patients are all admitted to a specialized cardiac arrest center as they have been resuscitated from a cardiac arrest outside hospital of presumed cardiac origin as defined by the Utstein template. Please look at the discussion section page 14.</p>
<p>Page 8, line 31-32 "The survivors from the coronary care units...". I'm not sure I understand the wording here, no can I find in Figure 1 what this refers to. Please clarify what this subgroup refers. It appears that these are patients who underwent percutaneous coronary intervention, had a brief arrest, and do not require ICU admission? Please be explicit.</p>	<p>The wording is re-phrased and hopefully more precise. Page 8.</p>
<p>Prior literature demonstrates neuropsychiatric and cognitive sequelae of OHCA survivors may be comparable to controls with general critical illness (e.g. as shown in substudies from the ABC Trial), STEMI (as shown in work by Lilja), etc. The authors should justify in this manuscript why they've not chosen to include any comparator arm (critical illness or major cardiac event, without cardiac arrest) to try to disentangle unique sequelae of anoxic brain injury from post-ICU syndrome.</p>	<p>Thank you for pointing this out. Please, see the discussion page 14.</p>
<p>Differential loss to follow-up is correctly identified by the authors as a potential major limitation. Given the feasibility aim of the study (The overall aim described at the top of Page 5), it may be</p>	<p>After consideration, we have chosen to take out the word feasible in the aim and hypothesis.</p>

<p>more appropriate for the primary outcome for patients to be: “Able to acquire the full battery of diagnostic testing at all timepoints” or something similar.</p> <p>The authors should briefly report their plans to look for missingness not at random. Based on what a priori thresholds will the authors conclude that their “novel screening procedure during hospitalization...is feasible”?</p>	<p>Loss to follow-up has been addressed in the discussion page 14.</p>
---	--

VERSION 2 – REVIEW

REVIEWER	Wioletta Mędrzycka-Dąbrowska Medical University of Gdansk
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	The work has been corrected according to all comments. I cannot see the added publication Czyż-Szypenbejl, K., Neurocognitive Testing-Do We Lack in Expertise? Critical Medicine 2019, although the authors write that the work has been added. I would ask for verification
-------------------------	--

REVIEWER	Jonathan Elmer University of Pittsburgh, USA
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	The authors have addressed my comments.
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

We have revised the manuscript, and apologise for the missing publication. The publication by Czyż-Szypenbejl K, Mędrzycka-Dąbrowska W, Sak-Dankosky N. Neurocognitive Testing—Do We Lack in Expertise? Crit Care Med. 2019;47(6):e530–1 has been added as reference 40 at page 9.