PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Review of Novel Therapeutics in Cardiac Arrest (ReNTICA) - Systematic Review Protocol
AUTHORS	Murphy, Travis; Snipes, Garrett; Chowdhury, Muhammad Abdul Baker; McCall-Wright, Patti; Aleong, Elizabeth; Taylor, Noelle; Messina, Maiya-Mari; Carrazana, Gabriela; Maciel, Carolina; Becker, Torben

VERSION 1 – REVIEW

REVIEWER	Endisch, Christian Charité Universitätsmedizin Berlin, Department of Neurology
REVIEW RETURNED	12-Sep-2021

GENERAL COMMENTS	I have no comments for the authors. Well-written manuscript.

REVIEWER	Hassager, Christian University Hospital of Copenhagen, Cardiology
REVIEW RETURNED	29-Sep-2021

GENERAL COMMENTS	The introduction gives the impression, that TTM works. This should be rewritten now that TTM2 has cast further doubt om this intervention. Why do you limit the data Collection to 2015-2020? This makes no sence to me. You define your population as patients that has been resuscitated - yet in the 'Comparisons' section you give epinephrine as an example. Please explain? In the 'Endpoint' par you mention several secondary endpoints. Will you report on these if the primary endpoint is neutral? The idea behind this project needs more explanation. Why do you think there will be any missed positive findings on a major endpoint, when the whole community have not identified any (the recent ILCOR+ERC guidelines have not reported anything) post resuscitation pharmocologic treatments tthat works?

REVIEWER	Berg, K Harvard University
REVIEW RETURNED	16-Nov-2021

GENERAL COMMENTS	Are there objective criteria other than study design that would lead to a study being included or excluded? For example, is there a minimum number of patients included for included studies? For study selection and quality assessment, how will disagreement

	between co-authors be dealt with? Also, full text review would usually be not only for quality assessment but to determine if a study meet criteria for inclusion, as this is often not apparent form the abstract only. I think more detail is needed on how "quality assessment" will be done. Will the authors do formal bias assessment, and if so by what method? For data extraction, would consider listing some of the data that will be extracted a little more specifically (number of patients, age, gender, cardiac arrest characteristics, medications used, outcomes, etc), and would state how the independent verification of data extraction will be done and how discrepancies will be resolved. Please note that most regard CPC/mRS etc as functional outcomes rather than neurologic outcomes. They are good outcomes to look at but would adjust the language somewhat since they are not purely neurologic outcome measures. Would include how the authors will determine whether meta-analysis is possible (based on statistical heterogeneity of studies, risk of bias in included studies, etc). At the end of the analysis section there is a small section on "confidence in cumulative evidence." This section really belongs in the preceding section as it is part of the methods/data collection. This does answer some of my questions above about how quality assessment will be done, but would move it to the quality assessment section of the protocol. Will GRADE or other method be used to assess certainty of evidence?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Christian Endisch, Charité Universitätsmedizin Berlin
Comments to the Author:

I have no comments for the authors. Well-written manuscript.
We thank Dr Endisch for his compliments and support.

Reviewer: 2
Dr. Christian Hassager, University Hospital of Copenhagen
Comments to the Author:

The introduction gives the impression, that TTM works. This should be rewritten now that TTM2 has cast further doubt on this intervention.
While the results of the trial were not available during the initial draft of this manuscript, the introduction has been updated accordingly as follows: “Aside from targeted temperature management, therapeutic options targeting improvement in neurologic outcome are scarce and recent data has cast doubt on even this guideline-recommended therapy.[2,3]”

Why do you limit the data Collection to 2015-2020? This makes no sence to me.

This review is designed as an evaluation of the most recent practices following the American Heart Association guideline updates and serves to expand upon prior work with a specific focus on functional outcomes. This rationale has been summarized in the manuscript as follows:

“A similar review of the literature was performed in 2015, though this was focused on cataloging the therapies utilized and did not focus on studies that included functional outcome measurements.[8] Another recent systematic review reported the rate of translation from animal models to human trials for therapies targeted at cardiac arrest.[7] Though again, this review did not have a specific focus on functional neurologic outcome. While the review published by Lind et al. identified the large number of experimental therapies targeted at post-cardiac arrest physiology, the authors noted a relative dearth of clinical trials investigating those same therapies in humans.[7] Additionally, the review published in 2021 did not compare the effects of different pharmacologic agents.[7] The review proposed here seeks to compile the best available evidence for pharmacologic interventions that will improve functional neurologic outcomes in humans following cardiac arrest and compare this directly to current practice guidelines.”

You define your population as patients that has been resuscitated - yet in the 'Comparisons' section you give epinephrine as an example. Please explain?
The population studies will include patients that are able to regain return of spontaneous circulation. The comparitors will be current standard of care, which includes the administration of epinephrine in nearly all scenarios. The role of this review is to evaluate the added benefit of therapies beyond what is currently standard practice and has been updated in the manuscript as follows: “The added benefit of the interventions identified will be compared to current international practice guidelines and the pharmacologic agents advocated there (epinephrine/adrenaline, amiodarone, and lidocaine/lignocaine).”

In the 'Endpoint' par you mention several secondary endpoints. Will you report on these if the primary endpoint is neutral?
Yes, we intend to evaluate these secondary endpoints whether the primary endpoint is positive or not and will report these findings with the appropriate context.

The idea behind this project needs more explanation. Why do you think there will be any missed positive findings on a major endpoint, when the whole community have not identified any (the recent ILCOR+ERC guidelines have not reported anything) post resuscitation pharmocologic treatments that works?
We appreciate the opportunity to expand on our rationale. The role of this review is to evaluate the added benefit of therapies beyond what is currently standard practice, with a particular focus on functional outcomes and provide a look into potential therapies that may not have been mentioned explicitly in international guidelines. This clarification has been added to the manuscript as follows: “The review proposed here will focus on identifying the best available data from human studies and report on therapies that may not have been explicitly mentioned in international guidelines to date.”

Reviewer: 3
Dr. K Berg, Harvard University
Comments to the Author:

Are there objective criteria other than study design that would lead to a study being included or excluded? For example, is there a minimum number of patients included for included studies?
No, no minimum number of patients will be required. Study design is the main determination of inclusion. This has been added to the study design section. This has been updated as follows:

“Studies that compare one intervention to standard resuscitation as the control will be included. No minimum number of included subjects will be required.”
For study selection and quality assessment, how will disagreement between co-authors be dealt with?
This has been made more explicit, disagreements will be adjudicated by a senior author and has been updated in the manuscript as follows: “Study titles and abstracts will be screened for relevance in duplicate, blindly and independently, by four reviewers (EA, NT, GC, MM) and adjudicated by a senior author (TM, CM).”

Also, full text review would usually be not only for quality assessment but to determine if a study meet criteria for inclusion, as this is often not apparent form the abstract only.
This has been more explicitly stated as follows: “Eligible studies will then be assessed again for inclusion and for quality in secondary screening through review of full-text manuscripts before data abstraction.”

I think more detail is needed on how "quality assessment" will be done. Will the authors do formal bias assessment, and if so by what method?
Yes, see comments below
For data extraction, would consider listing some of the data that will be extracted a little more specifically (number of patients, age, gender, cardiac arrest characteristics, medications used, outcomes, etc), and would state how the independent verification of data extraction will be done and how discrepancies will be resolved.
This has been stated more explicitly as follows: “Data extracted will be specifically those pertinent to the systematic review and all others that fit into the synthesis of outcome parameters from all studies and meets the potential for inclusion in a meta-analysis. This will include demographics, characteristics of cardiac arrest, medications administered, and outcome parameters as well as any data that are available across all included studies. Data extraction will be independently cross-checked by a senior author and discrepancies resolved through discussion with other senior authors.”

Please note that most regard CPC/mRS etc as functional outcomes rather than neurologic outcomes. They are good outcomes to look at but would adjust the language somewhat since they are not purely neurologic outcome measures.
This has been rephrased as follows: “The primary outcomes will be survival and neurologic function as defined by one of the following performance scales: Cerebral Performance Category, modified Rankin Scale, Glasgow Outcome Scale/Glasgow Outcome Scale-Extended.”

Would include how the authors will determine whether meta-analysis is possible (based on statistical heterogeneity of studies, risk of bias in included studies, etc).
This has been expressed in the revised “Quality Assessment” section as follows: “Each article will undergo initial screening in parallel by two independent reviewers to minimize bias. All selected articles will be reviewed with senior authors during full-text review. Cochrane tools for assessment of study quality will be utilized as appropriate. (ROBINS-1 and RoB 2.0). Two independent authors will assess the risks of bias in studies considered for full-text review in order to determine feasibility of a meta-analysis. Conflicts will be adjudicated with discussion and involvement of a third author (TM or CM) as necessary.”

At the end of the analysis section there is a small section on "confidence in cumulative evidence." This section really belongs in the preceding section as it is part of the methods/data collection. This does answer some of my questions above about how quality assessment will be done, but would move it to the quality assessment section of the protocol.
This has been revised as above

Will GRADE or other method be used to assess certainty of evidence?

Cochrane tools will be used – ROBINS-1 and RoB 2.0 based on the nature of the studies found in our literature search. This has been included in the manuscript as noted as above.

Reviewer: 1
Competing interests of Reviewer: None.

Reviewer: 2
Competing interests of Reviewer: No relevant.

I have received payment for lectures by Abiomed regarding their Impella system.

Reviewer: 3
Competing interests of Reviewer: None

VERSION 2 – REVIEW

REVIEWER	Berg, K Harvard University
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	Thank you to the authors for addressing my queries and adding some clarifying text. I think the protocol manuscript is improved and appropriate for publication.