PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis
AUTHORS	Sethi, Naqash; Naqash, Arushma; Nielsen, Niklas; Jakobsen, Janus

VERSION 1 – REVIEW

REVIEWER	Yoann LAUNEY Dpt Anaesthesia and Critical Care Medicine Centre Hospitalier Universitaire de Rennes Rennes, France
REVIEW RETURNED	07-Jul-2019

GENERAL COMMENTS	Reviewing for « Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis « Thanks to the authors for this well-written protocol. I find the manuscript adequately detailed especially on the pre-defined methodology that makes stronger the systematic review compared to previous systematic reviews. That may be a valuable contribution to this topic of great interest. However, I have several concerns. As a general remark, my overall concern is the high risk of heterogeneity amongst the included studies. Even if subgroup analysis are planned, the heterogeneity in the patients populations, the methods of cooling or underlying conditions may distort the validity of the meta-analysis results. For instance, by gathering all population of patients treated for fever, the risk is to include a bias in the physiological response to fever which might be different when comparing critically ill and non-critically ill patients. In other words, a multi-organ failure patient population may have different response to temperature control compare to patients with no organ failure, because o the dramatic change in the metabolic demand. Except of my misreading of the manuscript, it seems that the authors have not mentioned the subgroup analysis splitting these 2 types of patient populations. Another pitfall might be to consider that underlying physiological triggers of fever are similar amongst the patients with infectious and non-infectious fever. In some cases (neurological injuries, drug-induced fever) the stimuli of fever may persist longer and

	may require a longer period of temperature control, which could alter the final conclusions of the meta-analysis. For citing an other example, when considering patients with intra-cranial haemorrhage, whatever the cause is, the core body temperature may be in the desired range of clinical target but the brain temperature may vary up to a previously reported maximal difference of 2°C compared to body-core temperature. Then, one should probably consider the target of fever treatment in the included studies and, as planned by the authors, make the distinction between underlying conditions (neurological injury or not) This latter comment leads to another issue: what is the device used to monitor the body core temperature ? As the authors mentioned in the introduction, different devices are available for core temperature measurement. However, some of these methods have better accuracy than others, such as the urinary or oesophageal temperature. I suspect that point to be a source of bias and it should be probably reported in the Syst Review and mentioned in the final discussion.

REVIEWER	Hildy Schell-Chaple, PhD, RN, CCNS University of California, San Francisco Health United States
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	This is a very thorough and detailed study protocol that addresses an important clinical question. I would recommend that they include a sub analysis of the neurologically injured population as the source of fever and fever response to antipyretic interventions may be different in that population.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thanks to the authors for this well-written protocol.

I find the manuscript adequately detailed especially on the pre-defined methodology that makes stronger the systematic review compared to previous systematic reviews. That may be a valuable contribution to this topic of great interest.

Our response: We thank the peer-reviewer for the fine words!

However, I have several concerns. As a general remark, my overall concern is the high risk of heterogeneity amongst the included studies.
Even if subgroup analysis are planned, the heterogeneity in the patients populations, the methods of cooling or underlying conditions may distort the validity of the meta-analysis results. For instance, by gathering all population of patients treated for fever, the risk is to include a bias in the physiological response to fever which might be different when comparing critically ill and non-critically ill patients. In other words, a multi-organ failure patient population may have different response to temperature control compare to patients with no organ failure, because o the dramatic change in the metabolic demand. Except of my misreading of the manuscript, it seems that the authors have not mentioned the subgroup analysis splitting these 2 types of patient populations.

Our response: We agree that a potential limitation of the review might be clinical and statistical heterogeneity due to our broad inclusion criteria. Nevertheless, our broad inclusion criteria is also a major strength, as no previous review has assessed whether there actually exists any heterogeneity between different patient populations and different fever control interventions, respectively. It might be valid to pool all available trials if the intervention effect seems similar which would increase the statistical power. Furthermore, if we find considerable heterogeneity, we may ultimately decide that meta-analysis should be avoided. These strengths and limitations have now been highlighted in our revised manuscript.

To assess possible heterogeneity, we have planned to conduct four different subgroup analyses. One of these ('Comparison of the effects between trials with different inclusion criteria based on an underlying condition (e.g. neurological injury and infection) of the adult') was thought to divide all of the included trials in different subgroups based on their inclusion criteria. Hence, trials including critically ill participants would be included in one subgroup. Nevertheless, trials with non-critically ill participants would likely be split up in several other subgroups such as a subgroup including trials with infection, etc.
We therefore thank the peer-reviewer for reminding us to include such an important subgroup analysis. We have therefore now included a subgroup analysis comparing trials with critically ill participants to trials with non-critically ill participants.

Another pitfall might be to consider that underlying physiological triggers of fever are similar amongst the patients with infectious and non-infectious fever. In some cases (neurological injuries, drug-induced fever) the stimuli of fever may persist longer and may require a longer period of temperature control, which could alter the final conclusions of the meta-analysis.

Our response: We agree on this being another possible reason for heterogeneity. On the other hand, these theoretical considerations may not result in intervention effect differences between trials, and hence it might be valid to pool all trials. As mentioned above, we had planned to include trials with different inclusion criteria in the planned subgroup analysis ('Comparison of the effects between trials with different inclusion criteria based on an underlying condition (e.g. neurological injury and infection) of the adult'). However, a further limitation beside the above mentioned might be that trials with several inclusion criteria will belong to several subgroups in the planned subgroup analysis. There is therefore a high risk of multiple subgroups with only few trials included. Hence, the planned subgroup analysis will become redundant. We have therefore removed this subgroup analysis. Instead, we have now included a subgroup analysis comparing infectious fever to non-infectious fever.

For citing an other example, when considering patients with intra-cranial haemorrhage, whatever the cause is, the core body temperature may be in the desired range of clinical target but the brain temperature may vary up to a previously reported maximal difference of 2°C compared to body-core temperature. Then, one should probably consider the target of fever treatment in the included studies and, as planned by the authors, make the distinction between underlying conditions (neurological injury or not)

Our response: We agree with the peer-reviewer. We will therefore extract data on the temperature target of fever treatment in each included study. We will report this in a table and in the discussion section of the systematic review paper discuss whether this had any influence on our primary results.

This latter comment leads to another issue: what is the device used to monitor the body core temperature ? As the authors mentioned in the introduction, different devices are available for core temperature measurement. However, some of these methods have better accuracy than others, such

as the urinary or oesophageal temperature. I suspect that point to be a source of bias and it should be probably reported in the Syst Review and mentioned in the final discussion.

Our response: We agree with the peer-reviewer. We will therefore extract data on which device each trial used to monitor or measure temperature. We will report this in a table and in the discussion section of the systematic review paper discuss whether this had any influence on our primary results.

Reviewer: 2

This is a very thorough and detailed study protocol that addresses an important clinical question. I would recommend that they include a sub analysis of the neurologically injured population as the source of fever and fever response to antipyretic interventions may be different in that population.

Our response: We thank the peer-reviewer for the fine words. We agree with the peer-reviewer and have as mentioned above included a subgroup analyses comparing infectious fever to non-infectious fever (e.g. neurological injury or drug-induced fever).

VERSION 2 – REVIEW

REVIEWER	LAUNEY Yoann Critical care Unit Centre Hospitalier Universitaire de Rennes Rennes, France
REVIEW RETURNED	07-Sep-2019

GENERAL COMMENTS	Thank you to the authors for having answered to all comments anf for changes in the manuscript. I really think that this protocol deserves publication as it will review an important topic. I have no more comments to make.

REVIEWER	Hildy M. Schell-Chaple, PhD, RN University of California, San Francisco United States
REVIEW RETURNED	25-Sep-2019

GENERAL COMMENTS	Thank you for addressing the reviewers' feedback and the subset analysis for these heterogenic populations/studies will improve the contribution of the meta analysis.