BMJ Open

Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032389
Article Type:	Protocol
Date Submitted by the Author:	16-Jun-2019
Complete List of Authors:	Sethi, Naqash; Rigshospitalet, Copenhagen Trial Unit Naqash, Arushma; Rigshospitalet, Copenhagen Trial Unit Nielsen, Niklas; Lund University, Dept of Clinical Sciences Jakobsen, Janus; Rigshospitalet, Copenhagen Trial Unit; University of Southern Denmark, Department of Regional Health Research
Keywords:	INTERNAL MEDICINE, PRIMARY CARE, PUBLIC HEALTH

Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Naqash J Sethi[1*], Arushma I Naqash[1], Niklas Nielsen[2], Janus C Jakobsen[1, 3, 4]

[1] Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

[2] Department of Clinical Sciences Lund, Anesthesia and Intensive Care, Lund University, Helsingborg Hospital, S-251 87, Helsingborg, Sweden.

[3] Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.

[4] Department of Cardiology, Holbæk Hospital, Holbæk, Denmark.

Corresponding author

Naqash J Sethi (NJS)

Lundtoftegade 88, st. tv., 2200 København N, Denmark

naqash.sethi@ctu.dk

Co-authors

Arushma I Naqash (AIN) – arushma.naqash@ctu.dk

Niklas Nielsen (NN) – niklas.nielsen@telia.com

Janus C Jakobsen (JCJ) – jcj_ctu@icloud.com

Keywords

Fever; Fever control; Systematic review; Meta-analysis

Word count

28 6723 words

Abstract

Introduction

Fever is an integral part of the inflammatory response and has therefore likely a physiological role in fighting infections. Nevertheless, whether fever in itself is beneficial or harmful in adults is unknown. This protocol for a systematic review aims at identifying the beneficial and harmful effects of fever control interventions in adults.

Methods and analysis

This protocol for a systematic review was conducted following the recommendations of Cochrane and the eight-step assessment suggested by Jakobsen and colleagues for better validation of meta-analytic results in systematic reviews. We plan to include all relevant randomised clinical trials comparing any fever control intervention with placebo, sham, or no intervention in adults. We plan to search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, BIOSIS, CINAHL, SCOPUS, and Web of Science Core Collection to identify relevant trials. Any eligible trial will be assessed and classified as either at high risk of bias or low risk of bias, and our primary conclusions will be based on trials at low risk of bias. We will perform our meta-analyses of the extracted data using Review Manager 5.3 and Trial Sequential Analysis. For all our outcomes, we will create a 'Summary of Findings' table based on GRADE assessments of the certainty of the evidence.

Ethics and dissemination

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included. This systematic review has the potential to highlight 1) whether one should believe fever to be beneficial, harmful, or neither in adults; 2) the existing knowledge gaps on this topic; and 3) whether the recommendations from guidelines and daily clinical practice are correct. These results will be disseminated through publication in a leading peer-reviewed journal.

PROSPERO registration number

CRD42019134006

Article summary

Strengths and limitations of this study

- This systematic review will highlight 1) the evidence regarding the beneficial and harmful effects of fever control in adults; 2) the existing knowledge gaps on this topic; and 3) whether the recommendations from guidelines and daily clinical practice are correct.
- The methodology of this systematic review is based on the Cochrane Handbook; GRADE; and Trial Sequential Analysis – hence, this systematic review considers both risks of random errors and risks of systematic errors.
- There is a risk of statistical and clinical heterogeneity because of the various types of fever control interventions and participants included in the systematic review.
- There is a risk of type 1 error because of the large number of comparisons.

Introduction

Description of the condition

Fever is defined as having an elevated core temperature above the normal range. The normal range differs between individuals and currently no universal definition for fever exists (1, 2). Fever is common in several medical conditions that range from non-serious to life-threatening. Fever is primarily caused by infection, but fever may also occur in non-infectious states, such as autoimmune diseases, autoinflammatory diseases, trauma, reperfusion injury, and systemic inflammatory response (3, 4).

Normal body temperature is circadian and typically varies 0.5 °C over the course of the day (with the lowest temperature in the morning) (5). The body temperature is controlled by a thermoregulatory centre in the hypothalamus regulating the body temperature around a temperature set-point by balanced activities of temperature-sensitive neurons (6). These neurons evoke behavioural and physiologic responses, which balances excess heat production derived from metabolic activity in muscle and liver with heat dissipation from the skin and lungs (6).

Fever is triggered by infectious agents, microbial products, and inflammatory processes that induce macrophages, endothelial cells, and the reticuloendothelial system to produce and secrete pyrogenic cytokines into the circulation (7). These pyrogenic cytokines induce the synthesis of prostaglandin E2 (PGE_2) leading to elevated levels of PGE_2 in the thermoregulatory centre in the hypothalamus, where the normal temperature set-point is raised to a febrile temperature set-point (7, 8). The febrile temperature set-point creates physiologic and behavioural responses that seek to increase heat production and heat retention until the febrile temperature set-point is reached (8). Typical physiologic responses are cutaneous vasoconstriction, shivering, and non-shivering thermogenesis, while typical behavioural responses are to seek a warmer environment and adding clothing (8). When the febrile temperature set-point is reached, an increase or decrease in body temperature will stimulate thermoregulatory mechanisms alike those at normal body temperature. After the febrile temperature set-point begins to decline, as a cause of a reduction in the concentration of pyrogens or the use of antipyretics, the processes of heat loss are accelerated through vasodilation, sweating, and behavioural responses like removal of clothing (9). This continues until the new lower temperature set-point is reached.

The body temperature can be monitored by various types of peripheral (e.g. oral, tympanic membrane, axillary, cutaneous, and temporal artery thermometry) and central methods (e.g. rectal, urinary bladder, blood catheter, and oesophageal thermometry). Central methods are more accurate but less practical to use compared to peripheral methods (10).

Fever is, as described, an integral part of the inflammatory response and has therefore likely a physiological role in fighting infections (11, 12). Potential benefits of fever may be reduced growth and reproduction of some bacteria and viruses, enhanced immunologic function, and increased activity of antimicrobial drugs (11, 13, 14). Potential harms of fever may be increased level of discomfort, increased risk of neurological and cognitive sequelae, and increased metabolic demand (13, 15).

Description of the intervention

Fever may be controlled by both pharmacological and non-pharmacological interventions. Pharmacological interventions are the main choice for treating most cases of fever, while non-pharmacological interventions are recommended in cases of refractory fever or in cases where rapid temperature decrease is needed (15).

Pharmacological fever control interventions

Pharmacological fever control interventions, called antipyretics, consist of drugs able to inhibit the enzyme cyclooxygenase (COX-1 or COX-2) and thereby interrupt the synthesis of PGE_2 (16, 17). The following reduction in the concentration of PGE_2 causes the febrile temperature set-point to reach the normal temperature set-point (16, 17). Antipyretics may also limit the febrile response by suppressing tissue inflammation, reduce pyrogenic cytokine production, enhance expression of anti-inflammatory molecules, and boost the activity of endogenous antipyretics (18). Commonly used antipyretics are salicylates (e.g. aspirin), paracetamol, and nonsteroidal anti-inflammatory drugs (NSAID) (19). Adverse effects of antipyretics may be gastrointestinal symptoms and renal toxicity (e.g. caused by NSAID), bleeding (e.g. caused by aspirin and NSAID), and hepatic injury (e.g. caused by paracetamol) (20). Patients receiving high or prolonged doses of antipyretic agents should therefore, depending on which antipyretic they receive, be monitored for gastrointestinal adverse effects, renal dysfunction, signs of bleeding, and elevated liver enzymes (20).

Non-pharmacological fever control interventions

Non-pharmacological fever control interventions consist of various surface and endovascular cooling interventions (21). Cooling reduces the body temperature by removing heat without decreasing the febrile temperature set-point (15, 22). Thus, the use of cooling may result in increased heat production, metabolic rate, and oxygen consumption, as the body tries to counter the cooling effects by shivering which increases the body temperature (15, 22). Hence, control of these unintended consequences (e.g. shivering) is crucial when performing the cooling procedure (15, 22). Before commencement of a cooling intervention, common practice includes administration of sedation (including alpha-2-agonists), analgesics (e.g. meperidine), muscle relaxants (paralytics), and antipyretics (15, 22).

Surface cooling interventions work through conduction, convection, or evaporation (15). Conduction occurs when heat is exchanged between two objects in contact with one another; convection occurs when cold fluids, such as gases and liquids, flow along the skin transferring heat from the skin to the fluid around it; and evaporation occurs when there is heat loss from cold water being evaporated from the skin (15). Surface cooling interventions consist of both conventional interventions such as crushed ice, ice bags, fans, or sponging with tepid water or alcohol, and more advanced interventions such as circulating blankets with cold fluid or cold air which are wrapped around the patient (21).

Endovascular (catheter containing fluids is inserted through the skin into a blood vessel) cooling interventions might also be used to control fever, but are mostly used for targeted temperature management within intensive care (22). Examples of endovascular cooling interventions are heat exchange catheter devices and infusion of cold fluids (23). The primary advantage of endovascular cooling is more rapid cooling, but heat exchange catheter devices are difficult to use outside intensive care units, and infusions of cold fluids expose patients to unnecessary volume expansion and imprecise temperature control (22, 23).

Why it is important to do this review

Whether fever in itself is beneficial or harmful in adults is unknown. Arguments for treating fever is that fever control leads to increased patient comfort, reduced neurologic and cognitive impairment, and reduced metabolic cost (13, 15). Arguments against treating fever is that fever leads to reduced growth and reproduction of some bacteria and virus, enhanced immunologic function, and increased activity of antimicrobial drugs (11, 13, 14).

Four systematic reviews of randomised clinical trials have previously assessed the effects of fever control interventions in febrile adults (24-27).

- Dallimore et al. from 2018 included 13 trials with 1780 participants assessing the effects of any fever control intervention but the review only included critically ill adults (24). Dallimore et al. showed that 1) active temperature management versus placebo or standard care did not significantly affect mortality (OR 1.01; 95% CI 0.81 to 1.28), ICU length of stay, nor hospital length of stay; and 2) active temperature management was superior to placebo or standard care in reducing body temperature (24). Dallimore et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).
- Hammond et al. from 2011 included 11 trials with 801 participants assessing the effects of any fever control intervention but the review only included critically ill adults (25). Hammond et al. showed that 1) newer cooling methods (intravascular and hydrogel cooling) were superior to

conventional cooling methods (surface cooling) in reducing body temperature, but with a trend toward higher mortality in the patients receiving the newer cooling methods (RR 1.42; 95% CI 0.99 to 2.03); 2) surface cooling was superior to no surface cooling in reducing body temperature; 3) continuous infusions were superior to bolus dosing in reducing body temperature; and 4) aggressive (treatment ≥38.5 °C) was superior to permissive (treatment ≥40.0 °C) antipyretic treatment in reducing the mean daily temperature (25). Hammond et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).

- Niven et al. from 2013 included five trials with 399 participants assessing the effects of any fever control intervention but this review only included critically ill adults without any neurological injury (26). Niven et al. showed that fever control at ≥38.3-38.5 °C versus fever control at ≥40.0 °C or no fever control did not significantly affect mortality (RR 0.98; 95% CI 0.58 to 1.63) (26). Niven et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).
- Chan et al. from 2010 included six trials with 474 participants assessing the effects of surface cooling versus no surface cooling in febrile adults (27). Chan et al. showed that surface cooling versus no surface cooling did not significantly affect body temperature, but increased the risk of shivering (27). Chan et al. assessed the risk of bias in the included trials according to the recommendations from the Joanna Briggs Institute (30) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).

The impact of fever control interventions on mortality and other clinically important outcomes in febrile adults regardless of e.g. being critically ill or having neurological injury or infection is still unknown. A small number of trials have been included in previous reviews, and hence previously there has not been sufficient information to confirm or reject if fever control interventions affect the risk of death or other serious adverse events. It may result in sufficient power if all types of participants are included in a meta-analysis, and it would also be possible to compare the effects of fever control interventions between different types of participants using subgroup analyses (31). No former relevant review has taken into account both risks of random errors and risk of systematic errors (updated Cochrane methodology, Trial Sequential Analysis, and GRADE assessment) (29, 31-34).

Objective

To assess the beneficial and harmful effects of fever control interventions versus placebo, sham, or no intervention in adults when assessing mortality, both serious and non-serious adverse events, and quality of life.

Methods and analysis

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions (35). A PRISMA-P checklist file is attached (**Additional file 1**).

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of trial design, setting, blinding, publication status, publication year, language, and reporting of outcomes. We will not specifically search for non-randomised studies. However, if we during our literature searches identify non-randomised studies (quasi-randomised studies or observational studies) with adequate reports of harmful effects, we will narratively report these results.

Types of participants

We will include adult participants diagnosed with fever. We will accept the definitions used by the individual trialists. We will include participants irrespective of age, sex, and comorbidities. Furthermore, we will include participants regardless of underlying conditions such as being critically ill or having neurological injury or infection.

Trials that only include a subset of eligible participants will only be included if: 1) separate data on the eligible participants are available or 2) more than 90% are eligible.

Types of interventions

We will include three types of comparisons:

- any fever control intervention compared with placebo or sham;
- any fever control intervention compared with no intervention; and
- any fever control intervention added to a co-intervention compared with a similar co-intervention (with or without placebo or sham).

As experimental intervention, we will accept any type of pharmacological or non-pharmacological fever control intervention (as defined by trialists) irrespective of dose, route of administration, and duration of administration.

We will include all control interventions (placebo, sham, or no intervention) irrespective of dose, route of administration, and duration of administration.

We will accept any type of co-intervention when such co-intervention is intended to be delivered similarly to the experimental and control group.

We will separately include trials that compare more aggressive fever control with less aggressive fever control. By doing this, we will be able to discuss if the aggressivity of fever control has a beneficial or harmful impact on the patient.

Outcome measures

Primary outcomes

- All-cause mortality.
- Serious adverse events. We will define a serious adverse event as any untoward medical occurrence that resulted in death; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the patient (36). As we expect the reporting of serious adverse events to be very heterogeneous and not strictly according to the ICH-GCP recommendations in many trials, we will include the event as a serious adverse event if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider fulfil the ICH-GCP definition. If several of such event are reported, then we will choose the highest proportion reported in each trial. We will secondly analyse each component of serious adverse events separately.

Secondary outcomes

- Quality of life (measured on any valid continuous scale).
- Non-serious adverse events (defined as those leading to discontinuation of the intervention or defined as 'adverse events' by the trialists). Each adverse event will be analysed separately.

Exploratory outcomes

- Resolution of fever (as defined by the trialists).
- Temperature change (measured by body temperature).
- Number of serious adverse events (analysed as count data).
- Number of non-serious adverse events (analysed as count data).

'All-cause mortality', 'serious adverse events', 'non-serious adverse events', and 'resolution of fever' will be analysed as proportion of participants in each group. 'Quality of life' and 'temperature change' will be analysed as the mean difference between the groups.

As exploratory analyses, 'serious adverse events' and 'non-serious adverse events' will also be analysed as number of events in each group.

We will assess all outcomes at maximal follow-up.

Search methods for identification of studies

Electronic searches

We will search for eligible randomised clinical trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid, from 1946 and onwards).
- Embase (Ovid, from 1980 and onwards).
- LILACS (Bireme, 1982 and onwards).
- BIOSIS (Thomson Reuters, 1926 and onwards).
- CINAHL.
- SCOPUS.
- Web of Science Core Collection.

A preliminary search strategy for MEDLINE (Ovid) is given in **Additional file 2**.

We will adapt the preliminary search strategy for MEDLINE (Ovid) for use in these databases. We will apply the Cochrane sensitivity-maximising randomised clinical trial filter to MEDLINE (Ovid) and adaptations of it to all the other databases, except CENTRAL (37).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status. We will assess non-English language papers by asking individuals that fluently speak the language for help.

Searching other resources

We will search the reference lists of included randomised clinical trials, previous systematic reviews, and other types of reviews for any unidentified randomised clinical trials. We will also contact authors

of included randomised clinical trials for further information by email. Further, we will search for ongoing and unidentified randomised clinical trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/);
- Google Scholar (https://scholar.google.com/); and
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/).

We will also include unpublished and grey literature trials if we identify these and assess relevant retraction statements and errata for included studies.

Data collection and analysis

We will perform the review following the recommendations of Cochrane (31). The analyses will be performed using Review Manager 5.3 (38) and Trial Sequential Analysis (39). In case of Review Manager statistical software not being sufficient, we will use STATA 15 (40).

Selection of studies

Two review authors (NJS and AIN) will independently screen titles and abstracts for inclusion of all the potentially eligible trials. We will code all these studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (JCJ). We will retrieve all relevant full-text study reports/publications and two review authors (NJS and AIN) will independently screen the full-text and identify trials for inclusion. We will report reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (JCJ). We will identify and exclude duplicated and collated multiple reports of the same trial so that each trial rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (35).

Data extraction and management

We will use a data collection from for study characteristics and outcome data, which has been piloted on at least one study in the review. Two authors (NJS and AIN) will extract and validate data independently from the included trials. Any disagreement concerning the extracted data will be discussed between the two authors. If no agreement can be reached, a third author (JCJ) will resolve the issue. We will assess duplicate publications and companion papers of a trial together in order to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication. We will extract the following data:

- Trial characteristics: bias risks components (as defined below); trial design (parallel, factorial, or cross-over); trial period; number of trial sites; name of countries in which the trial was conducted; number of intervention arms; length of follow-up; and inclusion and exclusion criteria.
- Participants characteristics and diagnosis: number of randomised participants; number of analysed participants; number of participants lost to follow-up; mean age; age range; sex ratio; definition of fever; and specific inclusion criteria based on the condition of the adult (e.g. critically ill, neurological injury, infection).
- Experimental intervention characteristics: type of fever control intervention; dose of fever control intervention; duration of fever control intervention; and mode of administration.
- Control intervention characteristics: type of control intervention; dose of intervention; duration of intervention; and mode of administration.
- Co-intervention characteristics: type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.
- Outcomes: primary and secondary outcomes specified and collected; time points reported; and differences in planned and reported outcomes.
- Notes: funding of the trial, and notable conflicts of interest of trial authors, if available.

Assessment of risk of bias in included studies

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* in our evaluation of the methodology and hence the risk of bias of the included trials (28). Two review authors (NJS and AIN) will assess the risk of bias in the included trials independently. We will evaluate the methodology in respect of:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other risks of bias.

These domains enable classification of randomised clinical trials at low risk of bias and at high risk of bias. The latter trials tend to overestimate positive intervention effects (benefits) and underestimate negative effects (harms) (41-47).

We will classify the trials according to the following criteria:

Random sequence generation

- Low risk: if sequence generation was achieved using computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- Unclear risk: if the method of randomisation was not specified, but the trial was still presented as being randomised.
- High risk: If the allocation sequence was not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

- Low risk: if the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
- Uncertain risk: if the trial was classified as randomised but the allocation concealment process was not described.
- High risk: if the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and personnel

- Low risk: if the participants and the personnel were blinded to intervention allocation and this was described.
- Uncertain risk: if the procedure of blinding was insufficiently described.
- High risk: if blinding of participants and the personnel was not performed.

Blinding of outcome assessment

- Low risk: if it was mentioned that outcome assessors were blinded, and this was described.
- Uncertain risk: if it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was insufficiently described.

- High risk: if no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- Low risk: if missing data were unlikely to make treatment effects depart from plausible values. This could either be: 1) there were no dropouts or withdrawals for all outcomes, or 2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups. Generally, the trial will be judged as at a low risk of bias due to incomplete outcome data if dropouts are less than 5%. However, the 5% cut-off is not definitive.

- Uncertain risk: if there was insufficient information to assess whether missing data were likely to induce bias on the results.

- High risk: if the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- Low risk: if a protocol was published/registered before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial had begun, reporting of all-cause mortality and various types of serious adverse events will grant the trial a grade of low risk of bias.

- Uncertain risk: if no protocol was published and the outcomes all-cause mortality and various types of serious adverse events were not reported on.

- High risk: if the outcomes in the protocol were not reported on.

Other risks of bias

- Low risk: if the trial appears to be free of other components that could put it at risk of bias.

- Unclear risk: if the trial may or may not be free of other components that could put it at risk of bias.

- High risk: if there are other factors in the trial that could put it at risk of bias.

Overall risk of bias

- Low risk: the trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.

- High risk: the trial will be classified 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome. This will enable us to assess the bias risk for each outcome result in addition to each trial.

We will grade each potential source of bias as high, low, or unclear and provide evidence from the trial report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different trials for each of the domains listed.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see paragraphs below).

Continuous outcomes

We will calculate the mean differences (MDs) and if necessary, as a hypothesis generating analysis, the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see paragraphs below).

Count outcomes

We will calculate rate ratios with 95% confidence interval (CI) for count outcomes.

Unit of analysis issues

We will only include randomised clinical trials. For trials using cross-over design, only data from the first period will be included (48, 49). For trials where multiple trial intervention groups are reported, we will only include the relevant groups. If two comparisons from the same trial are combined in the same meta-analysis, we will halve the control group to avoid double-counting (49). We will not include cluster randomised trials, as these have a high risk of biased results due to confounding (31).

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing information and data.

Dichotomous outcomes

We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only change from baseline scores are reported, we will analyse the results together with follow-up scores (31). If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by the Chi^2-test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2-statistic (50, 51).

We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided (49).

Assessment of reporting biases

We will use a funnel plot to assess reporting bias in the meta-analyses including ten or more trials. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size, and asymmetry of a funnel plot is not necessarily caused by reporting bias. From this information, we assess possible reporting bias). For dichotomous outcomes, we will test asymmetry with the Harbord test (52) if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test (53) and the adjusted rank correlation (54).

Data synthesis

Meta-analysis and assessment of significance

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions (49), Keus et al. (33), and the eight-step assessment suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29). We will use the statistical software Review Manager 5.3 (38) provided by Cochrane to analyse data and STATA 15.

We will assess our intervention effects with both random-effects meta-analyses (55) and fixed-effect meta-analyses (56) and report the more conservative result as our primary result (29). The more conservative point estimate is the result with the highest P value and the widest 95% CI. In case that few trials (1-3) make up >90% of the weight in the meta-analysis, we will use fixed-effect meta-analysis. If there is substantial discrepancy between the results of the two methods, we will report and discuss the results (29).

We will adjust our thresholds for statistical significance due to problems with multiplicity (family-wise error rate), by dividing the pre-specified P value threshold with the value halfway between 1 (no adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment) (29). We will assess a total of four primary and secondary outcomes in the review and, hence, consider a P value of 0.02 or less as the threshold for statistical significance (29).

If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial Sequential Analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (32, 39, 57-65). Therefore, Trial Sequential Analysis (39) can be applied to control these risks (http://www.ctu.dk/tsa/) (62). Similar to a sample size calculation in a randomised clinical trial, Trial Sequential Analysis estimates the diversity-adjusted required information size (DARIS) (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors (60). The DARIS takes into account the anticipated intervention effect, the variance of the anticipated difference in intervention effects, the acceptable risk of falsely rejecting the null hypothesis (alpha), the acceptable risk of falsely confirming the null hypothesis (beta), and the variance of the intervention effect estimates between trials (29, 60, 66). We searched for suitable empirical data to determine and predefine the anticipated intervention effects (29). However, no suitable data could be found. Instead, we pragmatically hypothesised the anticipated intervention effects:

- When analysing all-cause mortality, serious adverse events, and non-serious adverse events, we will pragmatically anticipate an intervention effect equal to a risk ratio reduction (RRR) of 25%.
- When analysing resolution of fever, we will pragmatically anticipate an intervention effect equal to a RRR of 30%.
- When analysing quality of life and temperature change, we will pragmatically anticipate an intervention effect equal to the mean difference of the observed SD/2 (67).

Trial Sequential Analysis enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the DARIS, trial sequential monitoring boundaries are

constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the DARIS (32, 60).

Firm evidence for benefit or harm may be established if a trial sequential monitoring boundary (i.e. upper boundary of benefit or lower boundary of harm) is crossed before reaching the DARIS, in which case further trials may turn out to be superfluous. In contrast, if a boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with Trial Sequential Analysis. This occurs when the cumulative Z-score crosses the trial sequential boundaries for futility.

The Trial Sequential Analysis program is also able to calculate TSA-adjusted CIs, which we will report in addition to the unadjusted naïve 95% CI. TSA-adjusted CI compared to unadjusted naïve 95% CI gives a more correct estimation of the true CI, as it is adjusted for lack of information (62). If the Trial Sequential Analysis cannot be conducted because of too little information, we will conduct a more lenient analysis by increasing the anticipated intervention effect (in these cases, the TSA-adjusted CI is overly optimistic).

For dichotomous outcomes, we will estimate the DARIS based on an anticipated intervention effect (our anticipated intervention effect for each dichotomous outcome is stated above), the observed proportion of participants with an outcome in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of significance' above), a beta of 10%, and diversity as suggested by the trials in the meta-analysis (29, 60, 68). In case there is some evidence or effect of the intervention, a supplementary Trial Sequential Analysis using the limit of the CI closest to 1.00 as the anticipated intervention effect will be conducted (29).

For continuous outcomes, we will estimate the DARIS based on a minimal clinically important difference of SD/2, the standard deviation observed in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of significance' above), a beta of 10%, and a diversity as suggested by the trials in the meta-analysis (29, 60, 68). In case there is some evidence or effect of the intervention, a supplementary Trial Sequential Analysis using the limit of the CI closest to 0.00 as the anticipated intervention effect will be conducted (29).

We will document difficult decisions in the review and sensitivity analyses will assess the impact of these decisions on the findings of the review.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses on all our outcomes.

A. Comparison of the effects between trials with different types of fever control interventions.

B. Comparison of the effects between trials with different inclusion criteria based on an underlying condition (e.g. neurological injury and infection) of the adult.

C. Comparison of the effects between trials with different maximal follow-ups:

- Up to 1 year; or
- 1 year and above.

D. Comparison of the effects between industry funded trials or trials with unknown funding compared to non-industry funded trials:

- industry funded trials or unknown funding; or
- non-industry funded trials.

We will use the formal test for subgroup differences in Review Manager (38).

Other post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (29).

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis in which we exclude trials with overall 'high risk of bias'.

To assess the potential impact of the participants being critically ill, we will perform a sensitivity analysis in which we exclude trials that do not include critically ill participants.

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the following two sensitivity analyses when assessing each dichotomous outcome (all-cause mortality, serious adverse events, non-serious adverse events, and resolution of fever):

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group have survived, had no serious adverse event, had no non-serious adverse events, and had resolution of fever; and all those participants lost to follow-up in the control group have not survived, had a serious adverse event, had a non-serious adverse event, and did not have resolution of fever.

- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group have not survived, had a serious adverse event, had a non-serious adverse event, and did not have resolution of fever; and that all those participants lost to follow-up in the control group have survived, had no serious adverse event, had no non-serious adverse event, and had resolution of fever.

We will present results of both scenarios in our review.

To assess the potential impact of the missing data for continuous outcomes, we will perform the following two sensitivity analyses when assessing each continuous outcome (quality of life and temperature change):

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group and control group have had a 'beneficial outcome' or 'harmful outcome', respectively. A 'beneficial outcome' will be the group mean plus one standard deviation (SD) of the group mean. A 'harmful outcome' will be the group mean minus one SD of the group mean (29).

- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group and control group have had a 'harmful outcome' or 'beneficial outcome', respectively. A 'harmful outcome' will be the group mean minus one standard deviation (SD) of the group mean. A 'beneficial outcome' will be the group mean plus one SD of the group mean (29).

We will present results of both scenarios in our review.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population.

We will present results of this scenario in our review.

Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (29).

Summary of findings

We will use the GRADE system to assess the certainty of the body of evidence associated with each of our outcomes constructing 'Summary of Findings' (SoF) tables using the GRADEpro software (34, 69-

71). The GRADE approach appraises the certainty of the body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed (34, 69, 70). We will assess the GRADE levels of evidence as high, moderate, low, and very low and downgrade the evidence by one or two levels depending on the following certainty measures: within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (34, 69, 70). We will use TSA to assess the 'imprecision' of effect estimates (29). We will use methods and recommendations described in Chapter 8 (Section 8.5) (28) and Chapter 12 (72) of the Cochrane Handbook for Systematic Reviews of Interventions (31). We will justify all decisions to downgrade the certainty of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

We will include all trials in our analyses and conduct a sensitivity analysis excluding trials at high risk of bias. If the results are similar, we will base our SoF table and conclusions on the overall analysis. If they differ, we will base our SoF table and conclusions on trials at low risk of bias.

Differences between the protocol and the review

We will conduct the review according to this protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Patient and Public Involvement

We conducted this protocol for a systematic review without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this protocol for readability or accuracy.

Discussion

This protocol aims to assess the effects of fever control interventions in adults regardless of any underlying condition to determine whether fever control interventions are beneficial or harmful. The outcomes will be all-cause mortality, serious adverse events, quality of life, non-serious adverse events, resolution of fever, and temperature change.

This protocol has a number of strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions (49), the eight-step assessment suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29), Trial Sequential Analysis (62), and GRADE (34, 69, 70). Hence, this protocol takes into account both risks of random errors and risks of systematic errors.

Our protocol also has a number of limitations. The primary limitation is that we will include various types of pharmacological and non-pharmacological fever control interventions, and it is likely that different interventions have different effects. Another limitation is that we will include various types of participants regardless of their underlying condition, and it is possible that fever control interventions affect participants differently depending on their condition. To minimise this limitation, we have planned to carefully assess clinical and statistical heterogeneity including several subgroup analyses. Another limitation is the large number of comparisons, which increase the risk of type 1 error. To minimise this limitation, we have adjusted our thresholds for significance according to the total number of our primary and secondary outcomes. Nevertheless, the large risk of type 1 error will be taken into account when interpreting the review results.

Ethics and dissemination

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included. The results of this systematic review will be disseminated through publication in a leading peer-reviewed journal.

References

1. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. Jama. 1992;268(12):1578-80.

2. Obermeyer Z, Samra JK, Mullainathan S. Individual differences in normal body temperature: longitudinal big data analysis of patient records. BMJ (Clinical research ed). 2017;359:j5468.

3. Steele GM, Franco-Paredes C, Chastain DB. Noninfectious causes of fever in adults. The Nurse practitioner. 2018;43(4):38-44.

4. McGregor AC, Moore DA. Infectious causes of fever of unknown origin. Clinical medicine (London, England). 2015;15(3):285-7.

5. Chan MC, Spieth PM, Quinn K, Parotto M, Zhang H, Slutsky AS. Circadian rhythms: from basic mechanisms to the intensive care unit. Critical care medicine. 2012;40(1):246-53.

6. Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. American journal of physiology Regulatory, integrative and comparative physiology. 2007;292(1):R37-46.

7. Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31 Suppl 5:S178-84.

8. Saper CB, Breder CD. The neurologic basis of fever. The New England journal of medicine. 1994;330(26):1880-6.

9. Porat R, Dinarello CA. Pathophysiology and treatment of fever in adults. In A. Bloom (Ed.), *UpToDate*. Retrived 02.08.18, from https://www.uptodate.com/contents/pathophysiology-and-treatment-of-fever-in-adults. 2018.

10. Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Annals of internal medicine. 2015;163(10):768-77.

11. Kluger MJ, Kozak W, Conn CA, Leon LR, Soszynski D. The adaptive value of fever. Infectious disease clinics of North America. 1996;10(1):1-20.

12. Mackowiak PA. Fever: blessing or curse? A unifying hypothesis. Annals of internal medicine. 1994;120(12):1037-40.

13. Greisman LA, Mackowiak PA. Fever: beneficial and detrimental effects of antipyretics. Current opinion in infectious diseases. 2002;15(3):241-5.

14. Mackowiak PA, Ruderman AE, Martin RM, Many WJ, Smith JW, Luby JP. Effects of physiologic variations in temperature on the rate of antibiotic-induced bacterial killing. American journal of clinical pathology. 1981;76(1):57-62.

15. Plaisance KI, Mackowiak PA. Antipyretic therapy: physiologic rationale, diagnostic implications, and clinical consequences. Archives of internal medicine. 2000;160(4):449-56.

16. Vane JR. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs. Nature New Biology. 1971;231:232.

17. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature. 1972;240(5381):410-1.

18. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. The American journal of medicine. 2001;111(4):304-15.

19. Niven DJ, Laupland KB, Tabah A, Vesin A, Rello J, Koulenti D, et al. Diagnosis and management of temperature abnormality in ICUs: a EUROBACT investigators' survey. Critical care (London, England). 2013;17(6):R289.

20. Plaisance KI. Toxicities of drugs used in the management of fever. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31 Suppl 5:S219-23.

21. Polderman KH. How to Stay Cool in the Intensive Care Unit? Endovascular Versus Surface Cooling. Circulation. 2015;132(3):152-7.

22. Doyle JF, Schortgen F. Should we treat pyrexia? And how do we do it? Critical care (London, England). 2016;20(1):303.

23. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Critical care medicine. 2009;37(3):1101-20.

24. Dallimore J, Ebmeier S, Thayabaran D, Bellomo R, Bernard G, Schortgen F, et al. Effect of active temperature management on mortality in intensive care unit patients. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2018;20(2):150-63.

25. Hammond NE, Boyle M. Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: a systematic review and meta-analysis. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses. 2011;24(1):4-17.

26. Niven DJ, Stelfox HT, Laupland KB. Antipyretic therapy in febrile critically ill adults: A systematic review and meta-analysis. Journal of critical care. 2013;28(3):303-10.

27. Chan EY, Chen WT, Assam PN. External cooling methods for treatment of fever in adults: a systematic review. JBI library of systematic reviews. 2010;8(20):793-825.

28. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 520 (updated June 2017), Cochrane, 2017 Available from wwwtrainingcochraneorg/handbook.

29. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC medical research methodology. 2014;14:120.

30. Joanna Briggs Institute. Checklist for randomized controlled trials. Available at http://joannabriggs.org/assets/docs/critical-appraisal-tools/JBI_RCTs_Appraisal_tool2017.pdf [

31. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration. 2011;www.handbook.cochrane.org.

32. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of clinical epidemiology. 2008;61(1):64-75.

33. Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. BMC medical research methodology. 2010;10:90.

34. Schünemann H, Brozek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdtguidelinedevelopmentorg/app/handbook/handbookhtml.

35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9, w64.

36. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) adopts consolidated guideline on good clinical practice in the conduct of clinical trials on medicinal products for human use. International digest of health legislation. 1997;48(2):231-4.

37. Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbookcochraneorg.

38. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014.

39. Copenhagen Trial Unit. TSA - Trial Sequential Analysis. http://www.ctu.dk/tsa/.

40. StataCorp. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LP. 2017;http://www.stata.com.

41. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.

42. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of internal medicine. 2001;135(11):982-9.

43. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet (London, England). 1998;352(9128):609-13.

44. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Jama. 1995;273(5):408-12.

45. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ (Clinical research ed). 2008;336(7644):601-5.

46. Savovic J, Jones H, Altman D, Harris R, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technology Assessment. 2012;16(35):1-82.

47. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database of Systematic Reviews. 2017;2:Mr000033.

48. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International journal of epidemiology. 2002;31(1):140-9.

49. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

50. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.

51. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.

52. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Statistics in medicine. 2006;25(20):3443-57.

53. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-34.

54. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.

55. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.

56. Demets DL. Methods for combining randomized clinical trials: strengths and limitations. Statistics in medicine. 1987;6(3):341-50.

57. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of clinical epidemiology. 2008;61(8):763-9.

58. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International journal of epidemiology. 2009;38(1):287-98.

59. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? International journal of epidemiology. 2009;38(1):276-86.

60. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC medical research methodology. 2009;9:86.

61. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clinical epidemiology. 2010;2:57-66.

62. Thorlund K EJ, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). 2011. http://www.ctu.dk/tsa/files/tsa_manual.pdf.

63. Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic reviews of anesthesiologic interventions reported as statistically significant: problems with power, precision, and type 1 error protection. Anesthesia and analgesia. 2015;121(6):1611-22.

64. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ open. 2016;6(8):e011890.

65. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC medical research methodology. 2017;17(1):39.

66. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. PloS one. 2013;8(3):e59202.

67. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003;41(5):582-92.

68. Castellini G, Nielsen EE, Gluud C. Comment on: "Cell therapy for heart disease: Trial sequential analyses of two cochrane reviews". Clinical pharmacology and therapeutics. 2016.

69. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6.

70. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.

71. GRADEpro GDT. McMaster University (developed by Evidence Prime)2015.

72. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from wwwtrainingcochraneorg/handbook.

Footnotes

Authors' contributions

NJS and JCJ equally contributed in conception and design of the protocol. NJS drafted the protocol. AIN, NN, and JCJ amended the protocol. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy is hugely appreciated.

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION 1					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	58
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-22
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	799-801
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	802-804
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	802-804
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	802-804
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	149-202
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	203-206
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	211-240
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	269-299

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	281
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	300-314
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	304-314
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	315-323
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	324-340
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	241-268
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	341-417
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	460-478
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	418-531
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	532-587
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	478
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	394 – 401 AND 452-459
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	588-603

Additional file 2

Search strategy for MEDLINE (Ovid)

1. exp Fever/

4. exp Infection/

5. exp Sepsis/

6. exp Temperature/

8. (fever or pyrexia or febrile or infection or sepsis or temperature or hyperthermia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp Antipyretics/

11. exp Acetaminophen/

12. exp Anti-inflammatory Agents, Non-steroidal/

13. exp Ibuprofen/

14. exp Salicylates/

15. exp Cryotherapy/

16. ("fever control" or antipyretics or antipyresis or paracetamol or acetaminophen or NSAID or "non-steroidal anti-inflammatory drugs" or ibuprofen or "cyclo-oxygenase inhibitors" or "cox-inhibitor" or salicylates or aspirin or diclofenac or naproxen or indomethacin or ketorolac or metamizole or "induced hypothermia" or "targeted temperature management" or cooling or "external cooling" or "surface cooling" or "physical cooling" or "endovascular cooling" or sponges or fan or baths or blanket or ice or fluid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17. 10 or 11 or 12 or 13 or 14 or 15 or 16

18. 9 and 17

19. exp Clinical trial/

20. (randomized or randomised or clinical or controlled or placebo or "no intervention" or sham or trial or systematic review or meta-analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21. 19 or 20

20. 18 and 21

BMJ Open

Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032389.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2019
Complete List of Authors:	Sethi, Naqash; Rigshospitalet, Copenhagen Trial Unit Naqash, Arushma; Rigshospitalet, Copenhagen Trial Unit Nielsen, Niklas; Lund University, Dept of Clinical Sciences Jakobsen, Janus; Rigshospitalet, Copenhagen Trial Unit; University of Southern Denmark, Department of Regional Health Research
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice, Intensive care
Keywords:	INTERNAL MEDICINE, PRIMARY CARE, PUBLIC HEALTH

Fever control interventions versus placebo, sham, or no intervention in adults. A protocol for a systematic review with meta-analysis and Trial Sequential Analysis

Naqash J Sethi[1*], Arushma I Naqash[1], Niklas Nielsen[2], Janus C Jakobsen[1, 3, 4]

[1] Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

[2] Department of Clinical Sciences Lund, Anesthesia and Intensive Care, Lund University, Helsingborg Hospital, S-251 87, Helsingborg, Sweden.

[3] Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.

[4] Department of Cardiology, Holbæk Hospital, Holbæk, Denmark.

Corresponding author

Naqash J Sethi (NJS)

Lundtoftegade 88, st. tv., 2200 København N, Denmark

naqash.sethi@ctu.dk

Co-authors

Arushma I Naqash (AIN) – arushma.naqash@ctu.dk

Niklas Nielsen (NN) – niklas.nielsen@telia.com

Janus C Jakobsen (JCJ) – jcj_ctu@icloud.com

Keywords

Fever; Fever control; Systematic review; Meta-analysis

Word count

28 6795 words

Abstract

Introduction

Fever is an integral part of the inflammatory response and has therefore likely a physiological role in fighting infections. Nevertheless, whether fever in itself is beneficial or harmful in adults is unknown. This protocol for a systematic review aims at identifying the beneficial and harmful effects of fever control interventions in adults.

Methods and analysis

This protocol for a systematic review was conducted following the recommendations of Cochrane, GRADE, and the eight-step assessment suggested by Jakobsen and colleagues for better validation of meta-analytic results in systematic reviews. We plan to include all relevant randomised clinical trials comparing any fever control intervention with placebo, sham, or no intervention in adults. We plan to search CENTRAL, MEDLINE, Embase, LILACS, BIOSIS, CINAHL, SCOPUS, and Web of Science Core Collection to identify relevant trials. Any eligible trial will be assessed and classified as either at high risk of bias or low risk of bias, and our primary conclusions will be based on trials at low risk of bias. We will perform our meta-analyses of the extracted data using Review Manager 5.3 and Trial Sequential Analysis. For all our outcomes, we will create a 'Summary of Findings' table based on GRADE assessments of the certainty of the evidence.

Ethics and dissemination

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included. This systematic review has the potential to highlight 1) whether one should believe fever to be beneficial, harmful, or neither in adults; 2) the existing knowledge gaps on this topic; and 3) whether the recommendations from guidelines and daily clinical practice are correct. These results will be disseminated through publication in a leading peer-reviewed journal.

PROSPERO registration number

CRD42019134006

Article summary

Strengths and limitations of this study

- Methodology based on the Cochrane Handbook, GRADE, and Trial Sequential Analysis.
- Broad inclusion criteria including all trials assessing fever control interventions in adults.
- Broad search strategy including ten databases and two clinical trial registries.
- Risk of statistical and clinical heterogeneity due to various types of fever control interventions and participants included.
- High risk of family-wise error due to the large number of analyses included.

Introduction

Description of the condition

Fever is defined as having an elevated core temperature above the normal range. The normal range differs between individuals and currently no universal definition for fever exists (1, 2). Fever is common in several medical conditions that range from non-serious to life-threatening. Fever is primarily caused by infection, but fever may also occur in non-infectious states, such as autoimmune diseases, autoinflammatory diseases, trauma, reperfusion injury, and systemic inflammatory response (3, 4).

Normal body temperature is circadian and typically varies 0.5 °C over the course of the day (with the lowest temperature in the morning) (5). The body temperature is controlled by a thermoregulatory centre in the hypothalamus regulating the body temperature around a temperature set-point by balanced activities of temperature-sensitive neurons (6). These neurons evoke behavioural and physiologic responses, which balances excess heat production derived from metabolic activity in muscle and liver with heat dissipation from the skin and lungs (6).

Fever is triggered by infectious agents, microbial products, and inflammatory processes that induce macrophages, endothelial cells, and the reticuloendothelial system to produce and secrete pyrogenic cytokines into the circulation (7). These pyrogenic cytokines induce the synthesis of prostaglandin E2 (PGE_2) leading to elevated levels of PGE_2 in the thermoregulatory centre in the hypothalamus, where the normal temperature set-point is raised to a febrile temperature set-point (7, 8). The febrile temperature set-point creates physiologic and behavioural responses that seek to increase heat production and heat retention until the febrile temperature set-point is reached (8). Typical physiologic responses are cutaneous vasoconstriction, shivering, and non-shivering thermogenesis, while typical behavioural responses are to seek a warmer environment and adding clothing (8). When the febrile temperature set-point is reached, an increase or decrease in body temperature will stimulate thermoregulatory mechanisms alike those at normal body temperature. After the febrile temperature set-point begins to decline, as a cause of a reduction in the concentration of pyrogens or the use of antipyretics, the processes of heat loss are accelerated through vasodilation, sweating, and behavioural responses like removal of clothing (9). This continues until the new lower temperature set-point is reached.

The body temperature can be monitored by various types of peripheral (e.g. oral, tympanic membrane, axillary, cutaneous, and temporal artery thermometry) and central methods (e.g. rectal, urinary bladder, blood catheter, and oesophageal thermometry). Central methods are more accurate but less practical to use compared to peripheral methods (10).

Fever is, as described, an integral part of the inflammatory response and has therefore likely a physiological role in fighting infections (11, 12). Potential benefits of fever may be reduced growth and reproduction of some bacteria and viruses, enhanced immunologic function, and increased activity of antimicrobial drugs (11, 13, 14). Potential harms of fever may be increased level of discomfort, increased risk of neurological and cognitive sequelae, and increased metabolic demand (13, 15).

Description of the intervention

Fever may be controlled by both pharmacological and non-pharmacological interventions. Pharmacological interventions are the main choice for treating most cases of fever, while non-pharmacological interventions are recommended in cases of refractory fever or in cases where rapid temperature decrease is needed (15).

Pharmacological fever control interventions

Pharmacological fever control interventions, called antipyretics, consist of drugs able to inhibit the enzyme cyclooxygenase (COX-1 or COX-2) and thereby interrupt the synthesis of PGE_2 (16, 17). The following reduction in the concentration of PGE_2 causes the febrile temperature set-point to reach the normal temperature set-point (16, 17). Antipyretics may also limit the febrile response by suppressing tissue inflammation, reduce pyrogenic cytokine production, enhance expression of anti-inflammatory molecules, and boost the activity of endogenous antipyretics (18). Commonly used antipyretics are salicylates (e.g. aspirin), paracetamol, and nonsteroidal anti-inflammatory drugs (NSAID) (19). Adverse effects of antipyretics may be gastrointestinal symptoms and renal toxicity (e.g. caused by NSAID), bleeding (e.g. caused by aspirin and NSAID), and hepatic injury (e.g. caused by paracetamol) (20). Patients receiving high or prolonged doses of antipyretic agents should therefore, depending on which antipyretic they receive, be monitored for gastrointestinal adverse effects, renal dysfunction, signs of bleeding, and elevated liver enzymes (20).

Non-pharmacological fever control interventions

Non-pharmacological fever control interventions consist of various surface and endovascular cooling interventions (21). Cooling reduces the body temperature by removing heat without decreasing the febrile temperature set-point (15, 22). Thus, the use of cooling may result in increased heat production, metabolic rate, and oxygen consumption, as the body tries to counter the cooling effects by shivering which increases the body temperature (15, 22). Hence, control of these unintended consequences (e.g. shivering) is crucial when performing the cooling procedure (15, 22). Before commencement of a cooling intervention, common practice includes administration of sedation (including alpha-2-agonists), analgesics (e.g. meperidine), muscle relaxants (paralytics), and antipyretics (15, 22).

Surface cooling interventions work through conduction, convection, or evaporation (15). Conduction occurs when heat is exchanged between two objects in contact with one another; convection occurs when cold fluids, such as gases and liquids, flow along the skin transferring heat from the skin to the fluid around it; and evaporation occurs when there is heat loss from cold water being evaporated from the skin (15). Surface cooling interventions consist of both conventional interventions such as crushed ice, ice bags, fans, or sponging with tepid water or alcohol, and more advanced interventions such as circulating blankets with cold fluid or cold air which are wrapped around the patient (21).

Endovascular (catheter containing fluids is inserted through the skin into a blood vessel) cooling interventions might also be used to control fever, but are mostly used for targeted temperature management within intensive care (22). Examples of endovascular cooling interventions are heat exchange catheter devices and infusion of cold fluids (23). The primary advantage of endovascular cooling is more rapid cooling, but heat exchange catheter devices are difficult to use outside intensive care units, and infusions of cold fluids expose patients to unnecessary volume expansion and imprecise temperature control (22, 23).

Why it is important to do this review

Whether fever in itself is beneficial or harmful in adults is unknown. Arguments for treating fever is that fever control leads to increased patient comfort, reduced neurologic and cognitive impairment, and reduced metabolic cost (13, 15). Arguments against treating fever is that fever leads to reduced growth and reproduction of some bacteria and virus, enhanced immunologic function, and increased activity of antimicrobial drugs (11, 13, 14).

Four systematic reviews of randomised clinical trials have previously assessed the effects of fever control interventions in febrile adults (24-27).

- Dallimore et al. from 2018 included 13 trials with 1780 participants assessing the effects of any fever control intervention but the review only included critically ill adults (24). Dallimore et al. showed that 1) active temperature management versus placebo or standard care did not significantly affect mortality (OR 1.01; 95% CI 0.81 to 1.28), ICU length of stay, nor hospital length of stay; and 2) active temperature management was superior to placebo or standard care in reducing body temperature (24). Dallimore et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).
- Hammond et al. from 2011 included 11 trials with 801 participants assessing the effects of any fever control intervention but the review only included critically ill adults (25). Hammond et al. showed that 1) newer cooling methods (intravascular and hydrogel cooling) were superior to

conventional cooling methods (surface cooling) in reducing body temperature, but with a trend toward higher mortality in the patients receiving the newer cooling methods (RR 1.42; 95% CI 0.99 to 2.03); 2) surface cooling was superior to no surface cooling in reducing body temperature; 3) continuous infusions were superior to bolus dosing in reducing body temperature; and 4) aggressive (treatment ≥38.5 °C) was superior to permissive (treatment ≥40.0 °C) antipyretic treatment in reducing the mean daily temperature (25). Hammond et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).

- Niven et al. from 2013 included five trials with 399 participants assessing the effects of any fever control intervention but this review only included critically ill adults without any neurological injury (26). Niven et al. showed that fever control at ≥38.3-38.5 °C versus fever control at ≥40.0 °C or no fever control did not significantly affect mortality (RR 0.98; 95% CI 0.58 to 1.63) (26). Niven et al. assessed the risk of bias in the included trials according to the recommendations in the Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).
- Chan et al. from 2010 included six trials with 474 participants assessing the effects of surface cooling versus no surface cooling in febrile adults (27). Chan et al. showed that surface cooling versus no surface cooling did not significantly affect body temperature, but increased the risk of shivering (27). Chan et al. assessed the risk of bias in the included trials according to the recommendations from the Joanna Briggs Institute (30) and a systematic search was conducted, however GRADE was not used to assess the certainty of the evidence, and the risks of random errors was not assessed (29).

The impact of fever control interventions on mortality and other clinically important outcomes in febrile adults regardless of e.g. being critically ill or having neurological injury or infection is still unknown. A small number of trials have been included in previous reviews, and hence previously there has not been sufficient information to confirm or reject if fever control interventions affect the risk of death or other serious adverse events. It may result in sufficient power if all types of participants are included in a meta-analysis, and it would also be possible to compare the effects of fever control interventions between different types of participants using subgroup analyses (31). No former relevant review has taken into account both risks of random errors and risk of systematic errors (Cochrane methodology, Trial Sequential Analysis (TSA), and GRADE assessment) (29, 31-34).

Objective

To assess the beneficial and harmful effects of fever control interventions versus placebo, sham, or no intervention in adults when assessing mortality, both serious and non-serious adverse events, and quality of life.

Methods and analysis

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions (35). A PRISMA-P checklist file is attached (**Additional file 1**).

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of trial design, setting, blinding, publication status, publication year, language, and reporting of outcomes. We will not specifically search for non-randomised studies. However, if we during our literature searches identify non-randomised studies (quasi-randomised studies or observational studies) with adequate reports of harmful effects, we will narratively report these results.

Types of participants

We will include adult participants diagnosed with fever. We will accept the definitions used by the individual trialists. We will include participants irrespective of age, sex, and comorbidities. Furthermore, we will include participants regardless of underlying conditions such as being critically ill or having neurological injury or infection.

Trials that only include a subset of eligible participants will only be included if: 1) separate data on the eligible participants are available or 2) more than 90% are eligible.

Types of interventions

We will include three types of comparisons:

- any fever control intervention compared with placebo or sham;
- any fever control intervention compared with no intervention; and
- any fever control intervention added to a co-intervention compared with a similar co-intervention (with or without placebo or sham).

As experimental intervention, we will accept any type of pharmacological or non-pharmacological fever control intervention (as defined by trialists) irrespective of dose, route of administration, and duration of administration.

We will include all control interventions (placebo, sham, or no intervention) irrespective of dose, route of administration, and duration of administration.

We will accept any type of co-intervention when such co-intervention is intended to be delivered similarly to the experimental and control group.

We will separately include trials that compare more aggressive fever control with less aggressive fever control. By doing this, we will be able to discuss if the aggressivity of fever control has a beneficial or harmful impact on the patient.

Outcome measures

Primary outcomes

- All-cause mortality.
- Serious adverse events. We will define a serious adverse event as any untoward medical occurrence that resulted in death; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the patient (36). As we expect the reporting of serious adverse events to be very heterogeneous and not strictly according to the ICH-GCP recommendations in many trials, we will include the event as a serious adverse event if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider fulfil the ICH-GCP definition. If several of such event are reported, then we will choose the highest proportion reported in each trial. We will secondly analyse each component of serious adverse events separately.

Secondary outcomes

- Quality of life (measured on any valid continuous scale).
- Non-serious adverse events (defined as those leading to discontinuation of the intervention or defined as 'adverse events' by the trialists). Each adverse event will be analysed separately.

Exploratory outcomes

- Resolution of fever (as defined by the trialists).
- Temperature change (measured by body temperature).
- Number of serious adverse events (analysed as count data).
- Number of non-serious adverse events (analysed as count data).

'All-cause mortality', 'serious adverse events', 'non-serious adverse events', and 'resolution of fever' will be analysed as proportion of participants in each group. 'Quality of life' and 'temperature change' will be analysed as the mean difference between the groups.

As exploratory analyses, 'serious adverse events' and 'non-serious adverse events' will also be analysed as number of events in each group.

We will assess all outcomes at maximal follow-up.

Search methods for identification of studies

Electronic searches

We will search for eligible randomised clinical trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid, from 1946 and onwards).
- Embase (Ovid, from 1980 and onwards).
- LILACS (Bireme, 1982 and onwards).
- BIOSIS (Thomson Reuters, 1926 and onwards).
- CINAHL.
- SCOPUS.
- Web of Science Core Collection.

A preliminary search strategy for MEDLINE (Ovid) is given in **Additional file 2**.

We will adapt the preliminary search strategy for MEDLINE (Ovid) for use in these databases. We will apply the Cochrane sensitivity-maximising randomised clinical trial filter to MEDLINE (Ovid) and adaptations of it to all the other databases, except CENTRAL (37).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status. We will assess non-English language papers by asking individuals that fluently speak the language for help.

Searching other resources

We will search the reference lists of included randomised clinical trials, previous systematic reviews, and other types of reviews for any unidentified randomised clinical trials. We will also contact authors

of included randomised clinical trials for further information by email. Further, we will search for ongoing and unidentified randomised clinical trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/);
- Google Scholar (https://scholar.google.com/); and
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/).

We will also include unpublished and grey literature trials if we identify these and assess relevant retraction statements and errata for included studies.

Data collection and analysis

We will perform the review following the recommendations of Cochrane (31). The analyses will be performed using Review Manager 5.3 (38) and TSA (39). In case of Review Manager statistical software not being sufficient, we will use STATA 15 (40).

Selection of studies

Two review authors (NJS and AIN) will independently screen titles and abstracts for inclusion of all the potentially eligible trials. We will code all these studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (JCJ). We will retrieve all relevant full-text study reports/publications and two review authors (NJS and AIN) will independently screen the full-text and identify trials for inclusion. We will report reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (JCJ). We will identify and exclude duplicated and collated multiple reports of the same trial so that each trial rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (35).

Data extraction and management

We will use a data collection from for study characteristics and outcome data, which has been piloted on at least one study in the review. Two authors (NJS and AIN) will extract and validate data independently from the included trials. Any disagreement concerning the extracted data will be discussed between the two authors. If no agreement can be reached, a third author (JCJ) will resolve the issue. We will assess duplicate publications and companion papers of a trial together in order to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication. We will extract the following data:

- Trial characteristics: bias risks components (as defined below); trial design (parallel, factorial, or cross-over); trial period; number of trial sites; name of countries in which the trial was conducted; number of intervention arms; length of follow-up; and inclusion and exclusion criteria.

- Participants characteristics and diagnosis: number of randomised participants; number of analysed participants; number of participants lost to follow-up; mean age; age range; sex ratio; definition of fever; and specific inclusion criteria based on the condition of the adult (e.g. critically ill, neurological injury, infection).

- Experimental intervention characteristics: type of fever control intervention; dose of fever control intervention; duration of fever control intervention; and mode of administration.

- Control intervention characteristics: type of control intervention; dose of intervention; duration of intervention; and mode of administration.

- Co-intervention characteristics: type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.

- Outcomes: primary and secondary outcomes specified and collected; time points reported; and differences in planned and reported outcomes.

- Notes: temperature target of fever treatment; type of temperature measuring device; funding of the trial, and notable conflicts of interest of trial authors, if available.

Assessment of risk of bias in included studies

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* in our evaluation of the methodology and hence the risk of bias of the included trials (28). Two review authors (NJS and AIN) will assess the risk of bias in the included trials independently. We will evaluate the methodology in respect of:

- random sequence generation;

- allocation concealment;

- blinding of participants and personnel;

- blinding of outcome assessment;

- incomplete outcome data;

- selective outcome reporting; and

- other risks of bias.

These domains enable classification of randomised clinical trials at low risk of bias and at high risk of bias. The latter trials tend to overestimate positive intervention effects (benefits) and underestimate negative effects (harms) (41-47).

We will classify the trials according to the following criteria:

Random sequence generation

- Low risk: if sequence generation was achieved using computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- Unclear risk: if the method of randomisation was not specified, but the trial was still presented as being randomised.
- High risk: If the allocation sequence was not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

- Low risk: if the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
- Uncertain risk: if the trial was classified as randomised but the allocation concealment process was not described.
- High risk: if the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and personnel

- Low risk: if the participants and the personnel were blinded to intervention allocation and this was described.
- Uncertain risk: if the procedure of blinding was insufficiently described.
- High risk: if blinding of participants and the personnel was not performed.

Blinding of outcome assessment

- Low risk: if it was mentioned that outcome assessors were blinded, and this was described.

- Uncertain risk: if it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was insufficiently described.

- High risk: if no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- Low risk: if missing data were unlikely to make treatment effects depart from plausible values. This could either be: 1) there were no dropouts or withdrawals for all outcomes, or 2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups. Generally, the trial will be judged as at a low risk of bias due to incomplete outcome data if dropouts are less than 5%. However, the 5% cut-off is not definitive.

- Uncertain risk: if there was insufficient information to assess whether missing data were likely to induce bias on the results.

- High risk: if the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- Low risk: if a protocol was published/registered before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial had begun, reporting of all-cause mortality and various types of serious adverse events will grant the trial a grade of low risk of bias.

- Uncertain risk: if no protocol was published and the outcomes all-cause mortality and various types of serious adverse events were not reported on.

- High risk: if the outcomes in the protocol were not reported on.

Other risks of bias

- Low risk: if the trial appears to be free of other components that could put it at risk of bias.

- Unclear risk: if the trial may or may not be free of other components that could put it at risk of bias.

- High risk: if there are other factors in the trial that could put it at risk of bias.

Overall risk of bias

- Low risk: the trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.
- High risk: the trial will be classified 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome. This will enable us to assess the bias risk for each outcome result in addition to each trial.

We will grade each potential source of bias as high, low, or unclear and provide evidence from the trial report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different trials for each of the domains listed.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the TSA-adjusted CIs (see paragraphs below). We will calculate the absolute risk reduction (ARR) or increase (ARI) and number needed to treat (NNT) or harm (NNH) if the outcome result shows a beneficial or harmful effect, respectively.

Continuous outcomes

We will calculate the mean differences (MDs) and if necessary, as a hypothesis generating analysis, the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the TSA-adjusted CIs (see paragraphs below).

Count outcomes

We will calculate rate ratios with 95% confidence interval (CI) for count outcomes.

Unit of analysis issues

We will only include randomised clinical trials. For trials using cross-over design, only data from the first period will be included (48, 49). For trials where multiple trial intervention groups are reported, we will only include the relevant groups. If two comparisons from the same trial are combined in the same meta-analysis, we will halve the control group to avoid double-counting (49). We will not include cluster randomised trials, as these have a high risk of biased results due to confounding (31).

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing information and data.

Dichotomous outcomes

We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only change from baseline scores are reported, we will analyse the results together with follow-up scores (31). If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by the Chi^2-test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2-statistic (50, 51).

We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided (49).

Assessment of reporting biases

We will use a funnel plot to assess reporting bias in the meta-analyses including ten or more trials. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size, and asymmetry of a funnel plot is not necessarily caused by reporting bias. From this information, we assess possible reporting bias). For dichotomous outcomes, we will test asymmetry with the Harbord test (52) if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test (53) and the adjusted rank correlation (54).

Data synthesis

Meta-analysis and assessment of significance

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions (49), Keus et al. (33), and the eight-step assessment

suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29). We will use the statistical software Review Manager 5.3 (38) provided by Cochrane and STATA 15 (40) to analyse data.

We will assess our intervention effects with both random-effects meta-analyses (55) and fixed-effect meta-analyses (56) and report the more conservative result as our primary result (29). The more conservative point estimate is the result with the highest P value and the widest 95% CI. In case that few trials (1-3) make up >90% of the weight in the meta-analysis, we will use fixed-effect meta-analysis. If there is substantial discrepancy between the results of the two methods, we will report and discuss the results (29).

We will adjust our thresholds for statistical significance due to problems with multiplicity (family-wise error rate), by dividing the pre-specified P value threshold with the value halfway between 1 (no adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment) (29). We will assess a total of four primary and secondary outcomes in the review and, hence, consider a P value of 0.02 or less as the threshold for statistical significance (29). For our exploratory outcomes, we will consider a P value of 0.05 or less as the threshold for statistical significance.

If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial Sequential Analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (32, 39, 57-65). Therefore, TSA (39) can be applied to control these risks (http://www.ctu.dk/tsa/) (62). Similar to a sample size calculation in a randomised clinical trial, TSA estimates the diversity-adjusted required information size (DARIS) (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors (60). The DARIS takes into account the anticipated intervention effect, the variance of the anticipated difference in intervention effects, the acceptable risk of falsely rejecting the null hypothesis (alpha), the acceptable risk of falsely confirming the null hypothesis (beta), and the variance of the intervention effect estimates between trials (29, 60, 66). We searched for suitable empirical data to determine and predefine the anticipated intervention effects (29). However, no suitable data could be found. Instead, we pragmatically hypothesised the anticipated intervention effects:

- When analysing all-cause mortality, serious adverse events, and non-serious adverse events, we will pragmatically anticipate an intervention effect equal to a risk ratio reduction (RRR) of 25%.
- When analysing resolution of fever, we will pragmatically anticipate an intervention effect equal to a RRR of 30%.

- When analysing quality of life and temperature change, we will pragmatically anticipate an intervention effect equal to the mean difference of the observed SD/2 (67).

TSA enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the DARIS, trial sequential monitoring boundaries are constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the DARIS (32, 60).

Firm evidence for benefit or harm may be established if a trial sequential monitoring boundary (i.e. upper boundary of benefit or lower boundary of harm) is crossed before reaching the DARIS, in which case further trials may turn out to be superfluous. In contrast, if a boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential boundaries for futility.

The TSA program is also able to calculate TSA-adjusted CIs, which we will report in addition to the unadjusted naïve 95% CI. TSA-adjusted CI compared to unadjusted naïve 95% CI gives a more correct estimation of the true CI, as it is adjusted for lack of information (62). If the TSA cannot be conducted because of too little information, we will conduct a more lenient analysis by increasing the anticipated intervention effect (in these cases, the TSA-adjusted CI is overly optimistic).

For dichotomous outcomes, we will estimate the DARIS based on an anticipated intervention effect (our anticipated intervention effect for each dichotomous outcome is stated above), the observed proportion of participants with an outcome in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of significance' above), a beta of 10%, and diversity as suggested by the trials in the meta-analysis (29, 60, 68).

For continuous outcomes, we will estimate the DARIS based on a minimal clinically important difference of SD/2, the standard deviation observed in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of significance' above), a beta of 10%, and a diversity as suggested by the trials in the meta-analysis (29, 60, 68).

We will document difficult decisions in the review and sensitivity analyses will assess the impact of these decisions on the findings of the review.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses on all our outcomes.

A. Comparison of the effects between trials with different types of fever control interventions.

B. Comparison of the effects between critically ill and non-critically ill participants:

- Trials including critically ill participants; or
- Trials including non-critically ill participants.

C. Comparison of the effect between participants with infectious- and non-infectious fever (e.g. neurological injury or drug-induced fever):

- Trials including participants with infectious fever; or
- Trials including participants with non-infectious fever.

D. Comparison of the effects between trials with different maximal follow-ups:

- Up to 1 year; or
- 1 year and above.

E. Comparison of the effect between trials with different control interventions:

- Placebo-controlled trials; or
- No control intervention.

F. Comparison of the effects between industry funded trials or trials with unknown funding compared to non-industry funded trials:

- industry funded trials or unknown funding; or
- non-industry funded trials.

We will use the formal test for subgroup differences in Review Manager (38).

Other post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (29).

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis in which we exclude trials with overall 'high risk of bias'.

To assess the potential impact of the participants being critically ill, we will perform a sensitivity analysis in which we exclude trials that do not include critically ill participants.

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the following two sensitivity analyses when assessing each dichotomous outcome (all-cause mortality, serious adverse events, non-serious adverse events, and resolution of fever):

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group have survived, had no serious adverse event, had no non-serious adverse events, and had resolution of fever; and all those participants lost to follow-up in the control group have not survived, had a serious adverse event, had a non-serious adverse event, and did not have resolution of fever.
- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group have not survived, had a serious adverse event, had a non-serious adverse event, and did not have resolution of fever; and that all those participants lost to follow-up in the control group have survived, had no serious adverse event, had no non-serious adverse event, and had resolution of fever.

We will present results of both scenarios in our review.

To assess the potential impact of the missing data for continuous outcomes, we will perform the following two sensitivity analyses when assessing each continuous outcome (quality of life and temperature change):

- 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group and control group have had a 'beneficial outcome' or 'harmful outcome', respectively. A 'beneficial outcome' will be the group mean plus one standard deviation (SD) of the group mean. A 'harmful outcome' will be the group mean minus one SD of the group mean (29).
- 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group and control group have had a 'harmful outcome' or 'beneficial outcome', respectively. A 'harmful outcome' will be the group mean minus one standard deviation (SD) of the group mean. A 'beneficial outcome' will be the group mean plus one SD of the group mean (29).

We will present results of both scenarios in our review.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population.

We will present results of this scenario in our review.

Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (29).

Summary of findings

We will use the GRADE system to assess the certainty of the body of evidence associated with each of our outcomes constructing 'Summary of Findings' (SoF) tables using the GRADEpro software (34, 69-71). The GRADE approach appraises the certainty of the body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed (34, 69, 70). We will assess the GRADE levels of evidence as high, moderate, low, and very low and downgrade the evidence by one or two levels depending on the following certainty measures: within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (34, 69, 70). We will use TSA to assess the 'imprecision' of effect estimates (29). We will use methods and recommendations described in Chapter 8 (Section 8.5) (28) and Chapter 12 (72) of the Cochrane Handbook for Systematic Reviews of Interventions (31). We will justify all decisions to downgrade the certainty of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

We will include all trials in our analyses and conduct a sensitivity analysis excluding trials at high risk of bias. If the results are similar, we will base our SoF table and conclusions on the overall analysis. If they differ, we will base our SoF table and conclusions on trials at low risk of bias.

Differences between the protocol and the review

We will conduct the review according to this protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Patient and Public Involvement

We conducted this protocol for a systematic review without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this protocol for readability or accuracy.

Discussion

This protocol aims to assess the effects of fever control interventions in adults regardless of any underlying condition to determine whether fever control interventions are beneficial or harmful. The outcomes will be all-cause mortality, serious adverse events, quality of life, non-serious adverse events, resolution of fever, and temperature change.

This protocol has a number of strengths. The predefined methodology is based on the Cochrane Handbook for Systematic Reviews of Interventions (49), GRADE (34, 69, 70), TSA (62), and the eight-step assessment suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29). Hence, this protocol takes into account both risks of random errors and risks of systematic errors.

Our protocol also has a number of limitations. The primary limitation is that we will include various types of pharmacological and non-pharmacological fever control interventions, and it is likely that different interventions have different effects. Another limitation is that we will include various types of participants regardless of their underlying condition, and it is possible that fever control interventions affect participants differently depending on their condition. To minimise this limitation, we have planned to carefully assess clinical and statistical heterogeneity including several subgroup analyses. Another limitation is the large number of comparisons, which increase the risk of family-wise error. To minimise this limitation, we have adjusted our thresholds for significance according to the total number of our primary and secondary outcomes. Nevertheless, the large risk of type 1 error will be taken into account when interpreting the review results.

Ethics and dissemination

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included. The results of this systematic review will be disseminated through publication in a leading peer-reviewed journal.

References

1. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. Jama. 1992;268(12):1578-80.
2. Obermeyer Z, Samra JK, Mullainathan S. Individual differences in normal body temperature: longitudinal big data analysis of patient records. BMJ (Clinical research ed). 2017;359:j5468.
3. Steele GM, Franco-Paredes C, Chastain DB. Noninfectious causes of fever in adults. The Nurse practitioner. 2018;43(4):38-44.
4. McGregor AC, Moore DA. Infectious causes of fever of unknown origin. Clinical medicine (London, England). 2015;15(3):285-7.
5. Chan MC, Spieth PM, Quinn K, Parotto M, Zhang H, Slutsky AS. Circadian rhythms: from basic mechanisms to the intensive care unit. Critical care medicine. 2012;40(1):246-53.
6. Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. American journal of physiology Regulatory, integrative and comparative physiology. 2007;292(1):R37-46.
7. Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31 Suppl 5:S178-84.
8. Saper CB, Breder CD. The neurologic basis of fever. The New England journal of medicine. 1994;330(26):1880-6.
9. Porat R, Dinarello CA. Pathophysiology and treatment of fever in adults. In A. Bloom (Ed.), *UpToDate*. Retrived 02.08.18, from https://www.uptodate.com/contents/pathophysiology-and-treatment-of-fever-in-adults. 2018.
10. Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Annals of internal medicine. 2015;163(10):768-77.
11. Kluger MJ, Kozak W, Conn CA, Leon LR, Soszynski D. The adaptive value of fever. Infectious disease clinics of North America. 1996;10(1):1-20.
12. Mackowiak PA. Fever: blessing or curse? A unifying hypothesis. Annals of internal medicine. 1994;120(12):1037-40.
13. Greisman LA, Mackowiak PA. Fever: beneficial and detrimental effects of antipyretics. Current opinion in infectious diseases. 2002;15(3):241-5.
14. Mackowiak PA, Ruderman AE, Martin RM, Many WJ, Smith JW, Luby JP. Effects of physiologic variations in temperature on the rate of antibiotic-induced bacterial killing. American journal of clinical pathology. 1981;76(1):57-62.
15. Plaisance KI, Mackowiak PA. Antipyretic therapy: physiologic rationale, diagnostic implications, and clinical consequences. Archives of internal medicine. 2000;160(4):449-56.
16. Vane JR. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs. Nature New Biology. 1971;231:232.
17. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature. 1972;240(5381):410-1.
18. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. The American journal of medicine. 2001;111(4):304-15.
19. Niven DJ, Laupland KB, Tabah A, Vesin A, Rello J, Koulenti D, et al. Diagnosis and management of temperature abnormality in ICUs: a EUROBACT investigators' survey. Critical care (London, England). 2013;17(6):R289.

20. Plaisance KI. Toxicities of drugs used in the management of fever. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31 Suppl 5:S219-23.
21. Polderman KH. How to Stay Cool in the Intensive Care Unit? Endovascular Versus Surface Cooling. Circulation. 2015;132(3):152-7.
22. Doyle JF, Schortgen F. Should we treat pyrexia? And how do we do it? Critical care (London, England). 2016;20(1):303.
23. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Critical care medicine. 2009;37(3):1101-20.
24. Dallimore J, Ebmeier S, Thayabaran D, Bellomo R, Bernard G, Schortgen F, et al. Effect of active temperature management on mortality in intensive care unit patients. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2018;20(2):150-63.
25. Hammond NE, Boyle M. Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: a systematic review and meta-analysis. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses. 2011;24(1):4-17.
26. Niven DJ, Stelfox HT, Laupland KB. Antipyretic therapy in febrile critically ill adults: A systematic review and meta-analysis. Journal of critical care. 2013;28(3):303-10.
27. Chan EY, Chen WT, Assam PN. External cooling methods for treatment of fever in adults: a systematic review. JBI library of systematic reviews. 2010;8(20):793-825.
28. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 520 (updated June 2017), Cochrane, 2017 Available from wwwtrainingcochraneorg/handbook.
29. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC medical research methodology. 2014;14:120.
30. Joanna Briggs Institute. Checklist for randomized controlled trials. Available at http://joannabriggs.org/assets/docs/critical-appraisal-tools/JBI_RCTs_Appraisal_tool2017.pdf [
31. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration. 2011;www.handbook.cochrane.org.
32. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of clinical epidemiology. 2008;61(1):64-75.
33. Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. BMC medical research methodology. 2010;10:90.
34. Schünemann H, Brozek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdtguidelinedevelopmentorg/app/handbook/handbookhtml.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9, w64.
36. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) adopts consolidated guideline on good clinical practice in the conduct of clinical trials on medicinal products for human use. International digest of health legislation. 1997;48(2):231-4.
37. Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbookcochraneorg.
38. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014.
39. Copenhagen Trial Unit. TSA - Trial Sequential Analysis. http://www.ctu.dk/tsa/.

40. StataCorp. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LP. 2017;http://www.stata.com.
41. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.
42. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of internal medicine. 2001;135(11):982-9.
43. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet (London, England). 1998;352(9128):609-13.
44. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Jama. 1995;273(5):408-12.
45. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ (Clinical research ed). 2008;336(7644):601-5.
46. Savovic J, Jones H, Altman D, Harris R, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technology Assessment. 2012;16(35):1-82.
47. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database of Systematic Reviews. 2017;2:Mr000033.
48. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International journal of epidemiology. 2002;31(1):140-9.
49. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.
50. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.
51. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.
52. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Statistics in medicine. 2006;25(20):3443-57.
53. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-34.
54. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
55. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
56. Demets DL. Methods for combining randomized clinical trials: strengths and limitations. Statistics in medicine. 1987;6(3):341-50.
57. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of clinical epidemiology. 2008;61(8):763-9.
58. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International journal of epidemiology. 2009;38(1):287-98.
59. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? International journal of epidemiology. 2009;38(1):276-86.
60. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC medical research methodology. 2009;9:86.

61. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clinical epidemiology. 2010;2:57-66.
62. Thorlund K EJ, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). 2011. http://www.ctu.dk/tsa/files/tsa_manual.pdf.
63. Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic reviews of anesthesiologic interventions reported as statistically significant: problems with power, precision, and type 1 error protection. Anesthesia and analgesia. 2015;121(6):1611-22.
64. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ open. 2016;6(8):e011890.
65. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC medical research methodology. 2017;17(1):39.
66. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. PloS one. 2013;8(3):e59202.
67. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003;41(5):582-92.
68. Castellini G, Nielsen EE, Gluud C. Comment on: "Cell therapy for heart disease: Trial sequential analyses of two cochrane reviews". Clinical pharmacology and therapeutics. 2016.
69. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6.
70. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.
71. GRADEpro GDT. McMaster University (developed by Evidence Prime)2015.
72. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from wwwtrainingcochraneorg/handbook.

Footnotes

Authors' contributions

NJS and JCJ equally contributed in conception and design of the protocol. NJS drafted the protocol. AIN, NN, and JCJ amended the protocol. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy is hugely appreciated.

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION 1					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	54
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-22
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	803-805
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	806-808
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	806-808
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	806-808
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	143-196
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	197-200
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	205-234

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	263-293
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	275
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	294-308
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	298-308
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	309-317
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	318-335
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	235-262
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	336-412
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	457-476
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	413-522
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	523-586
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	476
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	389 – 396 AND 449-456
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	587-602

Additional file 2

Search strategy for MEDLINE (Ovid)

1. exp Fever/

4. exp Infection/

5. exp Sepsis/

6. exp Temperature/

8. (fever or pyrexia or febrile or infection or sepsis or temperature or hyperthermia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp Antipyretics/

11. exp Acetaminophen/

12. exp Anti-inflammatory Agents, Non-steroidal/

13. exp Ibuprofen/

14. exp Salicylates/

15. exp Cryotherapy/

16. ("fever control" or antipyretics or antipyresis or paracetamol or acetaminophen or NSAID or "non-steroidal anti-inflammatory drugs" or ibuprofen or "cyclo-oxygenase inhibitors" or "cox-inhibitor" or salicylates or aspirin or diclofenac or naproxen or indomethacin or ketorolac or metamizole or "induced hypothermia" or "targeted temperature management" or cooling or "external cooling" or "surface cooling" or "physical cooling" or "endovascular cooling" or sponges or fan or baths or blanket or ice or fluid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17. 10 or 11 or 12 or 13 or 14 or 15 or 16

18. 9 and 17

19. exp Clinical trial/

20. (randomized or randomised or clinical or controlled or placebo or "no intervention" or sham or trial or systematic review or meta-analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21. 19 or 20

20. 18 and 21