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

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Manuscripts

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

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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

56 Article summary

57 Strengths and limitations of this study

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

67 Introduction

68 Description of the condition

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

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

80 Fever is triggered by infectious agents, microbial products, and inflammatory processes that induce
81 macrophages, endothelial cells, and the reticuloendothelial system to produce and secrete pyrogenic
82 cytokines into the circulation (7). These pyrogenic cytokines induce the synthesis of prostaglandin E2
83 (PGE₂) leading to elevated levels of PGE₂ in the thermoregulatory centre in the hypothalamus, where
84 the normal temperature set-point is raised to a febrile temperature set-point (7, 8). The febrile
85 temperature set-point creates physiologic and behavioural responses that seek to increase heat
86 production and heat retention until the febrile temperature set-point is reached (8). Typical physiologic
87 responses are cutaneous vasoconstriction, shivering, and non-shivering thermogenesis, while typical
88 behavioural responses are to seek a warmer environment and adding clothing (8). When the febrile
89 temperature set-point is reached, an increase or decrease in body temperature will stimulate
90 thermoregulatory mechanisms alike those at normal body temperature. After the febrile temperature
91 set-point begins to decline, as a cause of a reduction in the concentration of pyrogens or the use of
92 antipyretics, the processes of heat loss are accelerated through vasodilation, sweating, and behavioural
93 responses like removal of clothing (9). This continues until the new lower temperature set-point is
94 reached.

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

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4 99 Fever is, as described, an integral part of the inflammatory response and has therefore likely a
5 physiological role in fighting infections (11, 12). Potential benefits of fever may be reduced growth and
6 100 reproduction of some bacteria and viruses, enhanced immunologic function, and increased activity of
7 101 antimicrobial drugs (11, 13, 14). Potential harms of fever may be increased level of discomfort,
8 102 increased risk of neurological and cognitive sequelae, and increased metabolic demand (13, 15).
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12 104 **Description of the intervention**

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14 105 Fever may be controlled by both pharmacological and non-pharmacological interventions.
15 106 Pharmacological interventions are the main choice for treating most cases of fever, while non-
16 107 pharmacological interventions are recommended in cases of refractory fever or in cases where rapid
17 108 temperature decrease is needed (15).
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20 109 **Pharmacological fever control interventions**

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22 110 Pharmacological fever control interventions, called antipyretics, consist of drugs able to inhibit the
23 111 enzyme cyclooxygenase (COX-1 or COX-2) and thereby interrupt the synthesis of PGE₂ (16, 17). The
24 112 following reduction in the concentration of PGE₂ causes the febrile temperature set-point to reach the
25 113 normal temperature set-point (16, 17). Antipyretics may also limit the febrile response by suppressing
26 114 tissue inflammation, reduce pyrogenic cytokine production, enhance expression of anti-inflammatory
27 115 molecules, and boost the activity of endogenous antipyretics (18). Commonly used antipyretics are
28 116 salicylates (e.g. aspirin), paracetamol, and nonsteroidal anti-inflammatory drugs (NSAID) (19). Adverse
29 117 effects of antipyretics may be gastrointestinal symptoms and renal toxicity (e.g. caused by NSAID),
30 118 bleeding (e.g. caused by aspirin and NSAID), and hepatic injury (e.g. caused by paracetamol) (20).
31 119 Patients receiving high or prolonged doses of antipyretic agents should therefore, depending on which
32 120 antipyretic they receive, be monitored for gastrointestinal adverse effects, renal dysfunction, signs of
33 121 bleeding, and elevated liver enzymes (20).
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40 122 **Non-pharmacological fever control interventions**

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42 123 Non-pharmacological fever control interventions consist of various surface and endovascular cooling
43 124 interventions (21). Cooling reduces the body temperature by removing heat without decreasing the
44 125 febrile temperature set-point (15, 22). Thus, the use of cooling may result in increased heat production,
45 126 metabolic rate, and oxygen consumption, as the body tries to counter the cooling effects by shivering
46 127 which increases the body temperature (15, 22). Hence, control of these unintended consequences (e.g.
47 128 shivering) is crucial when performing the cooling procedure (15, 22). Before commencement of a
48 129 cooling intervention, common practice includes administration of sedation (including alpha-2-agonists),
49 130 analgesics (e.g. meperidine), muscle relaxants (paralytics), and antipyretics (15, 22).
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4 131 Surface cooling interventions work through conduction, convection, or evaporation (15). Conduction
5 132 occurs when heat is exchanged between two objects in contact with one another; convection occurs
6 133 when cold fluids, such as gases and liquids, flow along the skin transferring heat from the skin to the
7 134 fluid around it; and evaporation occurs when there is heat loss from cold water being evaporated from
8 135 the skin (15). Surface cooling interventions consist of both conventional interventions such as crushed
9 136 ice, ice bags, fans, or sponging with tepid water or alcohol, and more advanced interventions such as
10 137 circulating blankets with cold fluid or cold air which are wrapped around the patient (21).

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15 138 Endovascular (catheter containing fluids is inserted through the skin into a blood vessel) cooling
16 139 interventions might also be used to control fever, but are mostly used for targeted temperature
17 140 management within intensive care (22). Examples of endovascular cooling interventions are heat
18 141 exchange catheter devices and infusion of cold fluids (23). The primary advantage of endovascular
19 142 cooling is more rapid cooling, but heat exchange catheter devices are difficult to use outside intensive
20 143 care units, and infusions of cold fluids expose patients to unnecessary volume expansion and imprecise
21 144 temperature control (22, 23).

25 145 **Why it is important to do this review**

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28 146 Whether fever in itself is beneficial or harmful in adults is unknown. Arguments for treating fever is that
29 147 fever control leads to increased patient comfort, reduced neurologic and cognitive impairment, and
30 148 reduced metabolic cost (13, 15). Arguments against treating fever is that fever leads to reduced growth
31 149 and reproduction of some bacteria and virus, enhanced immunologic function, and increased activity
32 150 of antimicrobial drugs (11, 13, 14).

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35 151 Four systematic reviews of randomised clinical trials have previously assessed the effects of fever
36 152 control interventions in febrile adults (24-27).

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39 153 - Dallimore et al. from 2018 included 13 trials with 1780 participants assessing the effects of any
40 154 fever control intervention but the review only included critically ill adults (24). Dallimore et al.
41 155 showed that 1) active temperature management versus placebo or standard care did not
42 156 significantly affect mortality (OR 1.01; 95% CI 0.81 to 1.28), ICU length of stay, nor hospital
43 157 length of stay; and 2) active temperature management was superior to placebo or standard
44 158 care in reducing body temperature (24). Dallimore et al. assessed the risk of bias in the included
45 159 trials according to the recommendations in the Cochrane Handbook (28) and a systematic
46 160 search was conducted, however GRADE was not used to assess the certainty of the evidence,
47 161 and the risks of random errors was not assessed (29).
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51 162 - Hammond et al. from 2011 included 11 trials with 801 participants assessing the effects of any
52 163 fever control intervention but the review only included critically ill adults (25). Hammond et al.
53 164 showed that 1) newer cooling methods (intravascular and hydrogel cooling) were superior to
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4 165 conventional cooling methods (surface cooling) in reducing body temperature, but with a trend
5 166 toward higher mortality in the patients receiving the newer cooling methods (RR 1.42; 95% CI
6 167 0.99 to 2.03); 2) surface cooling was superior to no surface cooling in reducing body
7 168 temperature; 3) continuous infusions were superior to bolus dosing in reducing body
8 169 temperature; and 4) aggressive (treatment ≥ 38.5 °C) was superior to permissive (treatment
9 170 ≥ 40.0 °C) antipyretic treatment in reducing the mean daily temperature (25). Hammond et al.
10 171 assessed the risk of bias in the included trials according to the recommendations in the
11 172 Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not
12 173 used to assess the certainty of the evidence, and the risks of random errors was not assessed
13 174 (29).

- 14 175 - Niven et al. from 2013 included five trials with 399 participants assessing the effects of any
15 176 fever control intervention but this review only included critically ill adults without any
16 177 neurological injury (26). Niven et al. showed that fever control at ≥ 38.3 - 38.5 °C versus fever
17 178 control at ≥ 40.0 °C or no fever control did not significantly affect mortality (RR 0.98; 95% CI 0.58
18 179 to 1.63) (26). Niven et al. assessed the risk of bias in the included trials according to the
19 180 recommendations in the Cochrane Handbook (28) and a systematic search was conducted,
20 181 however GRADE was not used to assess the certainty of the evidence, and the risks of random
21 182 errors was not assessed (29).
- 22 183 - Chan et al. from 2010 included six trials with 474 participants assessing the effects of surface
23 184 cooling versus no surface cooling in febrile adults (27). Chan et al. showed that surface cooling
24 185 versus no surface cooling did not significantly affect body temperature, but increased the risk
25 186 of shivering (27). Chan et al. assessed the risk of bias in the included trials according to the
26 187 recommendations from the Joanna Briggs Institute (30) and a systematic search was conducted,
27 188 however GRADE was not used to assess the certainty of the evidence, and the risks of random
28 189 errors was not assessed (29).

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31 190 The impact of fever control interventions on mortality and other clinically important outcomes in febrile
32 191 adults regardless of e.g. being critically ill or having neurological injury or infection is still unknown. A
33 192 small number of trials have been included in previous reviews, and hence previously there has not been
34 193 sufficient information to confirm or reject if fever control interventions affect the risk of death or other
35 194 serious adverse events. It may result in sufficient power if all types of participants are included in a
36 195 meta-analysis, and it would also be possible to compare the effects of fever control interventions
37 196 between different types of participants using subgroup analyses (31). No former relevant review has
38 197 taken into account both risks of random errors and risk of systematic errors (updated Cochrane
39 198 methodology, Trial Sequential Analysis, and GRADE assessment) (29, 31-34).

33 34 199 **Objective**

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4 200 To assess the beneficial and harmful effects of fever control interventions versus placebo, sham, or no
5 201 intervention in adults when assessing mortality, both serious and non-serious adverse events, and
6 202 quality of life.
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9 203 **Methods and analysis**

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12 204 This systematic review protocol has been developed based on Preferred Reporting Items for Systematic
13 205 Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews
14 206 evaluating healthcare interventions (35). A PRISMA-P checklist file is attached (**Additional file 1**).
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17 207 **Criteria for considering studies for this review**

18 19 208 **Types of studies**

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21 209 We will include randomised clinical trials irrespective of trial design, setting, blinding, publication status,
22 210 publication year, language, and reporting of outcomes. We will not specifically search for non-
23 211 randomised studies. However, if we during our literature searches identify non-randomised studies
24 212 (quasi-randomised studies or observational studies) with adequate reports of harmful effects, we will
25 213 narratively report these results.
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29 214 **Types of participants**

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31 215 We will include adult participants diagnosed with fever. We will accept the definitions used by the
32 216 individual trialists. We will include participants irrespective of age, sex, and comorbidities. Furthermore,
33 217 we will include participants regardless of underlying conditions such as being critically ill or having
34 218 neurological injury or infection.
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37 219 Trials that only include a subset of eligible participants will only be included if: 1) separate data on the
38 220 eligible participants are available or 2) more than 90% are eligible.
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41 221 **Types of interventions**

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43 222 We will include three types of comparisons:

- 44 223 - any fever control intervention compared with placebo or sham;
- 45 224 - any fever control intervention compared with no intervention; and
- 46 225 - any fever control intervention added to a co-intervention compared with a similar co-
47 226 intervention (with or without placebo or sham).
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51 227 As experimental intervention, we will accept any type of pharmacological or non-pharmacological fever
52 228 control intervention (as defined by trialists) irrespective of dose, route of administration, and duration
53 229 of administration.
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4 230 We will include all control interventions (placebo, sham, or no intervention) irrespective of dose, route
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6 231 of administration, and duration of administration.

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8 232 We will accept any type of co-intervention when such co-intervention is intended to be delivered
9 233 similarly to the experimental and control group.

10
11 234 We will separately include trials that compare more aggressive fever control with less aggressive fever
12 235 control. By doing this, we will be able to discuss if the aggressivity of fever control has a beneficial or
13
14 236 harmful impact on the patient.

15 16 237 **Outcome measures**

17 18 238 Primary outcomes

- 19
20 239 - All-cause mortality.
- 21
22 240 - Serious adverse events. We will define a serious adverse event as any untoward medical
23 241 occurrence that resulted in death; was life-threatening; required hospitalisation or prolongation
24 242 of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the
25 243 patient (36). As we expect the reporting of serious adverse events to be very heterogeneous
26 244 and not strictly according to the ICH-GCP recommendations in many trials, we will include the
27 245 event as a serious adverse event if the trialists either: 1) use the term 'serious adverse event'
28 246 but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider
29 247 fulfil the ICH-GCP definition. If several of such event are reported, then we will choose the
30 248 highest proportion reported in each trial. We will secondly analyse each component of serious
31 249 adverse events separately.

32 33 250 Secondary outcomes

- 34
35 251 - Quality of life (measured on any valid continuous scale).
- 36
37 252 - Non-serious adverse events (defined as those leading to discontinuation of the intervention or
38 253 defined as 'adverse events' by the trialists). Each adverse event will be analysed separately.

39 40 254 Exploratory outcomes

- 41
42 255 - Resolution of fever (as defined by the trialists).
- 43
44 256 - Temperature change (measured by body temperature).
- 45
46 257 - Number of serious adverse events (analysed as count data).
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48 258 - Number of non-serious adverse events (analysed as count data).
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259 'All-cause mortality', 'serious adverse events', 'non-serious adverse events', and 'resolution of fever'
260 will be analysed as proportion of participants in each group. 'Quality of life' and 'temperature change'
261 will be analysed as the mean difference between the groups.

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

264 We will assess all outcomes at maximal follow-up.

265 **Search methods for identification of studies**

266 **Electronic searches**

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

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

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

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

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

284 **Searching other resources**

285 We will search the reference lists of included randomised clinical trials, previous systematic reviews,
286 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 form 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:

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- 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.

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4 349 These domains enable classification of randomised clinical trials at low risk of bias and at high risk of
5 350 bias. The latter trials tend to overestimate positive intervention effects (benefits) and underestimate
6 351 negative effects (harms) (41-47).
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9 352 We will classify the trials according to the following criteria:
10

11 353 Random sequence generation

- 12
13 354 - Low risk: if sequence generation was achieved using computer random number generator or a
14 355 random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were
15 356 also considered adequate if performed by an independent adjudicator.
16
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18 357 - Unclear risk: if the method of randomisation was not specified, but the trial was still presented
19 358 as being randomised.
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22 359 - High risk: If the allocation sequence was not randomised or only quasi-randomised. These trials
23 360 will be excluded.
24

25 361 Allocation concealment

- 26
27 362 - Low risk: if the allocation of patients was performed by a central independent unit, on-site
28 363 locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers
29 364 prepared by an independent pharmacist or investigator.
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32 365 - Uncertain risk: if the trial was classified as randomised but the allocation concealment process
33 366 was not described.
- 34
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36 367 - High risk: if the allocation sequence was familiar to the investigators who assigned participants.
37

38 368 Blinding of participants and personnel

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40 369 - Low risk: if the participants and the personnel were blinded to intervention allocation and this
41 370 was described.
42
- 43 371 - Uncertain risk: if the procedure of blinding was insufficiently described.
- 44
45 372 - High risk: if blinding of participants and the personnel was not performed.
46

47 373 Blinding of outcome assessment

- 48
49 374 - Low risk: if it was mentioned that outcome assessors were blinded, and this was described.
- 50
51 375 - Uncertain risk: if it was not mentioned if the outcome assessors in the trial were blinded, or the
52 376 extent of blinding was insufficiently described.
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- 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'.

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4 406 - High risk: the trial will be classified 'high risk of bias' if any of the bias risk domains described in
5 407 the above are classified as 'unclear' or 'high risk of bias'.

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8 408 We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and
9 409 'selective outcome reporting' for each outcome. This will enable us to assess the bias risk for each
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11 410 outcome result in addition to each trial.

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13 411 We will grade each potential source of bias as high, low, or unclear and provide evidence from the trial
14 412 report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the
15 413 risk of bias judgements across different trials for each of the domains listed.

17 18 414 **Measures of treatment effect**

19 20 415 Dichotomous outcomes

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22 416 We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well
23 417 as the Trial Sequential Analysis-adjusted CIs (see paragraphs below).

24 25 418 Continuous outcomes

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27 419 We will calculate the mean differences (MDs) and if necessary, as a hypothesis generating analysis, the
28 420 standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the Trial
29 421 Sequential Analysis-adjusted CIs (see paragraphs below).

30 31 32 422 Count outcomes

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34 423 We will calculate rate ratios with 95% confidence interval (CI) for count outcomes.

35 36 424 **Unit of analysis issues**

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38 425 We will only include randomised clinical trials. For trials using cross-over design, only data from the first
39 426 period will be included (48, 49). For trials where multiple trial intervention groups are reported, we will
40 427 only include the relevant groups. If two comparisons from the same trial are combined in the same
41 428 meta-analysis, we will halve the control group to avoid double-counting (49). We will not include cluster
42 429 randomised trials, as these have a high risk of biased results due to confounding (31).

43 44 45 46 430 **Dealing with missing data**

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48 431 We will, as first option, contact all trial authors to obtain any relevant missing information and data.
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4 432 Dichotomous outcomes

6 433 We will not use intention-to-treat data if the original report did not contain such data. We will not
7 434 impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see
8 435 paragraph below), we will impute data.

11 436 Continuous outcomes

13 437 We will primarily analyse scores assessed at single time points. If only change from baseline scores are
14 438 reported, we will analyse the results together with follow-up scores (31). If standard deviations (SDs)
15 439 are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat
16 440 data if the original report did not contain such data. We will not impute missing values for any outcomes
17 441 in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

21 442 **Assessment of heterogeneity**

23 443 We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly
24 444 assess the presence of statistical heterogeneity by the Chi²-test (threshold P < 0.10) and measure the
25 445 quantities of heterogeneity by the I²-statistic (50, 51).

28 446 We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that
29 447 a meta-analysis should be avoided (49).

31 448 **Assessment of reporting biases**

33 449 We will use a funnel plot to assess reporting bias in the meta-analyses including ten or more trials. We
34 450 will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel
35 451 plot (i.e. a funnel plot assesses bias due to small sample size, and asymmetry of a funnel plot is not
36 452 necessarily caused by reporting bias. From this information, we assess possible reporting bias). For
37 453 dichotomous outcomes, we will test asymmetry with the Harbord test (52) if τ^2 is less than 0.1 and with
38 454 the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry
39 455 test (53) and the adjusted rank correlation (54).

44 456 **Data synthesis**

46 457 Meta-analysis and assessment of significance

48 458 We will undertake this meta-analysis according to the recommendations stated in the Cochrane
49 459 Handbook for Systematic Reviews of Interventions (49), Keus et al. (33), and the eight-step assessment
50 460 suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29).
51 461 We will use the statistical software Review Manager 5.3 (38) provided by Cochrane to analyse data and
52 462 STATA 15.

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4 463 We will assess our intervention effects with both random-effects meta-analyses (55) and fixed-effect
5 464 meta-analyses (56) and report the more conservative result as our primary result (29). The more
6 465 conservative point estimate is the result with the highest P value and the widest 95% CI. In case that
7 466 few trials (1-3) make up >90% of the weight in the meta-analysis, we will use fixed-effect meta-analysis.
8 467 If there is substantial discrepancy between the results of the two methods, we will report and discuss
9 468 the results (29).

10 469 We will adjust our thresholds for statistical significance due to problems with multiplicity (family-wise
11 470 error rate), by dividing the pre-specified P value threshold with the value halfway between 1 (no
12 471 adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment)
13 472 (29). We will assess a total of four primary and secondary outcomes in the review and, hence, consider
14 473 a P value of 0.02 or less as the threshold for statistical significance (29).

15 474 If quantitative synthesis is not appropriate, we will report the results in a narrative way.

16 475 Trial Sequential Analysis

17 476 Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple
18 477 testing of accumulating data (32, 39, 57-65). Therefore, Trial Sequential Analysis (39) can be applied to
19 478 control these risks (<http://www.ctu.dk/tsa/>) (62). Similar to a sample size calculation in a randomised
20 479 clinical trial, Trial Sequential Analysis estimates the diversity-adjusted required information size (DARIS)
21 480 (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention
22 481 effect) in order to minimise random errors (60). The DARIS takes into account the anticipated
23 482 intervention effect, the variance of the anticipated difference in intervention effects, the acceptable
24 483 risk of falsely rejecting the null hypothesis (alpha), the acceptable risk of falsely confirming the null
25 484 hypothesis (beta), and the variance of the intervention effect estimates between trials (29, 60, 66). We
26 485 searched for suitable empirical data to determine and predefine the anticipated intervention effects
27 486 (29). However, no suitable data could be found. Instead, we pragmatically hypothesised the anticipated
28 487 intervention effects:

- 29 488 - When analysing all-cause mortality, serious adverse events, and non-serious adverse events, we
30 489 will pragmatically anticipate an intervention effect equal to a risk ratio reduction (RRR) of 25%.
- 31 490 - When analysing resolution of fever, we will pragmatically anticipate an intervention effect equal
32 491 to a RRR of 30%.
- 33 492 - When analysing quality of life and temperature change, we will pragmatically anticipate an
34 493 intervention effect equal to the mean difference of the observed SD/2 (67).

35 494 Trial Sequential Analysis enables testing for significance to be conducted each time a new trial is
36 495 included in the meta-analysis. On the basis of the DARIS, trial sequential monitoring boundaries are

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4 496 constructed. This enables one to determine the statistical inference concerning cumulative meta-
5 497 analysis that has not yet reached the DARIS (32, 60).

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8 498 Firm evidence for benefit or harm may be established if a trial sequential monitoring boundary (i.e.
9 499 upper boundary of benefit or lower boundary of harm) is crossed before reaching the DARIS, in which
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11 500 case further trials may turn out to be superfluous. In contrast, if a boundary is not surpassed, one may
12 501 conclude that it is necessary to continue with further trials before a certain intervention effect can be
13 502 detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed
14 503 with Trial Sequential Analysis. This occurs when the cumulative Z-score crosses the trial sequential
15 504 boundaries for futility.

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18 505 The Trial Sequential Analysis program is also able to calculate TSA-adjusted CIs, which we will report in
19 506 addition to the unadjusted naïve 95% CI. TSA-adjusted CI compared to unadjusted naïve 95% CI gives a
20 507 more correct estimation of the true CI, as it is adjusted for lack of information (62). If the Trial Sequential
21 507 Analysis cannot be conducted because of too little information, we will conduct a more lenient analysis
22 508 by increasing the anticipated intervention effect (in these cases, the TSA-adjusted CI is overly
23 509 optimistic).

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27 511 For dichotomous outcomes, we will estimate the DARIS based on an anticipated intervention effect
28 512 (our anticipated intervention effect for each dichotomous outcome is stated above), the observed
29 513 proportion of participants with an outcome in the control group, an alpha of 2.0% for our primary and
30 513 secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of
31 514 significance' above), a beta of 10%, and diversity as suggested by the trials in the meta-analysis (29, 60,
32 515 68). In case there is some evidence or effect of the intervention, a supplementary Trial Sequential
33 516 Analysis using the limit of the CI closest to 1.00 as the anticipated intervention effect will be conducted
34 517 (29).

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39 519 For continuous outcomes, we will estimate the DARIS based on a minimal clinically important difference
40 520 of $SD/2$, the standard deviation observed in the control group, an alpha of 2.0% for our primary and
41 520 secondary outcomes and 5.0% for our exploratory outcomes (see 'Meta-analysis and assessment of
42 521 significance' above), a beta of 10%, and a diversity as suggested by the trials in the meta-analysis (29,
43 522 60, 68). In case there is some evidence or effect of the intervention, a supplementary Trial Sequential
44 523 Analysis using the limit of the CI closest to 0.00 as the anticipated intervention effect will be conducted
45 524 (29).

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50 526 We will document difficult decisions in the review and sensitivity analyses will assess the impact of
51 527 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.

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4 556 • 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the
5 557 experimental group have not survived, had a serious adverse event, had a non-serious adverse
6 558 event, and did not have resolution of fever; and that all those participants lost to follow-up in
7 559 the control group have survived, had no serious adverse event, had no non-serious adverse
8 560 event, and had resolution of fever.
9 561

10 561 We will present results of both scenarios in our review.
11 562

12 562 To assess the potential impact of the missing data for continuous outcomes, we will perform the
13 563 following two sensitivity analyses when assessing each continuous outcome (quality of life and
14 564 temperature change):
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- 16 565 • 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the
17 566 experimental group and control group have had a 'beneficial outcome' or 'harmful outcome',
18 567 respectively. A 'beneficial outcome' will be the group mean plus one standard deviation (SD) of
19 568 the group mean. A 'harmful outcome' will be the group mean minus one SD of the group mean
20 569 (29).
21 570
- 22 570 • 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the
23 571 experimental group and control group have had a 'harmful outcome' or 'beneficial outcome',
24 572 respectively. A 'harmful outcome' will be the group mean minus one standard deviation (SD) of
25 573 the group mean. A 'beneficial outcome' will be the group mean plus one SD of the group mean
26 574 (29).
27 575

28 575 We will present results of both scenarios in our review.
29 576

30 576 To assess the potential impact of missing SDs for continuous outcomes, we will perform the following
31 577 sensitivity analysis.
32 578

- 33 578 • Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials
34 579 with similar populations and low risk of bias. If we find no such trials, we will impute SDs from
35 580 trials with a similar population.
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37 581 We will present results of this scenario in our review.
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39 582 Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical
40 583 heterogeneity is identified during the analysis of the review results (29).
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42 584 **Summary of findings**

43 585 We will use the GRADE system to assess the certainty of the body of evidence associated with each of
44 586 our outcomes constructing 'Summary of Findings' (SoF) tables using the GRADEpro software (34, 69-
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4 587 71). The GRADE approach appraises the certainty of the body of evidence based on the extent to which
5 588 one can be confident that an estimate of effect or association reflects the item being assessed (34, 69,
6 589 70). We will assess the GRADE levels of evidence as high, moderate, low, and very low and downgrade
7 590 the evidence by one or two levels depending on the following certainty measures: within-study risk of
8 591 bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk
9 592 of publication bias (34, 69, 70). We will use TSA to assess the 'imprecision' of effect estimates (29). We
10 593 will use methods and recommendations described in Chapter 8 (Section 8.5) (28) and Chapter 12 (72)
11 594 of the Cochrane Handbook for Systematic Reviews of Interventions (31). We will justify all decisions to
12 595 downgrade the certainty of studies using footnotes and we will make comments to aid the reader's
13 596 understanding of the review where necessary.
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19 597 We will include all trials in our analyses and conduct a sensitivity analysis excluding trials at high risk of
20 598 bias. If the results are similar, we will base our SoF table and conclusions on the overall analysis. If they
21 599 differ, we will base our SoF table and conclusions on trials at low risk of bias.
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24 600 **Differences between the protocol and the review**

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26 601 We will conduct the review according to this protocol and report any deviations from it in the
27 602 'Differences between protocol and review' section of the systematic review.
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30 603 **Patient and Public Involvement**

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32 604 We conducted this protocol for a systematic review without patient involvement. Patients were not
33 605 invited to comment on the study design and were not consulted to develop patient relevant outcomes.
34 606 Patients were not invited to contribute to the writing or editing of this protocol for readability or
35 607 accuracy.
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38 608 **Discussion**

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41 609 This protocol aims to assess the effects of fever control interventions in adults regardless of any
42 610 underlying condition to determine whether fever control interventions are beneficial or harmful. The
43 611 outcomes will be all-cause mortality, serious adverse events, quality of life, non-serious adverse events,
44 612 resolution of fever, and temperature change.
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47 613 This protocol has a number of strengths. The predefined methodology is based on the Cochrane
48 614 Handbook for Systematic Reviews of Interventions (49), the eight-step assessment suggested by
49 615 Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29), Trial Sequential
50 616 Analysis (62), and GRADE (34, 69, 70). Hence, this protocol takes into account both risks of random
51 617 errors and risks of systematic errors.
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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.

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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.

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Competing interests

The authors declare that they have no competing interests.

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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	58
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-22
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	802-804
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	802-804
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	802-804
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	281
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	341-417
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	418-531
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	532-587
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	478
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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]

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For peer review only

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:	<i>BMJ Open</i>
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice, Intensive care
Keywords:	INTERNAL MEDICINE, PRIMARY CARE, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

1 Fever control interventions versus placebo, sham, or no 2 intervention in adults. A protocol for a systematic review with 3 meta-analysis and Trial Sequential Analysis

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23 24 Keywords

25 Fever; Fever control; Systematic review; Meta-analysis

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4 28 6795 words
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30 Abstract

31 Introduction

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

36 Methods and analysis

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

47 Ethics and dissemination

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

53 PROSPERO registration number

54 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.

65 Introduction

66 Description of the condition

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

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

78 Fever is triggered by infectious agents, microbial products, and inflammatory processes that induce
79 macrophages, endothelial cells, and the reticuloendothelial system to produce and secrete pyrogenic
80 cytokines into the circulation (7). These pyrogenic cytokines induce the synthesis of prostaglandin E2
81 (PGE₂) leading to elevated levels of PGE₂ in the thermoregulatory centre in the hypothalamus, where
82 the normal temperature set-point is raised to a febrile temperature set-point (7, 8). The febrile
83 temperature set-point creates physiologic and behavioural responses that seek to increase heat
84 production and heat retention until the febrile temperature set-point is reached (8). Typical physiologic
85 responses are cutaneous vasoconstriction, shivering, and non-shivering thermogenesis, while typical
86 behavioural responses are to seek a warmer environment and adding clothing (8). When the febrile
87 temperature set-point is reached, an increase or decrease in body temperature will stimulate
88 thermoregulatory mechanisms alike those at normal body temperature. After the febrile temperature
89 set-point begins to decline, as a cause of a reduction in the concentration of pyrogens or the use of
90 antipyretics, the processes of heat loss are accelerated through vasodilation, sweating, and behavioural
91 responses like removal of clothing (9). This continues until the new lower temperature set-point is
92 reached.

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

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4 97 Fever is, as described, an integral part of the inflammatory response and has therefore likely a
5 98 physiological role in fighting infections (11, 12). Potential benefits of fever may be reduced growth and
6 99 reproduction of some bacteria and viruses, enhanced immunologic function, and increased activity of
7 100 antimicrobial drugs (11, 13, 14). Potential harms of fever may be increased level of discomfort,
8 101 increased risk of neurological and cognitive sequelae, and increased metabolic demand (13, 15).
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12 102 **Description of the intervention**

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14 103 Fever may be controlled by both pharmacological and non-pharmacological interventions.
15 104 Pharmacological interventions are the main choice for treating most cases of fever, while non-
16 105 pharmacological interventions are recommended in cases of refractory fever or in cases where rapid
17 106 temperature decrease is needed (15).
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20 107 **Pharmacological fever control interventions**

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22 108 Pharmacological fever control interventions, called antipyretics, consist of drugs able to inhibit the
23 109 enzyme cyclooxygenase (COX-1 or COX-2) and thereby interrupt the synthesis of PGE₂ (16, 17). The
24 110 following reduction in the concentration of PGE₂ causes the febrile temperature set-point to reach the
25 111 normal temperature set-point (16, 17). Antipyretics may also limit the febrile response by suppressing
26 112 tissue inflammation, reduce pyrogenic cytokine production, enhance expression of anti-inflammatory
27 113 molecules, and boost the activity of endogenous antipyretics (18). Commonly used antipyretics are
28 114 salicylates (e.g. aspirin), paracetamol, and nonsteroidal anti-inflammatory drugs (NSAID) (19). Adverse
29 115 effects of antipyretics may be gastrointestinal symptoms and renal toxicity (e.g. caused by NSAID),
30 116 bleeding (e.g. caused by aspirin and NSAID), and hepatic injury (e.g. caused by paracetamol) (20).
31 117 Patients receiving high or prolonged doses of antipyretic agents should therefore, depending on which
32 118 antipyretic they receive, be monitored for gastrointestinal adverse effects, renal dysfunction, signs of
33 119 bleeding, and elevated liver enzymes (20).
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40 120 **Non-pharmacological fever control interventions**

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42 121 Non-pharmacological fever control interventions consist of various surface and endovascular cooling
43 122 interventions (21). Cooling reduces the body temperature by removing heat without decreasing the
44 123 febrile temperature set-point (15, 22). Thus, the use of cooling may result in increased heat production,
45 124 metabolic rate, and oxygen consumption, as the body tries to counter the cooling effects by shivering
46 125 which increases the body temperature (15, 22). Hence, control of these unintended consequences (e.g.
47 126 shivering) is crucial when performing the cooling procedure (15, 22). Before commencement of a
48 127 cooling intervention, common practice includes administration of sedation (including alpha-2-agonists),
49 128 analgesics (e.g. meperidine), muscle relaxants (paralytics), and antipyretics (15, 22).
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4 129 Surface cooling interventions work through conduction, convection, or evaporation (15). Conduction
5 130 occurs when heat is exchanged between two objects in contact with one another; convection occurs
6 131 when cold fluids, such as gases and liquids, flow along the skin transferring heat from the skin to the
7 132 fluid around it; and evaporation occurs when there is heat loss from cold water being evaporated from
8 133 the skin (15). Surface cooling interventions consist of both conventional interventions such as crushed
9 134 ice, ice bags, fans, or sponging with tepid water or alcohol, and more advanced interventions such as
10 135 circulating blankets with cold fluid or cold air which are wrapped around the patient (21).

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15 136 Endovascular (catheter containing fluids is inserted through the skin into a blood vessel) cooling
16 137 interventions might also be used to control fever, but are mostly used for targeted temperature
17 138 management within intensive care (22). Examples of endovascular cooling interventions are heat
18 139 exchange catheter devices and infusion of cold fluids (23). The primary advantage of endovascular
19 140 cooling is more rapid cooling, but heat exchange catheter devices are difficult to use outside intensive
20 141 care units, and infusions of cold fluids expose patients to unnecessary volume expansion and imprecise
21 142 temperature control (22, 23).

22 143 **Why it is important to do this review**

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27 144 Whether fever in itself is beneficial or harmful in adults is unknown. Arguments for treating fever is that
28 145 fever control leads to increased patient comfort, reduced neurologic and cognitive impairment, and
29 146 reduced metabolic cost (13, 15). Arguments against treating fever is that fever leads to reduced growth
30 147 and reproduction of some bacteria and virus, enhanced immunologic function, and increased activity
31 148 of antimicrobial drugs (11, 13, 14).

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35 149 Four systematic reviews of randomised clinical trials have previously assessed the effects of fever
36 150 control interventions in febrile adults (24-27).

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39 151 - Dallimore et al. from 2018 included 13 trials with 1780 participants assessing the effects of any
40 152 fever control intervention but the review only included critically ill adults (24). Dallimore et al.
41 153 showed that 1) active temperature management versus placebo or standard care did not
42 154 significantly affect mortality (OR 1.01; 95% CI 0.81 to 1.28), ICU length of stay, nor hospital
43 155 length of stay; and 2) active temperature management was superior to placebo or standard
44 156 care in reducing body temperature (24). Dallimore et al. assessed the risk of bias in the included
45 157 trials according to the recommendations in the Cochrane Handbook (28) and a systematic
46 158 search was conducted, however GRADE was not used to assess the certainty of the evidence,
47 159 and the risks of random errors was not assessed (29).
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51 160 - Hammond et al. from 2011 included 11 trials with 801 participants assessing the effects of any
52 161 fever control intervention but the review only included critically ill adults (25). Hammond et al.
53 162 showed that 1) newer cooling methods (intravascular and hydrogel cooling) were superior to
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4 163 conventional cooling methods (surface cooling) in reducing body temperature, but with a trend
5 164 toward higher mortality in the patients receiving the newer cooling methods (RR 1.42; 95% CI
6 165 0.99 to 2.03); 2) surface cooling was superior to no surface cooling in reducing body
7 166 temperature; 3) continuous infusions were superior to bolus dosing in reducing body
8 167 temperature; and 4) aggressive (treatment ≥ 38.5 °C) was superior to permissive (treatment
9 168 ≥ 40.0 °C) antipyretic treatment in reducing the mean daily temperature (25). Hammond et al.
10 169 assessed the risk of bias in the included trials according to the recommendations in the
11 170 Cochrane Handbook (28) and a systematic search was conducted, however GRADE was not
12 171 used to assess the certainty of the evidence, and the risks of random errors was not assessed
13 172 (29).

- 14 173 - Niven et al. from 2013 included five trials with 399 participants assessing the effects of any
15 174 fever control intervention but this review only included critically ill adults without any
16 175 neurological injury (26). Niven et al. showed that fever control at ≥ 38.3 - 38.5 °C versus fever
17 176 control at ≥ 40.0 °C or no fever control did not significantly affect mortality (RR 0.98; 95% CI 0.58
18 177 to 1.63) (26). Niven et al. assessed the risk of bias in the included trials according to the
19 178 recommendations in the Cochrane Handbook (28) and a systematic search was conducted,
20 179 however GRADE was not used to assess the certainty of the evidence, and the risks of random
21 180 errors was not assessed (29).
- 22 181 - Chan et al. from 2010 included six trials with 474 participants assessing the effects of surface
23 182 cooling versus no surface cooling in febrile adults (27). Chan et al. showed that surface cooling
24 183 versus no surface cooling did not significantly affect body temperature, but increased the risk
25 184 of shivering (27). Chan et al. assessed the risk of bias in the included trials according to the
26 185 recommendations from the Joanna Briggs Institute (30) and a systematic search was conducted,
27 186 however GRADE was not used to assess the certainty of the evidence, and the risks of random
28 187 errors was not assessed (29).

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31 188 The impact of fever control interventions on mortality and other clinically important outcomes in febrile
32 189 adults regardless of e.g. being critically ill or having neurological injury or infection is still unknown. A
33 190 small number of trials have been included in previous reviews, and hence previously there has not been
34 191 sufficient information to confirm or reject if fever control interventions affect the risk of death or other
35 192 serious adverse events. It may result in sufficient power if all types of participants are included in a
36 193 meta-analysis, and it would also be possible to compare the effects of fever control interventions
37 194 between different types of participants using subgroup analyses (31). No former relevant review has
38 195 taken into account both risks of random errors and risk of systematic errors (Cochrane methodology,
39 196 Trial Sequential Analysis (TSA), and GRADE assessment) (29, 31-34).

40 197 **Objective**

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4 198 To assess the beneficial and harmful effects of fever control interventions versus placebo, sham, or no
5 199 intervention in adults when assessing mortality, both serious and non-serious adverse events, and
6 200 quality of life.
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9 201 **Methods and analysis**

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12 202 This systematic review protocol has been developed based on Preferred Reporting Items for Systematic
13 203 Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews
14 204 evaluating healthcare interventions (35). A PRISMA-P checklist file is attached (**Additional file 1**).
15

16 17 205 **Criteria for considering studies for this review**

18 19 206 **Types of studies**

20
21 207 We will include randomised clinical trials irrespective of trial design, setting, blinding, publication status,
22 208 publication year, language, and reporting of outcomes. We will not specifically search for non-
23 209 randomised studies. However, if we during our literature searches identify non-randomised studies
24 210 (quasi-randomised studies or observational studies) with adequate reports of harmful effects, we will
25 211 narratively report these results.
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28 29 212 **Types of participants**

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31 213 We will include adult participants diagnosed with fever. We will accept the definitions used by the
32 214 individual trialists. We will include participants irrespective of age, sex, and comorbidities. Furthermore,
33 215 we will include participants regardless of underlying conditions such as being critically ill or having
34 216 neurological injury or infection.
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37 217 Trials that only include a subset of eligible participants will only be included if: 1) separate data on the
38 218 eligible participants are available or 2) more than 90% are eligible.
39

40 41 219 **Types of interventions**

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43 220 We will include three types of comparisons:

- 44 221 - any fever control intervention compared with placebo or sham;
- 45 222 - any fever control intervention compared with no intervention; and
- 46 223 - any fever control intervention added to a co-intervention compared with a similar co-
47 224 intervention (with or without placebo or sham).
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51 225 As experimental intervention, we will accept any type of pharmacological or non-pharmacological fever
52 226 control intervention (as defined by trialists) irrespective of dose, route of administration, and duration
53 227 of administration.
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4 228 We will include all control interventions (placebo, sham, or no intervention) irrespective of dose, route
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6 229 of administration, and duration of administration.

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8 230 We will accept any type of co-intervention when such co-intervention is intended to be delivered
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10 231 similarly to the experimental and control group.

11 232 We will separately include trials that compare more aggressive fever control with less aggressive fever
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13 233 control. By doing this, we will be able to discuss if the aggressivity of fever control has a beneficial or
14 234 harmful impact on the patient.
15

16 235 **Outcome measures**

17 18 236 Primary outcomes

- 19
20 237 - All-cause mortality.
21
22 238 - Serious adverse events. We will define a serious adverse event as any untoward medical
23 239 occurrence that resulted in death; was life-threatening; required hospitalisation or prolongation
24 240 of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the
25 241 patient (36). As we expect the reporting of serious adverse events to be very heterogeneous
26 242 and not strictly according to the ICH-GCP recommendations in many trials, we will include the
27 243 event as a serious adverse event if the trialists either: 1) use the term 'serious adverse event'
28 244 but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider
29 245 fulfil the ICH-GCP definition. If several of such event are reported, then we will choose the
30 246 highest proportion reported in each trial. We will secondly analyse each component of serious
31 247 adverse events separately.
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37 248 Secondary outcomes

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39 249 - Quality of life (measured on any valid continuous scale).
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41 250 - Non-serious adverse events (defined as those leading to discontinuation of the intervention or
42 251 defined as 'adverse events' by the trialists). Each adverse event will be analysed separately.
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45 252 Exploratory outcomes

- 46
47 253 - Resolution of fever (as defined by the trialists).
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49 254 - Temperature change (measured by body temperature).
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51 255 - Number of serious adverse events (analysed as count data).
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53 256 - Number of non-serious adverse events (analysed as count data).
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'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

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4 285 of included randomised clinical trials for further information by email. Further, we will search for
5
6 286 ongoing and unidentified randomised clinical trials on:

- 7
8 287 - ClinicalTrials.gov (www.clinicaltrials.gov);
9 288 - the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP)
10
11 289 search portal (<http://apps.who.int/trialsearch/>);
12 290 - Google Scholar (<https://scholar.google.com/>); and
13
14 291 - The Turning Research into Practice (TRIP) Database (<https://www.tripdatabase.com/>).

15
16 292 We will also include unpublished and grey literature trials if we identify these and assess relevant
17 293 retraction statements and errata for included studies.
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19 294 **Data collection and analysis**

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21 295 We will perform the review following the recommendations of Cochrane (31). The analyses will be
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23 296 performed using Review Manager 5.3 (38) and TSA (39). In case of Review Manager statistical software
24 297 not being sufficient, we will use STATA 15 (40).
25

26 298 **Selection of studies**

27
28 299 Two review authors (NJS and AIN) will independently screen titles and abstracts for inclusion of all the
29
30 300 potentially eligible trials. We will code all these studies as 'retrieve' (eligible or potentially
31 301 eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to
32
33 302 arbitrate (JCJ). We will retrieve all relevant full-text study reports/publications and two review authors
34 303 (NJS and AIN) will independently screen the full-text and identify trials for inclusion. We will report
35 304 reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or,
36
37 305 if required, we will consult a third person (JCJ). We will identify and exclude duplicated and collated
38 306 multiple reports of the same trial so that each trial rather than each report is the unit of interest in the
39
40 307 review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram
41 308 (35).
42

43 309 **Data extraction and management**

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45 310 We will use a data collection form for study characteristics and outcome data, which has been piloted
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47 311 on at least one study in the review. Two authors (NJS and AIN) will extract and validate data
48 312 independently from the included trials. Any disagreement concerning the extracted data will be
49 313 discussed between the two authors. If no agreement can be reached, a third author (JCJ) will resolve
50
51 314 the issue. We will assess duplicate publications and companion papers of a trial together in order to
52 315 evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will
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54 316 contact the trial authors by email to specify any additional data, which may not have been reported
55 317 sufficiently or at all in the publication. We will extract the following data:
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- 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

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4 347 - other risks of bias.
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6 348 These domains enable classification of randomised clinical trials at low risk of bias and at high risk of
7 bias. The latter trials tend to overestimate positive intervention effects (benefits) and underestimate
8 349 negative effects (harms) (41-47).
9 350

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11 351 We will classify the trials according to the following criteria:
12

13 352 Random sequence generation
14

- 15 353 - Low risk: if sequence generation was achieved using computer random number generator or a
16 random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were
17 354 also considered adequate if performed by an independent adjudicator.
18 355
19
20 356 - Unclear risk: if the method of randomisation was not specified, but the trial was still presented
21 as being randomised.
22 357
23
24 358 - High risk: If the allocation sequence was not randomised or only quasi-randomised. These trials
25 359 will be excluded.
26

27 360 Allocation concealment
28

- 29 361 - Low risk: if the allocation of patients was performed by a central independent unit, on-site
30 locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers
31 362 prepared by an independent pharmacist or investigator.
32 363
33
34 364 - Uncertain risk: if the trial was classified as randomised but the allocation concealment process
35 was not described.
36 365
37
38 366 - High risk: if the allocation sequence was familiar to the investigators who assigned participants.
39

40 367 Blinding of participants and personnel
41

- 42 368 - Low risk: if the participants and the personnel were blinded to intervention allocation and this
43 369 was described.
44
45 370 - Uncertain risk: if the procedure of blinding was insufficiently described.
46
47 371 - High risk: if blinding of participants and the personnel was not performed.
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49 372 Blinding of outcome assessment
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- 51 373 - Low risk: if it was mentioned that outcome assessors were blinded, and this was described.
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374 - Uncertain risk: if it was not mentioned if the outcome assessors in the trial were blinded, or the
375 extent of blinding was insufficiently described.

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

Incomplete outcome data

378 - Low risk: if missing data were unlikely to make treatment effects depart from plausible values.
379 This could either be: 1) there were no dropouts or withdrawals for all outcomes, or 2) the
380 numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated
381 and could be described as being similar in both groups. Generally, the trial will be judged as at
382 a low risk of bias due to incomplete outcome data if dropouts are less than 5%. However, the
383 5% cut-off is not definitive.

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

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

Selective outcome reporting

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

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

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

Other risks of bias

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

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

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

Overall risk of bias

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4 403 - Low risk: the trial will be classified as overall 'low risk of bias' only if all of the bias domains
5 404 described in the above paragraphs are classified as 'low risk of bias'.
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8 405 - High risk: the trial will be classified 'high risk of bias' if any of the bias risk domains described in
9 406 the above are classified as 'unclear' or 'high risk of bias'.
10

11 407 We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and
12 'selective outcome reporting' for each outcome. This will enable us to assess the bias risk for each
13 408 outcome result in addition to each trial.
14 409
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16 410 We will grade each potential source of bias as high, low, or unclear and provide evidence from the trial
17 report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the
18 411 risk of bias judgements across different trials for each of the domains listed.
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21 413 **Measures of treatment effect**

22 23 414 Dichotomous outcomes

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26 415 We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well
27 416 as the TSA-adjusted CIs (see paragraphs below). We will calculate the absolute risk reduction (ARR) or
28 increase (ARI) and number needed to treat (NNT) or harm (NNH) if the outcome result shows a
29 417 beneficial or harmful effect, respectively.
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32 419 Continuous outcomes

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34 420 We will calculate the mean differences (MDs) and if necessary, as a hypothesis generating analysis, the
35 421 standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the TSA-adjusted
36 422 CIs (see paragraphs below).
37
38

39 423 Count outcomes

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41 424 We will calculate rate ratios with 95% confidence interval (CI) for count outcomes.
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44 425 **Unit of analysis issues**

45 426 We will only include randomised clinical trials. For trials using cross-over design, only data from the first
46 427 period will be included (48, 49). For trials where multiple trial intervention groups are reported, we will
47 428 only include the relevant groups. If two comparisons from the same trial are combined in the same
48 429 meta-analysis, we will halve the control group to avoid double-counting (49). We will not include cluster
49 430 randomised trials, as these have a high risk of biased results due to confounding (31).
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431 **Dealing with missing data**

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

433 Dichotomous outcomes

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

437 Continuous outcomes

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

443 **Assessment of heterogeneity**

444 We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly
445 assess the presence of statistical heterogeneity by the Chi²-test (threshold P < 0.10) and measure the
446 quantities of heterogeneity by the I²-statistic (50, 51).

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

449 **Assessment of reporting biases**

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

457 **Data synthesis**

458 Meta-analysis and assessment of significance

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

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4 461 suggested by Jakobsen et al. for better validation of meta-analytic results in systematic reviews (29).
5 462 We will use the statistical software Review Manager 5.3 (38) provided by Cochrane and STATA 15 (40)
6 463 to analyse data.
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9 464 We will assess our intervention effects with both random-effects meta-analyses (55) and fixed-effect
10 465 meta-analyses (56) and report the more conservative result as our primary result (29). The more
11 466 conservative point estimate is the result with the highest P value and the widest 95% CI. In case that
12 467 few trials (1-3) make up >90% of the weight in the meta-analysis, we will use fixed-effect meta-analysis.
13 468 If there is substantial discrepancy between the results of the two methods, we will report and discuss
14 469 the results (29).
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18 470 We will adjust our thresholds for statistical significance due to problems with multiplicity (family-wise
19 471 error rate), by dividing the pre-specified P value threshold with the value halfway between 1 (no
20 472 adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment)
21 473 (29). We will assess a total of four primary and secondary outcomes in the review and, hence, consider
22 474 a P value of 0.02 or less as the threshold for statistical significance (29). For our exploratory outcomes,
23 475 we will consider a P value of 0.05 or less as the threshold for statistical significance.
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27 476 If quantitative synthesis is not appropriate, we will report the results in a narrative way.
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29 477 Trial Sequential Analysis

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31 478 Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple
32 479 testing of accumulating data (32, 39, 57-65). Therefore, TSA (39) can be applied to control these risks
33 480 (<http://www.ctu.dk/tsa/>) (62). Similar to a sample size calculation in a randomised clinical trial, TSA
34 481 estimates the diversity-adjusted required information size (DARIS) (that is, the number of participants
35 482 needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random
36 483 errors (60). The DARIS takes into account the anticipated intervention effect, the variance of the
37 484 anticipated difference in intervention effects, the acceptable risk of falsely rejecting the null hypothesis
38 485 (alpha), the acceptable risk of falsely confirming the null hypothesis (beta), and the variance of the
39 486 intervention effect estimates between trials (29, 60, 66). We searched for suitable empirical data to
40 487 determine and predefine the anticipated intervention effects (29). However, no suitable data could be
41 488 found. Instead, we pragmatically hypothesised the anticipated intervention effects:
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- 47 489 - When analysing all-cause mortality, serious adverse events, and non-serious adverse events, we
48 490 will pragmatically anticipate an intervention effect equal to a risk ratio reduction (RRR) of 25%.
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- 50 492 - When analysing resolution of fever, we will pragmatically anticipate an intervention effect equal
51 493 to a RRR of 30%.
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- 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.

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- 525 A. Comparison of the effects between trials with different types of fever control interventions.
- 526 B. Comparison of the effects between critically ill and non-critically ill participants:
- 527 • Trials including critically ill participants; or
 - 528 • Trials including non-critically ill participants.
- 529 C. Comparison of the effect between participants with infectious- and non-infectious fever (e.g.
530 neurological injury or drug-induced fever):
- 531 • Trials including participants with infectious fever; or
 - 532 • Trials including participants with non-infectious fever.
- 533 D. Comparison of the effects between trials with different maximal follow-ups:
- 534 • Up to 1 year; or
 - 535 • 1 year and above.
- 536 E. Comparison of the effect between trials with different control interventions:
- 537 • Placebo-controlled trials; or
 - 538 • No control intervention.
- 539 F. Comparison of the effects between industry funded trials or trials with unknown funding compared
540 to non-industry funded trials:
- 541 • industry funded trials or unknown funding; or
 - 542 • non-industry funded trials.

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

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

546 **Sensitivity analysis**

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

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

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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.

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4 581 • Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials
5 582 with similar populations and low risk of bias. If we find no such trials, we will impute SDs from
6 583 trials with a similar population.
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9 584 We will present results of this scenario in our review.
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11 585 Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical
12 586 heterogeneity is identified during the analysis of the review results (29).
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15 587 **Summary of findings**

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17 588 We will use the GRADE system to assess the certainty of the body of evidence associated with each of
18 589 our outcomes constructing 'Summary of Findings' (SoF) tables using the GRADEpro software (34, 69-
19 590 71). The GRADE approach appraises the certainty of the body of evidence based on the extent to which
20 591 one can be confident that an estimate of effect or association reflects the item being assessed (34, 69,
21 592 70). We will assess the GRADE levels of evidence as high, moderate, low, and very low and downgrade
22 593 the evidence by one or two levels depending on the following certainty measures: within-study risk of
23 594 bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk
24 595 of publication bias (34, 69, 70). We will use TSA to assess the 'imprecision' of effect estimates (29). We
25 596 will use methods and recommendations described in Chapter 8 (Section 8.5) (28) and Chapter 12 (72)
26 597 of the Cochrane Handbook for Systematic Reviews of Interventions (31). We will justify all decisions to
27 598 downgrade the certainty of studies using footnotes and we will make comments to aid the reader's
28 599 understanding of the review where necessary.
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34 600 We will include all trials in our analyses and conduct a sensitivity analysis excluding trials at high risk of
35 601 bias. If the results are similar, we will base our SoF table and conclusions on the overall analysis. If they
36 602 differ, we will base our SoF table and conclusions on trials at low risk of bias.
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39 603 **Differences between the protocol and the review**

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41 604 We will conduct the review according to this protocol and report any deviations from it in the
42 605 'Differences between protocol and review' section of the systematic review.
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45 606 **Patient and Public Involvement**

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47 607 We conducted this protocol for a systematic review without patient involvement. Patients were not
48 608 invited to comment on the study design and were not consulted to develop patient relevant outcomes.
49 609 Patients were not invited to contribute to the writing or editing of this protocol for readability or
50 610 accuracy.
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53 611 **Discussion**

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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.

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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.

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Competing interests

The authors declare that they have no competing interests.

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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	54
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-22
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	806-808
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	806-808
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	806-808
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	275
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	336-412
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	413-522
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	523-586
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	476
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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

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20. 18 and 21

For peer review only