

A survey of fever management for febrile intensive care patients without neurological injury

Manoj K Saxena, Naomi E Hammond, Colman Taylor, Paul Young, Michael C Reade, Rinaldo Bellomo and John Myburgh

Fever is a common observation during critical illness¹⁻⁴ and may be due to infection, sterile inflammation or neurological injury. Although fever may be immunologically beneficial,⁵⁻⁹ maintaining a high core temperature can convey a metabolic burden.^{10,11} Experimental and observational human data suggest that fever may exacerbate neurological injury.¹¹⁻¹⁴ Clinical trials of fever management lack sufficient methodological quality to determine whether attempts at reduction in temperature improve patient-centred outcomes among patients with sepsis, inflammation or neurological injury (Egi M, Morita K. Fever and antipyretic therapy in critically ill patients: a systematic review. Manuscript in preparation).^{10,15-18} The Surviving Sepsis guidelines¹⁹ and the Brain Trauma Foundation guidelines²⁰ reflect this uncertainty by the absence of specific recommendations on the management of fever.

We undertook a survey to describe the attitudes of intensive care clinicians in Australia and New Zealand about fever management for critically ill patients without neurological injury or hyperthermic syndromes.

Methods

We designed a scenario-based survey instrument that asked respondents to consider their approach to two clinical situations, stating that all questions within the survey related to temperature management in the absence of neurological pathological features (eg, stroke or head injury) and hyperthermic syndromes (eg, malignant hyperthermia).

The first scenario was that of a mechanically ventilated patient with pneumonia, severe sepsis and a temperature of 38.0°C. Respondents were asked to identify a temperature threshold for intervention (with options presented in 0.5°C bands), and to indicate which first- and second-line interventions they would use to reduce temperature. Respondents were able to select more than one intervention.

The second scenario related to a hypothetical clinical trial in which critically ill patients would be randomised to a group that received intensive temperature control and a group that had a permissive approach. Respondents were asked their opinions of acceptable temperature thresholds for each trial group and for their opinion on the importance of the proposed trial. The survey tool is provided in Appendix 1.

ABSTRACT

Objective: To determine the attitudes of critical care clinicians in Australia and New Zealand towards fever management for critically ill patients with sepsis but without neurological injury.

Design: Online scenario-based survey distributed to members of the Australian and New Zealand Intensive Care Society Clinical Trials Group and their intensive care colleagues.

Main outcome measures: The choice of intervention and preferred threshold temperature for modification of temperature in clinical practice and in a clinical trial.

Results: Most respondents indicated a preference for the use of interventions to lower temperature at or below 39.0°C (80%; 337/423), with first-line preference being a combination of paracetamol and physical cooling. Second-line interventions included the addition of intensive physical cooling. Doctors chose higher temperature thresholds for intervention (32% [43/134] below 38.5°C and 27% [36/134] above 39.5°C) than nurses (78% [226/289] and 7% [19/289], respectively), who, in turn, indicated stronger preferences for the use of physical cooling. There is support (78%) for a clinical trial of fever management, with respondents suggesting randomising patients to a mean intensive control of temperature to 38.0°C versus a permissive approach with a threshold for intervention of between 38.8°C (SD, 0.6°C) (nurses) and 39.5°C (SD, 0.7°C) (doctors).

Conclusion: There is considerable variability in attitudes to fever management with a reported tendency to act to reduce fever in febrile patients with sepsis. There was broad support for a clinical trial of fever management.

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The survey instrument was piloted in one intensive care unit, with revisions made to increase clarity and to provide all possible answers. A link to the online self-administered survey (SurveyMonkey, Palo Alto, Calif, USA), was distributed via email to doctors in the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and to nurses in the ANZICS CTG Research Coordinator

Table 1. Demographics of 447 intensive care clinician respondents to the survey*

	No. (%)
Profession	
Nurse	308 (69%)
Doctor	137 (31%)
Postgraduate qualifications	
Yes	358 (80%)
No	86 (19%)
Experience	
1–8 years	171 (38%)
> 8 years	275 (62%)
Hospital level	
Tertiary	343 (77%)
Rural	14 (3%)
Metropolitan	88 (20%)
Casemix	
Predominantly medical	26 (6%)
Predominantly surgical	40 (9%)
Mixed medical/surgical	371 (83%)
Single specialty unit	1 (< 1%)
Other	5 (1%)

* Missing data not imputed.

Interest Group. The survey invitations were emailed three times from 6 December 2010 to 11 January 2011. Recipients were asked to distribute the electronic link for the survey to nursing and medical staff in their ICU.

Statistical analysis was carried out using SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). Data were inspected for normality and are presented in parametric or non-parametric form as appropriate. An a-priori subgroup was defined according to profession (doctor or nurse). Differences in the proportion of responses between subgroups were examined using χ^2 tests, *t* tests or linear regression with *P* < 0.05 considered statistically significant. The survey was assessed as low/negligible risk and approved by the Human Research Ethics Committee, South Eastern Sydney Local Health Network (approval no. HREC/11/STG/89).

Results

There were 588 email invitations distributed through the ANZICS CTG and Research Coordinator Interest Group mailing list. We received 447 responses, from 308 nurses (69%) and 137 doctors (31%). Most respondents had more than 8 years of experience (62%) and worked in mixed medical and surgical units (83%) in a metropolitan (20%) or tertiary (77%) hospital setting (Table 1).

Figure 1. Thresholds for initiation of antipyretic interventions between professions (nurse/other, n = 289; doctor, n = 134; P < 0.001)

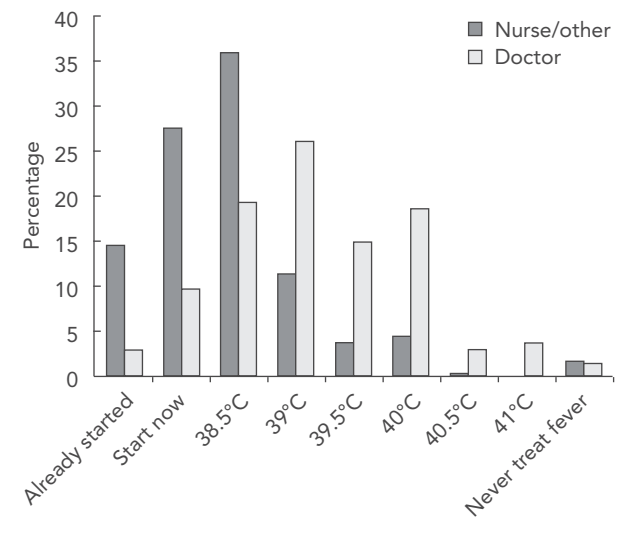
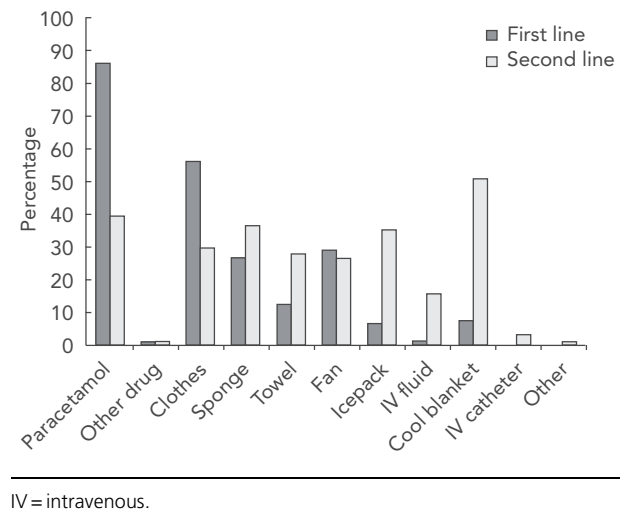


Figure 2. First- and second-line treatment preferences for fever management



IV = intravenous.

Figure 1 displays the temperature threshold at which the respondents would intervene with cooling interventions for a mechanically ventilated patient with pneumonia, severe sepsis, and a temperature of 38.0°C. Sixty-four per cent of respondents (269/423) indicated they would intervene at or below a temperature of 38.5°C and 80% (337/423) at or below 39.0°C. Between professions, nurses indicated a preference to intervene at lower temperatures than doctors (*P* < 0.01). Most nurses indicated a preference to intervene at or below 38.5°C (78%; 226/289); 7% (19/289) preferred

Table 2. Preference of first- and second-line interventional category of antipyretic by profession (n = 439)

	Nurse, no. (%)	Doctor, no. (%)	P
First-line intervention, n	286	132	—
Pharmacological only	65 (23%)	53 (40%)	<0.01
Paracetamol	238 (83%)	121 (92%)	—
Physical only	37 (13%)	6 (5%)	<0.01
Clothing removal	184 (64%)	50 (38%)	—
Sponge	90 (31%)	21 (16%)	—
Towel	39 (14%)	13 (10%)	—
Fan	94 (33%)	27 (20%)	—
Ice pack	22 (8%)	6 (5%)	—
Intravenous fluid	3 (1%)	3 (2%)	—
Cooling blanket	18 (6%)	14 (11%)	—
Pharmacological and physical	184 (64%)	73 (55%)	0.08
Second-line intervention, n	280	130	
Pharmacological only	15 (5%)	6 (5%)	0.87
Paracetamol	117 (42%)	46 (35%)	—
Physical only	161 (58%)	82 (63%)	0.36
Clothing removal	85 (30%)	37 (28%)	—
Sponge	115 (41%)	35 (27%)	—
Towel	83 (30%)	32 (25%)	—
Fan	83 (30%)	36 (28%)	—
Ice pack	108 (39%)	36 (28%)	—
Intravenous fluid	37 (13%)	70 (54%)	—
Cooling blanket	138 (49%)	70 (54%)	—
Pharmacological and physical	104 (37%)	41 (32%)	0.39

— = no statistical comparison undertaken.

Table 3. Mean temperature thresholds (SD) for a clinical trial of fever management: whole group and by profession

	Whole group (n = 399)	Doctors (n = 130)	Nurses (n = 269)	P
Mean intensive threshold	38.0°C (SD, 0.8°C)	38.1°C (SD, 0.6°C)	38.0°C (SD, 0.8°C)	0.03
Mean permissive threshold	39.0°C (SD, 0.7°C)	39.5°C (SD, 0.7°C)	38.8°C (SD, 0.6°C)	<0.01

to wait until the temperature was above 39.5°C or preferred not to treat fever at all. For doctors the corresponding percentages were 32% (43/134) and 27% (36/134), respectively.

Most respondents (360/419; 86%) chose paracetamol as their first-line antipyretic intervention (Figure 2), but simple physical cooling techniques were also a common choice, as indicated by preferences for the removal of clothing (56% [235/419]), sponging (27% [112/419]), and use of fans

(29% [122/419]). Rare responses for first-line preferences included the use of ice packs (7% [28/419]), cooling blankets (8% [32/419]) and cold intravenous fluids (1% [6/419]).

Respondents were asked to indicate second-line antipyretic interventions if fever persisted and, although paracetamol and simple physical cooling techniques remained common, respondents indicated an increase in use of ice packs (35% [145/411]) and cooling blankets (51% [209/411]). Respondents rarely indicated a preference for the use of a non-steroidal anti-inflammatory drug or cyclo-oxygenase 2 inhibitor (1% [5/411]) as a first-line or second-line intervention.

Analysis by profession indicated that the preferences of nursing and medical staff for antipyretic interventions were different (Table 2). For first-line interventions, doctors were more likely than nurses to specify the use of pharmacological agents (predominantly paracetamol) only (40% v 23%; $P < 0.01$) and nurses were more likely to use either a physical cooling technique alone (13% v 5%; $P < 0.01$) or a combination of physical cooling technique and paracetamol (64% v 55%; $P = 0.08$).

For second-line interventions, both professional groups indicated they would use physical cooling either alone (nurse 58%; doctor 62%; $P = 0.36$) or in combination with paracetamol (nurse 38%; doctor 33%; $P = 0.39$). Cooling blankets were indicated as a second-line therapy by 49% of nurses and 54% of doctors, whereas ice packs were indicated as second-line therapy by 39% of nurses and 28% of doctors.

Doctors expressed a stronger inclination than nurses for the use of cold intravenous fluids as a second-line therapy (nurse 13%; doctor 54%). Nursing staff generally indicated increased (first- and second-line) preference for the use of physical cooling techniques compared with medical staff (Table 2).

Table 3 shows respondents' attitudes towards temperature targets for permissive and intensive treatment groups in a clinical trial. For the intensive treatment group, the respondents specified a mean target temperature of 38.0°C

(SD, 0.75°C) and for the permissive group, 39.0°C (SD, 0.7°C). There was a statistically significant difference for the mean target temperature of the permissive group when analysed by the subgroup of profession (doctor, 39.5°C [SD, 0.7°C]; nurse, 38.8°C [SD, 0.6°C]; $P < 0.01$).

Seventy-eight per cent of respondents agreed (49% agreed; 29% strongly agreed) that a clinical trial of fever management was warranted; 19% of respondents were unsure, 3% disagreed, and 2% strongly disagreed.

Discussion

This survey reports on the preferences of intensive care clinicians for fever management in febrile patients with severe infection without neurological injury. Our primary findings suggest that fever management is highly variable. Most clinicians administer an intervention to reduce temperature at or below 39.0°C, and initially use a combination of pharmacological and physical interventions, with an increase in intensity of physical interventions for persistent fever. There were differences between the professions with doctors choosing higher temperature thresholds for intervention and nurses generally using more physical cooling; temperature thresholds for a clinical trial were 39.0°C (SD, 0.7°C) for a permissive strategy and 38.0°C (SD, 0.8°C) for an intensive strategy; finally, there was broad support for a clinical trial of fever management.

The range of thresholds for treatment in both the clinical scenario and the clinical trial are consistent with consensus guideline for the definition of fever,^{21,22} definitions of fever used in observational studies,³ and thresholds used for entry criteria in randomised, controlled clinical trials (38.3°C and 38.5°C),^{16,23,24} In the only study that evaluated a permissive approach to fever management, the temperature threshold for intervention in the permissive arm was 40.0°C.¹⁶ Historical data^{25,26} contemporary observational studies (Egi M, on behalf of the Japan–Korea Intensive Care Study Group and the Fever and Antipyretic in Critically Ill Patients Evaluation Study Group. The association of body temperature and antipyretics with mortality in non-neurological critically ill patients. Manuscript in preparation), consensus discussions¹⁶ and surveys (Young P, Medical Research Institute of New Zealand, Wellington, New Zealand unpublished data) also support the range of thresholds indicated by respondents.

The variability of attitudes to fever management for patients with an infection demonstrated in our survey is consistent with previous surveys of fever management practice in neurosurgical ICUs in international surveys.^{27,28} The use of interventions to modify temperature in our survey is also consistent with the protocol of the study by Schulman and colleagues¹⁶ and recent multicentre prospec-

tive cohort studies in Australia and New Zealand,²⁹ Japan and Korea (Egi M, Morita K. Fever and antipyretic therapy in critically ill patients: a systematic review. Manuscript in preparation) of non-neurologically injured patients with febrile sepsis and inflammation.

In the absence of high-quality randomised controlled clinical trials evaluating the safety and efficacy of temperature modification on patient-centred outcomes (Egi M, Morita K. Fever and antipyretic therapy in critically ill patients: a systematic review. Manuscript in preparation),^{15,18} there remains the possibility that the use of antipyretic interventions may be associated with harm. Randomised controlled clinical trials are needed to resolve the clinical uncertainty for this ubiquitous, everyday clinical issue and our survey suggests that clinicians have equipoise for a study comparing intensive control and a permissive approach to fever management.

The results of our survey may have implications for both the design and conduct of a potential randomised controlled clinical trial, and suggest that a temperature threshold of 38.0°C may be acceptable for an intensive fever management arm and that a temperature threshold between 38.8 and 39.5°C may be acceptable for a permissive arm. The survey results also suggest that paracetamol (with simple physical cooling) may be an appropriate first-line response, with the addition of more intensive cooling techniques if fever persisted. The differences observed between doctors and nurses may relate to training, ability to prescribe drugs and physical interventions, or personal preferences, and will be important to take into consideration when providing education before conduct of a clinical trial.

Clinicians may have concerns regarding temperature thresholds for the permissive arm of a hypothetical trial of fever management based on potential adverse neurological effects. These effects were originally described in the pre-antibiotic era in the context of “fever therapy”, where induced temperatures in excess of 40.5°C were noted to be associated with widespread systemic and neurological histopathological damage at autopsy.^{26,30} Comparisons of observational data before and after the introduction of antipyretics and antibiotics into clinical practice suggest that the upper limit for measured temperatures in clinical practice has reduced from 41.0°C and now rarely exceeds 40.0°C. In addition it is possible that, based on experimental models of neurological injury¹² and observational clinical studies^{14,31,32} of stroke and head injury, fever control has become increasingly extrapolated to non-neurological disorders such as sepsis and inflammation.³³

A strength of our study is that through the ANZICS CTG, we were able to survey a large group of doctors and nurses working across Australia and New Zealand, potentially

representing contemporary clinical practice and attitudes to a clinical trial of fever management. An additional strength is the number of responses returned as a proportion of the number of health care professionals on the ANZICS CTG member and Research Coordinator mailing lists, and that the survey was scenario-based.³⁴

The main weakness of our survey is the unknown response rate (at best, the response rate was 76% [447/588]) given that the survey was electronically forwarded on to an unknown number of intensive care staff. Additionally, we are unable to conclude that the opinions are generalisable to the broader ICU community, as there may be undetected responder bias towards the ANZICS CTG research community and metropolitan and tertiary hospitals. However, ICUs are mostly staffed by trained intensive care physicians and nurses, who work collaboratively in multidisciplinary teams in closed ICUs, and intensive care training in Australia and New Zealand is standardised.

Also, the possible bias towards the ANZICS CTG research community may favour the representation of the responses of the research community (including opinion leaders) with an interest in clinical trials. The support of this group for a clinical trial is essential. We did not explore the method of temperature measurement in this survey and this may affect the interpretation of thresholds for intervention. Several studies have documented that core temperature measurements may exceed non-core measurements by up to 0.5°C.³⁵ However, we are planning to collect observational data on temperature measurement practice in Australia and New Zealand (to be published separately), and, for the purposes of this survey, it is likely that the choice of temperature threshold chosen by respondents includes consideration of their usual method of measurement.

Finally, although surveys reflect perceptions of participants' clinical practice, they may not reflect their actual behaviour in clinical practice, as the use of physical cooling may be restricted by availability, cost or the license to prescribe in clinical practice. Although observational studies are required to describe actual clinical practice and to compare this with the results of our survey, our survey provides insight into attitudes of clinicians on fever management in patients with sepsis.

Conclusions

In conclusion, our survey suggests that there is variability in the attitudes of doctors and nurses to fever management in patients with sepsis and without neurological injury or hyperthermic syndromes. In a clinical scenario, clinicians choose to reduce temperature at a threshold below 39.0°C and use paracetamol and simple physical

cooling techniques first, followed by the addition of more intensive physical cooling if fever persists. At present, no particular management strategy is known to be superior to any other, and it remains possible that current practice may be harming substantial numbers of patients. The respondents supported a randomised controlled trial of intensively controlling temperature to 38.0°C versus a permissive approach with a threshold for intervention between 38.8 and 39.5°C of fever management. Further observational data may be informative for the design of such clinical trials.

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Competing interests

None declared.

Author details

Manoj K Saxena, Honorary Research Fellow,¹ and Intensive Care Physician^{2,3}

Naomi E Hammond, Research Fellow^{1,3}

Colman Taylor, Research Fellow^{1,4}

Paul Young, Honorary Senior Research Fellow⁵

Michael C Reade, Intensive Care Physician,⁶ and Associate Professor⁷

Rinaldo Bellomo, Director of Intensive Care Research⁶

John Myburgh, Director, Division of Critical Care and Trauma,¹ Professor of Critical Care Medicine,² and Intensive Care Physician³

¹ The George Institute for Global Health, Sydney, NSW, Australia.

² St George Hospital, Sydney, NSW, Australia.

³ St George Clinical School, University of New South Wales, Sydney, NSW, Australia.

⁴ Sydney Medical School, University of Sydney, Sydney, NSW, Australia.

⁵ Medical Research Institute of New Zealand, Wellington, New Zealand.

⁶ Austin Hospital, Melbourne, VIC, Australia.

⁷ University of Melbourne, Melbourne, VIC, Australia.

Correspondence: m.saxena@unsw.edu.au

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Appendix 1. Questionnaire

Introduction:

Your responses to the below questions will help us plan a clinical trial evaluating fever management in intensive care patients

This survey should take no longer than 5 minutes to complete.

Your participation is completely anonymous.

Thank you for your valuable contribution.

Q1: (a) I am a:

- Nurse
- Doctor
- Other (specify)

(b) Do you have post-graduate qualifications in Intensive Care?

- No/Yes

Q2: I have been working in intensive care for:

(a): ___ Years

Q3: (a) Does the majority of your intensive care practice take place in a:

- Tertiary hospital
- Rural hospital
- Metropolitan hospital

(b) Which of the following terms best describes your case mix in the hospital specified above?

- Predominantly medical (> 70% case-mix)
- Predominantly surgical (> 70% case-mix)
- Mixed medical and surgical (close to 50 : 50 case-mix)
- Single speciality unit
- Other (please specify)

The following questions ALL relate to how fever is managed in a typical intensive care patient without a neurological injury or a hyperthermic syndrome (e.g. malignant hyperthermia, heat stroke, serotonin syndrome etc).

Clinical Scenario

Q4: A 46 year-old man is in the ICU with a diagnosis of community acquired pneumonia — blood cultures are growing *S. pneumoniae*. He has severe sepsis and is mechanically ventilated, and right now he has a core temperature of 38°C.

(a) How would you respond to his temperature?

- Start treatment to reduce it now
- I would have already had such patient on prophylactic anti-fever therapy
- Wait until 38.5 and then treat,
- Wait until 39 and then treat
- Wait until 39.5 and then treat
- Wait until 40 and then treat,
- Wait until 40.5 and then treat
- Wait until 41 and then treat,
- Never treat fever

(b) If your answer to (a) involved modifying temperature, what would you normally use as your “first-line” intervention(s) to modify the temperature that you specified in (a)?

- Drugs only:
 - Paracetamol
 - diclofenac,
 - ibuprofen,
 - indomethacin
 - celecoxib
 - Paracoxib
 - Other: Please specify
- Physical cooling only:
 - Removal of clothes/coverings
 - Tepid sponging
 - Wet towel/blanket
 - Fan
 - Ice packs
 - Intravenous cold fluids
 - Cooling blanket/wrap
 - Intravenous cooling catheter
 - Other: Please specify
- Both drugs and physical cooling:
 - Paracetamol
 - diclofenac,
 - ibuprofen,
 - indomethacin
 - celecoxib
 - paracoxib
 - Removal of clothes/coverings
 - Tepid sponging
 - Wet towel/blanket
 - Fan
 - Ice packs
 - Intravenous cold fluids
 - Cooling blanket/wrap
 - Intravenous cooling catheter
 - Other: Please specify

(c) If your first technique “did not work”, what intervention(s) would you use next?

- Drugs only:
 - Paracetamol
 - diclofenac,
 - ibuprofen,
 - indomethacin
 - celecoxib
 - Paracoxib
 - Other: Please specify

• Physical cooling only:

- Removal of clothes/coverings
- Tepid sponging
- Wet towel/blanket
- Fan
- Ice packs
- Intravenous cold fluids
- Cooling blanket/wrap
- Intravenous cooling catheter
- Other: Please specify

• Both drugs and physical cooling:

- Paracetamol
- diclofenac
- ibuprofen,
- indomethacin
- celecoxib
- paracoxib
- Removal of clothes/coverings
- Tepid sponging
- Wet towel/blanket
- Fan
- Ice packs
- Intravenous cold fluids
- Cooling blanket/wrap
- Intravenous cooling catheter
- Other: Please specify

Attitude to participation in a clinical trial

We would like an indication of your thoughts about aspects of a planned trial.

In the planned clinical trial we anticipate randomising patients that are admitted to intensive care and have a core temperature of 38.5 degrees C, to permissive or intensive temperature management strategies. Patients with neurological injury will be excluded from the trial:

Q5: In the permissive arm, the protocol will specify that anti-pyretic interventions will be allowed if an upper core temperature threshold is breached. What do you think this upper core temperature threshold value should be?

Q6: In the intensive arm, we are planning on constructing an algorithm, (based on evidence from current practice), with the aim of reducing core temperature below a specified value. What do you think this value should be?

Q7: Do you believe a clinical trial comparing a permissive temperature management strategy to an intensive strategy for fever reduction in febrile critically ill patients is warranted?

Strongly agree, agree, unsure, disagree, strongly disagree

Q8: Are there any further comments you would like to add?

(Free text)