Different temperature thresholds for antipyretic intervention in critically ill children with fever due to infection: the FEVER feasibility RCT

Mark J Peters,1* Imran Khan,2 Kerry Woolfall,3 Elizabeth Deja,3 Paul R Mouncey,2 Jerome Wulff,2 Alexina Mason,2 Rachel Agbeko,4 Elizabeth S Draper,5 Blaise Fenn,6 Doug W Gould,2 Abby Koelewyn,2 Nigel Klein,7 Christine Mackerness,4 Sian Martin,2 Lauran O’Neill,1 Padmanabhan Ramnarayan,8 Shane Tibby,9 Lyvonne Tume,10 Jason Watkins,6 Kent Thorburn,11 Paul Wellman,9 David A Harrison2 and Kathryn M Rowan2

1Respiratory, Critical Care and Anaesthesia Unit, University College London Great Ormond Street Institute of Child Health, London, UK
2Clinical Trials Unit, Intensive Care National Audit and Research Centre, London, UK
3Department of Psychological Sciences, North West Hub for Trials Methodology, University of Liverpool, Liverpool, UK
4Paediatric Intensive Care Unit, Great North Children’s Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
5Department of Health Sciences, University of Leicester, Leicester, UK
6Patient/Parent Representative, London, UK
7Institute of Child Health, University College London, London, UK
8Children’s Acute Transport Service, Great Ormond Street Hospital, London, UK
9Evelina London Children’s Hospital, Guy’s and St Thomas’ NHS Foundation Trust, London, UK
10Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK
11Alder Hey Children’s NHS Foundation Trust, Liverpool, UK

*Corresponding author mark.peters@ucl.ac.uk

Declared competing interests of authors: Mark J Peters is a member of the National Institute for Health Research (NIHR) Health Technology Assessment General Board. Kathryn M Rowan is a member of the NIHR Health Services and Delivery Research Board.

Published February 2019
DOI: 10.3310/hta23050
Scientific summary

The FEVER feasibility RCT
Health Technology Assessment 2019; Vol. 23: No. 5
DOI: 10.3310/hta23050

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Fever is a host response that helps to control infections and is known to increase numerous basic immunological processes. This is recognised by the National Institute for Health and Care Excellence in guidance for the management of feverish illness in children [National Institute for Health and Care Excellence (NICE). Fever in Under 5s: Assessment and Initial Management. London: NICE; 2013. URL: www.nice.org.uk/guidance/cg160 (accessed 16 November 2018)], which recommends against the use of antipyretics with the sole aim of reducing body temperature. However, this advice is not aimed at critically ill children.

The FEVER feasibility study aimed to evaluate whether or not raising the temperature threshold at which clinicians deliver antipyretic interventions improves outcomes. A mixed-methods approach was used to determine if a large-scale trial would be feasible.

The FEVER qualitative study

Objectives

To review, with input from parents/legal representatives:

- the acceptability of the selection of temperature thresholds and options for analgesia for a definitive FEVER randomised controlled trial (RCT)
- potential barriers to recruitment, the proposed process of decision-making and research without prior consent (RWPC) and co-develop information and documentation for a definitive FEVER RCT
- the selection of important, relevant, patient-centred outcomes for a definitive FEVER RCT.

To review and explore, with input from clinicians:

- the acceptability of temperature thresholds and options for analgesia for a definitive FEVER RCT
- potential barriers to recruitment, RWPC and associated training needs for a definitive FEVER RCT.

Methods

Study design

This was a qualitative study using semistructured interviews with parents of children with relevant experience and focus groups with clinicians (nurses and doctors) working in four paediatric intensive care units (PICUs)/retrieval services.

Recruitment

It was anticipated that 15–25 parents/legal representatives would be recruited to reach data saturation and that a minimum of 4 and a maximum of 10 clinicians would attend each of the four focus groups (16–40 in total).

Parents/legal representatives with a child admitted to a PICU with severe infection within the preceding 3 years were recruited via postal contact and poster advertising in PICUs, using an existing database of parents recruited for a similar study and social media.

Clinicians were recruited via an e-mail invitation with the participant information sheet, which was sent by lead clinicians in paediatric critical care medicine at the four PICUs taking part in the pilot RCT.
**Interviews with parents/legal representatives**
Informed consent was taken. Screening and interviews stopped when saturation was reached.

**Focus groups with clinicians**
Informed consent was taken. At least one focus group was conducted at each of the four participating PICUs.

**Data analysis**
Analysis was interpretative and iterative and informed by the constant comparative approach. NVivo 10 software (QSR International, Warrington, UK) was used to assist the coding of data.

**Results**
A total of 46 parents registered interest, of whom 34 were screened. Data saturation was reached when 25 parents had been interviewed. Seventeen parents were recruited via social media, six by post, two by the existing database and none via advertising in PICUs. The sample included 20 mothers (four bereaved) and five fathers (two bereaved). Six focus groups were conducted involving 56 staff clinicians: 45 nurses and 11 doctors.

**Parent acceptability of the FEVER randomised control trial and temperature thresholds**
Parents found the proposed RCT to be acceptable. They would consent for the use of their child’s information in such a trial. Recommendations were made to reduce the higher temperature threshold to 39.5 °C rather than 40 °C, for tailored verbal explanations to be made by site staff and for adjustments of the participant information sheet for ease of reading and to address potential concerns.

**Consent approach**
Parents’ views on RWPC in a FEVER RCT were in line with previous research and guidance.

**Outcomes of importance to parents**
Parents prioritised the following outcomes: (1) long-term morbidity, (2) looking and behaving more normally, (3) length of time on breathing support, (4) time in a PICU and hospital and (5) how quickly vital signs are back to normal.

**Clinicians’ perspectives**
Focus groups with site staff revealed a concern regarding temperature thresholds, suggesting that 37.5 °C for the restrictive temperature was too low. Staff also showed concern about the permissive threshold and about not using paracetamol for analgesia in the less unwell, spontaneously breathing patients who may be in pain. Many staff found RWPC to be acceptable; however, concerns were raised regarding the acceptability to parents of participants randomised to the permissive group.

**Conclusions**
Findings suggested that parents and staff supported a FEVER RCT. These findings were used to develop the protocol, including reducing the permissive temperature threshold, narrowing the inclusion criteria to require that participants were mechanically ventilated, revising the participant information sheet and developing a staff training package, including parents’ perspectives observed in the FEVER qualitative study.

---

**The FEVER observational study**

**Objectives**
- To estimate the size of the potentially eligible population for the definitive FEVER RCT.
- To confirm, using empirical data, the temperature threshold(s) currently employed for a standard approach for antipyretic intervention in NHS PICUs.
- To estimate the characteristics (e.g. mean and standard deviation) of selected important, relevant, patient-centred primary outcome measure(s).
Methods

Study design and setting
This was an observational cohort study of the epidemiology of fever owing to infection in critically ill children following an unplanned admission to a PICU.

Sites
There were 22 PICUs in the Paediatric Intensive Care Audit Network (PICANet).

Target population
This was unplanned admissions to PICUs.

Data collection
The FEVER observational study was nested within PICANet and included routinely collected PICANet data and additional data.

All unplanned admissions were eligible. Data collection was split into three stages. Stages 1 and 2 aimed to identify potentially eligible patients for a FEVER RCT. Stage 3 provided infection, temperature and antipyretic management data.

Sample size
Approximately 4000 children were recruited from 22 PICUs over 6 months.

Data analysis
An interim analysis of the observational study data was conducted after 3 months to permit modifications to the design of the pilot RCT. In the final analysis, all potentially eligible patients for a FEVER RCT were included and the analyses were carried out based on the following populations:

- all patients with confirmed or suspected infection
- restricted to patients receiving any mode of mechanical ventilation (invasive, non-invasive or high-flow oxygen) on days 1–2 of PICU admission
- restricted to patients receiving invasive ventilation on days 1–2 of PICU admission.

Results
The FEVER observational study, conducted in 22 PICUs from April to August 2017, identified a potentially eligible population of 10.9 cases per site per month [95% confidence interval (CI) 10.3 to 11.5 cases]. The high number of potential participants permitted consideration of adjustments of study design by testing the impact of more stringent inclusion criteria. Importantly, mandating invasive mechanical ventilation rather than all forms of respiratory support reduced the eligible patient population to around 7.6 (95% CI 7.1 to 8.1 patients) per site per month.

Variation in the temperature thresholds associated with antipyretic interventions was observed across patients and sites; however, the majority of critically ill children with a maximum temperature of ≥ 37.5 °C received antipyretics. These findings remained consistent when the inclusion criteria were narrowed.

The PICU mortality was around 5%, increasing to 5.5% and 6.5% in mechanically ventilated and invasively mechanically ventilated patients, respectively. PICU length of stay and duration of mechanical ventilation and cardiovascular support also increased with narrowing inclusion criteria, whereas number of days alive and free from PICU/mechanical ventilation reduced.

Interim analysis at 3 months’ data collection
An interim analysis confirmed that a temperature threshold of 37.5 °C falls within usual care across UK PICUs and that restricting to mechanically ventilated patients only was possible in the planned recruitment time scales.
The FEVER pilot randomised controlled trial with integrated-perspectives study

Objectives

- Test the willingness of clinicians to screen, recruit and randomise eligible critically ill children.
- Estimate the recruitment rate of critically ill children.
- Test the acceptability of the deferred consenting procedure and participant information.
- Test, following randomisation, the delivery of and adherence to the selected temperature thresholds for antipyretic intervention and to demonstrate separation between the randomised groups in peak temperature measurement over the first 48 hours following randomisation.
- Test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event reporting.
- Inform the final selection of a patient-centred primary outcome measure.

Methods: pilot randomised controlled trial

Study design
This was a pragmatic, open, multicentre pilot RCT.

Sites
Four UK PICUs were used.

Recruitment

Inclusion criteria

- Unplanned PICU admission.
- Aged ≥ 28 days and < 16 years.
- Referral requiring PICU admission to a participating unit.
- Fever of ≥ 37.5 °C in the first 48 hours following contact with the paediatric retrieval service/PICU.
- New requirement for mechanical ventilation.
- Treating clinician presumes the cause of the fever is an infective process.

Exclusion criteria

- Acute encephalopathy, including convulsive status epilepticus.
- Postcardiopulmonary bypass or known/suspected cardiomyopathy/myocarditis.
- Rhabdomyolysis (defined as serum creatine kinase concentration at least 10 times the upper limit of normal).
- Malignant hyperthermia, neuroleptic malignant syndrome or drug-induced hyperthermia.
- Receiving palliative care or death perceived as imminent.
- Previously recruited to the pilot RCT.

Randomisation, allocation, intervention and consent
Eligible children were randomised 1:1 to a temperature threshold of 37.5 °C or 39.5 °C for the commencement of antipyretic intervention for the duration of their PICU stay while mechanically ventilated. A member of the site research team approached parents/legal representatives as soon as appropriate after randomisation to take consent.

Data collection
A secure, dedicated electronic case report form was set up and collection was nested within PICANet.
Sample size
It was anticipated that a sample size of 100 children would give 90% power to demonstrate a separation of 0.5 °C in mean peak temperature between temperature groups, allowing for a 16% withdrawal rate.

Statistical analysis
Statistical analyses were based on the intention-to-treat principle. Analyses were conducted using Stata®/SE version 14.0 (StataCorp LP, College Station, TX, USA).

Methods: integrated-perspectives study

Study design
This was an integrated-perspectives study, comprising questionnaires and interviews with parents/legal representatives and focus groups and online questionnaires with site staff. The aim was to explore parents/legal representatives’ and staff experiences and views of the FEVER pilot RCT.

Participants
Parents/legal representatives of children who participated in the FEVER pilot RCT were eligible, unless they were unable to speak or read English. Site staff involved in the pilot RCT were also eligible. There were no exclusion criteria. Informed consent was taken.

Interviews and focus groups
Parents/legal representatives: an interview topic guide was used to explore the views and experiences of parents of the pilot RCT.

Site staff
A topic guide was also used for the focus groups and interviews, to explore views and experiences of site staff. Key questions asked in the focus group were replicated in the questionnaire.

Data analysis
Analysis was undertaken in accordance with the methodology outlined in the qualitative study. Quantitative data from parent and staff questionnaires were cleaned and entered into IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented with percentages.

Results: pilot randomised controlled trial
Between September and December 2017, 100 eligible children were randomised from four sites: 49 to the permissive group and 51 to the restrictive group. The recruitment rate of 11.6 participants per site per month was greater than the pre-trial estimate of 6.25 participants. Consent was provided for 49 out of 51 participants in the restrictive group but only for 38 of 49 participants in the permissive group.

Maximum temperatures were a mean of 0.5 °C (95% CI 0.2 °C to 0.8 °C) higher in the permissive group over the first 48 hours of the intervention. A greater proportion of participants in the restrictive group received antipyretic intervention. Non-adherence was reported in 39 out of 628 6-hour time periods (6.2%) in the permissive group and 60 out of 810 time periods (7.4%) in the restrictive group. Overall, 39% of participants in the permissive group and 55% of participants in the restrictive group experienced at least one period of non-adherence. The main reason for receiving antipyretics early was paracetamol for pain or discomfort when receiving non-invasive or high-flow oxygen or being weaned from invasive ventilation.

As expected in a pilot trial, no differences were observed between groups for any of the outcome measures.
Results: integrated-perspectives study

Participants: parents/legal representatives
A total of 60 parents of 57 FEVER pilot RCT patients participated, of whom 41 completed a questionnaire, 12 took part in an interview and 7 took part in both.

Participants: clinicians
A total of 98 clinicians (77% nurses) were recruited from four sites. Half (n = 48) completed an online survey and the remainder attended a focus group.

Parents’ perspectives
Most parents supported the trial and felt that it was important. No parents referred to the temperature their child reached when discussing trial acceptability. However, parents viewed the permissive threshold as acceptable only if their child was not in pain or discomfort – these concerns were cited as reasons for withdrawal and non-consent. In general, parents found RWPC acceptable. Parents prioritised the following outcomes: length of time on mechanical ventilation, looking and/or behaving like their normal self, long-term effects of illness on child, not in discomfort and/or pain, number of days spent in the PICU and hospital, vital signs back to normal and effect on family. When combined with the qualitative study, the following outcomes should be prioritised for the FEVER RCT: length of time on mechanical ventilation, long-term effects of illness on child, looking and/or behaving like their normal self, not in discomfort and/or pain, number of days spent in the PICU and hospital, vital signs back to normal (e.g. heart rate, breathing rate and temperature) and effect on family. When prompted by the researcher, all except one parent stated that survival is the most important outcome measure.

Clinicians’ perspectives
Most clinicians viewed the trial as important and the use of RWPC to be acceptable as well as practically possible to conduct. In contrast to the qualitative study, staff viewed the restrictive temperature threshold to be acceptable. Approximately half indicated that the 39.5 °C threshold was acceptable.

Conclusions
The results identified a number of barriers to delivering the definitive FEVER RCT, but also informed how these barriers may be overcome.

A major concern is the acceptability of the temperature threshold in the permissive group. This was raised by both parents and clinicians in the qualitative elements of the study, suggesting that it is acceptable only when the child is not in pain or discomfort. The findings suggest that this could be addressed by restricting the inclusion criteria to only those patients who are receiving invasive ventilation. In addition, improved site staff training is needed to ensure a clear understanding of the rationale, the importance of approaching parents at an appropriate time, the ability of staff to address parents’ questions about the study and clarity around the definition and documentation of external/other cooling.

Recommendations for research
- A definitive FEVER RCT using the FEVER protocol tested here should not be conducted.
- A definitive FEVER RCT using a modified protocol should be conducted.
- Further work is required to agree the best outcome measures and/or develop new outcome measures for clinical trials of critically ill children.
Trial registration

The FEVER observational study is registered as NCT03028818 and the pilot RCT is registered as Current Controlled Trials ISRCTN16022198.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.
Health Technology Assessment

Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/44/01. The contractual start date was in November 2016. The draft report began editorial review in May 2018 and was accepted for publication in September 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen’s Printer and Controller of HMSO 2019. This work was produced by Peters et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
NIHR Journals Library Editor-in-Chief

Professor Ken Stein  Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK
Professor Andrée Le May  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)
Professor Matthias Beck  Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland
Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK
Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK
Dr Peter Davidson  Consultant Advisor, Wessex Institute, University of Southampton, UK
Ms Tara Lamont  Scientific Advisor, NETSCC, UK
Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK
Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK
Professor Geoffrey Meads  Professor of Wellbeing Research, University of Winchester, UK
Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, UK
Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK
Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK
Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Professor Helen Roberts  Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK
Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK
Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK
Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK
Professor Martin Underwood  Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK
Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk