An evaluation of the feasibility of conducting a randomised clinical trial to evaluate the clinical and cost-effectiveness of a more permissive temperature threshold for antipyretic intervention in critically ill children with fever due to infection:

FEVER Feasibility Study.
Research reference numbers

Sponsor name and reference
Intensive Care National Audit & Research Centre (01/04/16)

Funder name and reference
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (15/44/01)

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Fever Feasibility Study Summary

A fever (high temperature) is a normal response by the body to infection. When a very sick child has a fever, the usual reaction from clinicians (doctors/nurses) is to cool down the child. This can be done using drugs, such as paracetamol, or using a cooling mat, sponging the child with water, etc. The temperature at which clinicians usually start these treatments is about 37.5°C.

There is strong evidence, however, that fever may be an important bodily response and may actually help a child to recover from infection. In 2013, the National Institute for Health and Care Excellence (NICE) updated guidance for managing fever in children. It recommended that drugs should not be used only for the purpose of reducing a child’s temperature. Most of the evidence for this recommendation came from research in non-critically ill children, therefore, it is unknown whether this recommendation should be applied to very sick children.

Our aim is to compare giving treatments for fever at a higher temperature than usual, such as 39.5°C, with the usual temperature of around 37.5°C in children with infection admitted to an NHS paediatric intensive care unit (PICU).

As large clinical trials are expensive, it is important to be confident that this trial can be done and that the different components of the trial can work together. Before starting a full trial, we will conduct an 18-month feasibility study. A feasibility study is research done before a full trial to answer the question “can this trial be done?” It is used to estimate important factors such as willingness of parents/children to take part. A pilot trial, part of this feasibility study, is a smaller version of the full trial and this is done to check that the different components all run smoothly.

The first part of this study will involve conducting interviews with parents/legal guardians to understand whether the proposed trial is acceptable to them, how information should be written, what barriers they perceive to their child being included and what outcome measures are most important to them. We will discuss views on using deferred consent. Deferred consent is an approach which has successfully been used in previous emergency/critical care trials and involves including a child in a trial without prior consent from their parents/guardians and then seeking agreement later. The reason for considering this approach is that discussing a trial with parents/guardians when their child is in need of urgent treatment may be inappropriate and create an additional burden in an already very stressful situation.

The second part will involve observing and collecting data on children with fever from infection in 20 PICUs. We will also collect data on the outcomes identified as important by parents/guardians. These data will be used to tell us how many children would need to take part in a full trial and which are best outcomes to use.

The third part, the pilot trial, will be conducted in four PICUs and will recruit 100 children. We will test whether the deferred consent approach is acceptable to parents/guardians of participating children. This part will tell us, practically, if the trial can be done.

At the end, we will report a clear recommendation, or not, for continuation to a full trial.
Study 1: Fever Qualitative Study
RESEARCH REFERENCE NUMBERS

PROTOCOL VERSION NUMBER AND DATE
Version 2 01.03.17

IRAS NUMBER
217089

REC NUMBER

SPONSOR
Intensive Care National Audit & Research Centre (01/04/16)

FUNDER NAME AND REFERENCE
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project: 15/44/01)

CHIEF INVESTIGATOR
Professor Mark Peters

SPONSOR REPRESENTATIVE
Mr Kevin Hunt
Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ................................................................. Date: 17/10/2016
Name (please print): Mr Kevin Hunt
Position: Chief Executive

Chief Investigator:

Signature: ................................................................. Date: 17/10/2018
Name: (please print): Professor Mark Peters
Position: Chief Investigator
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General information

This document describes the FEVER qualitative study and provides information about procedures for the study. Participant recruitment will be undertaken in compliance with this document.

This protocol is part of the an evaluation of the feasibility of conducting a randomised clinical trial to evaluate the clinical and cost-effectiveness of a more permissive temperature threshold for antipyretic intervention in critically ill children with fever due to infection: the FEVER feasibility study.
## Study summary

### Protocol summary

| Title: | An evaluation of the feasibility of conducting a randomised clinical trial to evaluate the clinical and cost-effectiveness of a more permissive temperature threshold for antipyretic intervention in critically ill children with fever due to infection: FEVER qualitative study |
| Short title: | FEVER qualitative study |
| REC number: | 16/NW/16 |
| Sponsor name and reference: | ICNARC (01/04/16) |
| Funder name and reference: | NIHR Health Technology Assessment Programme |
| Study design: | Qualitative interview study |
| Study objectives: | |
| Objective 1: | To review and explore with parents the acceptability of selection of temperature thresholds and options for analgesia for a definitive RCT. |
| Objective 2: | To review and explore with parents the potential barriers to recruitment, the proposed process of decision-making and deferred consenting and co-develop information and documentation for a definitive RCT. |
| Objective 3: | To review and explore with parents the selection of important, relevant, patient-centred, primary and secondary outcomes for a definitive RCT. |
| Objective 4: | To review and explore with clinicians the acceptability of temperature thresholds and options for analgesia for a definitive RCT. |
| Objective 5: | To review and explore with clinicians the potential barriers to recruitment, deferred consenting and associated training needs for a definitive RCT. |
| Study centres: | Participants will be identified through four hospitals across the United Kingdom, an existing database of contacts held at the University of Liverpool and via social media/online support groups. |
| Population: | Parents (including legal representatives) with experience of their child being admitted to an Intensive Care Unit with a fever and suspected infection in the last |
Clinicians (nurses and doctors) at participating PICUs/retrieval services

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<td>Planned sample size:</td>
<td>15-25 parents and 16-40 clinicians</td>
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<td>Eight months</td>
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<td>No follow up</td>
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<td>Planned study period:</td>
<td>November 2016 – July 2017</td>
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Study flowchart

1. Identification of eligible families
   - Existing database (route 1)
   - Postal invitation (route 2)
   - Media advertising (route 3)

2. Provided with study information

3. Parents/Legal representatives register interest in participation by email/telephone and screened for eligibility

4. Example study information and list of outcomes emailed to parents

5. Informed consent obtained

6. Conduct interview

7. Copy of consent form sent and study exit
Background Information

Introduction and rationale

What is the problem being addressed?

Fever is a host response that helps to control infections with a very wide range of pathogens [1]. Fever has been very highly conserved throughout evolution for at least 580 million years [1]. Fever is seen across many species including reptiles, birds and mammals [2]. Recently even plants have been shown to raise core temperatures to control fungal infections [3].

Studies in non-critically ill patients with chickenpox [4], malaria [5] and rhinovirus [6] infections has led to a rediscovery of the potential beneficial effects of fever. This is recognised by the National Institute for Health and Care Excellence in their guidance for management of feverish illness in children (NICE CG160, May 2013) in which they recommend, “Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.” However, this advice is not aimed at the management of critically ill children.

Observational studies demonstrate that the treatment of fever in critically ill children is inconsistent [7]. In this population there is a lack of robust data to guide antipyretic intervention. This frequently leaves the decision whether/when to treat fever at the discretion of the bedside nurse. There is genuine uncertainty if the immunological advantages of a fever in defending the body against viruses and bacteria during critical illness outweigh the metabolic costs and cardiorespiratory consequences of a high fever [2]. In cases with underlying neurological pathology (e.g. traumatic brain injury, hypoxic-ischaemic encephalopathy, encephalomyelitis etc.) practice is to avoid fever because of consistent associations with worse outcomes, but in the much larger proportion of emergency admissions in whom other organ failures predominate (most commonly respiratory) the optimal approach is unknown. With emerging evidence that fever may be beneficial in critically ill adults but also cognisant of the physiological differences between adults and children, there is an important need to evaluate whether a more permissive approach to fever management in critically ill children improves outcomes.

A recent systematic review identified five, small, completed RCTs of antipyretic interventions in critically ill adults [8]. These trials were small (ranging from 26 to 200 patients) and the results of a meta-analysis on intensive care unit mortality were inconclusive (relative risk for fever control compared with no fever control or a more permissive threshold: 0.97, 95%
confidence interval 0.58 to 1.63). One larger RCT among adults – the HEAT trial in Australia and New Zealand – recently reported [9]. The HEAT trial examined the effect of acetaminophen (paracetamol) versus placebo to treat fever in 700 critically ill adults with known or suspected infection. No differences were seen in the primary outcome of the number of ICU-free days to day 28 or in mortality. One further RCT among adults– the FACEII Trial in Asia (UMIN000005593) – is currently ongoing. We are not aware of any completed or ongoing RCTs of antipyretic management in critically ill children.

A systematic review of observational studies of the association between fever and mortality in critically ill adults found wide variation in the definitions of fever and its association with mortality [10]. Two further, recent, observational studies in adults, not included in the systematic review, found different relationships between fever and mortality for patients with and without infection, with fever associated with lower mortality among admissions with infection unless the temperature exceeded 40°C [11,12]. Similar results have been found in small cohorts of critically ill children with infection [15].

The FEVER feasibility study aims to establish whether it is feasible to conduct a clinical trial to test different temperature thresholds at which clinicians deliver antipyretic intervention in critically ill children with fever due to infection.

Clinical trials, such as the proposed FEVER trial, are expensive and the chances of successful completion are improved if both the feasibility and pilot testing of certain key parameters can be clearly demonstrated. The FEVER feasibility study will use a mixed method approach comprising three separate studies, including a qualitative study (study 1), an observational study (study 2) and a pilot randomised controlled trial (study 3)

This protocol outlines work that will be undertaken for study 1. Studies 2 and 3 are outlined in separate protocols.
Aims and objectives

Aim
To explore important parameters needed to inform the design and successful conduct of the FEVER Trial.

Objectives
To review, with input from parents/legal representatives:

1. acceptability of selection of temperature thresholds and options for analgesia for a definitive RCT;
2. potential barriers to recruitment, the proposed process of decision-making and deferred consenting and co-develop information and documentation for a definitive RCT;
3. selection of important, relevant, patient-centred, primary and secondary outcomes for a definitive RCT.

To review and explore with input from clinicians:
4. acceptability of temperature thresholds and options for analgesia for a definitive RCT; and
5. potential barriers to recruitment, deferred consenting and associated training needs for a definitive RCT.
Study design and conduct

Study design and setting
Telephone interviews conducted at the University of Liverpool and focus groups conducted in four UK children’s hospitals by Dr Kerry Woolfall (KW) and the FEVER Study Research Associate (RA).

Eligibility criteria

Inclusion criteria:
Parents (including legal representatives) who have experienced their child being admitted to an intensive care unit with a fever and suspected infection in the last three years and clinicians (nurses and doctors) working in the four PICUs/retrieval services planned to be included in the pilot RCT (Study 3).

Exclusion criteria:
Parents/Legal representatives who do not speak English.

Recruitment and sampling

We will recruit parents/legal representatives through four routes to maximise the potential sample within the six-month active recruitment period.

Recruitment route 1: Existing database
Parents will be identified from an existing database held by KW at the University of Liverpool which contains contact details of parents who have participated in the Fluids in Shock (FiSh) feasibility study (HTA 13/04/105) and provided consent for contact for future related studies.

Recruitment route 2: Postal recruitment
PICU clinicians in each of the four participating hospitals (sites) will be invited to act as Principal Investigators (PI). These clinicians will use hospital medical records to identify 10-15 parents/legal representatives (including bereaved parents/legal representatives) who meet the inclusion criteria (starting with the most recent admission and working backwards). The clinician will send eligible parents/legal representatives a FEVER qualitative study Parent/Legal Representative postal invitation covering letter and copy of the PIS by post.
from the clinician/hospital. Bereaved parents/legal representatives (excluding those recently bereaved e.g. in the last 6 months) will be sent a FEVER qualitative study Participant postal invitation covering letter (Bereaved) and FEVER qualitative study Participant Information Sheet Bereaved (PIS- B).

The covering letter and PIS explains key aspects of the study and how parents/legal representatives can register their interest in taking part in an interview by contacting the FEVER researcher. A link to a FEVER website and Facebook page is also provided if parents/legal representatives wish to access further information about the study. Parents/Legal representatives living in North West England can choose to be interviewed at their home instead of a telephone interview.

**Recruitment route 3: Advertising in PICU**

Copies of the FEVER qualitative study Participant Information Leaflet and qualitative study Participant Information Poster will be sent to four participating hospitals (same as recruitment route 2) with a request for them to be placed in family rooms and on notice boards in the PICU. The FEVER qualitative study Participant Information Leaflet and Poster contain study information and contact details for parents/legal representatives to register their interest in taking part (as described in Recruitment Route 2). A link to the FEVER website will enable parents/legal representatives to access further information including the full PIS.

**Recruitment route 4: Media advertising including online and social media**

The RA will contact gatekeepers (e.g. charity leads/Chief Executive Officers) of support groups for parents/legal representatives whose children may have been admitted to PICU with a fever and suspected infection. The RA will ask them to post the FEVER qualitative study online recruitment advert on the support group’s website and/or social media pages (e.g. Facebook and Twitter). Examples of such groups could include: Children’s Hospital and Paediatric Intensive Care Charities (e.g. Great Ormond Street Hospital Charity, Children of St Mary’s Intensive Care (COSMIC), Children’s Acute Transport Service (CATS) Charity, UK Sepsis Trust, Meningitis Research Foundation). The advert will also be placed in a newspaper (e.g. Metro or Liverpool Echo)

Similarly to recruitment route 3, the advert will include a description the purpose of the study and what is involved. The advert will also contain information and contact details for
parents/legal representatives to register their interest in taking part (as described in Recruitment Route 2). A link to the study website will provide additional information about the study including the PIS.

We will recruit clinicians using an email invitation. The FEVER RA will send an email, including Participant Information Sheet (PIS) to clinicians at the four participating PICUs/retrieval services inviting them to take part in a focus group. One focus group will be conducted in each of the four participating hospitals.

**Arranging telephone interviews and focus groups**

The RA will identify a suitable date and location will be identified for each of the four focus groups. Details will be sent to clinicians who registered interest in attending.

In route 1, the RA will contact (either by telephone or email depending upon details given) parents/legal representatives on the University of Liverpool database. Emails will include a link to the study website and a description of the study including the PIS. The invitation will ask parents to contact the RA if they wish to participate in a telephone interview. If contact is by telephone, the RA will firstly describe the FEVER study to parents and obtain post or email contact to send details of the study, including a link to the study website and PIS. The RA will ask parents to consider the information and contact the RA if they wish to participate in a telephone interview.

In recruitment routes 2 and 3, the RA will respond to parents’/legal representatives’ requests to participate by contacting each parent/legal representative by email or telephone (depending on which contact details are provided). The researcher will check eligibility using questions listed in the FEVER qualitative study Participant registration document. Where parents meet the eligibility criteria, the researcher will arrange a convenient time and date for the telephone or home (in North West England only) interview. A copy of the example FEVER Pilot Study Participant Information Sheet and FEVER outcomes list will be sent to parents via email or post (whichever is preferred). Parents/Legal representatives will be asked to read this PIS and outcomes list before the scheduled interview.

Parents/Legal representatives who do not meet the eligibility criteria, or register after the target sample size (15-25 depending upon data saturation point) has been reached, will be thanked for their time and will take no further part in the study.
Informed consent

Focus groups

Written informed consent will be sought from clinicians prior to the commencement of focus groups.

Telephone interviews

The RA will begin the telephone interview by explaining the aims of the study, providing an opportunity for questions and verbally obtaining informed consent for the study. This will involve the RA reading each aspect of the FEVER qualitative study Participant Consent Form to participants, including consent for audio recording and to receive a copy of the findings when the study is complete. The RA will tick each box on the consent form when the participant provides verbal consent. Informed consent discussions will be audio recorded for auditing purposes.

After the interview is complete the RA will sign the consent form and send a FEVER qualitative study Participant thank you letter including a copy of consent from and a £30 Amazon voucher to the participant to thank them for their time.

Home interviews

The RA will seek written informed consent for the study using the FEVER qualitative study Participant Consent Form. The participant and the researcher will sign the consent form. At the end of the interview a £30 Amazon voucher will be given to the participant thank them for their time. A FEVER qualitative study Participant thank you letter will be posted to participants after the interview, including a copy of the consent form.

Focus group and interview conduct

Focus group conduct

Once informed consent is obtained, the focus groups will commence using the focus group topic guide to explore clinicians’ views on:

- acceptability of the proposed trial including selection of temperature thresholds and options for analgesia;
- potential barriers to recruitment and deferred consent in the trial and how these might be addressed; and
- associated training needs.
**Interview conduct**

The RA will check that the parent has had sufficient time to read the example FEVER Pilot Study Participant Information Sheet. The interview will then commence using the interview topic guide which will explore:

- acceptability of the proposed trial including selection of temperature thresholds and options for analgesia;
- identification of potential barriers for participation in the trial and how these might be addressed;
- parental decision-making in the emergency setting;
- acceptability of research without prior consent (deferred consent);
- length and content of the PIS and any proposed leaflets and posters; and
- trial design including selection of outcome measures.

Topic guides have been informed by previous trials conducted in paediatric emergency and critical care in the NHS [13,14] by earlier research (led by one of our co-investigators, KW)[15, 16] and by a review of all potential outcome measures conducted for the Fluids in Shock (FiSh) feasibility study (HTA 13/04/105). Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress.

**Sample size**

We anticipate a minimum of four and maximum of ten clinicians involved in FEVER will attend each of the four focus groups. The total focus group sample is therefore estimated to be approximately 16-40 clinicians.

Interviews will continue to be conducted until data saturation is reached. This is when the major themes identified in new data are reoccurring from previous participants/ transcripts and no new major themes are being discovered. Based on previous, similar studies[15] this is anticipated to be approximately 15-25 parents/legal representatives.

**Data analysis**

Interviews and focus groups will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst analysis will be informed by the constant comparison approach of
grounded theory, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (i.e. the design of the proposed pilot and definitive RCTs). Findings from the interviews and focus groups will be fed into the design (including patient information materials), approach to consent and training for site investigators for the pilot RCT (Study 3).
**Study management**

Professor Mark Peters will take overall responsibility for the FEVER qualitative study management and overseeing progress against timelines/milestones.

All day-to-day management of the FEVER qualitative study will be the responsibility of KW and the Study Management Group (SMG). The SMG will meet regularly to review progress of the study against timelines/milestones.
**Ethical approval**

This protocol, the PISs, consent forms and other study-related documents will be reviewed and approved by the NIHR HTA Programme and an NHS Research Ethics Committee (REC) with respect to scientific content and compliance with applicable research regulations involving human subjects. Any modification to the protocol and/or study-related documents which may impact on the conduct of the study, potential benefit to patients or patient safety will require a formal amendment. Such amendments will be submitted for approval by the NHS REC.

The Chief Investigator will require a copy of the relevant local approvals prior to any participant identification at the site. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.
Confidentiality, data storage and consent withdrawal

Names and full addresses (postal and email) will be collected from participants whom wish to take part in an interview. These details will be used to contact them to arrange interviews and send copies of the consent form and study findings (if participants request a copy). We will also seek consent to contact parents/legal representatives in the future about related studies. The contact details collected will not be used for any other purpose. All personal data will be held at the University of Liverpool. No personal data will be transferred electronically between sites. All files bearing participant identifiers (e.g. contact details) will be destroyed at the end of the study and only participants’ consent forms will be retained.

Audio recordings of interviews (not consent discussions) will be uploaded by the RA securely to a professional transcription company (Voicescript) website in accordance with the Data Protection Act 1998. Interview audio recordings will be anonymised by the FEVER RA as soon as the transcript is received from the professional transcription company. Any names or potentially identifying information will be removed. Audio recordings will be deleted when the FEVER researcher has checked transcripts against the audio recordings for accuracy. Audio recordings of consent for telephone interviews will be held for auditing purposes.

All data will be securely stored in a locket cabinet or in an encrypted electronic file. The digital audio recordings are likely to contain details that could identify participants. Audio recordings of interviews will be anonymised during transcription. All original files will labelled with a unique identity number, encrypted and held on password protected University of Liverpool desktop computers. As soon as the digital recordings have been transcribed, the digital files will be archived securely at the University of Liverpool. Publication of direct quotations from participants is necessary to report the results of qualitative research, but no identifying information will appear in transcripts and therefore none will appear in quotations. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Participation will be entirely voluntary and parents/guardians will be able to withdraw at any time without giving a reason by contacting the RA or KW. This is described in the PIS.
Risks and benefits

There is no foreseeable risk to participants. However, due to the emotive nature of the research setting it is acknowledged that there is a slight risk that the research may be burdensome. Therefore a number of steps have been taken to help minimise potential burden.

KW is experienced in the design and administration of interviews with vulnerable groups, including bereaved parents, on emotive topics, therefore all questions and prompts will be designed with the aim of reducing stress or personal intrusion. Participants will be able to select the time and date of the telephone interview. All interviews will be semi-structured yet conducted in a flexible manner to encourage narrative production and enable the interviewer to change topic if the participant seems to be upset[17]. Participants will be told that they can stop the interview at any time.

We do not anticipate that participants in this study will benefit directly, but many people find that taking part in studies of this sort is useful because they have a chance to air their views, reflect on their experiences and ultimately contribute to the design of a clinical trial to improve the treatment of seriously ill children.
Declaration of interests

None
Sponsorship and indemnity

ICNARC is the Sponsor for the FEVER qualitative study and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.
Dissemination policy

The progress and results of the FEVER qualitative study will be widely and actively disseminated.
Progress of the study

To ensure all stakeholders are kept aware and informed, ongoing progress of the FEVER qualitative study will be disseminated to: participating units through emails and telephone; to the wider critical care community through relevant professional newsletters, professional meetings; and to consumers/participants via the ICNARC or FEVER website/Twitter and Facebook page.
Study Results

Interim findings from this qualitative study will be fed into the FEVER External Pilot Study (starting April 201; described in a separate protocol). Overall findings will be fed into a report for the NIHR HTA Programme describing parents’ and legal representatives’ views on the acceptability of the trial, approach to consent and patient centred outcome measures. Findings from this qualitative study will also be written up for publication in an open access, peer-review journal and disseminated via social media and presentation at relevant medical conferences. A participant version of the findings will be written and sent to participants who consented to receiving a copy.
Audits

The study may be subject to inspection and audit by ICNARC under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
References


## Appendix 1 Protocol version history

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol version no.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of changes made</th>
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<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>Kerry Woolfall</td>
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</table>
Study 2: An observational study of the epidemiology of fever due to infection in critically ill children following an unplanned admission to a Paediatric Intensive Care Unit: Fever Observational Study
RESEARCH REFERENCE NUMBERS

PROTOCOL VERSION NUMBER AND DATE
v1.1
12 January 2017

IRAS NUMBER
209929

REC NUMBER
17/NW/0026

SPONSOR
Intensive Care National Audit & Research Centre (01/04/16)

FUNDER NAME AND REFERENCE
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project: 15/44/01)

CHIEF INVESTIGATOR
Professor Mark Peters

SPONSOR REPRESENTATIVE
Mr Kevin Hunt
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor’s Standard Operating Procedures (SOPs) and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: [Signature]
Date: 16/12/2016
Name (please print): Mr Kevin Hunt
Position: Chief Executive

Chief Investigator:

Signature: [Signature]
Date: 16/12/2016
Name (please print): Professor Mark Peters
Position: Professor of Paediatric Intensive Care
<table>
<thead>
<tr>
<th><strong>KEY CONTACTS</strong></th>
</tr>
</thead>
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## STUDY INVESTIGATORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
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<tbody>
<tr>
<td>Dr Rachel Agbeko</td>
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<td>Individual PCPIE member</td>
</tr>
<tr>
<td>Dr Kerry Woolfall</td>
<td>Department of Psychological Sciences</td>
<td>University of Liverpool</td>
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Abbreviations

CG  clinical guideline
CRF  case report form
CTU  Clinical Trials Unit
DARS  Data Access Request Service
GCP  Good Clinical Practice
HTA  Health Technology Assessment
ICH  International Conference on Harmonisation
ICNARC  Intensive Care National Audit and Research Centre
MRC  Medical Research Council
NIHR  National Institute for Health Research
PCPIE  Patient, Carer & Public Involvement & Engagement
PI  Principal Investigator
PICANet  Paediatric Intensive Care Audit Network
PICU  paediatric intensive care unit
PICOS  Paediatric Intensive Care Outcome Study
R&D  Research & Development
RCT  randomised control trial
REC  Research Ethics Committee
SMG  Study Management Group
SOP  Standard Operating Procedure

General information

This document describes the Fever Observational Study and provides information about procedures for the study. Data collection will be undertaken in compliance with this document.

This protocol is part of an evaluation of the feasibility of conducting a randomised clinical trial to evaluate the clinical and cost-effectiveness of a more permissive temperature threshold for antipyretic intervention in critically ill children with fever due to infection: the Fever feasibility study.
# STUDY SUMMARY

## Protocol summary

| Title: | An observational study of the epidemiology of fever due to infection in critically ill children following an unplanned admission to a Paediatric Intensive Care Unit. |
| Short title: | Fever Observational Study |
| REC number: | 17/NW/0026 |
| Sponsor name and reference: | ICNARC (01/04/16) |
| Funder name and reference: | NIHR Health Technology Assessment Programme (15/44/01) |
| Study design: | Observational study |
| Overall aim: | To inform the feasibility to conduct a study to test different temperature thresholds at which clinicians deliver antipyretic intervention in critically ill children with fever due to infection. |

### Study objectives:

- **Objective 1:** To estimate the size of the potentially eligible population for the definitive Randomised Controlled Trial (RCT), both overall and in subgroups defined by confirmed versus suspected infection and by site/type of infection.

- **Objective 2:** To confirm, using empirical data, the temperature threshold(s) currently employed for a standard approach for antipyretic intervention in NHS Paediatric Intensive Care Units (PICUs), and whether these vary according to confirmed versus suspected infection and site/type of infection.

- **Objective 3:** To estimate the characteristics (e.g. mean, standard deviation) of selected important, relevant, patient-centred primary outcome measure(s) to inform both selection of an ultimate primary outcome and for sample size calculation.

### Inclusion criteria:

- unplanned PICU admission;
- referral requiring PICU admission to a participating unit.

### Study centres:

20 NHS PICUs across the UK

### Population:

Children admitted to PICU with suspected or proven infection causing fever

### Duration: Six months

### Follow up duration: PICU discharge

### Definition of end of study: Last participant, last follow-up (after 30 days)

### Planned study period: February 2017 to August 2017
STUDY FLOW

1. Routine PICANet\(^1\) data collection
2. Screening for unplanned admissions to PICU
3. Data collection via additional PICANet screens
4. Routine PICANet follow-up at 30 days post-discharge from PICU

\(^1\) Paediatric Intensive Care Audit Network (PICANet)
BACKGROUND INFORMATION

Introduction and rationale
What is the problem being addressed?

Fever is a host response that helps to control infections with a very wide range of pathogens [1]. Fever has been very highly conserved throughout evolution for at least 580 million years [1]. Fever is seen across many species including reptiles, birds and mammals [2]. Recently even plants have been shown to raise core temperatures to control fungal infections [3].

Studies in non-critically ill patients with chickenpox [4], malaria [5] and rhinovirus [6] infections has led to a rediscovery of the potential beneficial effects of fever. This is recognised by the National Institute for Health and Care Excellence (NICE) in their guidance for management of feverish illness in children (NICE CG160, May 2013) in which they recommend, “Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.” However, this advice is not aimed at the management of critically ill children.

Observational studies demonstrate that the treatment of fever in critically ill children is inconsistent [7]. In this population there is a lack of robust data to guide antipyretic intervention. This frequently leaves the decision whether/when to treat fever at the discretion of the bedside nurse. There is genuine uncertainty if the immunological advantages of a fever in defending the body against viruses and bacteria during critical illness outweigh the metabolic costs and cardiorespiratory consequences of a high fever [2]. In cases with underlying neurological pathology (e.g. traumatic brain injury, hypoxic-ischaemic encephalopathy, encephalomyelitis etc.) practice is to avoid fever because of consistent associations with worse outcomes, but in the much larger proportion of emergency admissions in whom other organ failures predominate (most commonly respiratory) the optimal approach is unknown. With emerging evidence that fever may be beneficial in critically ill adults but also cognisant of the physiological differences between adults and children, there is an important need to evaluate whether a more permissive approach to fever management in critically ill children improves outcomes.

A recent systematic review identified five, small, completed RCTs of antipyretic interventions in critically ill adults [8]. These trials were small (ranging from 26 to 200 patients) and the results of a meta-analysis on intensive care unit mortality were inconclusive (relative risk for fever control compared with no fever control or a more permissive threshold: 0.97, 95% confidence interval 0.58 to 1.63). One larger RCT among adults – the HEAT trial in Australia and New Zealand – recently reported [9]. The HEAT trial examined the effect of acetaminophen (paracetamol) versus placebo to treat fever in 700 critically ill adults with known or suspected infection. No differences were seen in the primary outcome of the number of ICU-free days to day 28 or in mortality. One further RCT among adults – the FACEII Trial in Asia (UMIN000005593) – is currently ongoing. We are not aware of any completed or ongoing RCTs of antipyretic management in critically ill children.

A systematic review of observational studies of the association between fever and mortality in critically ill adults found wide variation in the definitions of fever and its association with
mortality [10]. Two further, recent, observational studies in adults, not included in the systematic review, found different relationships between fever and mortality for patients with and without infection, with fever associated with lower mortality among admissions with infection unless the temperature exceeded 40°C [11,12]. Similar results have been found in small cohorts of critically ill children with infection [13].

The Fever feasibility study aims to establish whether it is feasible to conduct a clinical trial to test different temperature thresholds at which clinicians deliver antipyretic intervention in critically ill children with fever due to infection.

Clinical trials, such as the proposed Fever trial, are expensive and the chances of successful completion are improved if both the feasibility and pilot testing of certain key parameters can be clearly demonstrated. The Fever feasibility study will use a mixed method approach comprising three separate studies, including a qualitative study (study 1), an observational study (study 2) and a pilot randomised controlled trial (study 3).

This protocol outlines work that will be undertaken for study 2. Studies 1 and 3 are outlined in separate protocols.

**Aims and objectives**

**Aim**

To inform the feasibility to conduct a study to test different temperature thresholds at which clinicians deliver antipyretic intervention in critically ill children with fever due to infection.

**Objectives**

1. To estimate the size of the potentially eligible population for the definitive RCT, both overall and in subgroups defined by confirmed versus suspected infection and by site/type of infection.

2. To confirm, using empirical data, the temperature threshold(s) currently employed for a standard approach for antipyretic intervention in NHS PICUs, and whether these vary according to confirmed versus suspected infection and site/type of infection.

3. To estimate the characteristics (e.g. mean, standard deviation) of selected important, relevant, patient-centred primary outcome measure(s) to inform both selection of an ultimate primary outcome and for sample size calculation.
STUDY DESIGN AND CONDUCT

Observational cohort study in infants and children admitted to paediatric intensive care units (PICU).

Study design and setting
20 PICUs representing a variety of configurations for UK PICUs (General or combined ICUs in general academic medical centres or within stand-alone children’s hospitals) who are actively participating in the Paediatric Intensive Care Audit Network (PICANet).

Study sites
In this protocol, ‘site’ refers to any hospital where the Fever Observational Study is conducted. Sites must be able to comply with:

- all responsibilities as stated in the Fever Statement of Activities and Schedule of Events;
- all requirements of the study protocol;
- the Research Governance Framework or Policy Framework for Health and Social Care Research (as applicable);
- data collection requirements; and
- International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP).

Site requirements
Sites must:

- identify and sign-up a local appropriate Principal Investigator (PI);
- agree to adhere to the Fever Observational Study data collection requirements; and
- agree to collect data on all eligible patients to the Fever Observational Study.

Site initiation and activation
Site initiations will be performed through site initiation teleconferences held with individual sites.

The following documentation must be in place prior to a site being opened to recruitment:

- all relevant institutional approvals (e.g. confirmation of capacity and capability); and
- a fully signed Fever Statement of Activities.

Once the ICNARC CTU have confirmed that all documentation is in place, a site activation e-mail will be issued to the PI, at which point, the site may start to collect data on eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- all study staff are trained appropriately, e.g. in study data collection processes; and
- timely data entry by staff authorised for PICANet data collection and entry.
Eligibility criteria

Study Population
Children admitted to PICU who fulfil all of the inclusion criteria.

Inclusion criteria
- unplanned PICU admission
- referral requiring PICU admission to a participating unit
All infants and children admitted to PICU will be recorded in routine PICAnet data collection. Patients who are recorded as an 'unplanned PICU admission' will be deemed eligible for the Fever Observational Study. There are no exclusion criteria.

Outcome measures
Primary
- the number of potentially eligible patients observed for a definitive trial (see Appendix A for eligibility criteria)
- the temperature thresholds employed
- the distribution of potential primary endpoints for a definitive study including: length of ventilation, length of PICU stay, PICU mortality, hospital mortality, duration of individual organ support.

Informed consent
Patient consent is not required as no patient identifiable data will be collected centrally during the course of the Fever Observational Study. Parents/legal guardians will be able to opt their child’s data out of the study. Posters and leaflets providing information about the study will be accessible in relative rooms within participating PICUs.

Interventions
None.
ASSESSMENTS

Data collection
The Fever Observational Study will be piggy-backed onto routine data collection for PICANet. Detailed guidance for the collection of data will be provided in the trial specific Standard Operating Procedure (SOP). All data items will be objectively defined according to relevant national and international guidelines. The additional data collected will comprise:

For all patients:
- confirmation of eligibility for the definitive trial (see Appendix A for the eligibility criteria)

If the patient does not have a suspected/confirmed infection or meets one of the exclusion criteria no further data will be collected. For patients who are potentially eligible for the definitive trial the following data will be collected:

- site and type of infection;
- daily data (for first four days in PICU) for the highest daily temperature and any antipyretic and analgesic interventions; and
- any important, relevant, patient-centred, potential primary outcome measures for the definitive RCT emerging from the previous systematic review and the qualitative study (Study 1) that are feasible to collect within the setting of a large observational study and part of routine PICANet data collection, e.g. organ dysfunction and specific treatments.

Follow-up
Routine PICANet follow-up data, collected at 30 days post-discharge from PICU will be collected only for those patients who are potentially eligible for the definitive trial.

Data management guidelines
Case report forms and data entry

All participant data collected will be entered onto paper case report forms (CRFs) prior to entry onto an additional data entry screen on the existing PICANet data entry software (in routine use in all UK PICUs). The Site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated by the Site PI to qualified members of the research team and should be recorded on the Delegation Log.

No patient identifiable data will be collected centrally during the course of the Fever Observational Study.

During the conduct of the study, all electronic participant data will be encrypted and all study documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the study, all participant data (electronic and paper) and other study documents will be archived securely and retained for five years at the site or at the ICNARC CTU, as appropriate (see study closure).

ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff have undergone data protection and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) training.
**Data validation**

Data entered onto the secure study database will undergo validation checks for completeness, accuracy and consistency of data.

**Adverse events**

Due to the fact that there is no interventional element to the Fever Observational Study no additional adverse event reporting will be required for the study to ensure maximum efficiency and reduce unnecessary data collection for participating sites.

**Study closure**

**End of study**

The end of the study will be when all available 30-day follow-up data has been provided to ICNARC CTU by PICANet. At this point the ‘declaration of end of trial’ form will be submitted by the ICNARC CTU.

**Archiving study documents**

At the end of the study, the ICNARC CTU will archive securely all centrally-held study-related documents for a minimum of five years in accordance with ICH GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The Site PI will be responsible for archiving all study-related documents (including CRFs and other essential documents) held at the participating site for a minimum of five years after the end of the study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

Guidance on archiving will be provided in the study-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.
STUDY MANAGEMENT & COMMITTEES

Good research practice
Fever Observational Study will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

Study Management Group
All day-to-day management of the Fever Observational Study will be the responsibility of the Study Management Group (SMG). Members of the SMG will include the Fever Study Coordinator, the Chief Investigator, the Research Assistant and the clinical co-investigators. The SMG will meet regularly to discuss management and progress of the study and findings from other related research.

Role of the ICNARC Clinical Trials Unit
The ICNARC CTU will be responsible for the day-to-day management of the study and will act as custodian of the data.
STATISTICS

Sampling
During the period 1 January 2011 to 31 December 2012, data submitted to PICANet indicate there were 21,326 emergency/unplanned admissions to the 27 UK PICUs. This corresponds to an anticipated overall sample size for the Fever Observational Study in 20 UK PICUs over a six month period of approximately 3960 (33 per PICU per month).

11,007 emergency/unplanned admissions to the 27 UK PICUs (51.6%) during the same period were admitted with a primary or secondary diagnosis consistent with a probable infection. Of these, 946 (8.6%) met one or more of the proposed Fever exclusion criteria. This will correspond to approximately 1900 admissions (16 per PICU per month) who require the additional Fever data collection on temperature and fever management.

Of admissions with probable infection, 1583 (14.4%) were readmissions of the same child. Based on data from the UK Paediatric Intensive Care Outcome Study (UK-PICOS) [14] approximately 70% of children admitted with infection will have a peak temperature ≥ 37.5°C. The resulting sample of approximately 1100 children will be sufficient to permit calculation of 30-day mortality (anticipated 6% based on data from PICANet) with a 95% confidence interval of ±1.4%.

Data analysis
Initial analysis of the data will take place half way through the data collection period to allow modifications to the design of the pilot RCT, specifically the temperature threshold in the control intervention. Final analysis will include assessment of longer-term outcomes and will be conducted following collection of all available 30-day follow-up data.

The size of the potentially eligible population for the definitive RCT (objective 1) will be estimated, both overall and for subgroups defined by: confirmed versus suspected infection; and by site and type of infection; according to the number of children screened for further data collection.

The temperature threshold(s) currently employed for a standard approach for antipyretic intervention in NHS PICUs (objective 2) will be explored by evaluating the proportion of children receiving antipyretic interventions according to their maximum daily temperature and number of days from admission to the PICU, both overall and according to confirmed versus suspected infection and site and type of infection.

The characteristics (e.g. mean, standard deviation) of selected important, relevant, patient-centred, potential primary outcome measures for the definitive RCT (objective 3) will be estimated from the observed data.
ETHICAL APPROVAL AND COMPLIANCE

The Fever Observational Study will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU’s research policies and procedures (see Study Design and Conduct).

The trial has received Health Research Authority Approval, including a favourable opinion from the Greater Manchester West REC. The ICNARC CTU will submit annual progress reports and all amendments to the Fever Observational Study Protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

It is the responsibility of the Site PI to obtain the necessary local approvals for the Fever Observational Study, including confirmation of capacity and capability from the Trust Research & Development (R&D) Department. The Site PI should submit the current approved versions of the Study Protocol and any other essential documents, to the R&D Department. It is also the responsibility of the Site PI to inform the R&D Department of any subsequent revisions to the Trial Protocol or other trial documents. Evidence of capacity and capability must be provided to the ICNARC CTU prior to recruitment of participants.

Participant confidentiality and data protection
No patient identifiable data will be held centrally by the ICNARC CTU. All data that is held by ICNARC will be stored securely. ICNARC is registered under the Data Protection Act (1998) and all ICNARC CTU staff have undergone Data Protection and ICH GCP training.

PICANet will collect patient identifiable data as part of their routine data collection and will ensure data is anonymised (date of birth converted to patient age) before being transferred to ICNARC CTU. PICANet has been approved to collect personal data by the National Information Governance Board (Formerly the Patient Information Advisory Group and now the Health Research Authority Confidentiality Advisory Group).
SPONSORSHIP AND INDEMNITY

Sponsor details

<table>
<thead>
<tr>
<th>Sponsor Name</th>
<th>Intensive Care National Audit &amp; Research Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Intensive Care National Audit &amp; Research Centre</td>
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<td></td>
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<td><a href="mailto:kevin.hunt@icnarc.org">kevin.hunt@icnarc.org</a></td>
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Indemnity

ICNARC holds Professional Indemnity insurance (Policy number: A05305/0816) and Excess Professional Indemnity insurance (Policy number: Epic 50548A / ExLayer1 / 10691144). These indemnities meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.
DECLARATION OF INTERESTS

None.
FUNDING

The Fever Observational Study is funded by the NIHR HTA programme as part of the Fever feasibility study grant (15/44/01).

PUBLICATION POLICY

The final report, a detailed description of the Fever Observational Study, the Fever qualitative study and the Fever external pilot study, results and recommendations for future policy and practice and future research, will be submitted to the NIHR HTA.

Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals.
AUDITS

The study may be subject to inspection and audit by ICNARC under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
REFERENCES


APPENDIX A:

Current eligibility criteria for the proposed definitive RCT:

Inclusion criteria

- unplanned PICU admission
- referral requiring PICU admission to a participating unit
- treating clinician presumes the cause of the fever is an infective process
- age ≥ 28 days and < 16 years (corrected gestational age)
- fever ≥ 37.5 °C in the first 48 hours following contact with the paediatric retrieval service/PICU.

Exclusion criteria

- acute encephalopathy, including convulsive status epilepticus
- post-cardiopulmonary bypass or known/suspected myocardial disease
- severe rhabdomyolysis
- malignant hyperthermia, neuroleptic malignant syndrome or drug-induced hyperthermia
- receiving palliative care or death perceived as imminent
Study 3: A multi-centre, pilot, randomised clinical trial of a more permissive temperature threshold for antipyretic intervention in critically ill children with known or suspected infection: Fever Pilot Trial
Research reference numbers

Protocol version number
v1.2, 04 October 2017

IRAS Number
209931

REC Number
17/LO/1139

Sponsor name and reference
Intensive Care National Audit & Research Centre (01/04/16)

Funder name and reference
National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (15/44/01)

Chief investigator
Professor Mark Peters

Sponsor representation
Ms Kerrie Gemmill

Please note: This protocol should not be applied to infants and children treated off trial. The trial will be monitored for adverse events and the ICNARC CTU can only ensure that active trial investigators are updated of any amendments to the protocol.
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance framework and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor’s Standard Operating Procedures (SOPs) and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Sponsor:

Signature:  
Date:  
14/06/2017

Name (please print):  
Ms Kerrie Gemmill  
Position:  
Managing Director

Chief Investigator:

Signature:  
Date:  
14/06/2017

Name (please print):  
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Position:  
Professor of Paediatric Intensive Care
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<td>Intensive Care National Audit &amp; Research Centre</td>
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<td>Professor Kathy Rowan</td>
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<td>Intensive Care National Audit &amp; Research Centre</td>
</tr>
<tr>
<td>Dr Kerry Woolfall</td>
<td>Department of Psychological Sciences</td>
<td>University of Liverpool</td>
</tr>
<tr>
<td><strong>PCPIE members</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ms Clara Francis</td>
<td>NA</td>
<td>Individual PCPIE member</td>
</tr>
<tr>
<td>Mr Jason Watkins</td>
<td>NA</td>
<td>Individual PCPIE member</td>
</tr>
<tr>
<td>Mr Blaise Fenn</td>
<td>NA</td>
<td>Individual PCPIE member</td>
</tr>
</tbody>
</table>
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<th>Description</th>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<td>CRF</td>
<td>case report form</td>
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<td>Clinical Trials Unit</td>
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<tr>
<td>DMEC</td>
<td>Data Monitoring and Ethics Committee</td>
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<td>GOSH</td>
<td>Great Ormond Street Hospital for Children</td>
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<td>Good Clinical Practice</td>
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<td>Health Technology Assessment</td>
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<td>International Conference on Harmonisation</td>
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<td>Intensive Care National Audit &amp; Research Centre</td>
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<tr>
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<td>Medical Research Council</td>
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<td>National Institute for Health Research</td>
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<tr>
<td>PCPIE</td>
<td>Patient, Carer &amp; Public Involvement &amp; Engagement</td>
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<tr>
<td>PICANet</td>
<td>Paediatric Intensive Care Audit Network</td>
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<tr>
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<td>paediatric intensive care unit</td>
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<tr>
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<tr>
<td>PIM2</td>
<td>Paediatric Index of Mortality version 2</td>
</tr>
<tr>
<td>PIS</td>
<td>Parents/Guardians Information Sheet</td>
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<td>RCT</td>
<td>randomised clinical trial</td>
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<td>Research Ethics Committee</td>
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<td>SAE</td>
<td>serious adverse event</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SMG</td>
<td>Study Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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</table>
General information

This document describes the Fever Pilot Trial and provides information about procedures for the Trial. Data collection will be undertaken in compliance with this document.

This protocol is part of an evaluation of the feasibility of conducting a definitive randomised clinical trial to evaluate the clinical and cost-effectiveness of a more permissive temperature threshold for antipyretic intervention in critically ill children with fever due to infection: the Fever Feasibility Study.
1 Trial summary

| Title: | A multi-centre randomised, parallel group pilot clinical trial investigating the feasibility of a definitive trial of a permissive temperature strategy against a restrictive temperature strategy in critically ill children with known or suspected infection |
| Short Title/acronym | Fever Pilot Trial |
| IRAS number | 209931 |
| REC number | 17/LO/1139 |
| Sponsor name & reference | Intensive Care National Audit & Research Centre (01/04/16) |
| Funder name & reference | NIHR HTA (15/44/01) |
| ISRCTN no | ISRCTN16022198 |
| Design | Pragmatic, open, randomised pilot clinical trial with integrated mixed method element |
| Overall aim | To assess the feasibility of a trial comparing a permissive approach to fever (treat at ≥39.5°C) with a standard restrictive approach (treat at >37.5°C) |
| Objectives | 1. To test the willingness of clinicians to screen, recruit and randomise eligible critically ill children  
2. To estimate the recruitment rate of critically ill children  
3. To test, following randomisation, delivery of, and adherence to the selected temperature thresholds (intervention and control) for antipyretic intervention, and demonstrate separation between the groups in peak temperature measurement over the first 48 hours following randomisation  
4. To test acceptability of the deferred consenting procedures and participant information  
5. To test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event (AE) reporting  
6. To inform final selection of a patient-centred primary outcome measure |
| Target accrual | 100 |
| Inclusion criteria |  
- Unplanned PICU admission  
- Age ≥ 28 days and < 16 years  
- Referral requiring PICU admission to a participating unit  
- Fever ≥ 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  
- Post-cardiopulmonary bypass or known/suspected cardiomyopathy/myocarditis  
- Rhabdomyolysis  
- Malignant hyperthermia, neuroleptic malignant syndrome or drug-induced hyperthermia  
- Receiving palliative care or death perceived as imminent  
- Previously recruited to the Fever Pilot Trial. |
<p>| Anticipated recruitment duration | 4 months |</p>
<table>
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<tr>
<th>Duration of participant follow up</th>
<th>30 days post randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of end of trial</td>
<td>End of trial is defined as, last participant, last follow-up</td>
</tr>
</tbody>
</table>
# 2 Trial flow

Figure 1.

**Initial assessment**
Infants and children assessed for eligibility at first face-to-face contact with ICU or retrieval teams:
- Emergency/unplanned admission to PICU
- Referral requiring PICU admission to a participating unit
- Age ≥ 28 days and ≤16 years
- Fever ≥37.5°C in the first 48 hours following first contact from paediatric retrieval service / PICU
- Cause of fever presumed to be due to an infective process
- New requirement for mechanical ventilation
- Meeting no exclusions (see section 5.2 for full exclusion criteria)

**Randomisation**
Web-based randomisation as soon as possible after meeting all eligibility criteria (within 6 hours of first temperature ≥37.5°C)
Minimised by: age (< 12 mths/≥12 mths)

**Restrictive Group**
Threshold of ≥ 37.5°C for institution of fever control

**Permissive Group**
Threshold of ≥ 39.5°C for institution of fever control

**Informed consent to continue in Trial from parent or legal representative**

**30 days post-randomisation**
3 Background information

3.1 Introduction and rationale

What is the problem being addressed?

Fever is a host response that helps to control infections with a very wide range of pathogens [1]. Fever has been very highly conserved throughout evolution for at least 580 million years [1]. Fever is seen across many species including reptiles, birds and mammals [2]. Recently even plants have been shown to raise core temperatures to control fungal infections [3].

Studies in non-critically ill patients with chickenpox [4], malaria [5] and rhinovirus [6] infections have led to a rediscovery of the potential beneficial effects of fever. This is recognised by the National Institute for Health and Care Excellence (NICE) in their guidance for management of feverish illness in children (NICE CG160, May 2013) in which they recommend, "Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever." However, this advice is not aimed at the management of critically ill children.

Observational studies demonstrate that the treatment of fever in critically ill children is inconsistent [7]. In this population there is a lack of robust data to guide antipyretic intervention. This frequently leaves the decision whether/when to treat fever at the discretion of the bedside nurse. There is genuine uncertainty if the immunological advantages of a fever in defending the body against viruses and bacteria during critical illness outweigh the metabolic costs and cardiorespiratory consequences of a high fever [2]. In cases with underlying neurological pathology (e.g. traumatic brain injury, hypoxic-ischaemic encephalopathy, encephalomyelitis etc.) practice is to avoid fever because of consistent associations with worse outcomes, but in the much larger proportion of emergency admissions in whom other organ failures predominate (most commonly respiratory) the optimal approach is unknown. With emerging evidence that fever may be beneficial in critically ill adults but also cognisant of the physiological differences between adults and children, there is an important need to evaluate whether a more permissive approach to fever management in critically ill children improves outcomes.

A recent systematic review identified five, small, completed RCTs of antipyretic interventions in critically ill adults [8]. These trials were small (ranging from 26 to 200 patients) and the results of a meta-analysis on intensive care unit mortality were inconclusive (relative risk for fever control compared with no fever control or a more permissive threshold: 0.97, 95% confidence interval 0.58 to 1.63). One larger RCT among adults – the HEAT trial in Australia and New Zealand – recently reported [9]. The HEAT trial examined the effect of acetaminophen (paracetamol) versus placebo to treat fever in 700 critically ill adults with known or suspected infection. No differences were seen in the primary outcome of the number of ICU-free days to day 28 or in mortality. One further RCT among adults – the FACEII Trial in Asia (UMIN000005593) – is currently ongoing. We are not aware of any completed or ongoing RCTs of antipyretic management in critically ill children.

A systematic review of observational studies of the association between fever and mortality in critically ill adults found wide variation in the definitions of fever and its association with mortality [10]. Two further, recent, observational studies in adults, not included in the systematic review, found different relationships between fever and mortality for patients with and without infection, with fever associated with lower mortality among admissions with infection unless the temperature exceeded 40°C [11,12]. Similar results have been found in small cohorts of critically ill children with infection [13].

The Fever feasibility study aims to establish whether it is feasible to conduct a clinical trial to
test different temperature thresholds at which clinicians deliver antipyretic intervention in critically ill children with fever due to infection.

Clinical trials, such as the proposed Fever trial, are expensive and the chances of successful completion are improved if both the feasibility and pilot testing of certain key parameters can be clearly demonstrated. The Fever feasibility study will use a mixed method approach comprising three separate studies, including a qualitative study (study 1), an observational study (study 2) and a pilot randomised controlled trial (study 3).

This protocol outlines work that will be undertaken for study 3. Studies 1 and 2 are outlined in separate protocols.

3.2 Aims and objectives

Aim

To inform the feasibility to conduct a definitive, multicenter RCT in critically ill children comparing different temperature thresholds at which clinicians deliver antipyretic interventions.

Objectives

1. To test the willingness of clinicians to screen, recruit and randomise eligible critically ill children
2. To estimate the recruitment rate of critically ill children
3. To test, following randomisation, delivery of, and adherence to the selected temperature thresholds (intervention and control) for antipyretic intervention, and demonstrate separation between the randomised groups in peak temperature measurement over the first 48 hours following randomisation
4. To test acceptability of the deferred consenting procedures and participant information
5. To test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event (AE) reporting
6. To inform final selection of a patient-centred primary outcome measure
4 Trial design and conduct

The Fever Pilot Trial is a pragmatic, open, pilot RCT in infants and children admitted to a paediatric intensive care unit (PICU).

4.1 Trial design and setting

Four UK PICUs and associated retrieval service. The trial sites are:

- Great Ormond Street Hospital for Children
  *Transport Team: Children’s Acute Transport Service (CATS)*

- Evelina London Children’s Hospital
  *Transport Team: South Thames Retrieval Service (STRS)*

- Alder Hey Children’s Hospital
  *Transport Team: The North West and North Wales Transport Service (NWTS)*

- Great North Children’s Hospital, Newcastle
  *Transport Team: North East Children’s Transport and Retrieval Service (NECTAR)*

Trial sites

In this protocol, ‘site’ refers to any hospital where the Fever Pilot Trial is conducted. Sites must be able to comply with:

- all responsibilities as stated in the Fever Pilot Trial Site Agreement;
- the trial treatments, follow-up schedules and all requirements of the trial protocol;
- the Research Governance Framework or Policy Framework for Health and Social Care Research (as applicable);
- data collection requirements; and
- International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP).

Site requirements

Sites must:

- identify and sign-up an appropriate local Principal Investigator (PI);
- identify a local Fever research team (including Research Nurse);
- agree to incorporate the Fever Pilot Trial into routine transport team and PICU activity particularly highlighting the importance of screening at first contact;
- agree to adhere to randomisation allocation and to ensure adherence to the protocol; and
- agree, where possible, to recruit all eligible patients to Fever and to maintain a screening log.
Site initiation and activation

Site initiations will be performed through site initiation meetings held at individual sites. The following documentation must be in place prior to a site being opened to recruitment:

- all relevant institutional approvals (e.g. confirmation of capacity and capability);
- a fully signed Fever Pilot Trial Site Agreement; and
- Fever Delegation Log.

Once the ICNARC CTU have confirmed that all documentation is in place, a site activation e-mail will be issued to the PI and Fever research team, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- all trial staff are trained appropriately, e.g. GCP;
- appropriate recruitment and care for patients in the trial;
- timely data entry; and
- prompt notification of all AEs (as specified in Section 11.0).

The PIs, other investigators and all local staff involved in the conduct of the trial at the site must be authorised on the Fever Delegation Log, held at site, and copied to the ICNARC CTU when any changes are made.
5 Trial population

Infants and children referred for paediatric intensive care admission at a participating site who fulfil all of the inclusion criteria and none of the exclusion criteria (indicated below).

5.1 Inclusion criteria

- unplanned PICU admission;
- age ≥ 28 days and < 16 years;
- referral requiring PICU admission to a participating unit;
- fever ≥ 37.5°C in the first 48 hours following contact with the paediatric retrieval service/PICU;
- new requirement for mechanical ventilation; and
- treating clinician presumes the cause of the fever is an infective process.

5.2 Exclusion criteria

- acute encephalopathy, including convulsive status epilepticus;
- post-cardiopulmonary 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; and/or
- previously recruited to the Fever Pilot Trial.

Screening

Potentially eligible infants and children will be screened against the inclusion/exclusion criteria by the transport team and PICU staff supported by the Fever research team. Randomisation will follow a ‘research without prior consent’ model and parents/guardians will be approached to discuss participation in Fever as soon as is reasonable and practical, but within 48 hours.

Infants and children who are eligible (fulfil all of the inclusion criteria and none of the exclusion criteria) but not randomised, or who fulfil all of the inclusion criteria but meet one or more of the exclusion criteria, will be recorded in the Fever Screening Log.
6 Enrolment

6.1 Recruitment and consent

Overview/Rationale

Children referred with a suspected infection and fever are a high-risk group of paediatric intensive care admissions. Fever is typically highest early in the clinical course before either treatment of the cause is attempted or specific treatment of fever is administered. Therefore any interventions to improve the management of fever will have the greatest impact if they are acted upon immediately after fever is detected. Any delay in the assignment of a fever treatment strategy will lessen its potential impact and may be detrimental to the patient.

During this time, staff priorities are to the assessment and emergency treatment of the patient.

Parents may not be present during this emergency life threatening situation; and even when parents are present, the distressing circumstances would compromise parents’ capacity to make an informed decision and provide consent.

This will make any attempt to obtain prospective fully informed consent from parents/legal representatives during an emergency both unpractical and inappropriate, and cause additional stress to families who are already distressed by their child’s illness. Considering these reasons, once a patient is identified as being eligible for the trial (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the assigned treatment will be applied as soon as possible. Informed consent will be sought from the parents/legal guardians at a more appropriate time. This method is known as ‘deferred’ or ‘retrospective’ consent and is recognised in European Law.

NB. The Fever Pilot Trial team recognises that the use of the terms ‘deferred’ and ‘retrospective’ are misnomers as a child will have already received an intervention as part of the trial before any information is given or consent is sought. Rather, the process should be understood, first, as the provision of information about what has already happened, and then as an invitation to consent for future procedures (where appropriate) and permission for the use of any data already collected.

Informed consent and assent

Once notified of the recruitment of a patient to the trial, a delegated member of the Fever site team will approach the parents/legal representatives as soon as practical and appropriate after randomisation to discuss the trial (usually within 24-48 hours of randomisation) in accordance with CONNECT guidance on research without prior consent in emergency care trials (see NIHR clinical trials Toolkit for CONNECT guidance: http://www.ct-toolkit.ac.uk/routemap/informed-consent/). Before approaching the participant/parent/legal representative/participant, the research team member will check with the relevant ward staff that the participant is stable and that timing is appropriate. If the participant’s condition has not stabilised additional time should be allowed before approaching the
participant/parent/legal representative. Checks conducted to assess appropriate timing for approach will be recorded in the patients' clinical notes.

If the participant has died or been discharged prior to their parents/legal representatives being approached, then the parents/legal representatives will be approached at a later point (see 6.2 Death prior to consent being sought and 6.3 Discharge prior to consent being sought).

A Participant Information Sheet (PIS - non-bereaved in-person) for parents/legal representatives will be provided. The PIS will identify the title of the trial, Chief Investigator and local Principal Investigator, and include information about: the purpose of the trial; the consequences of participating or not; participant confidentiality; contact details for the research team; and the future availability of the results of the trial.

A Consent Form (non-bereaved in-person) will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection. Parents/legal representatives will be allowed time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in Fever.

After the person seeking consent has checked that the PIS and Consent Form are understood, the member of the Fever site team taking consent will invite the parent/legal representative to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal representative, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to the severity of illness and its impact on the mental state of the target population, also considering the age of many of the participants, it will not be possible to involve trial participants in the consenting process. In addition to this, children cannot legally provide consent for their own participation in a trial, Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain capacity). Trial participants will then be provided with an age-appropriate PIS (where the content is adapted according to the child’s age to facilitate comprehension of the information) and asked to sign an Assent Form, if appropriate. Parents/legal representatives will be involved in this discussion. In all other respects, the assenting procedures will follow the consenting procedures as described above. Where appropriate, participants will be offered a sticker to thank them for their participation. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal representatives to discuss with the participant following recovery. The age appropriate PIS includes a description and link to the ‘You took part in research animation’ (https://youtu.be/_Fs1yUxeBFQ) which describes what happens when children are included in research without prior consent. The animation is based on the findings from 'The Children’s Voices project' which explored the views of 16 children aged 7-15 about research without prior consent.
6.2 Death prior to consent being sought

In a situation where a participant dies before consent has been sought, a site research team member will obtain information from colleagues and bereavement counsellors to establish the most appropriate research team member to notify the parents/legal representatives of the involvement in the research study. Consent can be sought from parents/legal representatives following the death of their child and prior to their departure from the hospital; however, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal representatives (B-PIS) (Parent/Guardian Information Sheet bereaved) and Consent Form (bereaved all and non-bereaved postal) would be used.

If consent is not sought prior to the parents'/legal representatives' departure from the hospital, then the parents/legal representatives will be sent a covering letter (bereaved), personalised by the most appropriate clinical team member, and a copy of the B-PIS (Parent/Guardian Information Sheet bereaved) and Consent Form (bereaved all and non-bereaved postal) by post four weeks after randomisation. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the trial, direct them to the B-PIS for detailed information on the trial and provide telephone contact details if parents/legal representatives wish to discuss the trial with a member of the site research team.

In line with the CONNECT guidance [14-16], if there is no response after four weeks of sending the initial letter, a follow up covering letter (bereaved) along with the B-PIS (Parent/Guardian Information Sheet bereaved) and Consent Form (bereaved all and non-bereaved postal) will be sent to the bereaved family. This second letter will provide the same information as the first letter. In addition, this letter will also confirm that if no Consent Form is received within four weeks of the letter being posted, then the participant’s data will be included in the study unless the family notify the site research team otherwise.

6.3 Discharge prior to consent being sought

In the unlikely situation where a participant is discharged from hospital before consent has been sought, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal representatives within five working days of hospital discharge to inform them of the participant’s involvement in the study and provide details of the study. If on this call, the parent/legal guardian agrees for their child’s data to be used in the study, it is to be indicated on the Telephone Agreement Form by the site research staff member making the call. In the event the parent/legal representative refuses to provide consent during the phone call, this will be treated the same as if they declined in hospital as part of a face to face discussion, and their child’s data will be excluded from the study and no further contact will be made. Those who: provisionally agree during the phone call; request further information; or cannot be reached, will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS (non-bereaved postal) and Consent Form (bereaved all and non-bereaved postal) by post. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the information sheet for detailed information on the study.
and provide telephone contact details if parents/legal representatives wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the PIS (postal version) and Consent Form will be sent. This second letter will provide the same information as the first letter. In addition, this letter will also confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant’s data will be included in the study unless the family notify the site research team otherwise.

6.4 Non-consent/Withdrawal

In consenting to the study, parents/legal representatives are consenting to the data already collected, continuation with the Trial treatment and assessment, and to follow-up. However, parents/legal representatives can refuse to give consent (non-consent) for either and withdraw from Fever at any time during the study. If a parent/legal representative explicitly states that they no longer wish for their child to take part or to contribute further data to the study, their decision must be respected. The Non-consent/Withdrawal of Consent Form should be completed and added onto the secure data entry system. Withdrawal of a child from the study should be recorded in their medical notes and no further data collected and any trial procedures stopped. All data collected up to the point of withdrawal will be retained and included in the study analysis unless indicated by the parent/legal representative, in which case the ICNARC CTU will be notified and all data collected will be withdrawn. In order to monitor non-consent, a minimal dataset will be collected for each parent/legal representative approached but not consented: a) Study site; b) Date/time randomised; c) Randomised intervention (including whether started on assigned treatment or not); d) Reason not consented (if parents/legal representatives are willing to provide reason for non-consent).

6.5 Co-enrolment

The SMG will consider co-enrolment with other interventional trials, where the management does not conflict with the Fever objectives, on a case-by-case basis. Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies). Details of any co-enrolment will be documented on the Fever enrolment log.
7 Randomisation

Randomisation must occur as soon as eligibility has been confirmed, within 6 hours of the infant or child’s temperature recorded as being ≥37.5°C.

Participants will be randomly allocated (1:1) to either the permissive group (see section 8.1) or to the restrictive group (see section 8.2) by an online computer generated dynamic procedure (minimisation) with a random component. There will be equal numbers of participants in each trial arm. After receiving login details, staff can access the randomisation website at: https://www.sealedenvelope.com/redpill/fever/

Minimisation will be performed on age (<12 months / ≥12 months). Each participant will be allocated with 70% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 30% probability. To randomise a participant, an authorised staff member will log onto a secure web-based randomisation system and enter the participant’s details to obtain a unique three-digit trial number and allocation to one of the two treatment groups.

In the event of any issues with eligibility or randomisation, one of the clinical members of the Study Management Group (SMG) will be available 24 hours/seven days per week to address any emergency recruitment/randomisation issues.

Emergency 24/7 telephone number: 0207 269 9295

Following screening and randomisation, the Fever Pilot Trial Case Report Form (CRF), will be made available to the clinical team. A Trial Number and treatment allocation will be assigned, and date and time of randomisation will be recorded on the Fever Pilot Trial CRF.
8 Treatment groups

The trial will incorporate a pragmatic approach to temperature control in both the permissive group and restrictive group.

8.1 Permissive group
Treatments to reduce temperature are only permitted in response to a temperature of 39.5°C or above while receiving mechanical ventilation.

8.2 Restrictive group
Treatments to reduce temperature are permitted in response to a temperature of 37.5°C or above while receiving mechanical ventilation.

The treatment strategies for the restrictive and permissive group will commence from randomisation until PICU discharge or death.
9 Outcome measures

The willingness of clinicians to screen, recruit and randomise eligible critically ill children (objective 1) will be assessed by:

- the proportion of eligible children recorded in trial screening logs that were recruited to the Fever Pilot Trial and the reported reasons for non-recruitment; and
- survey responses and focus groups with the clinicians screening and recruiting children to the Fever Pilot Trial.

The anticipated recruitment rate of eligible, critically ill children for the definitive RCT (objective 2) will be estimated from the proportion of eligible children recruited, combined with the size of the potentially eligible population estimated from the Fever Observational Study (IRAS 209929).

The acceptability of the information and documentation and of the consenting procedures (objective 3) will be assessed by:

- the proportion of recruited children whose parents subsequently declined to give consent or who withdrew their child from the Fever Pilot Trial having initially given consent;
- survey responses from parents who gave and declined to give consent; and
- qualitative evaluation of telephone interview transcripts from interviews with parents who gave and declined to give consent.

Adherence to the selected temperature thresholds for antipyretic intervention in both the higher temperature threshold (intervention) and standard care groups (objective 4) will be assessed by:

- the proportion of time spent below the allocated threshold; and
- the proportion of children that received antipyretic intervention on days when their maximum temperature did not reach the allocated threshold and that did not receive antipyretic intervention on days when their maximum temperature exceeded the allocated threshold.

Separation between the randomised groups in peak temperature measurement over the first 48 hours following randomisation (objective 5) will be assessed as the difference in the mean of the maximum temperature recorded during the first 48 hours following randomisation between the higher temperature threshold and standard care groups, presented with a 95% confidence interval.

The follow-up procedures for the selected outcome measures and for adverse event reporting (objective 6) will be assessed by the completeness of follow-up.
10 Assessments

10.1 Data collection

Detailed guidance for the collection of data will be provided in the trial specific Standard Operating Procedure (SOP). Routine linkage will be made with the Paediatric Intensive Care Audit Network (PICANet) through the PICANet ID and Trial Number.

10.2 Time points for data collection

1. Baseline/randomisation
2. Daily during PICU
3. At discharge from the PICU (where relevant) and hospital

Data collected at baseline/randomisation

Trial specific data collection:
- confirmation of eligibility criteria;
- age;
- first contact/admission to PICU details;
- previous treatment of fever; and
- physiology (e.g. heart rate, systolic BP, mean arterial pressure).

Via PICANet data linkage:
- type of admission to unit;
- source of admission;
- care area admitted from;
- retrieval/transfer;
- type of transport team;
- sex;
- PIM2 variables [17]; and
- primary diagnosis for this admission.

Data collected daily during PICU admission:

Trial specific data collection:
- periodic temperatures and physiology between randomisation and day 28;
- antipyretic and opioid interventions administered; and
- intubation status.

Where available, all recorded temperature values will be extracted from electronic charting systems at a minimum of hourly (for ISIP systems) or each 5 seconds where the high resolution data extraction and storage systems are available (currently only GOSH).

Via PICANet data linkage:
- interventions for organ support

Data collected at discharge from PICU/hospital:

Trial specific data collection:
- date of discharge (from PICU and acute hospital);
- survival status;
• adverse events;
• infection site and organism; and
• consent and assent details
  o if parental consent for telephone interview, and longer term contact/future research, parent/guardian contact details will be collected
11 Interviews and focus groups involving parents/legal representatives and site research staff

11.1 Design

The Fever Pilot Trial will include an integrated mixed method element, including questionnaires and interviews with parents/legal representatives during the Fever Pilot Trial, and a survey and focus groups with the site research staff towards the end of the recruitment period to:

- explore the willingness and experiences of site staff in screening, randomising and recruiting eligible participants, and

- explore, with input from parents/legal representatives and site staff, the acceptability of the Fever Trial and experiences of the consenting procedures and participant information materials.

Questionnaires (approximately n=50) and telephone interviews (n=15-25, depending upon data saturation – when major themes identified in new data are reoccurring from previous participants/transcripts, and no new major themes are being discovered) will be used to explore, with parents/legal representatives who do and do not consent to the Pilot Trial, the acceptability of the Fever Pilot Trial, including the approach to recruitment, consenting procedures and participant information materials. The aim will be to identify recruitment and consent issues and potential solutions to inform the proposed definitive Fever Trial.

Four focus groups and an online survey with staff from each participating PICU will also be carried out to explore their experiences of screening, recruiting, randomising and consenting parents/legal representatives/participants to the Fever Pilot Trial. The aim of the focus groups will be to add to data collected from parent/legal representative questionnaires and telephone interviews to identify recruitment and consent issues and potential solutions to inform the proposed Fever Trial.

11.2 Selection of participants

Parent/Legal representative

Inclusion criteria
- Parents/Legal representatives who do and do not consent to the Fever Pilot Trial

Exclusion criteria
- Parents/Legal representatives who do not speak English

Site research staff

Inclusion criteria
- Site research staff who are involved in screening, recruiting, randomising and consenting parents/legal representatives during the Fever Pilot Trial

Exclusion criteria
- None
11.3 Enrolment

All parents/legal representatives will be sampled as per inclusion criteria. As part of the Fever Pilot Trial PIS parents/legal representatives will be provided with information about the option to complete a questionnaire and/or take part in a telephone interview discussing their views on the consenting procedures for the Fever Pilot Trial. After consent discussions for the Fever Pilot Trial (see Section 6), the site research staff will ask the parents/legal representatives if they would like to complete the Fever Consent Questionnaire and/or provide contact details on the Consent Form if they wish to take part in a telephone interview. Parents/legal representatives contacted by post (see Death prior to consent being sought and Discharge prior to consent being sought) will be provided with information on the optional telephone interview only.

Research staff across all participating sites will be sent an email invitation to participate in a focus group (approximately 8-10 in each), or online questionnaire by the University of Liverpool Fever study team. Written consent will be sought from participants before the focus group begins. This will include consent for digital audio recording of the group discussion. The online introduction to the questionnaire will explain how completion of the questionnaire will constitute consent for participation.

Participation will be entirely voluntary and parents/legal representatives and site research staff will be able to withdraw at any time without giving a reason.

11.4 Procedures

Parent/legal representative questionnaires

Following the consent discussion one of the Fever site staff (a member of the healthcare team) will give a copy of the Fever Consent Questionnaire (see Appendix 4) to each parent/legal representative to complete (one questionnaire per parent).

The questionnaire will be placed in a stamped self-addressed envelope and returned by (e.g. within 12 hours) post to the University of Liverpool Fever study team.

Parent/legal representative telephone interviews

The University of Liverpool Fever study team will make contact with parents/legal representatives to arrange an interview within one month of consent. All interviews will be conducted by the team using the Fever parent/legal representative interview topic guide (see Appendix 3). Consent for audio recording of the interview will be checked verbally before the interview commences. The topic guide has been informed by previous trials conducted in paediatric emergency and critical care in the NHS and the Fever Qualitative Study (IRAS ID: 217089 - described in a separate protocol). Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress.

Any distress during the interviews will be managed with care and compassion. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview at any point. Any such families will be supported in obtaining appropriate help.
After the interview is complete, parents/legal representatives will be sent a letter and a £30 Amazon voucher to thank them for their time.

Interviews will continue to be conducted until data saturation is reached. This is when the major themes identified in new data are reoccurring from previous participants/ transcripts and no new major themes are being discovered. Based on previous, similar studies, this is anticipated to involve approximately 15-25 parents/legal representatives.

All parents/legal representatives who express an interest in taking part but are not selected for an interview will be contacted via telephone or email to thank them for their interest in the study.

Site staff focus groups

Focus groups will take place in a meeting room at the four selected sites towards the end of the Fever Pilot Trial recruitment period. The groups will be facilitated using a voting software package (Turning Point Technologies).

All focus groups will be conducted by the University of Liverpool Fever study team using the site research staff focus group topic guide (see Appendix 5). The site research staff focus group topic guide will be informed by the Fever Qualitative Study (IRAS ID: 217089 - described in a separate protocol) and early findings from parent/legal representative questionnaires and telephone interviews. Consent for audio recording will be checked verbally before the focus group begins.

After the focus groups are complete, site research staff will be sent a thank you letter.

Site staff online questionnaire

The invitation email will contain a link to the site staff online questionnaire (see Appendix 6) for completion. When the questionnaire is complete a message will thank staff for their time.

11.5 Analysis

Analysis of data from the interviews, questionnaires and focus groups will be assisted using NVivo 10 qualitative data analysis package and SPSS software for statistical analysis. Quantitative analysis will involve simple descriptive statistics and the chi-square test for trend. Qualitative data will be analysed thematically. Data from each method will be analysed separately then synthesised through the use of constant comparative analysis.
12 Data management guidelines

12.1 Case report forms and data entry

All participant data collected can be entered onto paper case report forms (CRFs) prior to entry onto a secure data entry system. The Site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated by the Site PI to qualified members of the research team and should be recorded on the Delegation Log.

No patient identifiable data will be collected centrally during the course of the Fever Pilot Trial.

During the conduct of the trial, all electronic participant data will be encrypted and all trial documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the trial, all participant data (electronic and paper) and other trial documents will be archived securely and retained for five years at the site or at the ICNARC CTU, as appropriate.

ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff have undergone data Protection and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) training.

12.2 Data validation

Data entered onto the secure trial database will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the research team at participating sites for resolution.

12.3 Trial monitoring

The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the trial.

Following a routine monitoring visit, a report will be sent, which will summarise the visit and the documents reviewed, along with any findings. The Site PI will be responsible for ensuring that all findings are addressed appropriately.

Additional site monitoring visits may be scheduled where necessary.
13 Safety monitoring

The following definitions have been adapted from Directive 2001/20/EC, of 4 April 2001, of the European Parliament (Clinical Trials Directive) and ICH GCP E6 guidelines:

13.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence or effect in a participant treated on a trial protocol, which does not necessarily have a causal relationship with trial treatment. An AE can therefore be any unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it is related to the trial treatment.

13.2 Serious adverse event

A serious adverse event (SAE) is defined as an AE that:

- results in death;
- is life threatening (the term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation or prolongs existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- consists of a congenital anomaly/birth defect.

Important AEs that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

Life threatening in the definition of a serious adverse event (SAE) refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Unexpected and Related Serious Adverse Event

A suspected AE related to the treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.
13.3 Severity

The Site PI, or other delegated investigator(s) (recorded in the Delegation of Trial Duties Log), must perform an assessment of severity for each AE using the following criteria:

0. **None**: indicates no event or complication.
1. **Mild**: complication results in only temporary harm and does not require clinical treatment.
2. **Moderate**: complication requires clinical treatment but does not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitation to the participant.
3. **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay, permanent functional limitation.
4. **Life-threatening**: complication that may lead to death.
5. **Fatal**: indicates that the participant died as a direct result of the complication/adverse event.

13.4 Relatedness

The Site PI or other delegated investigator(s) must perform an assessment of relatedness for each AE. This must be determined as follows:

- **None**: there is no evidence of any relationship to the trial treatment
- **Unlikely**: there is little evidence to suggest a relationship to the trial treatment, and there is another reasonable explanation of the event
- **Possibly**: there is some evidence to suggest a relationship to the trial treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the trial treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the trial treatment, and other possible contributing factors can be ruled out.

13.5 Expectedness

The Site PI or other delegated investigator(s) must perform an assessment of expectedness for each AE regardless of its relationship to the trial procedures. This assessment must be performed using the list of expected AEs in Appendix 2 and determined as follows:

- **Expected**
  The event is listed as an expected AE in Appendix 2, or is considered by a clinician to be an expected complication in this patient population (this would include rare complications).
- **Unexpected**
  The event is not listed as an expected AE in Appendix 2, or is considered by a clinician to be an unexpected event.
13.6 Recording and reporting procedures

All infants and children eligible for Fever are critically ill and due to the complexity of their condition are at increased risk of experiencing AEs. Many of these events are expected as a result of the infant/child's medical condition and standard treatment received in the PICU, but may not be related to participation in the trial. Consequently, any AEs occurring as a result of the infant/child's medical condition or standard critical care treatment will not be reported. Pre-existing conditions do not qualify as AEs unless they worsen, but should be documented in the infant/child's medical notes.

AEs that occur between randomisation and PICU discharge (or 30 days, whichever is earlier) post-randomisation must be recorded in the participant’s medical notes and on the Fever CRF. Information regarding date and time of event onset, severity and relatedness of the AE to trial treatment must be recorded (definitions below).

Those meeting the definition of a SAE (see section 13.2) must, in addition, be recorded in the SAE Log and reported to the ICNARC CTU, using the trial specific Fever SAE Reporting Form, by fax within **24 hours** of observing or learning of the SAE. All sections of the SAE Reporting Form must be completed.

The process for recording and reporting AEs and SAEs is summarised in Figure 2.

13.7 Follow-up of serious adverse events

All SAEs must be followed-up until resolution. The Site PI or other delegated investigator(s) must provide follow-up SAE report(s) if the SAE has not been resolved at the time of the initial report submission.

13.8 Central processing of serious adverse event reports

On receipt of the SAE report, a clinical member of the Fever Study Management Group (SMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the Fever SMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days. All decisions made by the SMG regarding expediting to the REC will be sent to the Data Monitoring and Ethics Committee (DMEC) for monitoring.

The ICNARC CTU will provide safety information to the Chief Investigator, SMG, Trial Steering Committee (TSC) and DMEC for review on a regular basis (as deemed necessary).

13.9 Additional safety monitoring

The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in AEs, the SMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC as appropriate.
13.10 Notifying the Research Ethics Committee

AEs that do not require expedited reporting will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC annually. This will commence one year from the date of approval for the trial.

*Figure 2. Adverse event recording and reporting*

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*If there is any uncertainty about whether the AE is associated with trial treatment, then it should be reported.*
14 Trial closure

14.1 End of trial

The end of the trial will be when the last participant has completed their 30-day follow-up, at which point the ‘declaration of end of trial’ form will be submitted to the REC by the ICNARC CTU.

14.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will archive securely all centrally-held trial-related documents for a minimum of ten years in accordance with ICH GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The Site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of ten years after the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

Guidance on archiving will be provided in the trial-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

14.3 Early discontinuation of the Trial

The trial may be stopped early upon recommendation of the TSC. In which case, the ICNARC CTU will inform all relevant staff working on Fever and advise on the actions to be taken as regards the treatment of participants. All randomised participants will continue to be followed up as per the Fever Protocol.
15 Statistics

15.1 Sample size calculation

The Fever Pilot Trial is set up without a defined primary outcome and, hence, without a usual power calculation to determine sample size. Instead, the sample size has been determined to be adequate to estimate critical parameters to be tested to a necessary degree of precision.

Data from 1,537 children admitted to PICU with a reason for admission associated with infection and a temperature ≥ 37.5°C in UK-PICUs indicate a mean peak temperature in the first 24 hours following PICU admission of 38.5°C with a standard deviation of 0.7°C. Based on this, a sample of 84 children will be sufficient to give 90% power to demonstrate a separation of 0.5°C in mean peak temperature between the higher temperature threshold group and standard care group. The Fever Trial will recruit 100 children to allow for up to 16% withdrawal following deferred consent

Allowing for a rate of non-recruitment of 30% of eligible children, the Fever Pilot Trial will be completed with four PICUs/retrieval teams recruiting for four months (anticipated recruitment rate 6.25 children per PICU per month).

15.2 Data analysis

Descriptive analysis will be carried out to assess the objectives of this Trial. Numbers of patients screened, eligible, randomised, consented and withdrawn from the Trial will be reported by site and by treatment group.

Baseline demographic and clinical data will be summarised for the ITT population, for each of the two treatment groups and overall. Continuous variables will be summarized as mean (standard deviation) and median (interquartile range) whilst categorical variables will be summarized as number (percent). There will be no statistical testing for any of the summary measures whilst comparing the baseline variables between the treatment groups.

Parent/legal representatives questionnaires and interviews, and site research staff focus groups and online survey

Analysis of data from the interviews, questionnaires and focus groups will be assisted using NVivo 10 qualitative data analysis package and SPSS software for statistical analysis. Quantitative analysis will involve simple descriptive statistics and the chi-square test for trend. Qualitative data will be analysed thematically. Data from each method will be analysed separately then synthesised through the use of constant comparative analysis.
16 Trial management and oversight committees

16.1 Good research practice

Fever will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

16.2 Study Management Group

All day-to-day management of the Fever Feasibility Study will be the responsibility of the SMG. Members of the SMG will include the Fever Study Coordinator, the Chief Investigator and the clinical co-investigators. The SMG will meet regularly to discuss management and progress of the Fever Feasibility Study and findings from other related research.

16.3 Trial Steering Committee

The progress of the Fever Pilot Trial will be monitored and supervised by the TSC. At least 75% of the members will be independent (including the Chair). It will also consist of at least one service user representative, experienced paediatric emergency medicine and critical care clinicians, trial methodologists, and the Chief Investigator.

16.4 Data Monitoring and Ethics Committee

The DMEC will include experienced paediatric emergency medicine and critical care clinicians and an experienced statistician. All members of the DMEC will be independent of both the SMG and the TSC. The DMEC will operate under the DAMOCLES Charter, and will report to the TSC, making recommendations on the continuation, or not, of the trial. Adherence to the intervention and safety will be monitored by the DMEC throughout the trial period.

16.5 Role of the ICNARC Clinical Trials Unit

ICNARC CTU will be responsible for the day-to-day management of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are reported, as appropriate, to the REC.
17 Ethical compliance

The Fever Pilot Trial will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU’s research policies and procedures.

17.1 Trial registration
This Trial has been registered with the ISRCTN Registry (ISRCTN16022198)

17.2 Central ethical compliance
The study has received a provisional favourable opinion from the Hampstead Research Ethics Committee (Reference: 17/LO/1139) and an initial assessment from the Health Research Authority. The ICNARC CTU will submit annual progress reports and all amendments to the Fever protocol to the REC for review. The ICNARC CTU will provide relevant approved study documents and other related materials to participating sites.

17.3 Local ethical compliance
It is the responsibility of the Site PI to obtain the necessary local approvals for the Fever Pilot Trial, including approval from the Trust Research & Development (R&D) Department. The Site PI should submit the current approved versions of the Trial Protocol, PIS, Consent Form, and any other written information to be given to participants, to the R&D Department. It is also the responsibility of the Site PI to inform the R&D Department of any subsequent revisions to the Trial Protocol or other trial documents. Evidence of NHS Trust R&D approval must be provided to the ICNARC CTU prior to recruitment of participants.

17.4 Participant confidentiality and data protection

No patient identifiable data will be collected as part of the study. If a parent/guardian consents for telephone interview, and/or longer term contact/future research then parent/guardian contact details will be required by the ICNARC CTU and the University of Liverpool to complete successful follow-up. The ICNARC CTU and University of Liverpool will act to preserve confidentiality and will not disclose or reproduce any information by which participant could be identified outside of that consented for. Data will be stored securely.

ICNARC is registered under the Data Protection Act (1998) and all ICNARC CTU staff have undergone data Protection and ICH GCP training.
18 Sponsorship and indemnity

18.1 Sponsor details

<table>
<thead>
<tr>
<th>Sponsor Name:</th>
<th>ICNARC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Intensive Care National Audit &amp; Research Centre</td>
</tr>
<tr>
<td></td>
<td>Napier House</td>
</tr>
<tr>
<td></td>
<td>24 High Holborn</td>
</tr>
<tr>
<td></td>
<td>London, WC1V 6AZ</td>
</tr>
<tr>
<td>Contact:</td>
<td>Kerrie Gemmill</td>
</tr>
<tr>
<td>Email:</td>
<td><a href="mailto:Kerrie.gemmill@icnarc.org">Kerrie.gemmill@icnarc.org</a></td>
</tr>
</tbody>
</table>

18.2 Indemnity

ICNARC holds Professional Indemnity insurance (Policy number: A05305/0816) and Excess Professional Indemnity insurance (Policy number: Epic 50548A / ESK03A12). These indemnities meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.
19 Funding

The trial is supported by grant funding from the NIHR Health Technology Assessment (HTA) Programme, as part of the Fever Feasibility Study grant (15/44/01).

A written agreement with the site PI and/or the PI’s institution and ICNARC will outline the funding arrangements to sites. The TSC will meet and review the financial aspects of the trial at least report to the Sponsor.
20 Publication policy

The final report, including a detailed description of the Fever Feasibility Study results and recommendations for future policy and practice and future research, will be submitted to the HTA.

Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All participant data will be anonymised before publication.
21 References


## Appendix 1 Protocol version history

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol version no.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of changes made</th>
</tr>
</thead>
</table>
| N/A          | 1.1                  | 27/07/2017    | Imran Khan           | • Minor clarification to the trial objectives  
• Added reference to a Telephone Agreement Form in the consent procedure  
• Minor elaborations in section 11  
• Inclusion of topic guides and questionnaires in appendix  
• Inclusion criterion added |
| 1            | 1.2                  | 05/10/2017    | Imran Khan           | • Minor clarification on Trial Flow to include modified eligibility criteria  
• Removal of “sickle cell disease” as exclusion criterion (Trial Summary; Section 5.2)  
• Added exclusion “previously recruited onto the Fever Pilot Trial” (Trial Summary; Section 5.2)  
• Amended existing exclusion “Severe rhabdomyolysis” to “Rhabdomyolysis” (Trial Summary; Section 5.2)  
• Defining Rhabdomyolysis (Section 5.2; Appendix 2)  
• Amended existing exclusion “Receiving or requiring mechanical ventilation” to “New requirement for mechanical ventilation” (Trial Summary; Section 5.1)  
• Added inclusion “Referral requiring PICU admission to a participating unit” (Trial Summary; Section 5.1)  
• Clarification of withdrawal of consent (Section 6.4)  
• Minor clarification in Randomisation (Section 7)  
• Clarified trial procedures applicable while patient is mechanically ventilated (Sections 8.1; 8.2)  
• Requirement to record intubation status as part of data collection (Section 10.2)  
• Addition to Severe Adverse Event reporting (Section 13.8) |
Appendix 2 Expected adverse events

Expected AEs that could be observed in participants up to PICU discharge (or 30 days whichever is earlier) following randomisation:

- seizures;
- rhabdomyolysis (Defined as serum creatine kinase concentration at least 10 times the upper limit of normal); and
- cerebral oedema.

[This list is not exhaustive. If an AE, as defined in Section 13.1, occurs this should be recorded and reported as described in Section 13.0]
Appendix 3 Parent/legal representative interview topic guide

Topic guide for interviewing parents in Fever

Please note: *Italic text indicates instruction for researcher and will not be read to participant*

**Intro:** My name is [researcher name] and I am a researcher from the University of Liverpool. Many thanks for agreeing to help us with the design of the Fever study.

Before we begin the interview I need to obtain your consent for the study is that ok? *(Refer to instructions (in box) on the Participant Consent form including consent for audio recording of this discussion).*

**Obtain consent here**

You can stop the interview at any time. Before we start do you have any questions?

**Bereaved:** I have some idea about your circumstances, if there is anything that you find difficult to talk about please don’t feel that you have to, or if you want to stop the interview at any point, then please let me know.

The reason that you were invited to take part in this interview study is because if we only ask those parents who have children who have recovered from their severe infection the information we gather won’t be complete. The findings will be biased. We know even less about what it is like for parents who have been bereaved to have discussions with doctors and nurses about the trial and what it was like to be involved in the trial. Doctors and nurses want to understand what it is like for parents in this situation and whether they should approach them about the trial. Does that make sense? Do you have any questions before I start?

I will start with some questions about you if that’s ok and then I will ask you about your experience of being invited to take part in Fever?
1. Experience

1.1 If known: My notes from when you registered interest in taking part in this interview state that your child received treatment for severe infection in *insert month and year*. Is that correct?

If not known: Please tell me a little bit about your child (name, age, gender)

When were they admitted to hospital for severe infection?

**Not bereaved**

How is [child name] now?

Has he/she recovered from his/her hospital visit?

1.2 Could you give me an outline of what happened for them to need emergency treatment for a fever and suspected infection? *(If bereaved say: I know this may be difficult, if you don’t wish to answer this question please say and I will go on to the next question)*

1.3 What hospital was this? (prompt explore if transferred)

1.4 Did the doctor give your child a diagnosis (e.g. did they tell you what had caused the illness?)

Section 2: The Fever recruitment process

2.1 Would you mind if I start by getting an overall picture of what happened when you first heard about the Fever trial… could you tell me a bit about that?

Explore any knowledge about the trial before admission. Explore where parents were/ when they first heard the trial mentioned. *(If Bereaved and received information by post go to section 4)*.

2.2 Did you give consent for your child to be in the trial?

This is a question I ask all parents and it’s not a test, but just so we can gage whether the trial is being explained clearly enough I wanted to know whether you;

Could you tell me what the Fever trial was looking at?

2.3 How were you introduced to the study?

Was it a doctor or nurse who spoke to you about the trial?

Did one of the nursing staff looking after your child introduce you to the research nurse or doctor?

2.4 Did the research nurse/doctor check with you that it was a good time to talk about research?

If so, when was this? Do you think that this was the best time?

If not, when would have been the best time?

How could this be improved?

2.5 Could you tell me what they explained about Fever?
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did they go through any of the potential risks or benefits of your child taking part in the trial at that point? If yes, how did they describe these?</td>
<td></td>
</tr>
<tr>
<td>2.6 Was there anything that you found: a) unclear b) surprising?</td>
<td></td>
</tr>
<tr>
<td>2.7 Is there anything else that sticks out in your mind about the discussion?</td>
<td></td>
</tr>
<tr>
<td>2.8 Do you have any suggestions about how this discussion could be improved in the future? If yes how?</td>
<td></td>
</tr>
<tr>
<td>2.9 Could you tell me about any written information you were given by a nurse or doctor about the trial? Explore whether they were given the information leaflet – short version and/or the full patient information sheet</td>
<td></td>
</tr>
<tr>
<td>2.10 When did you receive this information? (Prompt: explore written and verbal and time point)</td>
<td></td>
</tr>
<tr>
<td>2.11 Did you read the information leaflet/sheet? (Prompt: If they read the short information PIS leaflet or the full information PIS)</td>
<td></td>
</tr>
<tr>
<td>2.12 What did you think about the information leaflet/sheet?</td>
<td></td>
</tr>
<tr>
<td>2.13 Was there anything that you found: a) unclear? b) surprising?</td>
<td></td>
</tr>
<tr>
<td>2.14 Could the information leaflet be improved in any way? (Prompt: If so, how?)</td>
<td></td>
</tr>
<tr>
<td>2.16 Thinking about your experience of your child being admitted for a severe infection- what would you hope the Fever study would do to help your child? (Prompt: what effect would the treatment have to be useful?)</td>
<td></td>
</tr>
<tr>
<td>2.17 What would you be looking for as an indicator that your child was getting better?</td>
<td></td>
</tr>
</tbody>
</table>

**Section 3: Consent process**

*Explain:* Families involved in Fever provided consent after their child had already been actively involved in the Trial. This was to use the data already collected and for them to continue in the trial. We call this deferred consent or also known as research without prior consent.

The reason that this legislation is in place is because in situations like this (i.e., in paediatric critical care), there’s a belief that there’s no time to have a discussion about the research and that actually having that discussion might delay treatment.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 What did you think of the use of research without prior content in the Fever trial?</td>
<td></td>
</tr>
<tr>
<td>3.3 How long did you get to think about whether you wanted your child’s information to be used in Fever? Do you think this was long enough? Did you have the opportunity to ask any other questions about the study? Did you ask any? (Prompt, what questions did you ask?, if not, why not)</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Response</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>How long do you think people should be given to think about taking part in a trial?</td>
<td></td>
</tr>
<tr>
<td>3.4 In making the decision about your child’s participation in Fever, what sort of things went through your mind?</td>
<td></td>
</tr>
<tr>
<td>3.5 Was there anything you found particularly helpful in making up your mind?</td>
<td></td>
</tr>
<tr>
<td>3.6 Was there anything you found unhelpful?</td>
<td></td>
</tr>
<tr>
<td>3.7 How hard was this decision?</td>
<td></td>
</tr>
<tr>
<td>3.8 Was there anything specific that influenced your decision?</td>
<td></td>
</tr>
<tr>
<td>3.9 Would you mind telling me what were your reasons for (providing consent/not providing consent)?</td>
<td></td>
</tr>
<tr>
<td>3.10 If Fever goes to full trial do you think this is an acceptable way to obtain consent? (Explore response)</td>
<td></td>
</tr>
<tr>
<td>Section 4 Decision making (those who didn’t consent to Fever)</td>
<td></td>
</tr>
<tr>
<td>4.1 Would you mind telling me your reason for saying no to the trial?</td>
<td></td>
</tr>
<tr>
<td>4.2 Did you worry about how the doctor or nurse would respond?</td>
<td></td>
</tr>
<tr>
<td>4.3 How did they respond?</td>
<td></td>
</tr>
<tr>
<td>Section 5: Seeking child assent NOT BEREAVED PARENTS GO TO SECTION 6</td>
<td></td>
</tr>
<tr>
<td>5.1 Did the nurse or doctor explain the Fever trial to your child and give them an information sheet to seek their permission to take part? IF YES:</td>
<td></td>
</tr>
<tr>
<td>a) Could you tell me a bit more about that?</td>
<td></td>
</tr>
<tr>
<td>b) Do you think they understood the information they were given?</td>
<td></td>
</tr>
<tr>
<td>c) Did they give their permission to take part?</td>
<td></td>
</tr>
<tr>
<td>d) Did they ask any questions?</td>
<td></td>
</tr>
<tr>
<td>5.2 Did the nurse/doctor give you an information sheet to help you discuss the trial with your child when you got home? IF yes:</td>
<td></td>
</tr>
<tr>
<td>a) Did you discuss the Fever trial with your child? [Could you tell me about that?]</td>
<td></td>
</tr>
<tr>
<td>b) Could you tell me your reasons for discussing/not discussing the trial with them?</td>
<td></td>
</tr>
<tr>
<td>IF DISCUSSED WITH CHILD</td>
<td></td>
</tr>
<tr>
<td>a) Was the information sheet useful in helping you discuss the trial with your child?</td>
<td></td>
</tr>
<tr>
<td>b) how do you think the discussion went? EXPLORE (could you tell me a bit more about that)</td>
<td></td>
</tr>
<tr>
<td>c) Is there anything that could have helped you discuss the trial with you child?</td>
<td></td>
</tr>
</tbody>
</table>
d) Did your child ask any questions about the trial?

e) Did they want to take part?

f) Did they raise any concerns?

g) If your child had not wanted to take part in FEVER would their opinion have influenced your decision about the trial? [Could you tell me a bit more about that?]

5.3 What do you think involving children more in making the decision about the use of their information in a trial?

5.4 What do you think about children being involved in the trial discussion between doctors and parents as part of a family approach to consent?
   Or do you think it should discussion should be kept separate?

Section 6 Bereaved Parents only

We don't have much information about what parents who have lost a child think about how parents should be asked for consent. Even though some of these issues have been mentioned earlier, I'd like to check through these questions again and make sure I have your full answers, if its ok? (use judgement to see whether further probing here is appropriate)

6.1 (IF RECEIVED LETTER IN POST) How long after leaving hospital did you receive the letter about the Fever trial?

   - How did you feel when you first read the letter about the Fever trial?
   - Was this the first time you had heard about the trial?
   - Do you think that it is ok for doctors to send a letter to bereaved parents about their child’s involvement in a trial, or would have you preferred to have been told about the study before your left hospital?
   - Another option is for the doctor to phone bereaved parents to inform them about their child’s involvement in the study before a letter and information sheet is sent, what do you think about such a phone call? (Explore how you would have felt to receive such a phone call)
   - When you read the letter and Fever information sheet, what were your first thoughts?
   - Did you have any concerns about Fever? (Explore)

   - Did you contact the hospital to discuss the trial with the doctor or nurse? (if yes- were your concerns addressed (if applicable)
   - Did you want to know that your child had been entered into Fever?
   - How did you feel about the ‘opt out’ approach- which meant that you only had to contact the hospital if you didn’t want your child’s information to be included?

6.2 What advice would you give doctors and nurses on how to go about approaching bereaved parents to discuss Fever before they leave hospital?

6.3 When do you think is the best time for doctors and nurses to approach bereaved parents for deferred consent?

   Who approached you to discuss Fever? (Prompt: Was it a doctor or nurse? Did you know them?)

   Do you think that this was the most appropriate person to approach you?
If yes/no, what were your reasons for this? If not, who do you believe would have been the best person to approach you?

6.4 How do you think this should be done? Explore response and:

- **If letter**, do you think the letter should be 'opt in'- so parents would make contact with the hospital if they wanted their child’s data to be in the trial. Or 'opt out' where parents didn’t have to do anything if they wanted their child’s data to be in the trial (they are automatically enrolled)?

- **In person**, Do you think this should be done face to face or via a telephone call?

Out of all the options we have discussed which would you recommend?

In Fever we send parents a letter 4 weeks after they leave hospital to explain how their child was included in the trial and how their child's data will be included in the trial unless they contact the hospital to 'opt out'. There is a number for parents to contact the doctor if they have any questions. What do you think about this approach? Do you think it is OK to send a second letter in case of no response (e.g., in case the first letter was not opened by parents?) Explore 8 week timeframe. (Explore any concerns)

6.5 If the doctor or nurse had approached a parent about a trial before their child had passed away and left them to consider the information, do you think it is ok for the doctor or nurse to then contact the parent for their decision after their child has died? (Prompt, letter home or face to face?)

6.6 Some nurses have suggested involving a bereavement counsellor when contacting parents. What do you think about this? Did you take up the opportunity to speak to a bereavement counsellor?

Interview end- thank you for your time
Inform participant that their voucher and copy of the consent form will be sent via post. Check home address is on record from registration.
Appendix 4 Parent/legal representative questionnaire

Parent/Guardian Consent Questionnaire

Background

- The following questions are about the Fever study consent process that you took part in
- We refer to people agreeing to take part in research as ‘consenting’
- As your child received treatment as an emergency, consent for your child to take part in the Fever Study would have been sought after the emergency situation. This is known as research without prior consent, or deferred consent.

Completing this questionnaire

Today’s date

Are you the child’s

Mother  Father  Other ________________________________
(Please specify)

Your child’s age  days / weeks / months / years (circle as appropriate)
1. Please indicate how strongly you agree or disagree with the following statements by placing a circle around the answer that best fits your opinion.

<table>
<thead>
<tr>
<th>Statements</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. The doctor or nurse checked that it was a convenient time to discuss research before discussing Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b. I was initially surprised to find out that my child had already been entered into Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c. The information I received about Fever was clear and straightforward to understand</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>d. I understood why consent for my child’s participation in Fever was sought after the treatment had been given</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e. I had enough opportunity to ask questions about Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>f. I was satisfied with the consent process for Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g. It was difficult to take in the information I was given about Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h. It was difficult to make a decision about Fever</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>i. I made this decision</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>j. Someone took this decision away from me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>k. I was not in control of this decision</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>l. The decision about the research was inappropriately influenced by others</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

If the answer to this question is ‘Agree’, please state who you think influenced the decision about the research:
2. Did you consent for your child to participate in Fever?
   - Yes (Go to Question 3)
   - No (Go to Question 4)

3. What were your reasons for providing consent for your child to participate in Fever?
   Please tick all that apply and then circle your main reason (e.g. ☑)
   a. To help my child
   b. To help other children in the future
   c. I felt that medical studies like Fever are important
   d. Because I trusted the doctor or nurse who explained Fever
   e. The treatment had already started being given to my child
   f. My child recovered
   g. I didn’t feel comfortable saying no to the nurse or doctor who explained the study
   h. Other (Please state):

4. If you did not provide consent, please provide your reasons for deciding that your child would not take part in Fever
   (If you do not wish to do so, please leave this space blank)

5. Please tell us any comments or suggestions you have to improve the recruitment and consent process for Fever:

We would like to thank you for taking the time to complete this questionnaire.

Please place the questionnaire in the envelope provided, seal it and give it back to the doctor or research nurse.
Appendix 5 Site research staff focus group topic guide

Italic Black text = Actions/ prompts to facilitator
Black text = questions
Red text = voting handset

Tell the room: The main aim of the focus group is to find out how well you think the Fever Study has been going at your site, including what is working well and perhaps what isn't working so well. We will use these findings, alongside the rest of the data collected during the study, to establish the feasibility of conducting a larger trial.

We would really appreciate it if you can be as honest as possible – the questions you answer by the voting handsets are anonymous. We will ask you to introduce yourselves to help with facilitation. With your consent, we will audio record this session. An external company called Voicescript analyses the transcripts and we will remove any names, or identifiable information, before analysis.

Does anyone have any questions before we start?

Check consent for audio recording – press record

Practice voting question: If you were a vegetable, what vegetable would you be? Potato/carrot/asparagus/leek/pea

Section 1: role and involvement in the Fever Study

Please go round the room and introduce yourselves, your role and what you have contributed to the Fever Study?

Are you involved in: screening patients, helping with randomisation or consenting patients? (Explore research nurse full time/part time or split with clinical)

Please tell us what your role is at this hospital: Junior doctor/senior doctor/junior nurse/senior nurse

How much experience do you have in recruiting to paediatric clinical trials? (0-2 years/2-4/4-6/6-8/8-10/over 10)

Are you involved in clinical care of children (e.g. delivering medical interventions?) (Yes/No)

Section 2: Training

Who did you receive your Fever Study training from? 1) Trial team (e.g. ICNARC), 2) PI or member of your site team, 3) both

Overall how would you rate the Fever Study training? Excellent/good/fair/poor

Explore: What aspects, if any, of the training did you find useful? What was valued?

Do you think the site training prepared you for recruitment and consent in the Fever Study (YES/NO)

What aspects, if any, of the training did you think needed development?
Explore responses- what could be improved if we went to a larger study/ did you use any additional training or resources to prepare for Fever (e.g. EcliPSE consent video)

I will now go through each stage of the Fever recruitment process.
Section 3: Screening

When do you start screening? [Prompt: do start during phone call?]
Who usually screens?
Do you screen patients you may have missed?

Do you think the screening process could be improved? (Yes/No) Discuss potential challenges to screening or systems that have been put in place to assist screening.

Section 4: Randomisation

Did you experience any issues in randomising children to the FEVER Study? Yes / No. Explore answers including views on the web portal.

Do you have posters/ leaflets/stickers up on the wall? Do parents notice the leaflets, stickers or posters?

Have any parents asked about Fever before you mentioned it to them? If yes, what questions have parents asked? If yes, could you tell me what happened? Explore whether directed parents to poster/leaflets

In the patients randomised at this site so far, how long (in minutes) has there been between identifying eligibility and randomising patients using the web portal? (Explore if more than 15-20 minutes whether there is time to discuss Fever with parents)

Did you experience any issues in randomising children to the FEVER Study during transfer? Yes/No. Explore answers

Do you think the randomisation process could be improved? (Yes/No) Discuss potential challenges to the randomisation process or anything that has been put in places to assist randomisation.

Section 5: Protocol deviations and temperature thresholds

Have you experienced any difficulties in adhering to the protocol? (Yes/No)

If yes, could you tell me a bit more about what the major difficulties have been?

Explore:
- What is your understanding of the inclusion / exclusion criteria?
- Have you experienced difficulties with applying the inclusion / exclusion criteria? If yes, could you tell me a bit more about what the major barriers have been? Are they clear, too broad, too restrictive?

What have been the major barriers to delivering the intervention? Explore: lack of equipoise, inadequate training, protocol or CRF overly complex or difficult to follow?

How acceptable did you find waiting till 37.5°C to treat? Very acceptable/ acceptable/ not acceptable/ very unacceptable explore if there perception changed throughout the trial.

How acceptable did you find waiting till 39.5°C to treat? Very acceptable/ acceptable/ not acceptable/ very unacceptable explore if there perception changed throughout the trial.
Section 6: Recruitment and consent in the Fever Study

Before Fever, did you have any experience of research without prior consent? (Y/N)

What were your initial thoughts when you first heard that the Fever trial was to use a RWPC approach? Prompt: Did you have any concerns?

Have your views about research without prior consent in Fever changed over time? (Yes/No)
  If yes, could you tell me a bit more about that? At what point did they change before/after Site Initiation Visit? After experience of RWPC?

This next section is about your experience of discussing the trial with parents and seeking permission to use their child's data in Fever. These questions may only apply to a few or you.

Before you approach families to discuss Fever, do you speak to the clinical care team?
  • Have you ever asked the clinical team to introduce you to the parents?
  • At what time (post randomisation) have you usually approached parents? (Explore minimum and maximum time frames)
  • Have you included children in this discussion? If not, why?

When you approach families, will they have had an opportunity to discuss their child's condition with a member of the clinical team?
  • If no, explore why.

How have parents reacted to finding out that their child has been entered into a clinical trial without their prior consent? Have any parents been angry/upset etc. – what happened?

Do you check parents understanding of the trial?

Is there anything that you find particularly difficult about explaining the Fever Study to parents?

Section 7: Forms

Did you find the case report form easy to use? (Yes/No) How can it be improved? Explore: re: layout, data points, who completed it (front-line staff prospectively or research team retrospectively or both)

Did you find the consent form easy to use? (Yes/No) How can it be improved?

Have you involved children in Fever discussions? (Explore barriers and whether age appropriate PIS have been given/took home)
Section 9: Acceptability
Do you think a larger Fever trial is practically possible to conduct? Yes / no

Over all how acceptable do you think it is to conduct a larger Fever Trial?
Very acceptable / acceptable / not acceptable / very unacceptable / Not applicable
Explore answers

Section 8: Anything else

- Before we finish, is there anything you think is important for us to know if we conducted a larger Fever trial which we have not already covered?

- (If there is time) Could you please take a form and write down 3 things that have gone well with Fever and three things that could be improved.
Appendix 6 Site research staff questionnaire

Fever Study Site Staff Questionnaire

The aim of this short survey is to find out how well you think the Fever Study has been going at your site, including what is working well and perhaps what isn't working so well. We will use these findings, alongside the rest of the data collected during the Fever Study, to establish the feasibility of conducting a larger trial.

Please note that by returning this survey you are giving permission for your responses to be included in the Fever Study. All information will be anonymised and stored securely in compliance with the Data Protection Act 1998.

Background information

1. Please identify your hospital:
   Alder Hey / Evelina / Great Ormond Street Hospital / The Great North Children’s Hospital

2. What is your current role at this hospital?
   Junior doctor / Senior doctor / Junior nurse / Senior nurse
   Other (please state) _____________________________

3. How many years’ experience do you have in recruiting to paediatric clinical trials?
   0-2 / 2-4 / 4-6 / 6-8 / 8-10 / > 10

4. Are you involved in clinical care of children?
   Yes / No

5. How have you been involved in the Fever study (please tick all that apply)
   Screening patients
   Randomisation
   Consenting
   Involved in the clinical care of FEVER participants
   Other (please state) _____________________________
**Training**

11. Who provided your Fever training (please tick all that apply)
   - Trial team (e.g. ICNARC),
   - Member of your site team
   - Other (please state) ____________________________

12. Overall how would you rate the Fever Study site training from the trial team?
   - Excellent/ Good/ Fair/ Poor / Not applicable (did not attend)

13. Overall how would you rate the Fever Study training from your site team?
   - Excellent/ Good/ Fair/ Poor / Not applicable (did not attend)

14. Do you think the Fever site training could be improved? Yes/No
   - If yes, how? ___________________________________________
   - ____________________________________________________________________________
   - _______________________________________________________________________________
   - _______________________________________________________________________________

**Process**

6. Do you think the screening process could be improved?
   - Yes / No
   - If yes, please elaborate:
     ___________________________________________________
     ___________________________________________________
     ___________________________________________________

7. Do you think the randomisation process could be improved?
   - Yes / No
   - If yes, please elaborate:
     ___________________________________________________
     ___________________________________________________

8. Have you experienced any difficulties in adhering to the protocol?
   - Yes / No
   - If yes, please elaborate:
     ___________________________________________________
     ___________________________________________________
### Consent and comments

15. How acceptable did you find the use of Research without Prior Consent in Fever?
   - Very acceptable / Acceptable / Not acceptable / Very unacceptable / Not applicable

16. How have parents responded to the Fever consent discussion?
   - Very positively/ Positively/ Negatively/ Very negatively/ Not applicable.

   Please explain your answer ___________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

17. Did you find the case report form easy to use?
   - Yes / No/Not applicable

   If No, Please provide and suggestions for improving the case report form
   ___________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

18. Did you find the consent form easy to use?
   - Yes / No/Not applicable

   If No, Please provide and suggestions for improving the consent form
   ___________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

19. Do you think a larger Fever trial is practically possible to conduct?
   - Yes / No/Not applicable

   If No, Please provide and suggestions for improving the consent form
   ___________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

20. Overall how acceptable do you think it is to conduct a larger Fever Trial?
   - Very acceptable / Acceptable / Not acceptable / Very unacceptable / Not applicable

Thank you for taking the time to complete this questionnaire.