IRAS Number: 209931

Fever Study

A study about cooling down sick children when they reach different temperatures

Please ask your parent or carer or the nurse to explain any words that you don't understand.

1. What is research?

A research study is what you do when you want to learn about something or find out something new.

2. Why is this study being done?

We are doing this research study to find out the best way of treating sick children who have an infection and a high temperature.

3. Why was my parent or carer asked if I could take part?

Your parent or carer was asked if you could take part because you were very poorly and needed treatments. About 100 other children with similar problems will be taking part in this research.

If you have any questions about the research or what is involved, you can ask your parent or carer, or one of the nurses. You can also ask them to show you a short animation called 'You took part in research' which will help to explain what taking part in emergency research means. You can find the animation by searching 'You took part in Research' on You Tube, or typing in the following web address: https://youtu.be/_Fs1yUxeBFQ

4. What happened as part of the study?

The first thing that happened was that you were put into one of two groups.

★ **Group 1:** Children in this group were looked after by doctors and nurses, and were cooled down when their temperature was 37.5°C.

★ **Group 2:** Children in this group were looked after by doctors and nurses, and were cooled down when their temperature was slightly higher (39.5°C).

A computer decided at random which group you would be in. There was an equal chance that you would be in each group; nobody picked which group you went in. This makes it fair for everybody. We collected some information about your stay in hospital.

5. Will joining help me?

You are playing an important part in finding out what is the best way to help children like you to get better. We can't promise this research will help you, but you will be helping other children, just like you, who have the same problems in the future.

6. What happens when the research stops?

When we have collected information from all of the other children, we will tell you and your family what we found out.

7. Will anyone else know I am doing this?

No. All of your information will be kept safe and only people working on the study will be allowed to see it.

IRAS Number: 209931

Fever Study

A study looking at the best temperature at which to start cooling children and young people with a fever (high temperature) caused by an infection

Introduction

We are doing this research study to find out the best temperature at which to start cooling down children and young people who have a fever (high temperature) caused by an infection.

Why are we doing this research?

This is a pilot study which is done to find out whether it is possible to do a larger research study.

A fever (high temperature) is a normal bodily response to a severe infection. Across the UK, doctors usually start to try and cool down a child once their temperature reaches 38°C, using drugs like paracetamol or other methods like sponging them with cool water.

There is evidence that suggests fever is an important response which may help the body to recover from infection. However, this research looked at adults and children who were not very sick, so further research is needed to find out whether a fever might also help sick children recover from infection. We want to find out whether children and young people with an infection will recover more quickly if doctors allow their temperature to reach 39.5°C before trying to cool them down.

Before doing a large research study comparing the two temperatures, it is important that we first understand whether it is possible by doing a pilot study.

Why were parents or carers asked if I could take part in the study?

When you arrived in hospital, you had a fever and were showing symptoms of severe infection and needed immediate treatment. You were entered into the study and doctors and nurses either waited until 37.5°C or 39.5°C to start treating your fever. There was no time initially to discuss this

with your parents but it was explained to them as soon as possible afterwards. We were not able to ask you about the study at the time because you were too poorly. About 100 other children and young people will be taking part.

If you have any questions about the research or what is involved, you can ask your parent or carer, or one of the nurses. You can also ask them to show you a short animation called 'You took part in research' which will help explain what taking part in emergency research means. You can find the animation by searching 'You took part in Research' on You Tube, or typing in this address: https://youtu.be/_Fs1yUxeBFQ

What happened as part of the study?

You were put into one of two groups:

- **Group 1:** if you are in this group, doctors/nurses would have waited until your temperature reached 37.5°C before giving you any treatment (e.g. paracetamol) to cool you down. All of the other care you received was the same as usual.
- **Group 2:** if you are in this group, doctors/nurses would have waited until your temperature reached 39.5°C before giving you any treatment to cool you down. All of the other care you received was the same as usual.

A computer decided at random which group you would be in. There was an equal chance that you would be in each group; nobody picked which group you went in. This makes it fair for everyone. It doesn't matter which group you are in, you will always get the best possible care.

We collected some information about your stay in the hospital to be able to compare the two groups.

What are the possible benefits of taking part?

You are playing an important part in finding out what is the best way to help young people like you to get better. We can't promise this research will help you, but you will be helping others just like you who have the same problems in the future.

What happens when the research stops?

When we have collected information from everyone, we will tell you and your family what we found out.

Will anyone else know I am doing this?

No. All of your information will be kept strictly confidential and only people working on the study will be allowed to see it.

How will my data be kept confidential?

Your information is kept on a computer system which has passwords so it is secure. Nobody is allowed to share your personal information.

Thank you for reading this leaflet

This paediatric intensive care unit is participating in a research study to investigate the best temperature at which to start cooling a child with a fever due to infection.

If your child is taking part in this study, their progress will be carefully monitored and they will receive all the treatments they need to help them recover from their illness.

If you have any questions, please contact:
<RESEARCH NURSE NAME>

Telephone: <TO BE ADDED>

Email: <TO BE ADDED>
or

<PRINCIPAL INVESTIGATOR NAME>

Telephone: *<TO BE ADDED>*

Email: *<TO BE ADDED>*

IRAS Number: 209931

Research Ethics Committee
Reference Number: xx/xx/xxxx
Information Leaflet
(Parents or Guardians)
V1.0 16 June2017

PLEASE INSERT YOUR TRUST LOGO HERE

NHS
National Institute for Health Research

What is a fever?

A fever (high temperature) is a normal bodily response to a severe infection. There is evidence, in both humans and other animals, that fever is an important response by the body that may actually aid recovery from the illness causing the fever.

How are fevers treated?

When a very sick child has a fever, clinicians (doctors/nurses) usually cool down the child using drugs such as paracetamol, or physical methods such as a cooling mat, sponging with water etc.

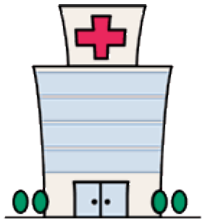
What is the purpose of the Fever Study?

The potential benefit of fever is not contested in minor illness and there is evidence that fever may actually help a child to recover from infection.

The National Institute for Health and Care Excellence (NICE) recommends that doctors should not use drugs or physical cooling methods solely for the purpose of reducing a child's temperature. However, the potential benefits of fever in children who are critically ill has not been properly studied and so the best approach is unknown.

This study aims to find out whether critically ill children with symptoms of severe infection should be given treatments for fever at a higher temperature (39.5°C) than usual (37.5°C).

This is a pilot study which will inform the design of a larger study, which we plan to run in hospitals across the UK.



What will happen if my child takes part?

As your child came to intensive care in an emergency it was important that they were treated as quickly as possible. Therefore, the doctors and nurses did not have time to discuss this research study with you beforehand.

If your child was eligible for the study, they would have been randomly allocated to one of two groups and either received cooling treatments when their temperature reached 37.5°C (group 1) or 39.5°C (group 2). Your child had an equal chance of being in either group.

As with all children in intensive care, your child would have been carefully monitored and given all other treatments, such as antibiotics, or medicines to treat any signs of pain or discomfort. They would have received all the other usual care they need to give them the best chance to recover from their illness.

What information will be collected?

If your child takes part in the study, we will collect information regarding your child's progress in hospital from their medical notes.

You may also be asked to complete a questionnaire or take part in a telephone interview.

All information collected will be kept completely confidential.

Do I have to take part?

No, you are free to leave the study at any time and this will not affect the standard of care your child receives.

What next?

If your child is eligible, you will be approached about this study by a member of the paediatric intensive care team.

An information sheet will be provided and a member of the team will go through this in detail with you.

If you have any concerns or want to know more about the Fever study, then please discuss this with a member of the health care team in this unit.

IRAS Number: 209931

Great Ormond Street Hospital for Children NHS Foundation Trust

icnarc intensive care national audit & research centre

University of Liverpool

Insert NHS logo
<Trust address 1> <Trust address 2>
<Trust address 3> <postcode>
<research team telephone number>

The Fever Study

Parent/Guardian Information Sheet

We invite you to provide consent for your child to be included in a research study

- We appreciate that this is a very difficult time for you and your family. We would like to ask you to spend a few minutes deciding on whether or not you would consent for your child's information to be included in a research study, which aims to improve the care of children in intensive care.
- Doctors and nurses currently use various methods to reduce fever in children, including drugs, such as paracetamol, and/or physical cooling methods, such as a cooling mat or sponging the child with water. These are known as antipyretic interventions. We hope to improve outcomes for critically ill children presenting with fever from infection by exploring what is the best temperature at which to start using these treatments. The Fever Study is a small study which is being done to inform the design of a future larger study (*i.e.,* a clinical trial). Before embarking on a large clinical trial, it is important to assess whether it is possible and acceptable to conduct this trial.
- Before you decide if you want to give your permission for your child's information to be included in this trial, it is important for you to understand why the research is being done and what it will involve.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish.
- Please ask the nurse or doctor who has spoken or written to you about the Fever Study if there is anything that is not clear or if you would like more information.

Important things that you need to know

- Your child was showing signs of fever thought likely to have resulted from an infection.
- Across the UK, children with fever are given cooling treatments. The temperature at which clinicians start these treatments is usually about 37.5°C. However, the best temperature at which to start treating fever is not known.
- There is evidence to suggest that fever may be an important bodily response and may actually help a child to recover from infection.
- We want to find out whether only giving cooling treatments for fever at a higher temperature (around 39.5°C) than usual (around 37.5°C) helps children's recovery.
- As this was a medical emergency, **there was no time to delay your child's treatment by asking for your consent**. Your child was entered into the Fever Study and received cooling treatments for fever at a temperature of either 37.5°C or 39.5°C. This is known as 'research without prior consent' or deferred consent.
- **Your child was carefully monitored and received all other treatments, such as antibiotics, or medicines to treat any signs of pain or discomfort.**
- Possible benefits of fever: fever may help resolve an infection more quickly.
- Possible risks of fever: a high temperature high uses extra energy and can make the heart beat more quickly.
- Young children may have seizures during a fever. But reducing a fever does not reduce this risk. The seizures are likely to be caused by the infection that the fever is trying to help the body heal.
- We are now asking for your permission for your child's information to be included in the Fever Study.

1) Why are we doing this study?

Infection is often present when a child needs intensive care as an emergency. Infection may be the main cause, or only a contributing factor. A fever (high temperature) is a normal response by the body to severe infection. When a very sick child has a fever, clinicians (doctors/nurses) would usually cool down the child. In the UK, this is done using drugs, such as paracetamol, and/or physical cooling methods, such as a cooling mat or sponging the child with water. The temperature at which clinicians usually start these treatments is about 37.5°C. However, the best temperature at which to start treating fever, is currently unknown.

There is a lot of evidence that fever may be an important bodily response and may actually help a child to recover from infection. The potential beneficial effects of fever are recognised by the National Institute for Health and Care Excellence (NICE) in their guidance for management of fever in children. It recommends that drugs should not be used if only for the purpose of reducing a child's temperature. However, this recommendation comes from research that involved children who were not critically ill. Therefore, it is unknown whether it should be applied to very sick children with severe infection. Further research is needed to find out which approach to fever management is best at treating critically ill children. Until this is done, current treatment recommendations cannot be improved.

Our aim is to find out whether critically ill children with symptoms of severe infection should be given treatments for fever at a higher temperature (around 39.5°C) than usual (around 37.5°C). The study will involve approximately 100 children and young people.

This is a pilot study – in other words, it is being done to inform the design of a larger study (a clinical trial), which we plan to run in hospitals across the UK.

2) What do I need to know about the treatment used and possible benefits and risks?

Children who are very ill and needing intensive care who develop a fever are frequently given cooling (antipyretic) interventions very quickly as part of their emergency treatment. This is part of a larger treatment package, which is thought to give them the best possible chance of recovery.

There is persuasive evidence in humans that fever is an important bodily response and may be beneficial in terms of surviving the infection causing the fever. The potential advantages of fever include a quicker recovery from minor childhood infections. However, it is uncertain whether the advantages of fever in defending the body against infection outweigh the risks in critically ill children. Our bodies respond to fever by using extra energy and oxygen and this can make the body work harder – seen by the heart going faster amongst other things. People worry about seizures with a fever. We now understand that treating fever does **not** reduce the risk of a seizure in children. This is because seizures are probably caused by the infections themselves rather than the fever.

The clinical and research teams carefully monitored your child for these risks, as they would with any child with fever from a suspected infection. They gave all treatments necessary to provide the best possible chance of recovery.

3) How was it decided which treatment my child received?

The Fever Study is a randomised controlled trial, which means that each child is randomly put into one of two groups (children allocated to group 1 receive antipyretic intervention at a temperature threshold of around 37.5°C and children allocated to group 2 receive antipyretic intervention at a higher temperature threshold of around 39.5°C). The temperature threshold your child was treated at was selected randomly by a computer programme, so your child had an equal chance of receiving intervention for fever at either around 37.5°C or around 39.5°C.

Your child would only have been entered into the study if they were feverish (≥37.5°C) for no longer than 48 hours prior to admission to intensive care and if the clinical team looking after them thought that the cause of fever was an infection.

4) Why am I being asked *after* my child has been given the treatment rather than before?

As this was a medical emergency, we could not delay giving the treatment your child needed. Explaining the study to you in advance would have caused a delay in giving your child urgent treatment. This is called 'research without prior consent' – an approach which has been used in other emergency studies to enable vital research to proceed.

We are now asking for your permission to use the information already collected about your child.

We would also like to know your views on the study and will ask you to take part in a telephone interview. This information will help the Fever Study team find out how best to run a larger research study in future.

5) What will happen next?

1. If you **agree** for your child's information to be included in the study, the hospital research team will collect anonymised information about your child's hospital stay, which will be sent to the Intensive Care National Audit & Research Centre (ICNARC) where it will be held securely. Even if you **agree**, you can change your mind at any time and can contact the research team using the contact details on the first page of this sheet.

2. Whether you do or do not agree for your child's information to be in the study, we are also interested in your views on the consent process for this study. This will involve taking part in a telephone interview (30-60 minutes) with a member of the Fever study team. You will be asked about how you felt about the Fever consent process, why you did or did not provide consent and how you think consent should be sought if we run a larger study. The views of parents/guardians are important to help us find the best way to do the study, including how we should explain the study to parents/guardians and how we should seek consent when a child has died. If you would like to help, we ask that you complete the relevant sections of the consent form and provide your contact details. A member of the Fever study team will then contact you within the next four weeks to arrange an interview.

3. Data collected from research studies can be used to address many important research questions beyond those planned in the original study. This has the potential to provide real benefit to patients and the scientific community. If possible, we would like your permission to keep your contact details on file after the study has ended and share anonymised data collected from the study if we feel it could contribute to answering other important health questions. Any information would be fully anonymised prior to being published or shared with other researchers.

The study results will be made available on the ICNARC website (www.icnarc.org) when it is finished.

6) Who is involved in this study?

This paediatric intensive care unit (PICU) is one of four NHS PICUs that are taking part in this study across the country. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is funding the study. Professor Mark Peters (University College London) is the Fever Study Chief Investigator. The study is sponsored and managed by ICNARC. Parents of children who have experienced fever with septic shock have been involved in the development of this study, including this information sheet and how you were asked to take part.

7) What if there is a problem?

Complaints: If you have a concern about any aspect of the Fever Study, you should ask to speak with the hospital principal investigator *(<INSERT NAME>)* or the research team (contact details are on top of the first page) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure – details can be obtained from your child's hospital.

Harm: For NHS service advice or support, please visit http://www.nhs.uk/ to find your local Patient Advice and Liaison Services (PALS) services contact details.

There are also a range of support groups for parents whose child has experienced severe infection. Some of these include:

UK Sepsis Trust
- Website: http://sepsistrust.org/
- Telephone: 0845 606 6255

Meningitis Research Foundation
- Website: http://www.meningitis.org/
- Telephone: 080 8800 3344

There are a number of support groups for anyone who has been affected by the death of child, including:

Sands (Still birth and neonatal death charity)
- Website: https://www.uk-sands.org/
- Telephone: 020 7436 5881

Child Bereavement UK
- Website: http://www.childbereavementuk.org/
- Telephone: 0800 02 888 40

If you are harmed due to someone's negligence or wish to complain about any aspect of the way you have been approached or treated during the course of this trial, contact the Hospital's PALS for further information.

8) How my personal data is kept confidential?

ICNARC, where your child's data will be kept, has a very secure computer system and a strict information security policy. As part of this policy, all staff sign a contract agreeing to keep data secure and confidential. ICNARC is also registered under the Data Protection Act.

If you decide to take part in a telephone interview or agree to have your contact details kept with us; identification data, including full name, telephone number(s) and email address, and transcripts will be encrypted and held on password protected University of Liverpool computer. Access to personal data will be limited to authorised staff members. Any results will be presented in a way that does not attribute information to individuals.

9) Who has reviewed the study?

The study has been reviewed by the NIHR HTA and the London Hampstead Research Ethics Committee (17/LO/1139), who have agreed that the study is being conducted in a correct and appropriate manner.

Thank you for your time.
We are very grateful that you are considering taking part in this study.

Great Ormond Street Hospital for Children NHS Foundation Trust

icnarc intensive care national audit & research centre

University of Liverpool

Insert NHS logo
<Trust address 1> <Trust address 2>
<Trust address 3> <postcode>
<research team telephone number>

The Fever Study

Parent/Guardian Information Sheet

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- Before you decide if you want to give your permission for your child's information to be included in this trial, and whether you want them to continue to be in the trial, it is important for you to understand why the research is being done and what it will involve.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish.
- Please ask the nurse or doctor who has spoken to you about the Fever Study if there is anything that is not clear or if you would like more information.

Important things that you need to know

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- Possible risks of fever: a high temperature high uses extra energy and can make the heart beat more quickly.
- Young children may have seizures during a fever. But reducing a fever does not reduce this risk. The seizures are likely to be caused by the infection that the fever is trying to help the body heal.
- We are now asking for your permission for your child's information to be included in the Fever Study and your consent for your child to continue to be in the trial.

1) Why are we doing this study?

Infection is often present when a child needs intensive care as an emergency. Infection may be the main cause, or only a contributing factor. A fever (high temperature) is a normal response by the body to severe infection. When a very sick child has a fever, clinicians (doctors/nurses) would usually cool down the child. In the UK, this is done using drugs, such as paracetamol, and/or physical cooling methods, such as a cooling mat or sponging the child with water. The temperature at which clinicians usually start these treatments is about 37.5°C. However, the best temperature at which to start treating fever, is currently unknown.

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Our aim is to find out whether critically ill children with symptoms of severe infection should be given treatments for fever at a higher temperature (around 39.5°C) than usual (around 37.5°C). The study will involve approximately 100 children and young people.

This is a pilot study – in other words, it is being done to inform the design of a larger study (a clinical trial), which we plan to run in hospitals across the UK.

2) What do I need to know about the treatment used and possible benefits and risks?

Children who are very ill and needing intensive care who develop a fever are frequently given cooling (antipyretic) interventions very quickly as part of their emergency treatment. This is part of a larger treatment package, which is thought to give them the best possible chance of recovery.

There is persuasive evidence in humans that fever is an important bodily response and may be beneficial in terms of surviving the infection causing the fever. The potential advantages of fever include a quicker recovery from minor childhood infections. However, it is uncertain whether the advantages of fever in defending the body against infection outweigh the risks in critically ill children. Our bodies respond to fever by using extra energy and oxygen and this can make the body work harder – seen by the heart going faster amongst other things. People worry about seizures with a fever. We now understand that treating fever does **not** reduce the risk of a seizure in children. This is because seizures are probably caused by the infections themselves rather than the fever.

The clinical and research teams carefully monitored your child for these risks, as they would with any child with fever from a suspected infection. <u>They gave and will continue to give all treatments necessary to provide the best possible chance of recovery.</u>

We cannot promise that your child benefited directly by participating in this study. However, ultimately this study will help to improve the future treatment of children with infection.

3) How was it decided which treatment my child received?

The Fever Study is a randomised controlled trial, which means that each child is randomly put into one of two groups (children allocated to group 1 receive antipyretic intervention at a temperature threshold of around 37.5°C and children allocated to group 2 receive antipyretic intervention at a higher temperature threshold of around 39.5°C). The temperature threshold your child was treated at was selected randomly by a computer programme, so your child had an equal chance of receiving intervention for fever at either around 37.5°C or around 39.5°C.

Your child would only have been entered into the study if they were feverish (≥37.5°C) for no longer than 48 hours prior to admission to intensive care and if the clinical team looking after them thought that the cause of fever was an infection.

4) Why am I being asked *after* my child has been started on the treatment rather than before?

As this was a medical emergency, we could not delay giving the treatment your child needed. Explaining the study to you in advance would have caused a delay in giving your child urgent treatment. This is called 'research without prior consent' – an approach which has been used in other emergency studies to enable vital research to proceed.

We are now asking for your permission to:

a) use the information already collected about your child;
b) continue to treat your child's fever according to the temperature threshold that has been assigned until your child has been discharged from intensive care; and
c) collect information for the study about your child's hospital stay.

We would also like to know your views on the study and will ask you to complete a brief questionnaire and/or take part in a telephone interview. This information will help the Fever Study team find out how best to run a larger research study in future.

5) What will happen next?

1. If you **agree** for your child to continue on the trial, and for their information to be included in the study, the hospital research team will collect anonymised information about your child's hospital stay, which will be sent to the Intensive Care National Audit & Research Centre (ICNARC) where it will be held securely. Even if you **agree**, you can change your mind at any time and can contact the research team using the contact details on the first page of this sheet.

2. Whether you do or do not agree for your child to continue on the trial or for your child's information to be in the study, we are also interested in your views on the consent process for this study. This will involve completing a questionnaire and/or taking part in a telephone interview (30-60 minutes) with a member of the Fever study team. You will be asked about how you felt about the Fever consent process, why you did or did not provide consent and how you think consent should be sought if we run a larger study. The views of parents/guardians are important to help us find the best way to do the study, including how we should explain the study to parents/guardians and how we should seek consent when a child has died. If you would like to help, we ask that you complete the relevant sections of the consent form and provide your contact details. A member of the Fever study team will then contact you within the next four weeks to arrange an interview.

3. Data collected from research studies can be used to address many important research questions beyond those planned in the original study. This has the potential to provide real benefit to patients and the scientific community. If possible, we would like your permission to keep your contact details on file after the study has ended and share anonymised data collected from the study if we feel it could contribute to answering other important health questions. Any information would be fully anonymised prior to being published or shared with other researchers.

The study results will be made available on the ICNARC website (www.icnarc.org) when it is finished.

6) Who is involved in this study?

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have experienced fever with septic shock have been involved in the development of this study, including this information sheet and how you were asked to take part.

7) What if there is a problem?

Complaints: If you have a concern about any aspect of the Fever Study, you should ask to speak with the hospital principal investigator *(<INSERT NAME>)* or the research team (contact details are on top of the first page) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure – details can be obtained from your child's hospital.

Harm:

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- Website: http://www.meningitis.org/
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- Website: http://www.childbereavementuk.org/
- Telephone: 0800 02 888 40

If you are harmed due to someone's negligence or wish to complain about any aspect of the way you have been approached or treated during the course of this trial, contact the Hospital's PALS for further information.

8) How my personal data is kept confidential?

ICNARC, where your child's data will be kept, has a very secure computer system and a strict information security policy. As part of this policy, all staff sign a contract agreeing to keep data secure and confidential. ICNARC is also registered under the Data Protection Act.

If you decide to take part in a telephone interview or agree to have your contact details kept with us; identification data, including full name, telephone number(s) and email address, and transcripts will be encrypted and held on password protected University of Liverpool computer. Access to personal data will be limited to authorised staff members. Any results will be presented in a way that does not attribute information to individuals.

9) Who has reviewed the study?

The study has been reviewed by the NIHR HTA and the London Hampstead Research Ethics Committee (17/LO/1139), who have agreed that the study is being conducted in a correct and appropriate manner.

Thank you for your time.
We are very grateful that you are considering taking part in this study.

Great Ormond Street Hospital for Children NHS Foundation Trust

icnarc intensive care national audit & research centre

University of Liverpool

Insert NHS logo
<Trust address 1> <Trust address 2>
<Trust address 3> <postcode>
<research team telephone number>

The Fever Study

Parent/Guardian Information Sheet

We invite you to provide consent for your child to be included in a research study

- Doctors and nurses currently use various methods to reduce fever in children, including drugs, such as paracetamol, and/or physical cooling methods, such as a cooling mat or sponging the child with water. These are known as antipyretic interventions. We hope to improve outcomes for critically ill children presenting with fever from infection by exploring what is the best temperature at which to start using these treatments. The Fever Study is a small study which is being done to inform the design of a future larger study (*i.e.,* a clinical trial). Before embarking on a large clinical trial, it is important to assess whether it is possible and acceptable to conduct this trial.
- Before you decide if you want to give your permission for your child's information to be included in this trial, and whether you want them to continue to be in the trial, it is important for you to understand why the research is being done and what it will involve.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish.
- Please ask the nurse or doctor who has spoken to you about the Fever Study if there is anything that is not clear or if you would like more information.

Important things that you need to know

- Your child was showing signs of fever thought likely to have resulted from an infection.
- Across the UK, children with fever are given cooling treatments. The temperature at which clinicians start these treatments is usually about 37.5°C. However, the best temperature at which to start treating fever is not known.
- There is evidence to suggest that fever may be an important bodily response and may actually help a child to recover from infection.
- We want to find out whether only giving cooling treatments for fever at a higher temperature (around 39.5°C) than usual (around 37.5°C) helps children's recovery.
- As this was a medical emergency, **there was no time to delay your child's treatment by asking for your consent**. Your child was entered into the Fever Study and received cooling treatments for fever at a temperature of either 37.5°C or 39.5°C. This is known as 'research without prior consent' or deferred consent.
- **Your child was carefully monitored and received all other treatments, such as antibiotics, or medicines to treat any signs of pain or discomfort.**
- Possible benefits of fever: fever may help resolve an infection more quickly.
- Possible risks of fever: a high temperature high uses extra energy and can make the heart beat more quickly.
- Young children may have seizures during a fever. But reducing a fever does not reduce this risk. The seizures are likely to be caused by the infection that the fever is trying to help the body heal.
- We are now asking for your permission for your child's information to be included in the Fever Study.

1) Why are we doing this study?

Infection is often present when a child needs intensive care as an emergency. Infection may be the main cause, or only a contributing factor. A fever (high temperature) is a normal response by the body to severe infection. When a very sick child has a fever, clinicians (doctors/nurses) would usually cool down the child. In the UK, this is done using drugs, such as paracetamol, and/or physical cooling methods, such as a cooling mat or sponging the child with water. The temperature at which clinicians usually start these treatments is about 37.5°C. However, the best temperature at which to start treating fever, is currently unknown.

There is a lot of evidence that fever may be an important bodily response and may actually help a child to recover from infection. The potential beneficial effects of fever are recognised by the National Institute for Health and Care Excellence (NICE) in their guidance for management of fever in children. It recommends that drugs should not be used if only for the purpose of reducing a child's temperature. However, this recommendation comes from research that involved children who were not critically ill. Therefore, it is unknown whether it should be applied to very sick children with severe infection. Further research is needed to find out which approach to fever management is best at treating critically ill children. Until this is done, current treatment recommendations cannot be improved.

Our aim is to find out whether critically ill children with symptoms of severe infection should be given treatments for fever at a higher temperature (around 39.5°C) than usual (around 37.5°C). The study will involve approximately 100 children and young people.

This is a pilot study – in other words, it is being done to inform the design of a larger study (a clinical trial), which we plan to run in hospitals across the UK.

2) What do I need to know about the treatment used and possible benefits and risks?

Children who are very ill and needing intensive care who develop a fever are frequently given cooling (antipyretic) interventions very quickly as part of their emergency treatment. This is part of a larger treatment package, which is thought to give them the best possible chance of recovery.

There is persuasive evidence in humans that fever is an important bodily response and may be beneficial in terms of surviving the infection causing the fever. The potential advantages of fever include a quicker recovery from minor childhood infections. However, it is uncertain whether the advantages of fever in defending the body against infection outweigh the risks in critically ill children. Our bodies respond to fever by using extra energy and oxygen and this can make the body work harder – seen by the heart going faster amongst other things. People worry about seizures with a fever. We now understand that treating fever does **not** reduce the risk of a seizure in children. This is because seizures are probably caused by the infections themselves rather than the fever.

The clinical and research teams carefully monitored your child for these risks, as they would with any child with fever from a suspected infection. <u>They gave and will continue to give all treatments necessary to provide the best possible chance of recovery.</u>

We cannot promise that your child benefited directly by participating in this study. However, ultimately this study will help to improve the future treatment of children with infection.

3) How was it decided which treatment my child received?

The Fever Study is a randomised controlled trial, which means that each child is randomly put into one of two groups (children allocated to group 1 receive antipyretic intervention at a temperature threshold of around 37.5°C and children allocated to group 2 receive antipyretic intervention at a higher temperature threshold of around 39.5°C). The temperature threshold your child was treated at was selected randomly by a computer programme, so your child had an equal chance of receiving intervention for fever at either around 37.5°C or around 39.5°C.

Your child would only have been entered into the study if they were feverish (≥37.5°C) for no longer than 48 hours prior to admission to intensive care and if the clinical team looking after them thought that the cause of fever was an infection.

4) Why am I being asked *after* my child has been started on the treatment rather than before?

As this was a medical emergency, we could not delay giving the treatment your child needed. Explaining the study to you in advance would have caused a delay in giving your child urgent treatment. This is called 'research without prior consent' – an approach which has been used in other emergency studies to enable vital research to proceed.

We are now asking for your permission to use the information already collected about your child.

We would also like to know your views on the study and will ask you to take part in a telephone interview. This information will help the Fever Study team find out how best to run a larger research study in future.

5) What will happen next?

1. If you **agree** for your child's information to be included in the study, the hospital research team will collect anonymised information about your child's hospital stay, which will be sent to the Intensive Care National Audit & Research Centre (ICNARC) where it will be held securely. Even if you **agree**, you can change your mind at any time and can contact the research team using the contact details on the first page of this sheet.

2. Whether you do or do not agree for your child's information to be in the study, we are also interested in your views on the consent process for this study. This will involve taking part in a telephone interview (30-60 minutes) with a member of the Fever study team. You will be asked about how you felt about the Fever consent process, why you did or did not provide consent and how you think consent should be sought if we run a larger study. The views of parents/guardians are important to help us find the best way to do the study, including how we should explain the study to parents/guardians and how we should seek consent when a child has died. If you would like to help, we ask that you complete the relevant sections of the consent form and provide your contact details. A member of the Fever study team will then contact you within the next four weeks to arrange an interview.

3. Data collected from research studies can be used to address many important research questions beyond those planned in the original study. This has the potential to provide real benefit to patients and the scientific community. If possible, we would like your permission to keep your contact details on file after the study has ended and share anonymised data collected from the study if we feel it could contribute to answering other important health questions. Any information would be fully anonymised prior to being published or shared with other researchers.

The study results will be made available on the ICNARC website (www.icnarc.org) when it is finished.

6) Who is involved in this study?

This paediatric intensive care unit (PICU) is one of four NHS PICUs that are taking part in this study across the country. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is funding the study. Professor Mark Peters (University College London) is the Fever Study Chief Investigator. The study is sponsored and managed by ICNARC. Parents of children who have experienced fever with septic shock have been involved in the development of this study, including this information sheet and how you were asked to take part.

7) What if there is a problem?

Complaints: If you have a concern about any aspect of the Fever Study, you should ask to speak with the hospital principal investigator *(<INSERT NAME>)* or the research team (contact details are on top of the first page) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure – details can be obtained from your child's hospital.

Harm:

For NHS service advice or support, please visit http://www.nhs.uk/ to find your local Patient Advice and Liaison Services (PALS) services contact details.

There are also a range of support groups for parents whose child has experienced severe infection. Some of these include:

UK Sepsis Trust
- Website: http://sepsistrust.org/
- Telephone: 0845 606 6255

Meningitis Research Foundation
- Website: http://www.meningitis.org/
- Telephone: 080 8800 3344

There are a number of support groups for anyone who has been affected by the death of child, including:

Sands (Still birth and neonatal death charity)
- Website: https://www.uk-sands.org/
- Telephone: 020 7436 5881

Child Bereavement UK
- Website: http://www.childbereavementuk.org/
- Telephone: 0800 02 888 40

If you are harmed due to someone's negligence or wish to complain about any aspect of the way you have been approached or treated during the course of this trial, contact the Hospital's PALS for further information.

8) How my personal data is kept confidential?

ICNARC, where your child's data will be kept, has a very secure computer system and a strict information security policy. As part of this policy, all staff sign a contract agreeing to keep data secure and confidential. ICNARC is also registered under the Data Protection Act.

If you decide to take part in a telephone interview or agree to have your contact details kept with us; identification data, including full name, telephone number(s) and email address, and transcripts will be encrypted and held on password protected University of Liverpool computer. Access to personal data will be limited to authorised staff members. Any results will be presented in a way that does not attribute information to individuals.

9) Who has reviewed the study?

The study has been reviewed by the NIHR HTA and the London Hampstead Research Ethics Committee (17/LO/1139), who have agreed that the study is being conducted in a correct and appropriate manner.

Thank you for your time.
We are very grateful that you are considering taking part in this study.

Fever Pilot Trial

Participant Information Sheet (Site Research Staff)

We invite you to take part in a research study

You are being invited to take part in a research study. Please ask us if there is anything that is not clear in this information sheet or if you would like more information (contact details overleaf).

The Fever Trial 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.

Before embarking on a large trial, it is important to assess whether it is possible to conduct such a trial. This study aims to gather that information, in terms of finding out if the trial procedures work smoothly and looking at the views of parents/legal representatives and clinicians involved in screening, recruiting, randomising and consenting parents/legal representatives during the pilot trial.

Your hospital is one of four taking part in this study across the country.

Why have I been chosen?

As you will be involved in recruiting children to research studies such as Fever, your views are very important to us. We are asking clinicians from each of the Fever Pilot Trial sites to take part in a focus group. For those who are unable to attend there will be an opportunity to complete a short online questionnaire.

What will happen if I take part?

We will ask you to register interest in taking part in a focus group.

Focus groups will take place in a meeting room at your hospital (<INSERT HOSPITAL NAMES>). Each focus group will take about 60-90 minutes and involve 8-10 site research staff. All focus groups will be conducted by the University of Liverpool Fever study team. The online questionnaire will be sent via email shortly after the focus group is complete.

What will I be asked about in the focus group?

We will ask you about the discussions you have had with families of children eligible to participate in the pilot RCT, including your thoughts on the consent process and your experience of explaining research without prior consent (deferred consent) to families. We will also ask you about what information families requested to help them make a decision about taking part in the pilot RCT. We are also interested in how you decided which children to approach for assent and any recommendations you have to inform the design of a future trial.

What are the possible benefits and risks of taking part?

This qualitative element of the study is very low risk. Should you want to discuss any aspect of the study, please contact Kerry Woolfall or Beth Deja (details below).

Findings of this study will be used to inform the design of a future larger trial. We cannot promise that you or the families you work with will benefit directly from this study, but many people find that taking part in studies of this sort is useful because they have a chance to air their views and to reflect on things.

Who is involved in this study?

This paediatric intensive care unit (PICU) is one of four NHS PICUs that are taking part in this study across the country. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is funding the study. Professor Mark Peters (University College London) is the FEVER Study Chief Investigator. The study is sponsored and managed by ICNARC. Parents of children who have experienced fever with septic shock have been involved in the development of this study, including this information sheet and how you were asked to take part.

What if there is a problem?

Any complaint about the conduct of this study, the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, then you should speak to the researchers who will do their best to answer your questions (see contact details below). If you remain unhappy and wish to complain formally, then you can do this through the NHS Complaints Procedure. Details can be obtained from your employer.

How to contact us

If you have any questions, please contact:

Dr Kerry Woolfall: K.Woolfall@liverpool.ac.uk Tel: 0151 794 4634
Dr Beth Deja: bdeja1@liverpool.ac.uk Tel: 0151 794

Thank you for your time.
We are very grateful that you are considering taking part in this study.