External pilot study of the Fluids in Shock (FiSh) trial

STUDY SHORT TITLE
FiSh External Pilot Study

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Chief investigator
Dr David Inwald

Sponsor representative
Ruth Nicholson

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 the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial 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:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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Contents

Abbreviations

AE	adverse event
CI	Chief Investigator
CRF	Case Report Form
CTU	clinical trials unit
DMEC	Data Monitoring and Ethics Committee
ED	emergency department
FiSh	Fluids in Shock
GCP	Good Clinical Practice
HSCIC	Health & Social Care Information Centre
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
MRC	Medical Research Council
NIHR	National Institute for Health Research
NHS	National Health Service
PAU	paediatric assessment unit
PPI	Patient and Public Involvement
PI	Principal Investigator
PICANet	Paediatric Intensive Care Audit Network
PICU	paediatric intensive care unit
PIM2	Paediatric Index of Mortality 2 score
PIS	Participant Information Sheet
R&D	Research & Development
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SMG	Study Management Group
SOP	Standard Operating Procedure
SSC	Study Steering Committee

Keywords

Child
Bolus fluid
Resuscitation
Critical care
Emergency medicine
Sepsis
Septic shock

General information

This document describes the Fluids in Shock (FiSh) External Pilot Study and provides information about procedures for the study. Participant recruitment will be undertaken in compliance with this document.

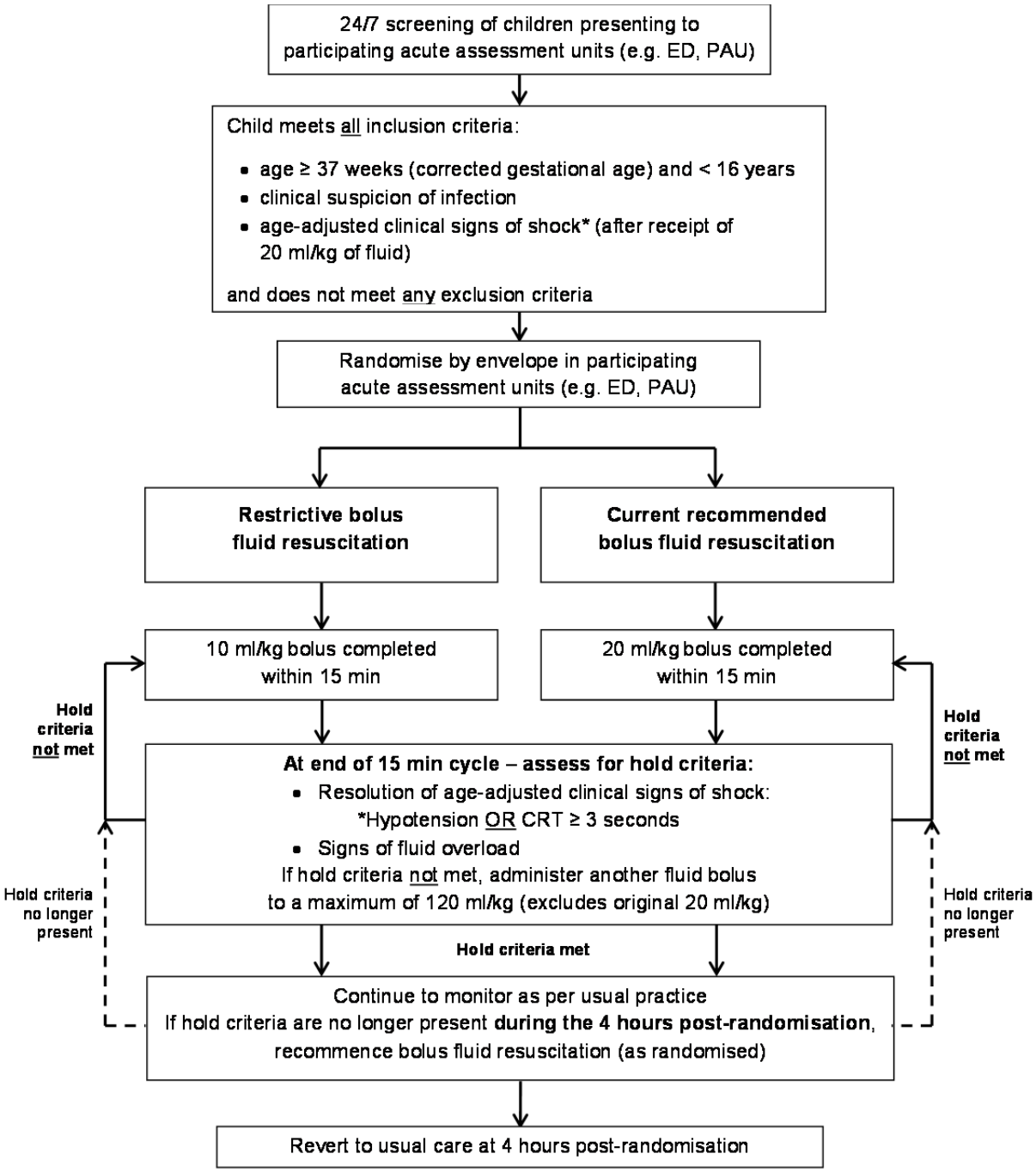
This protocol is part of the ‘Combined feasibility and external pilot study to inform the design and conduct of the Fluids in Shock (FiSh) trial’.

Study summary

Title	External pilot study of the Fluids in Shock (FiSh) trial
Short title	FiSh External Pilot Study
REC number	16/LO/0854
ISRCTN number	<*TO BE INSERTED*>
Sponsor name and reference	Imperial College London (16SM3292)
Funder name and reference	NIHR Health Technology Assessment Programme (13/04/105)
Design	Mixed methods: • Pilot randomised controlled trial (RCT) • Questionnaires, interviews and focus groups
Aim	To explore and test important key parameters needed to inform the design and ensure the successful conduct of the FiSh trial
Objectives	• To test the willingness of clinicians to screen, recruit and randomise eligible patients • To estimate the recruitment rate • To test, following randomisation, delivery of, and adherence to, the intervention and demonstrate separation between the groups • To test acceptability of the deferred consenting procedures and participant information • To test follow-up for the identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event reporting • To inform final selection of a patient-centred primary outcome measure • To estimate the characteristics of the selected patient-centred primary outcome measure to inform sample size estimation • To inform content and time needed for final data collection
Pilot randomised controlled trial	
Planned number of sites	Fourteen NHS hospitals, four with paediatric intensive care units
Planned sample size	108 children
Inclusion criteria	• Age ≥37 weeks (corrected gestational age) and <16 years • Clinical suspicion of infection • Clinical signs of shock after receipt of 20 ml/kg of fluid • Recruitment and randomisation to take place in an acute assessment area (e.g. ED, PAU)
Exclusion criteria	• Prior receipt of more than 20 ml/kg of fluid • Conditions in which bolus fluid resuscitation should be curtailed (e.g. raised intracranial pressure, diabetic ketoacidosis, known/suspected myocarditis/cardiomyopathy) • Full active resuscitation not within current goals of care
Intervention	Restrictive bolus fluid resuscitation of 10 ml/kg
Control	Bolus fluid resuscitation of 20 ml/kg
Duration of treatment	Every 15 mins for up to 4 hours

Duration of participant follow-up	30 days
Duration of recruitment	9 months
Definition of end of study	Last participant, last follow-up
Questionnaires, interviews and focus groups	
Planned sample size	100-150 questionnaires and 15-25 telephone interviews with parents/legal representatives 3 focus groups and 10 telephone interviews with site research staff
Inclusion criteria	*Parents/Legal representatives* • Approached for consent for the pilot RCT *Site research staff* • Involved in screening, recruiting, randomising and consenting parents/legal representatives during the pilot RCT
Exclusion criteria	*Parents/Legal representatives* • Non-English speaking *Site research staff* • None
Duration of procedures	Questionnaires: 10-15 minutes per participant Interviews: 30-60 minutes per participant Focus groups: 60 minutes per meeting
Duration of recruitment	Parents/Legal representatives: 6 months Site research staff: 2 months

Study flow chart



Age-adjusted clinical signs of shock:

a) Hypotension

Age	Systolic blood pressure
0 days – <1 week	<60
1 week – <1 year	<70
1-<2 years	<75
2-<5 years	<80
5-<12 years	<85
≥12 years	<90

b) Capillary refill time ≥ 3 seconds

1 Background and rationale

Infectious diseases remain a major cause of mortality and morbidity, accounting for more than 25% of deaths in children under the age of five years in Europe.[1] In the UK, approximately 1000 children present to paediatric intensive care units (PICUs) with severe sepsis each year, of which 8% die (Paediatric Intensive Care Audit Network (PICANet) data 2012/13). Mortality increases to 17% when children presenting to emergency departments (EDs) with severe sepsis are included.[2] In addition, serious morbidity in PICU survivors is high.[3]

Rapid, bolus fluid resuscitation is integral to UK management of children presenting to EDs with septic shock. In 2009, based on weak evidence, the ACCM-PALS guideline recommended bolus fluid resuscitation with bolus size of 20 ml/kg, up to a total of 200 ml/kg over the first hour, for the management of children and neonates with septic shock.[4]

In Africa, a recent, rigorous, multicentre randomised controlled trial (RCT), the FEAST study, compared bolus fluid resuscitation of 20 ml/kg with maintenance fluid in over 3000 children with severe infection.[5] The study reported a 30% increase in mortality associated with bolus fluid resuscitation. Though conducted in a low-income setting, FEAST has raised considerable uncertainty and highlighted the lack of evidence for bolus fluid resuscitation for children in middle- and high-income settings.

A recent systematic review of bolus fluid resuscitation in children with septic shock reported that fluid boluses were associated with increased mortality compared with maintenance fluid.[6] However, the only RCT comparing bolus with maintenance fluid identified in this review was the FEAST study. The systematic review additionally identified one RCT comparing different fluid volumes.[7] This trial compared an aggressive fluid resuscitation strategy (20-40 ml/kg over 15 minutes) with usual fluid resuscitation (20 ml/kg over 20 minutes up to a maximum of 60 ml/kg over 60 minutes) in 147 children, aged 1 month to 12 years, presenting with septic shock to a single ED in India. The total volume of fluid administered was higher in the aggressive fluid resuscitation group but there was no difference in mortality or in the other clinical outcomes measured, except for an increase in hepatomegaly at 20 minutes in the aggressive fluid resuscitation group.

Current situation

No trials to date have compared a restrictive bolus fluid resuscitation strategy with recommended bolus fluid resuscitation in children with septic shock. One single-centre pilot RCT is currently ongoing in Canada (Pilot Study for the SQUEEZE Trial, NCT01973907). This trial aims to achieve a 'fluid sparing' resuscitation strategy through earlier initiation of vasoactive medication (following initial bolus fluid resuscitation of at least 40 ml/kg within two hours prior to randomisation).

When considering a repeat of FEAST in the UK, the existence and adoption of clinical guidelines (such as the ACCM-PALS) and training courses (such as Advanced Paediatric Life Support) make it very unlikely that clinicians in UK EDs would accept a randomisation allocation to maintenance fluid. However, with accumulating adult and paediatric data suggesting that excessive fluid administration is associated with worse patient outcomes, and even increased risk of death[8], the optimal amount of fluid for children presenting with septic shock remains an important unanswered question.

The FiSh trial proposes to evaluate, in a pragmatic RCT, whether a restrictive strategy (bolus fluid resuscitation of 10 ml/kg), compared with current recommended strategy (bolus fluid resuscitation of 20 ml/kg), is associated with improved outcomes for children presenting to UK EDs with presumed septic shock.

Feasibility

Given the considerable uncertainty raised by FEAST and the lack of evidence for bolus fluid resuscitation for children in middle- and high-income settings, it is imperative to establish whether a large, multicentre RCT of a restrictive bolus fluid resuscitation strategy is feasible in the UK. The research question of this study is, would a full RCT using the FiSh trial protocol be feasible and practical? Clinical trials, such as the proposed FiSh 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.

This protocol outlines work that will be undertaken to establish the practicality of running the FiSh trial, including a pilot RCT and questionnaires, interviews and focus groups with parents/legal representatives and site research staff involved in the pilot RCT. The FiSh Feasibility Study, which looks at the feasibility of conducting the FiSh trial, will be examined prior to the FiSh External Pilot Study through qualitative interviews (see separate protocol).

2 Aims and objectives

Aim

To explore and test important key parameters needed to inform the design and ensure the successful conduct of the FiSh trial.

Objectives

1) To test the willingness of clinicians to screen, recruit and randomise eligible patients
2) To estimate the recruitment rate
3) To test, following randomisation, delivery of, and adherence to, the intervention and demonstrate separation between the groups
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
7) To estimate the characteristics (e.g. standard deviation) of the selected patient-centred primary outcome measure to inform sample size estimation
8) To inform content and time needed for final data collection

3 Pilot randomised controlled trial

3.1 Study design

Pilot randomised controlled trial.

3.2 Setting

Four regional hospitals representing three geographical regions will operate as three 'hubs' (two hospitals will be in the same hub). Three of these hospitals have an integral ED which will recruit patients within the hubs. Each hub will be networked with three feeder hospital EDs in district hospitals ('spokes'), which do not have an integral PICU. Participants recruited in these feeder EDs will be transferred via the regional PICU retrieval services into the hub PICUs. Thus, the feeder EDs, hub EDs, retrieval services and PICUs will operate in three separate hub/spoke models.

Regions

Bristol
Hub: Bristol Royal Hospital for Children

London (North Thames)
Joint-hubs: St Mary's Hospital and Great Ormond Street Hospital for Children

Southampton
Hub: Southampton General Hospital

Study sites

In this protocol, 'site' refers to any hospital where the FiSh External Pilot Study is conducted. Sites must be able to comply with:

- all responsibilities as stated in the FiSh Study Site Agreement;
- the study treatments, follow-up schedules and all requirements of the study protocol;
- the Research Governance Framework;
- 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);
- identify a responsible FiSh Research Nurse (to be funded, or part-funded, centrally);
- agree to incorporate FiSh into routine ED activity particularly highlighting the importance of screening at ED presentation;
- agree to adhere to randomisation allocation and to ensure adherence to the protocol; and

- agree, where possible, to recruit all eligible patients to FiSh and to maintain a screening log.

Site initiation and activation

Site initiations will be performed through two different methods: a central collaborators' meeting; and site initiation meetings held at hub or at individual site.

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

- all relevant institutional approvals (e.g. local Research and Development (R&D));
- a fully signed FiSh Study Site Agreement; and
- 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, 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 study staff are trained appropriately, including GCP trained;
- appropriate recruitment and care for patients in the study;
- timely data entry; and
- prompt notification of all AEs (as specified in Section 5).

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

3.3 Selection of participants

Inclusion criteria

- Age greater than or equal to 37 weeks (corrected gestational age) and less than 16 years
- Clinical suspicion of infection
- Clinical signs of shock after receipt of 20 ml/kg of bolus fluid (see Section 3.5 for age-adjusted shock criteria)
- Recruitment and randomisation to take place while child is in an acute assessment area (e.g. ED, paediatric assessment unit (PAU))

Exclusion criteria

- Prior receipt of more than 20 ml/kg of bolus fluid
- Conditions in which bolus fluid resuscitation should be curtailed (e.g. raised intracranial pressure, diabetic ketoacidosis, known/suspected myocarditis/cardiomyopathy)
- Full active resuscitation not within current goals of care

Screening

Potentially eligible infants and children will be screened against the inclusion/exclusion criteria by the clinical team looking after the patient in the ED, supported by the site research team. 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 on the FiSh screening log.

3.4 Enrolment

Consent

Patients requiring bolus fluid resuscitation as treatment for septic shock will most often need this treatment started in a life-threatening emergency, where any delay in commencing treatment will be detrimental. This will make any attempt to obtain fully informed consent from parents/legal representatives during an emergency inappropriate, and cause additional stress to families who are already distressed by their child's illness. Therefore, once a patient is identified as being eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment will be applied as soon as possible. This method is known as 'deferred' or 'retrospective' consent and which is recognised in European Law.[9]

NB. The FiSh study 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 study 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.

Once notified of the recruitment of a patient to the study, a delegated member of the site research team will approach the parents/legal representatives as soon as practically and appropriately possible after randomisation to discuss the study (usually within 24-48 hours of randomisation[10]). 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 *Death prior to consent being sought* and *Discharge prior to consent being sought*).

A Participant Information Sheet (PIS) for parents/legal representatives will be provided. The PIS will identify the title of the study and the Chief Investigator (CI), and include information about: the purpose of the study; the consequences of participating or not; participant confidentiality; use of personal data; data security; and the future availability of the results of the study. It will also provide information on completing an optional questionnaire and/or telephone interview (see Section 4).

A Consent Form 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 FiSh.

After the person seeking consent has checked that the PIS and Consent Form are understood, the doctor or nurse will invite the parent/legal representative to sign the Consent Form and will then add

their own name and countersign it. If parents/legal representatives are interested in taking part in a telephone interview (see Section 4), then their contact details will be recorded on the Consent Form. 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. The child's GP will be sent a letter to inform them of the child's participation in the study, provided consent has been given for this.

Due to the severity of illness and its impact on mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain capacity). Study participants will then be provided with an age-appropriate PIS 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. 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 same process will be followed if a participant turns 16 years old during the study period.

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. Deferred 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) and Consent Form would be used.

If deferred 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, personalised by the most appropriate clinical team member, and a copy of the B-PIS and Consent Form (postal version for bereaved parents/legal representatives) 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 study, direct them to the B-PIS 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 B-PIS and Consent Form (postal version for bereaved parents/legal representatives) 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 receipt of the letter, then the participant's data will be included in the study unless the family notify the site research team otherwise.

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. Following on from the call, as well as if there is no response to the call, the parents/legal representatives will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS and Consent Form (postal version) 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 and Consent Form (postal version) 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 receipt of the letter, then the participant's data will be included in the study unless the family notify the site research team otherwise.

Randomisation

Randomisation will be performed as soon as possible after identifying the patient as being eligible for the study. Eligible patients will be randomised on a 1:1 basis to bolus fluid resuscitation with either 20 ml/kg or 10 ml/kg boluses using sealed opaque envelopes available at each site. In addition, 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: 020 7269 9290

As the success of this study depends on the ability of front line clinicians to perform all study procedures in a resuscitation setting, the randomisation process will be as simple as possible and allocation will be by randomised permuted blocks (with variable block lengths), stratified by recruiting site only. Patient randomisation must be performed prior to commencement of any study intervention.

Following screening and randomisation, the FiSh Case Report Form (CRF), which will be contained in the randomisation pack, will be made available to the clinical team. A FiSh Trial Number and treatment allocation will be assigned, and time of randomisation will be recorded on the FiSh CRF.

Co-enrolment

The SMG will consider co-enrolment of FiSh participants onto other interventional studies where the management does not conflict with the FiSh 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 FiSh enrolment log.

Non-consent/Withdrawal

In consenting to the study, parents/legal representatives are consenting to the data already collected (on the study treatment and assessments) to be used and to follow-up. However, parents/legal representatives can refuse to give consent (non-consent) or withdraw from FiSh at any time during the study. If a parent/legal representative explicitly state 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. All data collected up to the point of withdrawal will be retained and included in the study analysis. 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).

3.5 Procedures

Children will be randomly allocated to bolus fluid resuscitation using boluses of two different sizes over a four-hour resuscitation period. The period will be divided up into 16 fifteen-minute cycles and one bolus of either 10 ml/kg (intervention) or 20 ml/kg (control) will be delivered within one cycle – at a rate left to the discretion of the treating clinician. Other interventions will proceed at the discretion of the treating clinician.

At the end of each cycle, should the age-adjusted clinical signs of shock (either low blood pressure or prolonged capillary refill time – see Table 1) persist, then another bolus of the same size (i.e. according to randomly allocated group) will be repeated – again, at a rate left to the discretion of the treating clinician but within the next fifteen-minute cycle.

The cycles repeat until either the end of the four-hour resuscitation period or any of the hold criteria occur (see *Hold criteria*). After the four-hour resuscitation period, any further treatment will be at the discretion of the treating clinician.

The maximum amount of fluid that can be given within the study protocol, regardless of allocation, will be 120 ml/kg (excludes the original 20 ml/kg bolus). If more than 120 ml/kg of fluid is required, then further treatment will be at the discretion of the treating clinician.

Table 1 Age-adjusted shock criteria

a) Hypotension

Age	Systolic blood pressure
0 days – <1 week	<60
1 week – <1 year	<70
1-<2 years	<75
2-<5 years	<80
5-<12 years	<85
≥12 years	<90

b) Capillary refill time ≥ 3 seconds (assessed using standard methods)

Intervention

Restrictive bolus fluid resuscitation of 10 ml/kg with selection of fluid type at the discretion of the treating clinician. To be given within 15 minutes, rate at discretion of treating clinician.

Control

Current recommended bolus fluid resuscitation of 20 ml/kg (as per the current ACCM-PALS guidelines[4]) with selection of fluid type at the discretion of the treating clinician. To be given within 15 minutes, rate at discretion of treating clinician.

Hold criteria

In participants whose age-adjusted clinical signs of shock resolve or who show signs of fluid overload (e.g. pulmonary oedema – either rales (crackles) on auscultation or pulmonary oedema fluid in the endotracheal tube; or new or increasing hepatomegaly), delivery of further fluid boluses will be withheld. If, within the four-hour resuscitation period, fluid boluses are indicated again, i.e. age-adjusted clinical signs of shock present in absence of signs of fluid overload, then the cycles will be recommenced with the allocated boluses until the end of the four-hour intervention period.

3.6 Outcomes

The combined objectives of the FiSh External Pilot Study are to test whether all of the processes can work together, and to inform the design and ensure the successful conduct of the FiSh trial (should this be the recommendation).

Objectives 1, 2, 4 will be measured by:

- proportion of eligible patients recruited
- number of patients recruited per site per month
- proportion of parents/legal representatives refusing deferred consent

Objective 3 will be measured by:

- proportion of fluid boluses delivered at correct volume and time during the intervention period
- to compare total volume of fluid received during the intervention period

Objectives 5 to 8 will be measured by:

- proportion of complete data for each outcome measure
- characteristics of potential outcome measures (e.g. standard deviation)
- observed AEs
- time taken for data collection and entry
- proportion of required data able to be linked to routine sources

3.7 Data collection

Data collection will be restricted to those data sufficient to address the objectives of the FiSh External Pilot Study. Detailed guidance for the collection of data will be provided in the study specific Standard Operating Procedure (SOP). All data items will be objectively defined according to relevant national and international guidelines. Routine linkage will be used as applicable, e.g. with PICANet and the Health & Social Care Information Centre (HSCIC).

Data collected will include:

Baseline

- Confirmation of eligibility criteria
    - Age
    - Shock criteria (including fluid bolus therapy)
    - Confirmation of suspected infection
    - Acute assessment area admission date/time
- Randomisation details
- Patient details (including parental contact details)
- Physiology (including Paediatric Index of Mortality 2 score (PIM2))
- Comorbidities

Hours 0-4 (every 15 minutes)

- Fluid bolus therapy (type and volume)
- Physiology (including shock criteria)

End of Hour 4

- Other relevant medical interventions (including mechanical ventilation and vasoactive agents)

Discharge (or death)

- Total fluids given (at hour 24)
- Receipt of antibiotics
- Location
- Infection diagnosis
- Survival status
- Length of stay in PICU and hospital
- Organ support

30 days

- Survival status
- Safety monitoring

Table 2 Data collection timeframe

	Baseline	Hours 0-4	End of Hour 4	Discharge (or death)	Day 30
Eligibility criteria	X				
Informed consent	X*				
Allocation	X				
Patient details	X				
Physiology	X	X	X	X	
Fluid bolus	X	X		X	
Interventions			X		
Hospital stay				X	
Outcomes				X	X
Safety monitoring					X

*as soon as feasible

3.8 Data management

All participant data collected will be entered onto paper CRFs prior to entry onto a secure electronic 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.

Data entered onto the secure study 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.

During the conduct of the study, all electronic participant data will be encrypted and all study documents stored securely at the site, the ICNARC CTU or the University of Liverpool, as appropriate.

3.9 Monitoring

The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the study. In addition, the Research Ethics Committee (REC) and the Sponsor may request access to source data/documents for audit and review. Study participants and their parents/legal representatives will be informed of this during the informed consent process.

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 there is evidence or suspicion of continued non-adherence with the FiSh protocol.

4 Interviews and focus groups involving parents/legal representatives and site research staff

4.1 Design

The FiSh External Pilot Study will include a mixed method element. This will involve questionnaires and interviews with parents/legal representatives during the first six months of the pilot RCT, and focus groups and interviews with the site research staff towards the end of the recruitment period.

Questionnaires (n=100-150) and telephone interviews (n=15-25) will be used to explore, with parents/legal representatives who do and do not consent to the pilot RCT, the acceptability of FiSh, 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 FiSh trial.

Three focus groups with site research staff will also be carried out to explore their experiences of screening, recruiting, randomising and consenting parents/legal representatives/participants to the pilot RCT. Up to 10 telephone interviews will be conducted to capture the views of site research staff who are unable to attend one of the three focus groups. The aim of the focus groups, with the telephone interviews, will be to add to data collected from parent/legal representative questionnaires and interviews to identify recruitment and consent issues and potential solutions to inform the proposed FiSh trial.

4.2 Selection of participants

Parent/Legal representative

Inclusion criteria

- Parents/Legal representatives who do and do not consent to the pilot RCT

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 pilot RCT

Exclusion criteria

- None

4.3 Enrolment

As part of the PIS (see Section 3.4), parents/legal representatives will be provided with information about the option to complete a questionnaire and/or a telephone interview discussing their views on the consenting procedures for the pilot RCT. After consent discussions for the pilot RCT (see Section 3.4), the site research staff will ask the parents/legal representatives if they would like to complete the FiSh 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 12 sites will be sent an email invitation to participate in a focus group by the University of Liverpool FiSh team. They will be given a copy of the PIS for staff, which includes information about: the purpose of the study; how the study is being funded; and the consequences of participating or not. Each site research team will identify two to three individuals from their team to participate in focus groups. Written consent will be sought from participants before the focus group, or the telephone interview, begins. This will include consent for digitally audio recording of the group discussion or interview. The University of Liverpool FiSh study team will email or post a copy of the consent form with a request to complete and return the form prior to the arranged focus group, or telephone interview, date.

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.

4.4 Procedures

Questionnaires

Following the consent discussion one of the hospital's local FiSh team (a member of the healthcare team) will give a copy of the FiSh Consent Questionnaire to each parent/legal representative to complete. The questionnaire will be placed in a stamped self-addressed envelope and returned by post to the University of Liverpool FiSh team.

Telephone interviews

The University of Liverpool FiSh 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 FiSh interview topic guide. 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[11, 12] and the FiSh Feasibility Study (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 thank you letter and a £20 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[13], this is anticipated to involve approximately 15-25 parents/legal representatives.

All families 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.

Focus groups and interviews

Focus groups will take place in a meeting room at the three selected sites towards the end of the pilot RCT recruitment period (months 7-8). Individual telephone interviews will be arranged for up to 10 site research staff who register interest in taking part, but are unable to attend a focus group. This should ensure that all FiSh site research staff have an opportunity to take part.

All interviews and focus groups will be conducted by the University of Liverpool FiSh team using the site research staff focus group/interview topic guide. The site research staff focus group/interview topic guide will be informed by the FiSh Feasibility Study (described in a separate protocol) and early findings from parent/legal representative questionnaires and telephone interviews. Consent for audio recording of interviews will be checked verbally before the focus group or interview begins.

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

5 Safety monitoring

5.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

Adverse Event

Any untoward medical occurrence or effect in a patient participating in a study, which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavourable symptom or disease temporally associated with the use of the study treatment, whether or not it is related to the allocated study treatment.

Serious Adverse Event

An AE is defined as serious if it:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- is 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.

5.2 Severity

The assessment of severity will be graded based on the PI's (or other delegated investigators') clinical judgement using the following definitions:

- **None**: indicates no event or complication
- **Mild**: complication results in only temporary harm and does not require clinical treatment
- **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 patient
- **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay and/or permanent functional limitation
- **Life threatening**: complication may lead to death
- **Fatal**: indicates that the patient died as a direct result of the complication/AE

5.3 Relatedness

The PI or other delegated investigator(s) should use clinical judgement to determine the relationship between the study treatment and the occurrence of each AE using the following definitions:

- **None**: there is no evidence of any relationship to the study treatment
- **Unlikely**: there is little evidence to suggest a relationship to the study treatment, and there is another reasonable explanation of the event

- **Possibly**: there is some evidence to suggest a relationship to the study treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the study treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the study treatment, and other possible contributing factors can be ruled out

5.4 Expectedness

The PI or other delegated investigator(s) must assess the expectedness for each SAE regardless of its relationship to the study procedures.

- **Expected**: the event is listed as an expected AE in Appendix 2
- **Unexpected**: the event is not listed as an expected AE in Appendix 2

5.5 Recording and reporting procedures

All children eligible for FiSh 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 child's medical condition and standard treatment received in the PICU, but may not be related to participation in the study. Consequently, any AEs occurring as a result of the 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 child's medical notes.

All other AEs that occur between randomisation and 30 days post-randomisation must be recorded in the participant's medical notes and on the FiSh CRF. Information regarding date and time of event onset, severity and relatedness of the AE to study treatment must be recorded.

Those meeting the definition of a SAE (see Section 5.1) must, in addition, be reported to the ICNARC CTU, using the FiSh 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 1.

5.6 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.

5.7 Central processing of serious adverse event reports

On receipt of the SAE report, a clinical member of the FiSh SMG will evaluate the event for relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the REC.

If the event is evaluated by either the CI or a clinical member of the FiSh SMG as an unexpected and related SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the CI, SMG, Study Steering Committee (SSC) and Data Monitoring and Ethics Committee (DMEC) for review on a regular basis (as deemed necessary).

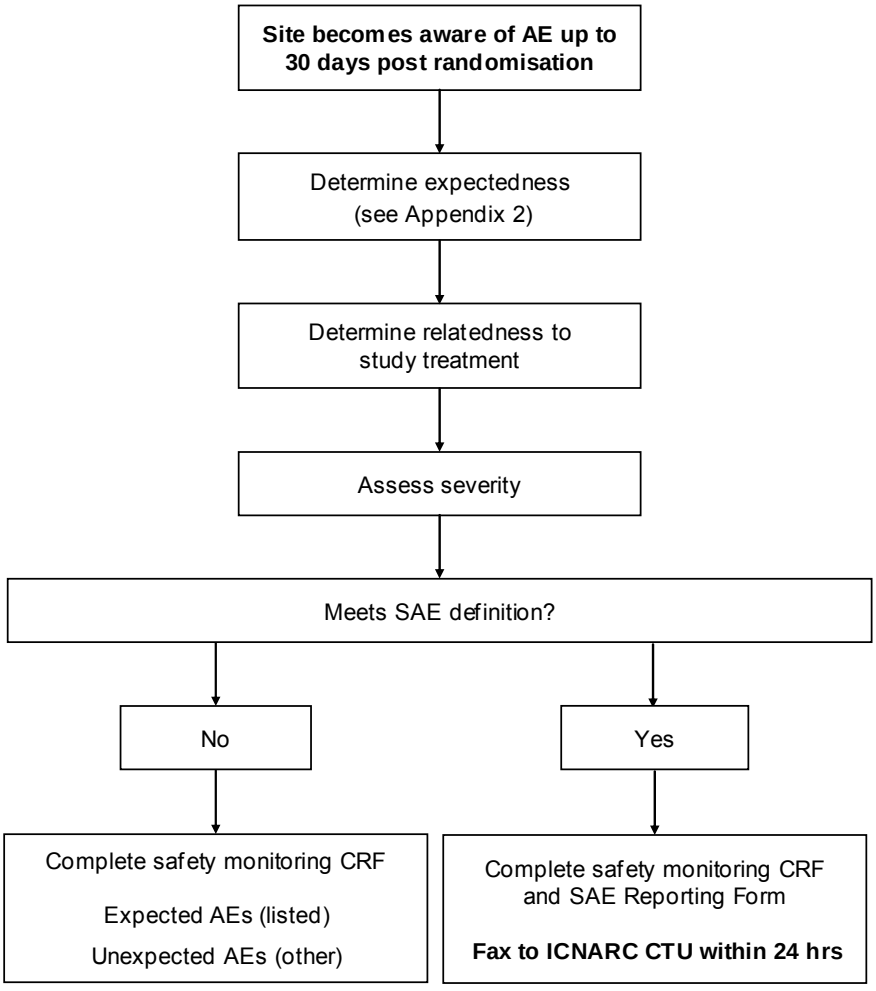
5.8 Additional safety monitoring

The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the study treatment. In the event that any study 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 study, the ICNARC CTU will inform the REC as appropriate.

5.9 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 study.

Figure 1 Adverse event recording and reporting



6 Study closure

6.1 End of study

The end of the study 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.

6.2 Archiving study documents

At the end of the study, the ICNARC CTU and University of Liverpool 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.

6.3 Early discontinuation of the study

The study may be stopped early upon recommendation of the SSC. In which case, the ICNARC CTU will inform all relevant staff working on FiSh and advise on the actions to be taken regarding the treatment of participants. All randomised participants will continue to be followed up as per the FiSh protocol.

7 Statistics and data analysis

7.1 Sample size calculation

The pilot RCT 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.

Based on available data from PICANet and the PICS-SG severe sepsis audit[2], it is anticipated that the participating sites will recruit approximately one child per month, providing a total of approximately 108 children.

Recent research[14] has demonstrated that a standard sample size for a pilot study (approximately 30 patients[15]) will result in an imprecise estimate of the standard deviation of a potential outcome measure which will frequently lead to definitive studies that are either underpowered (if the imprecision of the estimated SD is not taken into account in the sample size calculation) or inefficient (if it is). Sim and Lewis recommend a sample size of around 60 patients would usually be sufficient to estimate the SD for a continuous outcome measure; however, they note that estimating

the precision of a binary outcome will require a larger sample size, typically requiring between 98 and 260 patients.[14] For example, one potential outcome measure for the FiSh trial is 30-day all-cause mortality, which is anticipated to be in the region of between 8% (estimate from PICANet data) and 17% (estimate from PICS sepsis audit in ED). The proposed sample size of 108 patients for the FiSh pilot would enable the mortality to be calculated with a precision of approximately +/- 5%.

7.2 Statistical analysis plan

Pilot randomised controlled trial

Descriptive analysis will be conducted to assess the objectives of the FiSh External Pilot Study.

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

Analysis of data from the interviews, questionnaires and focus groups will be assisted using NVivo 8 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, as previously described.[16, 17]

8 Study management and oversight

8.1 Good research practice

FiSh 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.

8.2 Study Management Group

All day-to-day management of FiSh will be the responsibility of the SMG. Members of the SMG will include the FiSh Study Manager, the CI and the co-investigators. The SMG will meet regularly to discuss management and progress of the study and findings from other related research.

8.3 Study Steering Committee

The progress of the study will be monitored and supervised by the SSC. 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 and the CI.

8.4 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 SSC. The DMEC will operate under the DAMOCLES Charter, and will report to the SSC, making recommendations on the continuation, or not, of the study. Adherence to the intervention and safety will be monitored by the DMEC throughout the study period.

8.5 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. The ICNARC CTU will ensure that all SAEs are reported, as appropriate, to the REC.

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

9 Ethical compliance

FiSh will be conducted in accordance with the approved study 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.

9.1 Study registration

This study has been registered with the ISRCTN Registry (<*TO BE ADDED*>).

9.2 Central ethical compliance

The study has received a favourable opinion from the London - Stanmore REC (Reference: 16/LO/0854) and approval from the Health Research Authority. The ICNARC CTU will submit annual progress reports and all amendments to the FiSh protocol to the REC for review. The ICNARC CTU will provide relevant approved study documents and other related materials to participating sites.

9.3 Local ethical compliance

It is the responsibility of the site PI to obtain the necessary local approvals for FiSh, including approval from the Trust R&D Department. The site PI should submit the current approved versions of the study 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 study protocol or other study documents. Evidence of NHS Trust R&D approval must be provided to the ICNARC CTU prior to recruitment of participants.

9.4 Patient and Public Involvement

There are two Patient and Public Involvement (PPI) representatives as co-investigators on this study and who have been involved in its development. As members of the SMG, they are fully involved in the work planned as part of this study. In addition, independent PPI representatives will be sought for membership of the SSC.

Two clear strands of work have been identified as part of the combined FiSh feasibility and external pilot study to ensure full PPI involvement. One strand concerns the design of the external pilot study by involving parents/legal representatives in discussions covering:

- acceptability of the proposed study;
- identification of potential barriers for participation in the study and how these could be addressed;
- length and content of the parent/guardian information sheet;
- study design;
- parental/guardian decision-making in the emergency setting; and
- acceptability of and approach adopted to deferred consent.

The other strand concerns the selection of important patient-centred outcome measures (primary and secondary).

9.5 Data protection and participant confidentiality

Identifiable patient data, including full name, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored securely.

Names, telephone numbers and email addresses will be collected from parents/legal representatives whom wish to take part in a telephone interview. Consent will be obtained for these contact details to be held by the FiSh study team (ICNARC CTU and University of Liverpool) to be used to arrange the interview. We will also seek consent to share their child's de-identified data or to be contacted by the study team for future research. All files bearing participant identifiers (e.g. contact details) will be destroyed at the end of the study (unless consent given to be contacted for future research) and only the consent forms will be retained.

Audio recordings of interviews and focus groups are necessary to ensure full and accurate accounts. Audio recordings of interviews and focus groups will be uploaded securely to a professional transcription company (Voicescript) website in accordance with the Data Protection Act (1998). Original audio files will be deleted once the transcripts are anonymised and checked for accuracy.

All data will be securely stored in a locket cabinet or in an encrypted electronic file. Transcripts will be labelled with a unique identity number, encrypted and held on password protected University of Liverpool desktop computers. 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 CI will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act (1998).

9.6 Declaration of interests

All study investigators have confirmed that they do not have any financial or other conflicts of interest to declare in relation to this study.

9.7 Access to the final study dataset

Once the data from the combined feasibility and external pilot study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

10 Sponsorship and funding

10.1 Sponsor

Imperial College Healthcare NHS Trust will act as Sponsor for this study.

10.2 Indemnity

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

10.3 Funding

The study is supported by grant funding from the NIHR Health Technology Assessment (HTA) Programme.

A written agreement with the site PI and/or the PI's institution and Imperial College Healthcare NHS Trust will outline the funding arrangements to sites. The SSC will meet and review the financial aspects of the study at least annually and report to the Sponsor.

11 Dissemination

The final report, including a detailed description of the study, results and recommending the continuation, or not, to the FiSh trial, will be submitted to the NIHR HTA Programme for publication in Health Technology Assessment. 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.

Following initial presentation of the results to the collaborating sites, the results will be presented at national and international conferences/meetings. The results will also be disseminated to families (children and their parents/legal representatives).

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13 Appendices

Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	1.1		Ruth Canter	• Updated inclusion criteria • Minor administrative clarifications

Appendix 2 – Expected adverse events

Expected AEs that could be observed in participants up to 30 days following randomisation:

- Pulmonary oedema
- Cerebral oedema
- Extravasation injury
- Amputation
- Skin graft

[This list is not exhaustive. If an AE, as defined in Section 5.1, occurs this should be recorded and reported as described in Section 5.0]