# Restricted fluid bolus versus current practice in children with septic shock: the FiSh feasibility study and pilot RCT

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## Scientific summary

### The Fluids in Shock (FiSh) trial

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# Scientific summary

## Background

Fluid bolus therapy is integral to the management of children presenting to NHS hospitals with septic shock. Current guidelines recommend boluses of 20 ml/kg. However, this recommendation is based on weak evidence from small observational studies. In Africa, a recent large multicentre randomised controlled trial (RCT), Fluid Expansion as Supportive Therapy (FEAST) (Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, *et al.* Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;**364**:2483–95), compared fluid bolus resuscitation of 20 ml/kg with maintenance fluid in > 3000 children with severe infection. The FEAST trial showed a 35% increase in mortality associated with fluid bolus. Although conducted in a low-income setting with limited resources, the FEAST trial raised uncertainty and highlighted the lack of evidence in higher-income settings. No trials to date have investigated fluid bolus volumes given to children in a high-income setting.

To address this problem, we developed the Fluids in Shock (FiSh) trial. This was a RCT that aimed to evaluate whether or not a restrictive strategy (fluid bolus volume of 10 ml/kg), compared with the current recommended strategy (fluid bolus volume of 20 ml/kg), is associated with improved outcomes for children presenting to UK emergency departments (EDs) with presumed septic shock. We conducted a combined feasibility and external pilot RCT to determine if a large-scale trial would be feasible.

### *Objectives*

#### Feasibility study

1. To provide evidence of the willingness of clinicians to participate and the sign-up of sites.
2. To review and explore, with input from parents/legal representatives, acceptability, potential barriers, information/documentation, decision-making and research without prior consent (RWPC).
3. To review and explore, with input from parents/legal representatives, the potential, patient-centred primary and important secondary outcome measures.

#### External pilot trial

1. To test the willingness of clinicians to screen, recruit and randomise eligible patients.
2. To estimate recruitment rate.
3. To test, following randomisation, the delivery of and adherence to the intervention and demonstrate separation between the groups.
4. To test the acceptability of the deferred consenting procedures and documentation.
5. To test follow-up for identified, potential, patient-centred primary and other important secondary outcome measures and for adverse event (AE) reporting.
6. To inform the final selection of a patient-centred primary outcome measure.
7. To estimate the characteristics of the selected patient-centred primary outcome measure to inform sample size estimation.
8. To inform the content and time needed for final data collection.

## Feasibility study

### *Methods*

#### Study design
This was a qualitative semistructured interview study, seeking the views of parents/legal representatives with experience, in the previous 3 years, of a child with severe infection requiring hospital admission.

#### Design and development of the protocol
The protocol, sample size, recruitment strategy, draft trial documentation and interview topic guide were informed by our previous research.

#### Recruitment
It was anticipated that 15–25 parents/legal representatives would be recruited. Parents or legal representatives with a child presenting to an ED or admitted to a paediatric intensive care unit (PICU) with severe infection within the previous 3 years were eligible to take part, unless they were unable to speak and read English. Several recruitment strategies were employed: postal contact and posters advertising the study in PICUs in four participating hospitals, and social media.

#### Interviews
Informed consent was taken. Interviews aimed for data saturation, that is, the point at which no new major themes are discovered in analysis. No further interviews were conducted once data saturation was reached.

#### Data analysis
Analysis was interpretative and iterative and informed by the constant comparative approach. NVivo 10 (QSR International, Warrington, UK) was used to code data.

### *Results*
Of the 58 parents who registered interest, 29 were screened. Three were deemed ineligible and five did not confirm an interview date. Data saturation was reached when 21 parents had been interviewed. Seventeen parents were recruited via social media, four by post and none via advertising in PICUs. The sample included 18 mothers (five bereaved) and three fathers (two bereaved).

#### The trial in general
Overall, parents supported RWPC and the FiSh trial. Some parents were concerned that a change from current practice might jeopardise their child's chances of survival. In response, recommendations were made for tailored verbal explanations to be made by site staff and for adjustments to the participant information sheet (PIS).

#### When to ask for consent
Parents suggested that consent should occur after stabilisation of their child's condition. The majority of bereaved parents supported contact via post.

#### Outcomes of importance to parents
Parents prioritised the following outcomes: (1) long-term morbidity, (2) looking and behaving more normally, (3) organ/physiological functioning, (4) time spent on treatments and machines and (5) survival. Bereaved parents found it difficult to consider outcome measures other than survival.

### *Conclusions*
Overall, the feasibility study findings suggested that parents whose child had experienced severe infection supported the FiSh trial. Some specific concerns and misunderstandings were revealed. These findings were used to develop the pilot trial documentation, the site staff training package and guidance on consent. Parents' views on outcomes were incorporated into potential outcome measures collected in the pilot trial.

# Pilot randomised controlled trial with integrated perspectives study

## *Methods: pilot randomised controlled trial*

### Study design
Pragmatic, open, multicentre individual RCT.

### Sites
Sites were set up in a 'hub-and-spoke' model in three regions: (1) Bristol, (2) London (North Thames) and (3) Southampton. The 'hubs' were four regional hospitals with integral PICUs (two hospitals covered the same region), three of which also had an integrated ED. The 'spokes' were nine hospitals that had an ED but not a PICU.

### Recruitment

#### *Inclusion criteria*

- Aged ≥ 37 weeks (corrected gestational age) and < 16 years.
- Clinical suspicion of infection.
- Clinical signs of shock [defined as age-adjusted hypotension or prolonged capillary refill time (CRT) of ≥ 3 seconds] after receipt of 20 ml/kg of fluid bolus.
- Recruitment and randomisation to take place while child is in an acute assessment area (e.g. paediatric assessment unit or ED).

#### *Exclusion criteria*

- Prior receipt of > 20 ml/kg of fluid bolus.
- Conditions in which fluid bolus resuscitation should be curtailed.
- Full active resuscitation not within current goals of care.

### Randomisation, allocation, intervention and consent
Eligible children were randomised using sealed envelopes and allocated 1 : 1 to either 10-ml/kg or 20-ml/kg fluid bolus resuscitation over a 4-hour period. The period was divided up into 15-minute cycles and one bolus was delivered per cycle. At the end of each cycle, if signs of shock were present, then another bolus of the allocated volume was given within a cycle. Cycles were repeated until either the end of the 4-hour period or any of the hold criteria occurred (resolution of shock or signs of fluid overload). If hold criteria were present, the delivery of further fluid boluses was withheld. If, within the 4-hour resuscitation period, hold criteria were no longer present, then cycles were recommenced with the allocated fluid bolus volume. After 4 hours, further treatment was at clinical discretion.

The maximum volume of fluid within the pilot protocol was 120 ml/kg (excluding the 20-ml/kg fluid bolus pre randomisation). If > 120 ml/kg of fluid was required, then further treatment was at clinical discretion.

A member of the site research team approached parents/legal representatives as soon as appropriate after randomisation to take consent.

The combined objectives were to test whether or not all of the processes worked together, and to inform the design and ensure the successful conduct of the FiSh trial (should this be the recommendation).

Objectives 1, 2 and 4 were measured by the:

- proportion of eligible children recruited
- number of children recruited per site per month
- proportion of parents/legal representatives refusing consent.

Objective 3 was measured by the:

- proportion of fluid boluses delivered at the correct volume and time during the intervention period
- total volume of fluid received during the intervention period in each treatment group.

Objectives 5–8 were measured by the:

- proportion of complete data for each outcome measure
- characteristics of potential outcome measures
- observed AEs
- time taken for data collection and entry
- proportion of required data that could be linked to routine sources.

### Data collection

A secure, dedicated electronic case report form (eCRF) was set up for trial data, which were to be entered by site staff. Inclusion criteria, baseline characteristics, intervention, physiology and location of care data to the point of hospital discharge were collected by the sites. Death at 30 days was determined by linking the eCRF data with data from the NHS Spine web portal. For children admitted to a PICU, daily intervention data (mechanical ventilation, PICU length of stay, PICU mortality) were obtained via linkage with the Paediatric Intensive Care Audit Network (PICANet), the national clinical audit for paediatric intensive care.

### Sample size

Based on available data, it was anticipated that the 12 EDs would recruit approximately one child per month, that is, around 108 children over 9 months.

### Statistical analysis

Statistical analyses were based on the intention-to-treat principle. All tests used were two-sided with significance levels set at a $p$-value of $< 0.05$ and with no adjustment for multiplicity. The final analyses were conducted using Stata/SE™ version 14.0 (StataCorp LP, College Station, TX, USA).

## *Methods: integrated perspectives study*

### Study design

The integrated qualitative perspectives study comprised questionnaires and interviews with parents/legal representatives, and focus groups and interviews with site staff. The aim was to explore the experiences and views of parents/legal representatives and staff in relation to the pilot trial.

### Participants

The parents or legal representatives of children who were randomised into the pilot trial were eligible to take part, unless they were unable to speak and read English. Site staff who were involved in the pilot trial were also eligible to take part. There were no exclusion criteria for staff. Informed consent was taken.

### Interviews and focus groups

#### *Parents/legal representatives*

An interview topic guide was used to explore the views and experiences of parents about the FiSh trial in a similar manner to the feasibility study (see above).

#### *Site staff*

A topic guide was also used for the focus groups and interviews with site staff to explore their views and experiences of the FiSh trial.

### Data analysis
Analysis was performed in accordance with the methodology used in the feasibility study (see above).

## *Results: pilot randomised controlled trial*
The pilot trial was conducted in 13 hospitals from July 2016 to April 2017. Seventy-five children were randomised, 40 to the 10-ml/kg fluid bolus group and 35 to the 20-ml/kg fluid bolus group. Two children were withdrawn. The overall recruitment rate was 0.9 children per site per month [95% confidence interval (CI) 0.7 to 1.2 children per site per month]. Baseline characteristics were similar, with some imbalance in age and weight.

Most children (59% in the 10-ml/kg fluid bolus group and 74% in the 20-ml/kg fluid bolus group) required a single trial bolus before shock resolved. Fluid boluses were delivered in accordance with protocol in 79% of children in the 10-ml/kg fluid bolus group and in 55% in the 20-ml/kg fluid bolus group. The mean total volume of study fluid received was 23% lower in the 10-ml/kg fluid bolus group, at 188 ml [standard deviation (SD) 325 ml], compared with the 20-ml/kg fluid bolus group [243 ml (SD 275 ml); mean difference −54 ml, 95% CI −196 ml to 88 ml; $p = 0.44$]. However, when the children's weights were taken into account, the separation in study fluid volume was significant [14.5 ml/kg (SD 11.1 ml/kg) versus 25.7 ml/kg (SD 12.0 ml/kg); $p < 0.001$].

There were no deaths and no serious AEs. Overall, 29% of children were admitted to a PICU. Length of hospital stay, transfers to PICU, length of stay in PICU, and days alive and not in PICU at 30 days post randomisation did not differ significantly between the groups.

## *Results: integrated perspectives study*

### Participants: parents/legal representatives
A total of 52 out of 75 (69%) parents of the children enrolled in the pilot trial consented. Questionnaires were received from 45 out of 52 (87%) parents from 44 families.

### Participants: site staff
Three focus groups were conducted with 20 site staff from the three 'hub' pilot trial sites. In addition, seven telephone interviews were conducted with 7 out of 20 (35%) staff.

### Parental perspectives
Some parents [7/20 (35%) interviewed and 13/45 (29%) who completed a questionnaire] were surprised to discover that their child had been enrolled into the pilot trial without prior consent. However, all supported RWPC in the FiSh pilot trial. Many parents said that they consented for altruistic reasons. Parents felt that they were approached for consent at the appropriate time, when the emergency situation had passed. Parents described the FiSh trial PIS as comprehensive and generally clear. Ranked in order of importance, parents prioritised the following outcome measures: (1) organ/physiological functioning, (2) looking and behaving normally, (3) fewer machines, (4) less time spent on various treatments, such as mechanical ventilation, (5) long-term morbidity, (6) survival and (7) less time in hospital.

### Site staff perspectives
Site staff stated that the training had prepared them for the pilot trial. Of the site staff in focus groups, 65% (13/20) indicated that the screening process could be improved. Many staff found it difficult to complete the case report form while resuscitating a child. Suggestions for improvement included the following: 24/7 research nurse cover in the ED; making sure all staff are trained, including new staff on rotation; and ensuring that study posters are placed in the optimal location. The randomisation methodology was viewed as straightforward. Thirty per cent (6/20) of the site staff in focus groups experienced problems with adherence to the protocol. Protocol deviations related to a lack of equipoise when clinicians favoured 10-ml/kg, rather than 20-ml/kg, fluid boluses, and with difficulties in administering boluses within the 15-minute cycles.

### *Conclusions*

The population had lower severity of illness than expected and many sites struggled to recruit more than a handful of children. The majority of the recruitment was led by three sites. Most children required only one trial fluid bolus, fewer than one-third of children were transferred to PICU and all survived. There were more adherence issues in the 20-ml/kg fluid bolus group, mainly because of difficulties delivering the fluid boluses within the 15-minute cycles. Fewer than half of the children had confirmed infection and, of these, only 13 had confirmed bacterial infections in sterile sites. Overall, such results would have been impossible to imagine in the 1990s and 2000s, when the incidence of severe community-acquired sepsis was much higher. Possible reasons for this finding include both the comprehensive childhood vaccination programme now offered in the UK and implementation of 'sepsis bundles', which may have improved recognition and early management in those who present to an ED.

The findings from the integrated perspectives study indicated that the FiSh trial was, in general, acceptable to parents and site staff.

Data from both quantitative and qualitative analyses demonstrated that clinicians tended to favour the smaller bolus size, suggesting that equipoise may no longer exist. Further work is thus required to confirm that equipoise still exists before any trial on different volumes of fluid bolus is undertaken in the UK.

## Recommendations for research

1. The full FiSh trial, with the current design, is not feasible.
2. Further observational and epidemiological work is required to determine if there is still a population of children in the UK of whom this study question could usefully be asked.
3. Further work is required to elucidate current treatment and to determine whether or not equipoise still exists in relation to the research question among clinicians in the UK.

## Study registration

This trial is registered as ISRCTN15244462.

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