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Statistical Analysis Plan

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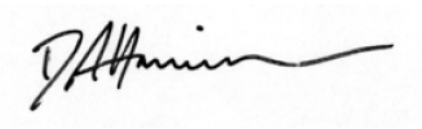
Senior Statistician: Dr David Harrison (Senior Statistician, ICNARC)		03/05/2017

Version history

Version number	Date	Summary of main changes from previous versions
1.0	03/05/2017	N/A

Contents

Abbreviations

AE	adverse event
CRT	capillary refill time
ED	emergency department
FiSh	Fluids in Shock
ICNARC	Intensive Care National Audit & Research Centre
IQR	Interquartile range
PAU	paediatric assessment unit
PICU	paediatric intensive care unit
PICANet	Paediatric Intensive Care Audit Network
PICS-SG	Paediatric Intensive Society – Study Group
PIM2r	Paediatric Index of Mortality version 2
RCT	randomised clinical trial
SAE	serious adverse event
SD	standard deviation

1 Background

The External Pilot Study of the Fluids in Shock trial (the FiSh Trial) is a pragmatic pilot randomised clinical trial (RCT) in infants and children presenting to UK emergency departments (EDs) with presumed septic shock.

The External Pilot Study comprises of a qualitative study and a quantitative pilot RCT (the External Pilot Trial).

This document describes the proposed statistical analyses for the External Pilot Trial. It is important to set these out and agree on them in advance of analysing the outcome data for the External Pilot Trial, so that data-derived decisions in the analyses are avoided.

2 Aim and objectives

2.1 Aim

The FiSh Trial sets out to evaluate 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 with presumed septic shock.

The aim of the External Pilot Trial is to explore and test important key parameters needed to inform the design and ensure the successful conduct of the FiSh Trial.

2.2 Objectives

1) To test the willingness of clinicians to screen, recruit and randomise eligible patients
2) To estimate the recruitment rate for the FiSh Trial
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 for the FiSh Trial
7) To estimate the characteristics of the selected patient-centred primary outcome measure to inform sample size estimation for the FiSh Trial
8) To inform content and time needed for final data collection for the FiSh Trial

3 Pilot trial design

3.1 Inclusion/exclusion

The External Pilot Trial population will consist of infants and children receiving treatment at a participating site who fulfil all of the inclusion criteria and none of the exclusion criteria below.

3.1.1 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 bolus fluid
- Recruitment and randomisation in an acute assessment area e.g. ED, paediatric assessment unit (PAU)

3.1.2 Exclusion criteria

- Prior receipt of > 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

3.2 Pilot trial treatment

Infants and 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. The maximum amount of fluid that can be given per bolus is either 500 ml (for those allocated to 10 ml/kg boluses) or 1000 ml (for those allocated to 20 ml/kg boluses). Other treatment is 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 (CRT) (Table 1) persist, then another bolus of the same size will be repeated within the next 15 minute cycle, again, at a rate left to the discretion of the treating clinician.

The cycles repeat until either the end of the four-hour resuscitation period or when any of the hold criteria occur (Table 2). Following the presence of any the hold criteria, 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. 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 (or) b) Capillary refill time ≥ 3 seconds (assessed using standard methods)

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

Table 2: 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.

3.3 Outcomes

Objectives 1, 2, 4 will be reported as:

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

Objective 3 will be reported as:

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

Objectives 5 to 8 will be reported as:

- 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

4 Sample size calculation

The External Pilot Trial was designed in the absence of a defined primary outcome and, hence, in the absence of a power calculation to estimate sample size. Instead, the sample size was determined to be adequate to estimate critical parameters to be tested to a necessary degree of precision.

Based on available data from the Paediatric Intensive Care Audit Network (PICANet) and the Paediatric Intensive Society – Study Group (PICS-SG) severe sepsis audit[1], it was anticipated that the participating sites will recruit approximately one child per month, providing a total of approximately 108 infants and children.

Recent research[2] has demonstrated that a standard sample size for a pilot trial (approximately 30 patients[3]) will result in an imprecise estimate of the standard deviation (SD) 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[2]. 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-SG sepsis audit in ED).

The proposed sample size of 108 infants and children for the External Pilot Trial would enable the mortality to be calculated with a precision of approximately ±5%.

5 End of trial

The end of the External Pilot Trial will be when the last participant has completed their 30-day follow-up.

6 Analysis principles

All analyses will be conducted by intention-to-treat. The infants and children will be analysed according to the treatment group they were randomised to, irrespective of whether the treatment allocated was received i.e. all infants and children will be included in the analysis, regardless of whether they have, or have not, adhered to the protocol.

7 Missing data

The proportion of variables included in the analyses that are missing will be reported.

8 Analyses

8.1 Screening, recruitment and randomisation of eligible infants and children

Recruitment to the External Pilot Trial, treatment allocation and completeness of follow-up will be illustrated using a CONSORT flow diagram. All participating sites have maintained Screening Logs of infants and children who are eligible (fulfil all of the inclusion criteria and

none of the exclusion criteria) but are not randomised, and who fulfil all of the inclusion criteria but meet one or more of the exclusion criteria. Reasons for non-recruitment will be categorised and summarised.

Numbers and percentages of screened and randomised infants and children will be presented. The following will be reported for each treatment group:

- number of infants and children screened;
- number of infants and children received 20 ml/kg bolus;
- number of infants and children resolved shock after initial 20 ml/kg bolus;
- number of infants and children not eligible;
- number of infants and children randomised; and
- number of infants and children, in those randomised, that did not meet inclusion criteria or met one or more of the exclusion criteria.

8.2 Rate of recruitment

Recruitment to the External Pilot Trial will be presented as a rate over the recruitment period and per month, overall and per site. The variation in recruitment rate across sites will be presented as a funnel plot (recruitment rate against months open to recruitment). Potential reasons for variation in recruitment rates will be explored.

8.3 Refused consent

Numbers and percentages within each treatment group will be reported for infants and children that had deferred consent either refused initially, or subsequently withdrawn.

8.4 Patient characteristics

The following baseline (pre-randomisation) demographic and clinical factors will be summarised by treatment group:

- age in months;
- gender;
- weight;
- met age-adjusted hypotension criterion;
- met prolonged CRT criterion;
- met both age-adjusted hypotension and prolonged CRT criterion;
- Paediatric Index of Mortality version 2 (PIM2r) score (2016 recalibration); and
- infection confirmed.

Numbers and percentages within each treatment group will be reported for categorical factors; means (with standard deviations - SD) and medians (with interquartile ranges - IQR) within each treatment group will be reported for continuous factors. P values will not be calculated or quoted.

8.5 Protocol deviations

Numbers and percentages of protocol deviations will be reported. The following protocol deviations will be reported for each treatment group:

- did not receive first bolus;
- for subsequent boluses, bolus given, shock criteria not met; and
- for subsequent boluses, shock criteria met, no bolus given.

8.6 Delivery of, and adherence to, the intervention and separation between groups

Numbers and percentages within each treatment group will be reported for the following treatment measures:

- receipt of bolus fluid resuscitation of 10 ml/kg (±10%);
- receipt of bolus fluid resuscitation of 20 ml/kg (±10%);
- delivery of boluses within 15 minutes (overall and by age group); and
- fluid boluses delivered at correct volume and within 15 minutes during the intervention period.

Overall adherence will be reported as the number and percentage of patients in each treatment group not meeting all of the above criteria dependent on the treatment group.

The distribution of the total volume of fluid received during the intervention period in each treatment group will be presented as a histogram and summarised by the median (IQR) and mean (SD) in each treatment group. Separation between the treatment groups will be assessed by the difference in the mean total volume of fluid, tested with a t test and reported difference in means with 95% confidence interval.

8.7 Outcome measures

The following potential outcome measures will be reported for each treatment group:

- hospital mortality;
- mortality within 30 days post-randomisation;
- length of hospital stay;
- transferred to PICU;
- length of stay in PICU among those admitted;
- days alive and free of PICU up to 30 days (deaths within 30 days score 0, infants and children not admitted to PICU score 30);
- receipt of mechanical ventilation;
- duration of mechanical ventilation among those ventilated; and
- days alive and free of mechanical ventilation up to 30 days (deaths within 30 days score 0, infants and children not receiving mechanical ventilation score 30).

While noting that this is a pilot RCT and not powered to detect differences in outcomes, the potential outcome measures will be tested between the groups to gain further understanding of the potential magnitude of any treatment effect from the width of the confidence intervals. Differences in binary outcomes will be tested with Fisher's exact test and presented as the number and percentage in each treatment group, absolute risk difference and relative risk

with 95% confidence intervals. Differences in lengths of stay and duration of organ support will be tested with the Wilcoxon rank sum test and presented as median (IQR) in each treatment group. Differences in days alive and free of PICU/mechanical ventilation will be tested with the t test and presented as difference in means with 95% confidence interval.

For all potential outcome measures, the number of infants and children with complete data in each treatment group will be reported. For measures requiring data linkage with routine data sources, the proportion of successfully linked records will be reported.

9 Subgroup analyses

Subgroup analyses are not appropriate due to the small sample size.

10 Interim

No interim analyses are planned due to the nature of the trial.

11 Safety

The number and percentage of AEs and serious adverse events (SAEs) within 30 days post-randomisation will be reported by treatment group.

References

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2. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of clinical epidemiology* 2012;**65**:301-8. http://dx.doi.org/10.1016/j.jclinepi.2011.07.011

3. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *Journal of evaluation in clinical practice* 2004;**10**:307-12. http://dx.doi.org/10.1111/j.2002.384.doc.x

Appendix: Dummy tables

Proposed tables

i. Table 1: Comparison of screening and randomisation by treatment group

Variables		Restricted bolus	Usual treatment
Screened	[N]	[XX]	[XX]
Received fluid bolus	20 ml/kg, n (%)	XX (XX.X)	XX (XX.X)
	<20 ml/kg, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Still in shock after 20 ml/kg bolus	Yes, n (%)	XX (XX.X)	XX (XX.X)
	No, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Met exclusion criteria	No, n (%)	XX.X (XX.X)	XX.X (XX.X)
	Yes, n (%)	XX.X (XX.X)	XX.X (XX.X)
	[N]	[XX]	[XX]
Randomised	Yes, n (% of those eligible)	XX (XX.X)	XX (XX.X)
	Missed, n (% of those eligible)	XX (XX.X)	XX (XX.X)
	Other, n (% of those eligible)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Randomised in error	Did not meet inclusion criteria,	XX	XX
	Met exclusion criteria, n	XX	XX

n: number of patients; %: percentage of patients; N: total number of patients

ii. Table 2: Comparison of baseline characteristics by treatment group

Variables		Restricted bolus	Usual treatment
		N=XX	N=XX
Age (months)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX (XX, XX)	XX (XX, XX)
	[N]	[XX]	[XX]
Gender	Male, n (%)	XX (XX.X)	XX (XX.X)
	Female, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Weight (kg)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	[N]	[XX]	[XX]
Met age-adjusted hypotension criterion	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Met prolonged CRT criterion*	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Met age-adjusted hypotension and prolonged CRT criterion	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
PIM2r (2016) score	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX (XX, XX)	XX (XX, XX)
	[N]	[XX]	[XX]
Infection confirmed	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]

*≥ 3 sec; n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range

iii. Table 3: Protocol adherence

Variables		Restricted bolus	Usual treatment
		N=XX	N=XX
Received first boluses	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Of subsequent boluses:			
Bolus given, shock criteria not met	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Shock criteria met, no bolus given	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]

n: number of patients; %: percentage of patients; N: total number of patients
Shock criteria: CRT ≥ 3 sec or met age adjusted hypotension

iv. Table 4: Treatment delivery

Variables		Restricted bolus	Usual treatment
		N=XX	N=XX
Receipt of bolus fluid resuscitation	10 ml/kg*, n (%)	XX (XX.X)	XX (XX.X)
	20 ml/kg*, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Delivery of boluses within 15 minutes	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
By age group:			
0 days – <1 week	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
1 week – <1 year	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
1-<2 years	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
2-<5 years	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
5-<12 years	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
≥12 years	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Fluid boluses delivered at correct volume and within 15 minutes	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Total volume of fluid received during the intervention period	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	[N]	[XX]	[XX]

*±10%; n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range

v. Table 5: Outcome measures

Potential outcomes	Restricted bolus N=XX	Usual treatment N=XX	Effect estimate (95% CI)	P value
Hospital mortality, n (%) [N]	XX (XX.X) [XX]	XX (XX.X) [XX]	Absolute risk difference: X.X (X.X, X.X) Relative risk difference: X.X (X.X, X.X)	0.XXX 0.XXX
Mortality within 30 days*, n (%) [N]	XX (XX.X) [XX]	XX (XX.X) [XX]	Absolute risk difference: X.X (X.X, X.X) Relative risk difference: X.X (X.X, X.X)	0.XXX 0.XXX
Length of hospital stay, median (IQR) [N]	XX (XX, XX) [XX]	XX (XX, XX) [XX]		0.XXX
Transferred to PICU, n (%) [N]	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]	Absolute risk difference: X.X (X.X, X.X) Relative risk difference: X.X (X.X, X.X)	0.XXX 0.XXX
Length of stay in PICU, median (IQR) [N]	XX (XX, XX) [XX]	XX.X (XX, XX) [XX]		0.XXX
Days alive and free of PICU up to 30 days*, mean (SD) [N]	XX (XX.X) [XX]	XX (XX.X) [XX]	Mean difference: X.X (X.X, X.X)	0.XXX
Receipt of mechanical ventilation, n (%) [N]	XX (XX.X) [XX]	XX (XX.X) [XX]	Absolute risk difference: X.X (X.X, X.X) Relative risk difference: X.X (X.X, X.X)	0.XXX 0.XXX
Duration of mechanical ventilation among those ventilated, median (IQR) [N]	XX (XX, XX) [XX]	XX (XX, XX) [XX]		0.XXX
Days alive and free of mechanical ventilation up to 30 days*, mean (SD) [N]	XX (XX.X) [XX]	XX (XX.X) [XX]	Mean difference: X.X (X.X, X.X)	0.XXX

*post-randomisation; N: patients with complete data; n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range