Randomised **S**tudy of Early **C**ontinuous Positive Airways Pressure in **A**cute **R**espiratory **F**ailure in Children with Impaired Immunity

REC number:	12/LO/1051
Trial Sponsor:	Great Ormond Street Hospital for Children NHS Foundation Trust
Sponsor reference:	10AR31
ISRCTN number:	ISRCTN82853500
Trial Funder:	Great Ormond Street Hospital Children's Charity. Registered Charity No. 235825
Protocol version:	1.2
Protocol version date:	5 August 2013
Chief Investigator:	Dr Mark Peters Reader in Paediatric Intensive Care and Hon Consultant Intensivist The UCL Institute of Child Health

Please note: This protocol should not be applied to infants and children treated off trial. The trial will be monitored for adverse events and the ICNARC CTU can only ensure that active trial investigators are updated of any amendments to the protocol.

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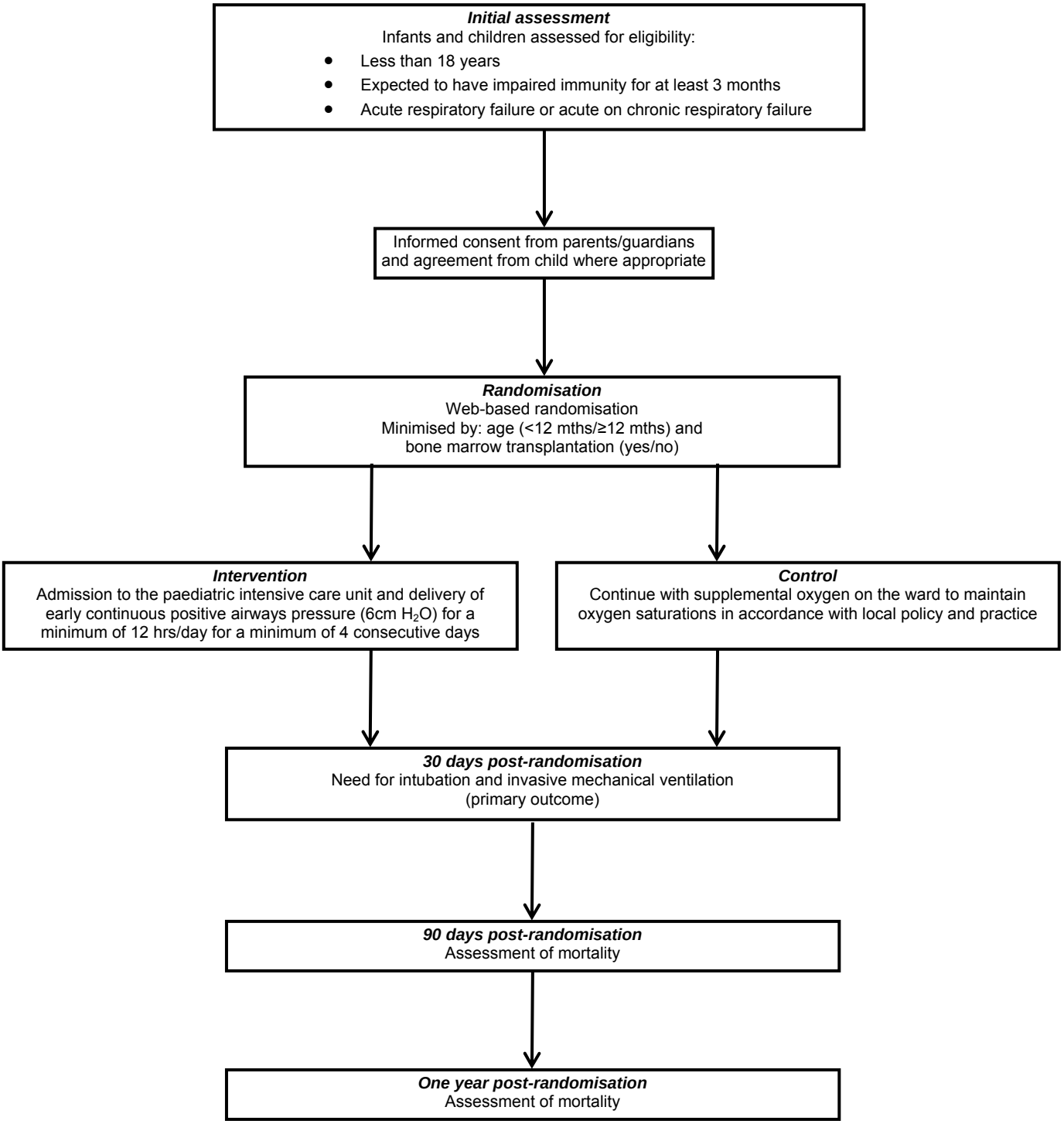
Abbreviations

AE	adverse event
ARDS	acute respiratory distress syndrome
CPAP	continuous positive airways pressure
CRF	case report form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
FiO_2	fraction of inspired oxygen
GOSH	Great Ormond Street Hospital for Children
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
MRC	Medical Research Council
PELOD	Paediatric Logistic Organ Dysfunction score
PICU	paediatric intensive care unit
PIM2	Paediatric Index of Mortality version 2
PIS	Parents/Guardians Information Sheet
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
$ScvO_2$	central venous oxygen saturation
SOP	Standard Operating Procedure
SpO_2	oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee

1.0 Protocol Summary

Title:	Randomised **S**tudy of Early **C**ontinuous Positive Airways Pressure in **A**cute **R**espiratory **F**ailure in Children with Impaired Immunity
Short Title/acronym:	SCARF
REC number:	12/LO/1051
Sponsor name & reference:	Great Ormond Street Hospital for Children NHS Trust, 10AR31
Funder name & reference:	Great Ormond Street Hospital for Children's Charity. Registered Charity No. 235825, 10AR31
ISRCTN no:	ISRCTN82853500
Design:	Pragmatic, open, randomised controlled trial
Overall aim:	To compare early admission to the paediatric intensive care unit (PICU) and continuous positive airways pressure vs. standard care in acute respiratory failure in children with impaired immunity
Primary outcome:	Requirement for intubation and invasive mechanical ventilation within 30 days post-randomisation
Secondary outcomes:	• Maximum and aggregate daily organ failure score • Mortality at 30 days post-randomisation • Requirement for Level 2 or Level 3 respiratory support within 30 days post-randomisation • Days free from any ventilator support at 30 days post-randomisation • Days free from supplemental oxygen (i.e. above pre-acute respiratory failure requirement) at 30 days post-randomisation • Hospital mortality • Mortality at 90 days post-randomisation • Mortality at one year post-randomisation
Target accrual:	148 infants and children
Inclusion criteria:	• Age less than 18 years • Expected to have impaired immunity for at least three months as a result of a primary diagnosis, therapy or a combination of both • Acute respiratory failure or acute on chronic respiratory failure
Exclusion criteria	• Already receiving invasive mechanical ventilation for non-respiratory indications • Other acute indication for emergency PICU admission and invasive mechanical ventilation, independent of the degree of respiratory failure (e.g. shock, reduced level of consciousness, seizures), as assessed by the PICU team • Recent oesophageal/gastric surgery • End-of-life care plan in place with limitation of resuscitation • Life expectancy less than 12 months • Already receiving treatment on PICU
Anticipated duration of recruitment:	36 months
Duration of participant follow up:	One year post-randomisation
Definition of end of trial:	End of trial is defined as, last participant, last follow-up

Figure 1 Trial schema



2.0 Background

Acute lung injury and acute respiratory distress syndrome (ARDS) are inflammatory lung conditions characterised by pulmonary oedema, reduced lung compliance, and hypoxaemia. Lung volumes are decreased and hypoxaemia results from ventilation-perfusion mismatch. Overall case fatality rates for children are around 20% but in the context of immunocompromise this approaches 50%[1-4].

Drug therapies have not proven effective in decreasing mortality from ARDS[5-8]. The only evidence-based interventions from adult studies are: a lung-protective strategy involving the use of small tidal volumes with limitation of the end-inspiratory lung stretch[6], avoidance of fluid overload[7], and early neuromuscular blockade[8].

In addition, three small randomised controlled trials (RCTs) of adults with impaired immunity and acute respiratory failure have suggested that using continuous positive airways pressure (CPAP), via facemask or helmet, *before* it is required to maintain gas exchange, reduces the risk of death by around 60%[9-11]. The mechanism by which such a survival benefit may be achieved is not clear but possibilities include: the prevention of further atelectasis and the associated risk of secondary respiratory infections; limitation of 'atelectrauma' (mechanical injury to lung tissue caused by repetitive cycles of opening and closing); or possibly non-specific effects of the closer monitoring and care that patients receiving non-invasive ventilation typically receive. These RCTs in adults were small and recruited different subsets of patients with impaired immunity (solid organ transplantation – n=40[9], haematological cancer with neutropenia – n=52[10] and haematological malignancy – n=40[11]). However, these data are consistent with an increasing literature that suggests that early aggressive care improves outcomes for many forms of critical illness, such as resuscitation from shock in adults and children[12-15].

None of the previous studies of early CPAP for managing acute respiratory failure in patients with impaired immunity have included children. The cost and benefit of early CPAP may be distinct in paediatric patients because of differences in respiratory mechanics and case mix. Infants and children differ significantly from adults with regard to lung volumes (e.g. functional residual capacity being closer to closing volume) and reduced chest wall stiffness, which means that they develop atelectasis and respiratory failure far more readily than adults. In addition, the spectrum of patients with impaired immunity in childhood is much wider than in adults, particularly with the array of congenital immunodeficiencies. Another important consideration is the practicality of administering CPAP to infants and young children, which can be challenging.

This trial therefore, will investigate if early admission to the paediatric intensive care unit (PICU) and early delivery of CPAP improves outcome in infants and children with impaired immunity and acute respiratory failure. It is a pragmatic trial that will assess the response of the clinical syndrome of acute respiratory failure (irrespective of the cause) to two different management strategies.

3.0 Aim

To determine if admission to the PICU for early delivery of CPAP – i.e. before it is required to maintain gas exchange – reduces the requirement for invasive mechanical ventilation and improves survival in infants and children with severely impaired immunity and acute respiratory failure.

The hypothesis is that early admission to the PICU for early delivery of CPAP will reduce the need for intubation and invasive mechanical ventilation within 30 days and improve survival from both acute and acute on chronic respiratory failure in children with impaired immunity.

4.0 Trial Design

SCARF is a pragmatic, open, RCT in infants and children with severely impaired immunity and acute respiratory failure.

Eligible infants and children, for whom written informed consent is available, will be randomly allocated, in equal numbers, to receive either, admission to the PICU for early CPAP or standard care on the ward. All other care will be at the discretion of the treating clinician.

Trial participants will be followed up to 30 days post-randomisation for assessment of requirement for intubation and invasive mechanical ventilation (primary outcome) and for adverse events.

In addition, participants will be followed up at 90 days and one year post-randomisation for assessment of secondary outcomes (see below).

Participant flow through the trial is summarised in Figure 1.

5.0 Outcome Measures

5.1 Primary

Requirement for intubation and invasive mechanical ventilation (Level 4 respiratory support – see section 10.3) within 30 days post-randomisation.

5.2 Secondary

The secondary outcome measures are:

- maximum and aggregate paediatric logistic organ dysfunction score (PELOD)[16] at 30 days post-randomisation;
- mortality at 30 days post-randomisation;
- requirement for Level 2 or Level 3 respiratory support (see section 10.3) within 30 days post-randomisation;
- days free from any ventilator support (Level 2, 3 or 4 respiratory support – see section 10.3) at 30 days post-randomisation;
- days free from supplemental oxygen (i.e. above pre-acute respiratory failure requirement) at 30 days post-randomisation;
- hospital mortality;
- mortality at 90 days post-randomisation;
- mortality at one year post-randomisation.

6.0 Trial Population

Infants and children receiving treatment at a participating site who fulfil all of the inclusion criteria and none of the exclusion criteria below.

6.1 Inclusion criteria

1) Age less than 18 years

and

2) expected to have severely impaired immunity (defined as a chronic state of a reduced ability to resist infection) for at least three months as a result of a primary diagnosis, therapy or a combination of both, including:

i. high-risk of severe neutropenia:
- receiving treatment for Acute Leukaemia or Myelodysplastic syndrome (either frontline or relapse therapy)
- receiving cyclical therapy for high grade lymphoma;
- receiving rapid COJEC (*cisplatin, vincristine, carboplatin, etoposide cyclophosphamide)* for neuroblastoma
- receiving cyclical chemotherapy
- postallo- or autologous stem cell transplantation;

ii. severe immunodeficiency;

iii. haemophagocytic lymphohistiocytosis;

iv. undergoing bone marrow transplantation;

v. other condition or therapy, or combination of the two, likely to lead to severely impaired immunity for at least three months.

and

3) either acute respiratory failure or acute on chronic respiratory failure as defined below.

Acute respiratory failure is defined as a new onset of hypoxaemia, tachypnoea and chest x-ray changes developing in the previous 48 hours. All of the following age specific criteria must be met:

i.*hypoxaemia*: arterial oxygen saturation (SpO_2) less than 90% in room air

and

ii.*tachypnoea*: respiratory rate greater than approximate 90th centile for age: 55 (<12 months); 45 (12 months – <2 years); 30 (≥2 years – <4 years); 25 (≥4 years – <10 years) and 20 (≥10 years – <18 years)[17]

[unless the child is receiving a continuous infusion of an opiate at any dose, in which case the tachypnoea criteria do not apply]

and

iii. *chest X-ray changes*: radiological evidence of acute pulmonary infiltrates developing in the previous 48 hours.

Acute on chronic respiratory failure is defined as a significant acute deterioration, in the previous 48 hours, in infants and children with pre-existing chronic lung disease

requiring long-term supplemental oxygen therapy. All of the following age-specific criteria must be met:

i. *hypoxaemia*: SpO_2 less than 90% in room air and a requirement for increased supplemental oxygen by ≥30% of baseline flow rate (or ≥30% increase from baseline fraction of inspired oxygen (FiO_2)where measured).

and

ii.*tachypnoea*: increased respiratory rate >20% above baseline and greater than approximate 90th centile for age: 55 (<12 months); 45 (12 months – <2 years); 30 (≥2 years – <4 years); 25 (≥4 years – <10 years) and 20 (≥10 years – <18 years)[17]

[unless the child is receiving a continuous infusion of an opiate at any dose, in which case the tachypnoea criteria do not apply]

and

iii. *new chest X-ray changes:* radiological evidence of acute pulmonary infiltrates developing in the previous 48 hours.

[The cause of acute or acute on chronic respiratory failure is not a consideration. This is a pragmatic trial to assess the response of the clinical syndrome of acute respiratory failure to two different management strategies. Acute respiratory failure might arise from an acute lower respiratory tract infection, systemic sepsis or inflammatory processes, such as veno-occlusive disease, or graft vs. host disease with varying degrees of fluid retention/overload.]

6.2 Exclusion criteria

- already receiving artificial mechanical ventilation for non-respiratory indications;
- other acute indication for emergency PICU admission and invasive mechanical ventilation, independent of the degree of respiratory failure (e.g. shock, reduced level of consciousness, seizures), as assessed by the PICU team;
- recent oesophageal/gastric surgery;
- end-of-life care plan in place with limitation of resuscitation;
- life expectancy less than 12 months;
- already receiving treatment on the PICU.

Potentially eligible infants and children will be screened against the inclusion/exclusion criteria prior to their parents/guardians being approached to discuss participation in SCARF. Infants and children who are eligible (fulfill all of the inclusion criteria and none of the exclusion criteria) but not randomised, or who fulfill all of the inclusion criteria but meet one or more of the exclusion criteria, will be recorded in the SCARF Screening Log.

7.0 Pre-randomisation care

Prior to randomisation, all care will be determined by the clinical team primarily responsible for the child's treatment and care.

8.0 Informed Consent Procedure

Informed consent must be obtained to enable randomisation to occur within 24 hours of the infant or child meeting the eligibility criteria. Once eligibility has been confirmed, staff (doctors or nurses) authorised by the Site Principle Investigator (PI) will describe SCARF to the parent/guardian. A standard Parent/Guardian Information Sheet (PIS) will be provided which will identify the title of the trial, the Chief Investigator and include information about: the purpose of the trial, the consequences of participating, or not (i.e. none), participant confidentiality, use of personal data, data security, the future availability of the results of the trial and funding. 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 collection and storage of personal information, for information to be gathered from the hospital patient management system/the NHS Central Database flagging system (Data Linkage Service – DLS) and for the General Practitioner (GP) to be contacted. Parents/guardians 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 SCARF.

After the doctor or nurse has checked that the PIS and Consent Form are understood, the doctor or nurse will invite the parent/guardian to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/guardian, the original placed in the child's medical notes, and a copy kept in the Investigator Site File.

9.0 Randomisation

Randomisation must occur as soon as eligibility has been confirmed and informed consent has been obtained with the aim of commencing treatment within 24 hours of the infant or child meeting all three criteria for acute respiratory failure. The 24-hour window commences when the last criterion is met. In most cases it is anticipated that this will be hypoxaemia and a requirement for supplementary oxygen.

Participants will be allocated to treatment groups by a computer generated dynamic procedure (minimisation) with a random component. Minimisation will be performed on age (<12 months / ≥12 months) and bone marrow transplantation (yes/no). Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To randomise a participant, an authorised staff member will log onto a secure web-based randomisation system (https://www.sealedenvelope.com/simple-randomiser/v1/trials/scarf) and enter the participant's details to obtain a unique four-digit trial number and allocation to one of the two treatment groups.

Participants will be randomly allocated (1:1) to either the intervention group (admission to the PICU and delivery of CPAP) or to the control group (usual care, i.e. remain on the ward and receive supplemental oxygen to maintain oxygen saturation). There will be equal numbers of participants in each trial arm.

10.0 Trial Procedures

10.1 Intervention group

Participants allocated to the intervention group will be admitted to the PICU and receive CPAP of at least 6cm H_2O with supplemental oxygen for a minimum of 12 hours per day for at least four consecutive days (Level 2 respiratory support – see section 10.3). The interface for delivering CPAP (i.e. via face mask, helmet or infant flow-driver) will be at the discretion of the clinical team responsible for the participant's care. All other care will be determined by the clinical team primarily responsible for the participant's care.

10.2 Control group

Participants allocated to the control group will remain on the ward and receive supplemental oxygen to maintain oxygen saturation in accordance with standard local practice (Level 1 respiratory support – see section 10.3). All other care (including antimicrobial therapy, fluid therapy, analgesia and sedative agents, bronchodilator therapy) will be determined by the clinical team primarily responsible for the child's care. Participants in the control group will be admitted to the PICU in accordance with standard acutely ill child protocols and as deemed necessary by the ICU outreach/Medical Rapid response teams and the clinical team responsible for the child's care.

10.3 Levels of respiratory support

The four levels of respiratory support are as follows:

- Level 1: inspired oxygen therapy on the ward (control group only);
- Level 2: CPAP at 6-10cm H_2O;
- Level 3: non-invasive bilevel positive airway pressure (BiPAP) via facemask or helmet;
- Level 4: intubation and mechanical ventilation.

Participants randomised to the intervention group will receive Level 2 respiratory support in the PICU unless their clinical condition changes (see sections 10.4 – 10.6). Participants randomised to the control group will continue to receive Level 1 respiratory support unless their clinical condition changes (see sections 10.4 – 10.6).

10.4 Changes to the level of respiratory support

The following applies to participants in both intervention and control groups:

- participants will progress between the levels in sequence (i.e. Levels 2, 3, 4 in the intervention group and Levels 1, 2, 3, 4, in the control group) unless they stabilise or develop an acute indication for intubation and ventilation (see section 10.6);
- the criteria to escalate from one group to the next or to go directly to intubation and mechanical ventilation are proscribed (see section 10.5);
- decisions to step down respiratory support are at the discretion of the clinical team, aside from a step down from Level 2 to Level 1 for the intervention group, which is not permitted before the end of the 4-day intervention period (unless the participant has progressed to a higher level during this period, in which case they can be stepped down at the discretion of the clinical team).
- the choice of settings *within* each of the four levels are at the discretion of the clinical team.

10.5 Criteria for escalating the level of respiratory support

The following criteria for escalating the level of respiratory support apply to participants in both intervention and control groups regardless of the current level of respiratory support.

Participant meets any of the following:

- *Respiratory acidosis:* defined as an increase in $PaCO_2$ accompanied by a pH of 7.20 or less for more than 1 hour;

- *Persistent moderate hypoxaemia:* defined as either
    - failure to maintain a PaO_2:FiO_2 >85mmHg (11.3kPa) for more than one hour, or
    - SpO_2/FiO_2 ratio of less than 98mmHg for more than one hour, or
    - SpO_2<90% for more than one hour despite optimised inspired oxygen therapy (e.g. 15l/min^{-1} via appropriately fitting reservoir mask for Level 1 respiratory support or FiO_2 of 1.0 via CPAP for Level 2 respiratory support);

- *Severe hypoxaemia:* defined as failure to maintain SpO_2 >80% at any time;

- *Evidence of persistent inadequate oxygen delivery:* defined as an increase in serum lactate or central venous oxygen saturation ($ScvO_2$) persistently below 65%.

10.6 Indications for Level 4 respiratory support (intubation and invasive mechanical ventilation

The following are indications for intubation and invasive mechanical ventilation regardless of the prior level of respiratory support:

- condition necessitating protection of the airway, e.g. a seizure disorder or severe encephalopathy with a modified Glasgow Coma Score of 8 or less, and/or loss of adequate airways reflexes;
- copious tracheal secretions;
- severe agitation requiring sedation;
- severe haemodynamic instability, e.g. progressive rise in serum lactate, increasing requirement for inotropic support;
- evidence on electrocardiography of ischaemia or clinically significant ventricular arrhythmias;
- acute haemofiltration in a child without prior suitable intravenous access;
- investigations/surgical procedures necessitating intubation.

11.0 Assessments

11.1 Data collection

Detailed guidance for the collection of data will be provided in the trial specific Standard Operating Procedure (SOP). All data items will be objectively defined according to relevant national and international guidelines.

11.2 Time points for data collection

- Baseline/randomisation;

- Daily during episode of acute respiratory failure;
- At discharge from the PICU (where relevant) and hospital;
- 30 days post-randomisation;
- 90 days post-randomisation;
- One year post-randomisation.

11.3 Data collected at baseline/randomisation

The following identifiers are required for flagging participants with the hospital patient management system/DLS and for follow-up at 30 days, 90 days and at one year post-randomisation:

- NHS number;
- date of birth;
- sex;
- forename;
- surname;
- full name, full address and telephone number of GP.

The following data are required for risk adjustment and stratification:

- chronic diagnosis;
- bone marrow transplantation (yes/no);
- suspected cause of acute respiratory failure;
- weight;
- PIM2 score[18].

11.4 Data collected daily during this episode of acute respiratory failure

- physiology data, including FiO_2, O_2 l/min^{-1}, PCO_2, $ScvO_2$, SpO_2, blood lactate, heart rate, respiratory rate, work of breathing (normal/increased/greatly increased), serum creatinine, platelet count, white blood count;
- Glasgow Coma Score;
- PELOD score[16];
- type of ventilation;
- interventions, including use of sedative drugs.

11.5 Data collected at discharge from PICU/hospital

- date of discharge;
- survival status;
- confirmed cause of acute respiratory failure.

11.6 Data collected at 30 days post-randomisation

- need for intubation and invasive mechanical ventilation (primary outcome);
- survival status;
- adverse events.

11.7 Data collected at 90 days post-randomisation

- survival status.

11.8 Data collected at one year post-randomisation

- survival status.

12.0 Follow-up

Following randomisation, the child's GP will be informed, by letter, of their participation in SCARF and provided with a brief description of the trial.

All participants discharged from hospital will be flagged with the hospital patient management system/DLS for subsequent reporting of mortality data at 30 days, 90 days and one year post-randomisation. Complete collection of participant identifiers (described in section 11.3) will allow the majority (>90%) of participants to be flagged.

13.0 Data management guidelines

13.1 Case report forms and data entry

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

Data collected during the course of SCARF will not be anonymised in order to allow participants to be traced for outcome data. This is detailed in the PIS and on the Consent Form.

During the conduct of the trial, all electronic participant data will be encrypted and all trial documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the trial, all participant data (electronic and paper) and other trial documents will be archived securely and retained for ten years at the site or at the ICNARC CTU, as appropriate (see section 17.0).

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

13.2 Data validation

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

14.0 Adverse events

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

14.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence or effect in a participant treated on a trial protocol, which does not necessarily have a causal

relationship with trial treatment. An AE can therefore be any unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it is related to the trial treatment.

14.2 Serious adverse event

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

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

14.3 Recording and reporting procedures

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

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

Those meeting the definition of a SAE (i.e. severity 3, 4 or 5 – see section 14.4) must, in addition, be recorded in the SAE Log and reported to the ICNARC CTU, using the trial specific SCARF SAE Reporting Form, by fax within **24 hours** of observing or learning of the SAE. All sections of the SAE Reporting Form must be completed.

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

14.4 Severity

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

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

5. **Fatal**: indicates that the participant died as a direct result of the complication/adverse event.

14.5 Relatedness

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

- **None**
  There is no evidence of any relationship.
- **Unlikely**
  There is little evidence to suggest a relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).
- **Possible**
  There is some evidence to suggest a relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).
- **Probable**
  There is evidence to suggest a relationship and the influence of other factors is unlikely.
- **Definitely**
  There is clear evidence to suggest a relationship and other possible contributing factors can be ruled out.

14.6 Expectedness

The Site PI or other delegated investigator(s) must perform an assessment of expectedness for each AE regardless of its relationship to the trial procedures. This assessment must be performed using the list of expected AEs in Appendix 1 and determined as follows:

- **Expected**
  The event is listed as an expected AE in Appendix 1, or is considered by a clinician to be an expected complication in this patient population (this would include rare complications).

- **Unexpected**
  The event is <u>not</u> listed as an expected AE in Appendix 1, or is considered by a clinician to be an unexpected event.

14.7 Follow-up of serious adverse events

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

14.8 Central processing of serious adverse event reports

On receipt of the SAE report, a clinical member of the SCARF Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC).

If the event is evaluated by either the Chief Investigator or a clinical member of the SCARF TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

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

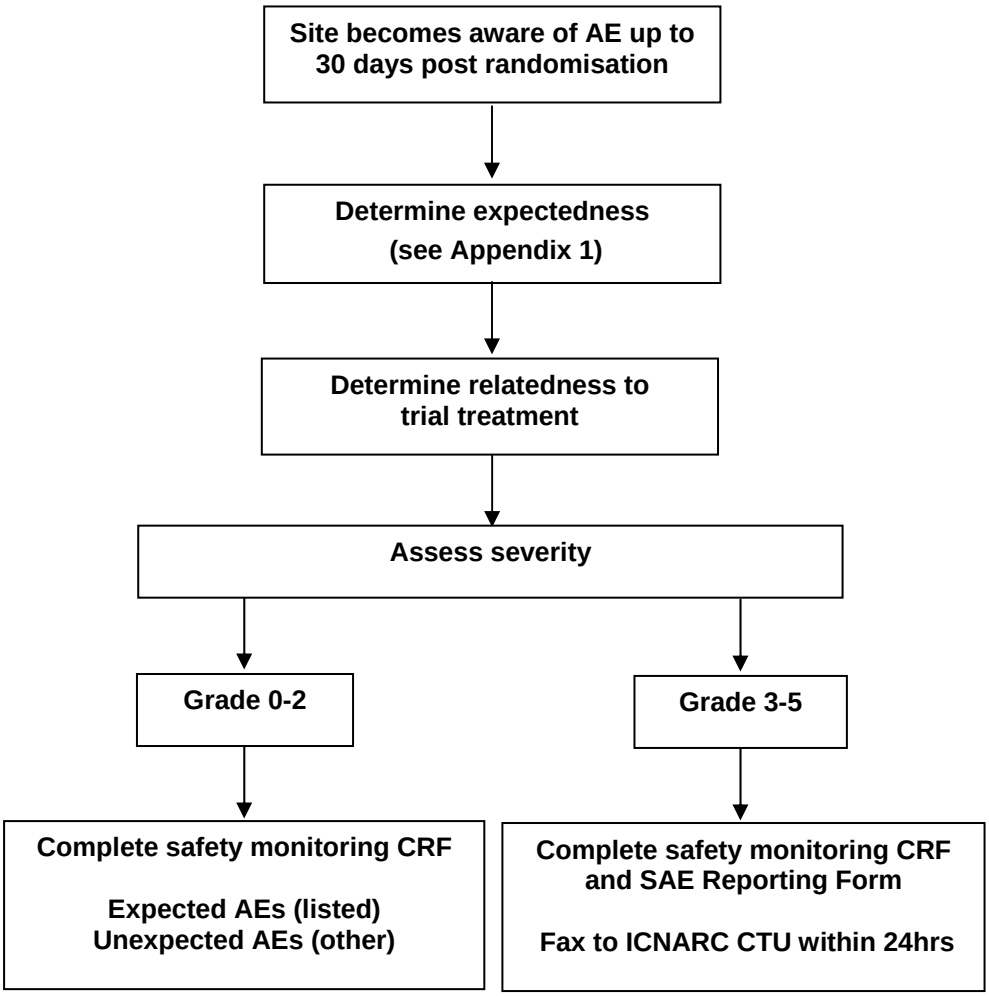
14.9 Additional safety monitoring

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

14.10 Notifying the Research Ethics Committee

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

Figure 2 Adverse event recording and reporting



15.0 Trial monitoring and oversight

The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the trial. In addition, the REC may request access to source data/documents for audit and review. Trial participants and their parents will be informed of this during the informed consent process (see section 8.0).

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 non-compliance with the SCARF Protocol.

16.0 Withdrawal

16.1 Withdrawal of a participant

In consenting/agreeing to the trial, parents/guardians and their children are consenting/agreeing to trial treatment, assessments, follow-up and data collection. However, children or their parents can withdraw from SCARF at anytime during the trial. If a child, or their parents, explicitly state that they no longer wish to take part or to contribute further data to the trial, their decision must be respected. The Withdrawal of Consent form should be completed and sent to the ICNARC CTU. Withdrawal of an infant or child from the trial should be recorded in their medical notes and no further data collected. To ensure the scientific validity of the trial and the safety of other participants, all data collected up to the point of withdrawal will be retained and primary outcome data (requirement for intubation and invasive mechanical ventilation within 30 days of randomisation) collected and included in the trial analysis. All identifiers will be removed at the end of the trial to ensure anonymity for all infants and children recruited into SCARF.

17.0 Trial closure

17.1 End of trial

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

17.2 Archiving trial documents

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

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

17.3 Early discontinuation of the trial

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

18.0 Trial management and committees

18.1 Good research practice

SCARF 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.

18.2 Trial Management Group

All day-to-day management of SCARF will be the responsibility of the TMG. Members of the TMG will include the SCARF Trial Manager, the Chief Investigator and the clinical co-investigators. The TMG will meet regularly to discuss management and progress of the trial and findings from other related research.

18.3 Trial Steering Committee

The trial will be supervised by the TSC, which will be chaired by an independent member, Dr Mark Rosenthal, Paediatric Respiratory Physician, Royal Brompton Hospital & Harefield NHS Foundation Trust. The TSC will include at least two additional independent members and a service user representative.

18.4 Data Monitoring and Ethics Committee

The DMEC will be chaired by Dr Shane Tibby, Consultant Paediatric Intensivist, Guy's and St Thomas' NHS Foundation Trust, who is an experienced statistician and paediatric intensivist. All members of the DMEC will be independent of both the SCARF TMG and the TSC. The DMEC will operate under the DAMOCLES Charter[19-20], and will report to the TSC, making recommendations on the continuation, or not, of the trial. Safety will be monitored by the DMEC through mandatory reporting of SAEs throughout the trial period.

18.5 Role of the ICNARC Clinical Trials Unit

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

19.0 Statistics

19.1 Sample size calculation

Data submissions to the Paediatric Intensive Care Audit Network, the national clinical audit for PICUs in the UK, report a mean of 3.3 patients per month with severely impaired immunity admitted to GOSH PICU over the last eight years. Two thirds were admitted with respiratory failure as the primary reason for admission and 75% of these received mechanical ventilation. We estimate that a similar number experience acute respiratory distress on the ward fitting our inclusion criteria that do not require ICU admission. Therefore we would be expecting to randomise around 4-5 participants per month and anticipate an intubation rate of around 35-40% in the control group. Assuming the same relative risk reduction (~60%) as observed in adult studies, a sample of 148 children (74 in each group) is required to detect a reduction in intubation rate from 35% to 14% with 80% power and a type 1 error rate of 5% (two-sided).

19.2 Statistical analysis

All analyses will be conducted by intention to treat, with a two-sided p value of <0.05 taken to indicate a statistically significant result. The primary effect estimate will be the relative risk of intubation for invasive mechanical ventilation at 30 days post-randomisation, with statistical significance assessed by Fisher's exact test. As a secondary analysis, the primary outcome will also be analysed by multivariable logistic regression adjusted for baseline covariates of age, chronic diagnosis, bone marrow transplantation, suspected cause of acute respiratory failure, weight and PIM2 score[18]. The baseline covariates have been selected *a priori* for their anticipated strong association with the outcome, no further selection of covariates will be performed based on imbalance at baseline or significance in univariable analyses. Secondary outcomes will be analysed by logistic regression for binary outcomes (mortality, requirement of level 2/3 respiratory support) or linear regression for continuous outcomes (PELOD[16], days free from ventilator support/supplemental oxygen) adjusted for the same baseline covariates as above. Due to the small sample size, no subgroup analyses are planned.

A single interim analysis will be conducted at 50% recruitment. The results of the interim analysis will be reviewed by the DMEC, using a Peto-Haybittle stopping rule (P<0.001) to recommend early termination of the trial due to harm[20]. It is not recommended that the trial should terminate early for efficacy, as any treatment effect that would be statistically significant at this level would be sufficiently large as to be clinically implausible and therefore unlikely to change clinical practice[20]. Additional interim analyses will be conducted if requested by the DMEC.

20.0 Ethical compliance

SCARF will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU's research policies and procedures (see section 18.0).

The trial has received a favourable opinion from the London Riverside REC. The ICNARC CTU will submit annual progress reports and all amendments to the SCARF Protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

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

20.1 Participant confidentiality and data protection

Identifiable participant 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 participant could be identified. Data will be stored securely.

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

21.0 Sponsorship and Indemnity

21.1 Sponsor details

Sponsor Name:	Great Ormond Street Hospital for Children NHS Foundation Trust
Address:	Great Ormond Street Hospital for Children NHS Foundation Trust Great Ormond Street London, WC1N 3JH
Contact:	Emma Pendleton
Email:	R&DGovernance@gosh.nhs.uk

21.2 Indemnity

University College London holds Professional Indemnity insurance (Policy number RKK423027/25, Royal & Sun Alliance) and Excess Professional Indemnity insurance (Policy number BR062932-003, Liberty Mutual Insurance Europe Limited). These indemnities meet the potential legal liability of the sponsor (GOSH) and employees for harm to participants arising from the design and management of the research.

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

22.0 Funding

SCARF is funded by Great Ormond Street Hospital Children's Charity, Registered Charity No. 235825.

23.0 Publication policy

The final report, including a detailed description of the trial, results and recommendations for future policy and practice and future research, will be submitted

to the Great Ormond Street Hospital Children's Charity. 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.

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Appendix 1: Expected adverse events

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

- Pneumothorax
- Facial pressure sores
- Sinusitis
- New nosebleed
- Corneal irritation
- Headache
- Abdominal bloating/distension
- Aspiration

[This list is not exhaustive. If an adverse event, as defined in section 14.1, occurs this should be recorded and reported as described in section 14.0]