NETSCC, HTA

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CATheter Infections in CHildren

A randomised controlled trial comparing the effectiveness of heparin bonded or antibiotic impregnated central venous catheters with standard central venous catheters for the prevention of hospital acquired blood stream infection in children

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Authorised on behalf of the Sponsor:

Signed: G. Lambert Date: 22/9/10

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CTRC

Clinical Trials Research Centre

General Information

This document describes the CATCH trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit, part of the University of Liverpool Clinical Trials Research Centre (CTRC)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator via the MCRN CTU.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or noted retrospectively (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments, and will be conducted in compliance with the protocol, Clinical Trials Research Centre Standard Operating Procedures, Good Clinical Practice (GCP) and published by the European Agency for the Evaluation of Medicinal Products as “Note for Guidance on Good Clinical Practice” (CPMP/ICH/135/95) (Approval 17 July 1996).

The trial involves the use of CE-marked medical devices employed for their intended purpose, therefore this trial is not considered to be a clinical investigation under the Medical Devices Regulations 2002, nor does it fall within the remit of the UK Statutory Instrument 2004 No. 1031(Medicines for Human Use (Clinical Trials) Regulations).

Relationship Statement

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Research Network Clinical Trials Unit; MCRN CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynaecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The National Institute for Health Research (NIHR) Medicines for Children Research Network and National Cancer Research Network is part of the NIHR Clinical Research Network.

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Glossary

AE	Adverse Event
AI	Adverse Incident
AIC	Adverse Incident Centre
Attempted insertion of CVC	Needle through skin
CATS	Children's Acute Transport Service
CE	French phrase "Conformité Européene" which literally means "European Conformity". The symbol CE is used by manufacturers to show that a medical device meets the relevant requirements of the regulations and that it is fit for its intended purpose.
CFU	Colony Forming Units
CI	Chief Investigator
CPA	Clinical Pathology Accreditation
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
CVC	Central Venous Catheters
GP	General Practitioner
HES	Hospital Episodes Statistics
HTA	Health Technology Assessment
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
Kg	Kilograms
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MHRA	Medicines and Healthcare products Regulatory Agency
NRES	National Research Ethics Service
ONS	Office of National Statistics
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse – although the protocol refers to a RN it may be anyone who has been delegated the relevant duties on the delegation log.
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

1 PROTOCOL SUMMARY

Title: CATCH: CATheter Infections in Children

A randomised controlled trial comparing the effectiveness of heparin bonded or antibiotic impregnated central venous catheters (CVCs) with standard CVCs for the prevention of hospital acquired blood stream infection in children

The trial is a pragmatic, 3-arm randomised controlled clinical trial. Treatment allocation cannot be blinded to the clinician responsible for randomising a patient and inserting the CVC but will be concealed from patients, their parents and PICU personnel responsible for their care.

Phase: III

Population: The trial population is 1200 children less than 16 years of age admitted to PICU, who require insertion of a CVC for at least 3 days.. We will recruit children from two broad clinical groups: children admitted as planned surgical admissions (about one-third of all admissions) and children admitted as an emergency from the same or another hospital. Approximately 40% of PICU admissions are expected to be eligible. As this trial involves treatment in an emergency situation, we will be requesting ethical approval for a deferred consent process for children admitted as an emergency. The line can then be inserted without any delay and consent/assent will be sought as soon as possible ideally within 48 hours post randomisation, once the patient's condition allows.

Centres: The trial will take place in Paediatric Intensive Care Units (PICUs) in the UK, which have access to microbiology laboratories with Clinical Pathology Accreditation. Most of the PICUs that will participate in the trial have more than 600 admissions per year and fall within the Medicines for Children Local Research Networks.

Trial Duration: Patient follow-up until 48 hours after removal of the randomised CVC will be based on routinely recorded clinical data collated by the research nurse. Follow-up at 6 months will be ascertained from routine administrative data.

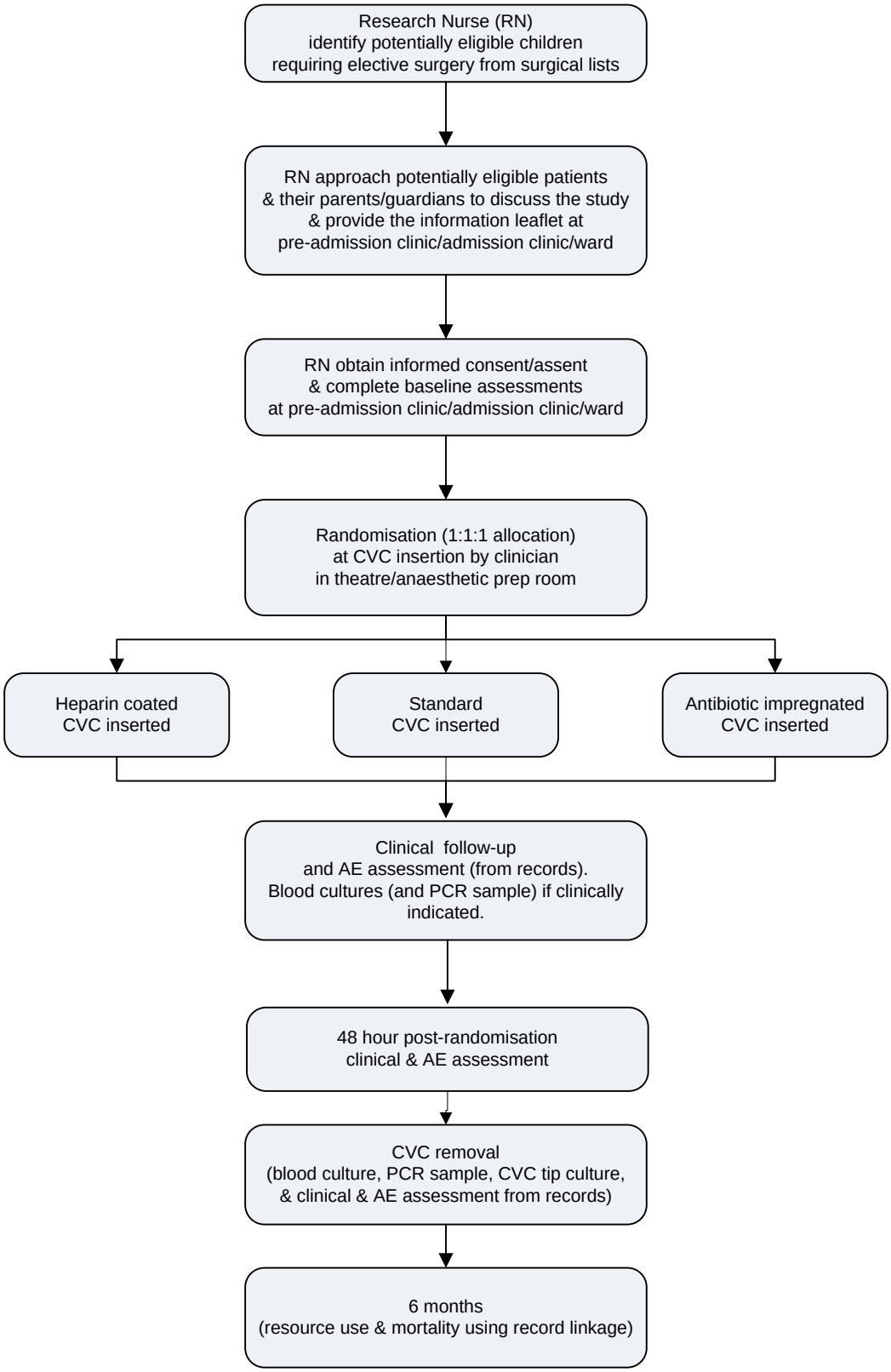
Description of Agent/ Intervention: We will randomly allocate children to a standard CVC, antibiotic impregnated CVC (minocycline and rifampicin), or heparin bonded CVC in a ratio of 1:1:1. All CVCs used in the trial are CE marked medical devices used for their intended purpose.

Objectives:

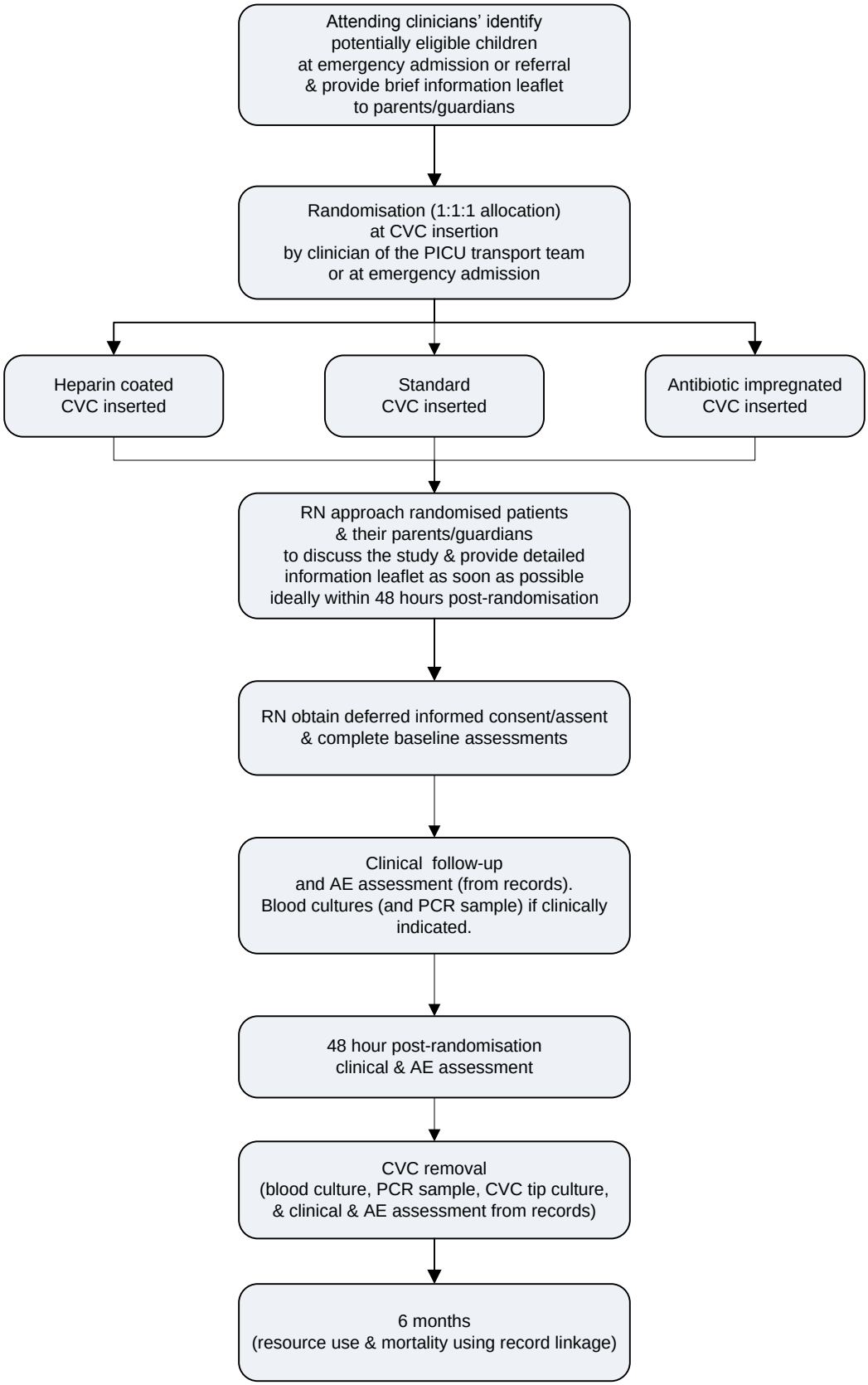
Primary: To determine the effectiveness of heparin bonded or antibiotic impregnated CVCs compared with standard CVCs for preventing hospital acquired blood stream infection.

Secondary Objectives include: Cost effectiveness, effectiveness of type of CVC in 3-way comparison for preventing hospital acquired blood stream infection, effect of type of CVC on clinical measures of care (duration of CVC insertion, antibiotic use, and stay), mortality at 30 days, adverse events on pathogen selection, antibiotic resistance, clinical evidence of CVC thrombosis, and thrombocytopenia.

Schematic of Trial Design: Elective Surgical Patients



Schematic of Trial Design: Emergency Admission Patients



2 BACKGROUND INFORMATION

2.1 Introduction

Review of the literature and rationale for the trial:
Central venous catheters (CVCs) are widely used in the NHS with an estimated 238,000 inserted each year (1). CVCs are used in intensive and high dependency care to provide venous access for resuscitation, drug delivery, intravenous feeding, monitoring, and blood sampling. Their main disadvantage is healthcare acquired infection. (2-5)

Nine systematic reviews and at least 37 randomised controlled trials (11,586 patients) demonstrate substantial benefits of impregnated compared with standard CVCs for catheter-related bloodstream infection.(1;6) The most recent review shows that heparin bonded or antibiotic impregnated CVCs offer the most effective options,(6) and a cost effectiveness analysis suggests that impregnated CVCs could be cost saving, though which type is most effective was not clear.(1) Heparin bonded CVCs act by reducing thrombus formation and bacterial adherence to thrombus, but the bonding agent, benzalkonium chloride, also has anti-infective properties. Antibiotic impregnated CVCs act by preventing biofilm formation and thereby prevent bacterial colonisation.

Despite the large number of trials of impregnated CVCs, uncertainty remains about the magnitude of any potential benefit for children in NHS Paediatric Intensive Care Units (PICUs) for the following reasons:

a) No trials have compared antibiotic impregnated with standard CVCs in children. CVCs used in children are much narrower than adult CVCs and the risk of thrombus formation, bacterial adhesion and infection is much higher. Consequently, the effect of antibiotic impregnated CVCs may be less.
b) Neither of the two trials of heparin bonded CVCs in children, and few of the trials of antibiotic impregnated CVCs in adults have been conducted in the context of strenuous efforts to reduce CVC infection through improved catheter care bundles. It is not known whether the relatively large reductions in relative risk and absolute risk seen in trials predating CVC care bundles would be sustained in PICUs where rates of infection have already been reduced by improved CVC care. Information is needed to address the policy question of whether investment in impregnated CVCs is warranted across PICUs in the UK.
c) Several systematic reviews raise concerns that the poor quality of previous studies means that the benefits of impregnated CVCs may have been overestimated. (1;6-8) Firstly, few trials reported good concealment of treatment allocation or blinding of clinicians to the intervention and many failed to account for losses or withdrawals, all factors that could lead to overestimation of the effect. (1;6)
d) Secondly, all previous trials relied on catheter related blood stream infection as the primary outcome measure, which requires positive cultures from the blood and catheter tip. This measure is highly susceptible to bias, as the tip can be easily contaminated during removal, and residual antibiotic in the catheter tip may inhibit culture in the laboratory.
e) Aside from the potential biases in measuring catheter related blood stream infection, impregnated CVCs may impact on all blood stream infections after CVC insertion and on the associated mortality, risk of complications and length of stay. No trials have determined the effect of impregnated CVCs on all blood stream infections in children in PICUs in the context of CVC care bundles.

Current practice

Antibiotic and heparin impregnated CVCs have been used for a long time in the USA. However, their use in NHS PICUs has been limited for several reasons. Firstly, lack of evidence for antibiotic impregnated CVCs in children; there is a single centre, company sponsored trial of antibiotic compared with standard CVCs that has recently started recruiting children undergoing elective cardiac surgery. The primary endpoint is catheter related blood stream infection (expected sample size of 500 over four years). Secondly, licensing; although heparin bonded CVCs had been used for several years under special arrangement by Great Ormond Street (for elective and emergency patients) and Birmingham Children's' Hospital (emergency patients only) they were not licensed in the UK until October 2006. Antibiotic impregnated CVCs were licensed in 2007. A pre-trial survey of 11 participating centres found that heparin bonded CVCs are used for all emergency and surgical patients by three units and for some patients in a further three units. Antibiotic impregnated CVCs are used for some patients in two units. Thirdly, timing; licensing of impregnated CVCs coincided with the introduction of CVC care bundles in many centres. The resulting fall in infection rates has blunted the drive for additional interventions. Finally, cost: the list price for standard CVCs is £38 compared with around £72 for heparin bonded or antibiotic impregnated CVCs. Despite these considerations and existing pattern of use, all 11 centres surveyed for the HTA ref: 08/13/47 trial stated that they would be willing to randomise children to a standard CVC, or to antibiotic impregnated or heparin bonded CVCs.

Clinical and policy questions addressed by the trial

The trial will address the policy question of whether impregnated CVCs should be adopted across all NHS PICUs and for which types of patients, based on evidence of clinical and cost effectiveness. It will provide valuable information that is currently not available for children and will address many of the problems associated with the quality of previous studies and their generalisability to the PICU and NHS setting. If impregnated CVCs are found to be superior, the trial will also inform the decision about which type of impregnated CVC to adopt. As the cost of purchasing both types of impregnated CVC is the same, decisions about which to adopt will be informed by differences in beneficial and adverse clinical outcomes (using primary and secondary outcome measures). The results will either clearly favour one option or will quantify the uncertainty underlying a trade-off of benefits and harms which can be used to inform decisions about the value of further 'head to head' comparisons.

2.2 Objectives

Primary objective:

1. To determine the effectiveness of heparin bonded or antibiotic impregnated CVCs compared with standard CVCs for preventing hospital acquired blood stream infection.

Secondary objectives:

2. To determine the cost effectiveness of heparin bonded or antibiotic impregnated CVCs compared with standard CVCs, based on the primary outcome and costs of acute care from the perspective of the NHS.

3. To determine the effectiveness of type of CVC in 3-way comparisons of heparin bonded versus antibiotic impregnated versus standard CVCs for preventing hospital acquired blood stream infection, based on culture, quantitative bacterial DNA, and clinical measures of infection.

4. To determine the effect of type of CVC on clinical measures of care (duration of CVC insertion, duration of antibiotic use, and duration of stay).

5. To determine the effect of type of CVC on mortality at 30 days.

6. To identify adverse effects of CVC type on pathogen selection, antibiotic resistance, clinical evidence of CVC thrombosis and thrombocytopenia.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Use of a standard CVC carries a small risk (about 10% for children with a CVC for three or more days) that the CVC will become infected and cause infection in the blood stream. This is usually treated rapidly but rarely can lead to complications. Most PICU's in the UK use standard lines.
Antibiotic impregnated CVCs have a theoretical but as yet unproven risk of generating infection with antibiotic resistant bacteria or encouraging the growth of certain pathogens.

Antibiotic impregnated CVCs contraindications described by Cook Medical Spectrum® and Spectrum Glide™ Central Venous Catheters Instructions for Use (September 2007), and from consultation with Cook Medical, are:

- Allergy or history of allergy to tetracyclines (including minocyline) or rifampin;
- Minocycline and rifampicin are agents that do not include any genotoxic effects except a possible teratogenic effect in pregnant women. They do not recommend the use of spectrum or spectrum glide CVCs in pregnant women.

Both of these contraindications are exclusion criteria for CATCH (see section 5.2).

There is a very small possibility that a patient may become sensitised to the antibiotics and develop an acute allergic reaction, but this is very rare and there are currently no known cases reported.

Heparin bonded CVCs have had no reported adverse events since their introduction in the 1980s. There is a theoretical risk of a rare platelet disorder that can occur with heparin therapy but this has never been reported to the manufacturer in association with heparin bonded CVCs.

Heparin bonded CVC contraindications described by Cook Medical Uncoated and Heparin-Coated Central Venous Catheters Instructions for Use (August 2007) are patients with a history of induced thrombocytopenia. This is an exclusion criterion for CATCH (see section 5.2).

There are no other risks involved in participating in the trial. No additional procedures will be involved over and above normal clinical care. A small amount of additional blood (approximately 0.5ml) will be drawn, whenever blood is taken for blood cultures, to allow PCR measurement of the amount of bacteria in the blood.

2.3.2 Known Potential Benefits

There is evidence from previous trials that antibiotic or heparin impregnated CVCs reduce the risk of infection. The pooled relative risk for catheter related blood stream infection with heparin bonded versus standard CVC is 0.16 (95%CI: 0.06, 0.43; 3 trials, 2 including children) and for antibiotic impregnated vs. standard CVC it is 0.28 (95%CI:0.15, 0.54; 7 trials, none in children).(1;7) However, the benefit for children in PICU is uncertain because CVC infections are being reduced anyway following a Department of Health initiative (Saving Lives) (9) to improve the care of CVCs.

3 SELECTION OF CENTRES/CLINICIANS

3.1 Centre/Clinician Inclusion Criteria

The trial will take place in PICUs in the UK. Any PICU can participate provided the following criteria are met:

a. Local R&D approval;
b. Signed non-commercial agreement between the centre and the sponsor;
c. Completion and return of 'Signature and Delegation Log' to the MCRN CTU;
d. Clinical Pathology Accreditation for their Microbiology Laboratories (www.cpa-uk.co.uk);
e. Receipt of evidence of (a), (b), (c) & (d) by MCRN CTU

3.2 Centre/Clinician Exclusion Criteria

a. Unable to fulfil the inclusion criteria

4 TRIAL DESIGN

4.1 Primary Endpoint

The primary outcome will be time to first blood stream infection defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC removal.

4.2 Secondary Endpoint(s)

a. Rate of blood stream infection during CVC insertion per 1000 CVC days
b. Time to CVC thrombosis - defined clinically
c. Time to a composite measure of blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria
d. Mortality by 30 days
e. Type of bacteria and fungi isolated from positive blood cultures
f. Resistance to minocycline or rifampicin of blood culture or CVC tip isolates
g. Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring
h. Time to randomised CVC removal
i. Length of stay requiring PICU
j. Total length of hospital stay for current episode (for up to 6 month post-randomisation)
k. Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVCs

Precise definitions of the outcomes and details of minimum quantities for blood samples are given below

Definitions of Primary Outcome

1. **Blood culture samples** will usually be taken from the central line in children to preserve venous access. It is not standard practice to routinely take peripheral blood samples for blood culture in PICUs. Practice guidelines for sampling will be circulated to all units. A minimum of 0.5ml will be taken from each lumen and inoculated into separate culture bottles for each lumen (note total volume is 1ml for neonates in whom double lumen CVCs are used). Sampling from multiple lumens will be used because sampling from one lumen reduces sensitivity for catheter related bloodstream infection.(10;11)
2. **Clinically indicated** means blood cultures taken because infection is suspected by the clinician either due to a change in the patient's condition (e.g. pyrexia, change in oxygen or inotrope requirements, hypotension, poor perfusion, increase white blood cell count and/or C–reactive protein) or a high likelihood of infection due to their risk status. Guidelines will be developed to improve standardisation of practice, but not to dictate what must ultimately be a clinical judgement. Blood cultures will be taken routinely at CVC removal, to allow comparison of isolate with the CVC tip culture. This culture will be counted as 'clinically indicated' if the line was removed for suspected infection.
3. **Positive blood culture** will be defined as: i) one or more positive blood cultures with a non-skin organism from a sample taken from one or more lumens of the CVC; or ii) the same organism isolated from 2 or more CVC lumens or from the same lumen within 48 hours. Skin organisms are coagulase-negative staphylococci, *Corynebacterium spp*. and *Proprionibacterium spp*. The primary outcome is the time to first occurrence of a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and before 48 hours after CVC removal.

Definitions of secondary outcomes

1. **Rate of blood stream infection - Second episode of blood stream infection** will be defined by a positive blood culture of a different isolate (in terms of species and antibiogram) from a sample taken more than 48 hours after the first positive culture and before 48 hours after CVC removal. Any positive blood cultures of the same isolate will be regarded as the same episode regardless of time since the first sample.
2. **A CVC related blood stream infection** will be defined by: i) the same isolate (species and antibiogram) from the CVC tip and from a blood culture sample taken more than 48 hours after CVC insertion and before 48 hours after CVC removal; ii) differential positivity of the same isolate in blood cultures taken from multiple lumens (i.e. not all positive or negative at the same sampling or the same skin commensal isolated from the same lumen but not all lumens on multiple occasions).
3. **High bacterial DNA load indicative of blood stream infection** will be defined as more than 0.25 pg of bacterial DNA per microlitre of whole blood detected from one or more CVC lumens taken more than 48 hours after CVC insertion and before 48 hours after CVC removal. High bacterial DNA load indicative of CVC related blood stream infection will be defined by differential results for high bacterial load from multiple lumens (i.e. not all above or below 0.25 pg/microlitre). Analysis of bacterial DNA load will be based on a minimum sample of 0.2ml from each lumen taken at the same time as the blood culture, placed in separate EDTA bottles for each lumen, and frozen at -20ºC till batching within 1 month of sampling. The rationale for using quantitative PCR measures of bacterial DNA is because most children in PICU will be on antibiotic treatment, which reduces the sensitivity of blood culture. PCR appears to be more sensitive than culture for detecting blood stream infection.(12-14)
4. **Culture negative infection** will be defined by a change in antibiotic treatment more than 48 hours after CVC insertion in the presence of negative blood cultures, no focus of infection, and clinical or laboratory signs of infection. The signs of infection should include ≥ 2 of the following: clinical signs - temperature >38^{o}C or temperature instability, haemodynamic instability (hypotension, mottled, poor perfusion, capillary refill>3s); or laboratory signs - C-reactive protein rising above normal range; white blood cell count (falling below 2 x 10^{9}/l or above 10 x 10^{9}/l or showing a rising trend).
5. **Positive CVC tip culture** will be based on a 4cm tip of the catheter, removed using a sterile procedure, and cultured according to standard methods.(15) A positive culture will be considered a secondary outcome only if the blood culture is positive for the same isolate and positive blood culture sample was taken within 7 days prior to the CVC removal. This is because CVCs are easily contaminated during removal.
6. **Exit site infection** will be defined by erythema extending 0.5cm or more for infants, 1cm for older children and 2cm for adolescents from the exit site of the CVC, or pus at the exit site.
7. **CVC thrombosis** will be defined clinically by: a) repeated failure to withdraw blood from the CVC; b) swollen limb due to suspected thrombosis; c) removal of the CVC because of clinical evidence of a blocked CVC; or d) ultrasound evidence of thrombus if routinely available.
8. **Antibiotic resistance** will be recorded as an **adverse event** if resistance is detected to minocycline or rifampicin using standard E tests on isolates from blood or the CVC tip. A recent review detected an excess of fungal infections associated with antibiotic impregnated CVCs,(3) but the difference was not significant due to small numbers. All microbiology laboratories supporting PICUs involved in the trial will be asked to use E strips to test for minocycline or rifampicin resistance in any isolates from blood cultures or CVC tips.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Patients with the following characteristics will be eligible for inclusion in the trial:

a. Less than 16 years of age;
b. Admitted to or being prepared for admission to an intensive care unit participating in the trial;
c. Require insertion of a CVC as part of good clinical management;
d. Require one of the CVC sizes available to the trial (see Appendix A for the list of CVCs);
e. Expected to require a CVC for at least 3 days;
f. Appropriate consent obtained (prospective consent for elective surgical patients, deferred consent for emergency admission patients).

5.2 Exclusion Criteria

Patients with the following characteristics will be excluded from the trial:

a. Patients previously enrolled in the CATCH trial;
b. Patients with a known allergy or hypersensitivity to tetracyclines (including minocycline), rifampicin or heparin;
c. Patients known to be pregnant;
d. Patients with a history of heparin induced thrombocytopenia;
e. Patients are in a randomised controlled trial that excludes participation in CATCH

6 RECRUITMENT AND RANDOMISATION

6.1 Screening

Surgical lists will be reviewed by clinical staff or the designated research nurse (RN) to identify potentially eligible elective surgical patients. Patients admitted as an emergency, who require a CVC, will be assessed by clinical staff, and randomised if they fulfil the eligibility criteria (see Section 5). A screening log of elective patients who are approached but not consented will be completed by the RN. Screening information on emergency patients who are randomised whether or not they consent will be collected by way of eligibility, randomisation and consent CRF (see section 6.6.2 for further details on CRF content).

6.2 Recruitment

Elective surgical patients and emergency admission patients will be recruited using different procedures.

6.2.1 Elective Surgical Patients

If a patient is assessed to be eligible for the trial (i.e. meets the eligibility criteria listed in section 5), the RN will provide written information (in advance if feasible) and will meet with patients and parents or legal representative at the earliest time that can be arranged pre-operatively to discuss participation. Where feasible, this will be at a clinic visit prior to admission, but may be during their pre-operative ward admission. The RN will allow the family sufficient time to discuss the trial and decide whether to consent to trial entry (see section 11.3 for consent procedures).

If written consent is provided by the parent or legal representative, and assent by the child where appropriate, the patient will be eligible to be randomised to the trial. The RN will inform the anaesthetist of the patient's participation and will complete the eligibility and randomisation CRF . The anaesthetist will randomise the patient and select the appropriate size and length of CVC to be inserted .

6.2.2 Emergency Admission Patients

All emergency admissions will be subject to the following procedures, even though in a few cases, time to CVC insertion may be less critical and there may be time to discuss the trial (see section 11.1 for ethical considerations).

Upon emergency admission to PICU or notification that an emergency retrieval is required and a patient is assessed to be eligible for trial participation by the clinical team (i.e. meets the eligibility criteria listed in section 5), the clinician responsible for inserting the CVC will take the randomisation pack and all three types of CVC in the appropriate length and size with them to the retrieval. At the patient's bedside, if the patient is still eligible for the trial, they will be randomised and insertion of the CVC of the type allocated will be attempted. The patient, parent or guardian will be given a leaflet containing brief details about the trial. Where feasible this will be prior to CVC insertion. For the reasons described in section 11.1 no attempt will be made to obtain fully informed consent for the trial from the parent/legal representative prior to CVC insertion. The RN will be notified of the randomisation and will approach parents/guardians as soon as possible ideally within the next 48 hours to discuss the trial, offer more detailed written information, and allow sufficient time for the parents/guardians and child to consider participation (see section 11.3 for consent procedures).

Written informed consent will be sought for data to be collected from routine medical records and for additional blood samples to be taken (see section 8). If written consent is provided, the patient will be followed-up in the trial. The RN will complete the admission details from clinical records (see section 0). Other clinical and laboratory data will be collected from the time of consent. As it will not be possible to involve critically ill children in the consenting process, assent by the child will be sought as their condition allows. If parent/legal representative consent is not provided, see section 6.6.

For children who die before consent can be obtained, we are sensitive to the needs of bereaved families and the attending clinician/RN and bereavement councillor as appropriate will notify parents/guardians of the research involvement. A parent/legal representative information sheet will be given to the parents/guardians specifically for when the child has died. Deferred informed consent to the trial will be sought as described in sections 11.3, and if obtained, data will be collected from clinical records (see section 8).

6.3 Randomisation

The allocated trial number and CVC type will be provided to centres in the form of a series of sequentially numbered randomisation packs. Separate series of randomisation packs will be provided for emergency and elective patients. The randomising clinician will select the next sequentially numbered, sealed pack from either the elective surgical or the emergency admission pack series as appropriate. Each pack will contain an opaque, pressure-sealed envelope that will give the randomisation allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. The pack will also contain an unblinding envelope and a pre-paid envelope.. This is so that page 1 of the randomisation envelope containing information on the allocation and details of the actual CVC inserted can be returned to the MCRN CTU in the pre-paid envelope, and pages 2 & 3 of the randomisation envelope containing details of the actual CVC type inserted can be stored securely in the unblinding envelope on site in an accessible location. The RN will also record the actual received CVC details onto the website www.catchtrial.org.uk/treatment.aspx. This information is stored as a back-up for the unblinding envelopes. For further details on the administration and recording of the allocated CVC see section 7.3.

The randomisation packs will be securely stored near to the boxes containing CVCs for trial use. The CVC boxes (sets) will be labelled as supplied by the manufacturer, but the RN will also stick a trial label containing a space for the randomisation number and patient initials onto the CVC set cover. The attending clinician will select and insert a device of the type allocated, and also of an appropriate length and size, estimated using the patient's weight and age (see appendix A for the list of CVC sizes available).

The RN will check daily to ensure that the correct number of randomisation packs is present, that they are intact and that the sequential numbering system is maintained. Any discrepancies will be immediately reported to the MCRN CTU. The RN will also ensure that there are an adequate selection of CVCs available for the trial, and will liaise with the local procurement department (and the MCRN CTU) as necessary.

Note: The randomised CVC or if this is not inserted, the first CVC inserted within 12 hours from randomisation will be classed as the trial CVC and followed up accordingly

If a trial participant requires an additional CVC(s) at the same time as the trial CVC (i.e. in parallel), the default CVC for that centre will be used.

If a trial participant requires a subsequent CVC(s) after the trial CVC has been removed (i.e. in series), the subsequent CVC(s) will not be randomised and the default CVC used at that centre will be used.

6.4 Patient Transfer

If a patient is transferred to another hospital with the trial CVC still in situ, and it is deemed appropriate by the centres involved and the MCRN CTU, the participating centre to whom the patient is transferred should take over responsibility for the patient to enable collection of follow-up data until 48 hours after the trial CVC is removed. The transfer of responsibility for the collection of follow-up data should be documented in the investigator site files of both centres involved and the MCRN CTU should be notified in writing. A copy of the CRFs and consent/assent forms should also be provided to the new centre. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs patient remains the responsibility of the original centre.

If transfer of responsibility is not possible, the research nurse should liaise with staff at the relevant hospital to collect follow up data from the routine clinical records until 48 hours after the CVC is removed.

In both cases, resource use and mortality will be obtained at six month follow-up using PICANet data, hospital episode statistics (HES) and the office of national statistics (ONS).

6.5 Patient Withdrawal

In consenting to the trial patients are consented to the trial intervention, and follow-up sample and data collection. Patients are free to withdraw consent at any time without providing a reason.

For elective patients they are free to withdraw from the trial intervention prior to CVC insertion. Once the CVC has been inserted it will be removed when clinically indicated. . They will also receive appropriate care under medical supervision until the symptoms of any adverse events resolve or the patient's condition becomes stable. Blood cultures and CVC tip culture would still be undertaken if clinically indicated and deemed necessary as part of routine clinical care. In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinical teams or the patients and their parent/legal representative.

Where the parent/legal representative (or patient where applicable) wishes to withdraw consent from any component of the trial there will be clarification whether this is withdrawal from follow-up sample or data collection, or a combination and a withdrawal CRF should be completed. Centres should explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the parent/legal representative (or patient where applicable) explicitly withdraws consent for follow-up.

Where the parent/legal representative (or patient where applicable) wishes to withdraw consent for the whole trial, the patient will not contribute further data to the trial and anonymised data collected up to the point of withdrawal of consent will be included in the analyses unless the patient explicitly states that this is not their wish.

6.6 Consent Not Provided

6.6.1 Elective Surgical Patients

If consent is not provided for elective surgical patients, they will not be randomised to the trial.

To enable monitoring of refusals to participate minimal data for each elective surgery patient who is approached but not randomised will be recorded by the RN and returned to the MRCN CTU on a monthly basis, including:

a. Centre/PICU;
b. Date approached;
c. Date of Birth (if parent/guardian provides permission);
d. Reason not randomised

Reasons for non-consent will be asked routinely but it will be made clear to the parents/legal guardian that they do not have to provide a reason unless happy to do so.

6.6.2 Emergency Admission Patients

If the parent/legal representative of an emergency admission patient does not consent, no further data will be collected and the child will be recorded as not consented. The CVC will be removed when clinically indicated. They will receive appropriate clinical care for any adverse events related to the CVC.

To enable monitoring of CVC insertion following randomisation, and approach and refusals to participate, minimal data for each patient who is randomised but is not consented will be collected on the Eligibility and Randomisation CRF and Consent CRF* by the RN and returned to the MRCN CTU on a weekly basis, including:

a. Centre/PICU;
b. Date randomised;
c. Patient Date of Birth
d. CVC details (including if not attempted, reason not attempted; if attempted but not inserted, reason not inserted)
e. Reason not consented

As for elective surgical patients, reasons for non-consent will be asked routinely but it will be made clear that they do not have to provide a reason unless happy to do so.

If a patient dies before consent can be obtained, the process described in section 6.2.2 will be followed. A death CRF detailing the date and time of death, and the relationship to the trial intervention will be completed by the RN and returned to the MCRN CTU within 7 days of the clinical research team becoming aware of the event (see section 10).

*Please note consent form is attached to the parent information sheet and is read and filled in by the parent. The consent CRF is completed by the RN and records whether consent was obtained and reasons if not consented (where provided).

7 TRIAL INTERVENTIONS

7.1 Introduction

Patients will be randomised to standard CVCs, antibiotic impregnated (minocycline and rifampicin) CVCs or heparin bonded CVCs in a ratio of 1:1:1. This ratio reflects uncertainty about which of these three types is best in terms of the risk of bloodstream infection and cost effectiveness.

7.2 Packaging, Labelling, Storage and Stability

The CVCs used in the trial will be sourced via usual NHS procurement arrangements from Cook Medical (http://www.cookgroup.com) according to Cook Medical's standard business procedures. Only the devices listed in Appendix A will be supplied for trial use as per the pricing structure detailed in section 15.1.2.

All variations allowed in the trial design are CE-marked medical devices used in accordance with the manufacturer's instructions for their intended purpose.

The following changes to the manufacture of the CVCs may occur during the course of CATCH:

- European regulatory approval for the addition of hydrophilic coating to Cook 4Fr and 5Fr antibiotic-impregnated CVCs is in progress.
- The current CLC200®Injection Caps may change to MicroCLAVE® Neutral Displacement Connectors (both manufactured by ICU Medical), which will result in a one component part change to Cook CVC sets.

Packaging of the CVC sets are identical, but to adhere to licensing requirements the manufacturer (Cook Medical) routinely labels the CVC package with the product code number and letters BH (indicating heparin bonded), ABRM (indicating antibiotic impregnation), or no additional letters (indicating standard).

The CVCs should be stored in accordance with local policy clearly marked for CATCH trial use, where they are readily accessible to the clinician responsible for randomisation and line insertion. In some centres, stocks for elective and emergency cases will be kept in separate locations. Cook Medical recommends that the CVCs should be stored in a dark, dry, cool place. All heparin-bonded CVC sets and antibiotic-impregnated CVC sets have a 12-month expiry date from the date of manufacture. All standard CVC sets have a 36-month expiry date from the date of manufacture. All European stock of Cook CVC sets is shipped from the USA and has a minimum lead time of 12 weeks. It will be the responsibility of the centre in liaison with the local procurement department to ensure the disposal of those supplies when the shelf life expires and arrange resupply where appropriate. The RN and MCRN CTU will monitor that trial allocated CVCs are being used within their shelf life.

7.3 Administration of Trial Interventions

To administer the randomly allocated CVC:

a. **The randomising clinician** will select and insert the allocated CVC type of an appropriate length, lumen number and gauge, estimated using the patient's weight and age (see Appendix A of a list of acceptable CVCs).

b. After insertion has been attempted, **the inserting clinician or RN** will complete the trial label on the CVC set cover (randomisation number and patient initials) and will remove the CVC set cover from the CVC set. The CVC set cover also has a large label provided by the manufacturer adhered to it. This label carries the CVC type, gauge, lumen, length, expiry date and product code number with the letters BH (indicating heparin bonded), ABRM (indicating antibiotic impregnation), or no additional letters (indicating standard). The barcode sticker will be peeled off this label and placed in the box provided on page 1 of the randomisation envelope. Page 1 of the randomisation envelope should then be placed into the prepaid envelope and posted to the MCRN CTU ideally within 24 hours so that correct allocation can be verified and use within the shelf life can be monitored.

c. Access the website www.catchtrial.org.uk/treatment.aspx using your password and login and input the CVC details the patient received. The process for updating the website will be provided in separate guidance as part of the Investigator Site file.

d. Pages 2 & 3 of the randomisation envelope will placed in the unblinding envelope together with the CVC set cover and stored securely on site in an accessible location.

   The allocated CVC type should not be disclosed to the rest of the clinical team. If any labels are placed in the patient's medical records identifying the CVC type (see b above), the identifying letters should crossed out of the medical records by the trial RN.

e. If the initial attempt at insertion is unsuccessful, or a different size is needed, the allocated CVC type will be used for the subsequent attempt on the same patient. Should an envelope be opened and the allocation subsequently not used, this will be recorded and the randomisation envelope returned to the MCRN CTU. It will not be retained at centre nor used for the next eligible patient.

The attempted insertion of the randomised CVC, or if not attempted, the first attempted CVC insertion within 12 hours from randomisation will be followed-up as part of the trial. The CVCs will be removed when clinically indicated. The time, date and reasons for removal will be recorded by the RN from the patient's medical records (see section 8).

Note: If a trial participant requires an additional CVC(s) at the same time as the trial CVC (i.e. in parallel), the default CVC for that centre will be used.

If a trial participant requires a subsequent CVC(s) after the trial CVC has been removed (i.e. in series), the subsequent CVC(s) will not be randomised and the default CVC used at that centre will be used.

7.4 Concealment of Allocation, Disclosure & Unblinding

Ideally, the allocation of CVC type would be completely blinded to all personnel involved in the trial. This is not possible because of:

- Differences in appearance that are visible at insertion or removal. Antibiotic CVCs can be distinguished by a gold strip and heparin/standard by a blue strip on the part of the CVC that is inside the patient when the catheter is in situ.
- Packaging of the CVC sets are identical but licensing requirements are such that the items carry a label coded to indicate the CVC type.
- Costs of manufacturing coded, identical CVCs, solely for the trial and ensuring adequate supplies of all sizes and types would be prohibitive.

Whilst blinding is not possible, it is possible to minimise disclosure of allocation because the three types of CVC look identical after insertion into the vein and the clinician inserting the CVC is unlikely to be directly involved in day to day care of the patient on PICU. The importance of non disclosure of this information will be stressed during trial training.

- For elective surgical patients, the CVC will be inserted by the anaesthetist in the pre-operation room.
- For emergency patients retrieved from other hospitals, the CVC will be inserted at the referring hospital by a member of the retrieval team. Where designated retrieval teams exist (e.g. the Children's Acute Transport Service - CATS team in London), retrieval is undertaken by staff based outside the PICU using a supply of CVCs kept in the CATS office. In other centres, practice will vary and retrieval may be undertaken by a member of PICU staff who may contribute to the care of the child at some point during their stay. This will be recorded.
- For emergency patients admitted from the same hospital, the CVC will be inserted on PICU. Hence, in these instances, the same clinician may be involved in insertion and ongoing care. This will be recorded.

The clinician and any assistant present during insertion or removal will be requested to not disclose the allocation unless deliberate unblinding is required (see section 7.4.2). When the person involved in insertion contributes to the subsequent care of the child, the information will be documented with their involvement in the decision process relating to clinically defined bloodstream infections.

7.4.1 Accidental Disclosure to Staff and Parents and/or Patients

If the CVC allocation is accidentally disclosed to staff at any other time during the patient's participation in the trial, an Unblinding CRF (see section 7.4.2) should be completed and returned to the MCRN CTU within 24 hours of the disclosure.

7.4.2 Deliberate Unblinding of Individual Patients During Trial Conduct

If simply removing the CVC is a viable option for the patient's care, it should not be necessary for unblinding to occur.

Unblinding to the clinical team, RN, parent or participant should be considered only when knowledge of the allocation is deemed essential for the participant's ongoing care to enable treatment of a serious adverse event(s) (e.g. in the case of an allergic reaction to the CVC). In general, unblinding during conduct of the clinical trial should only occur when there are compelling medical or safety reasons to do so.

If unblinding is deemed necessary, the following unblinding procedure should be followed:

a. Where possible (during office hours), consent for individual unblinding should be made via the Trial Coordinator at MCRN CTU who will seek agreement of the Chief Investigator.
b. The unblinding envelope prepared by the inserting clinician or trial RN containing pages 2 & 3 of the randomisation envelope and the CVC set cover, which has been stored on site in an accessible location, can be used to obtain the CVC allocation.
c. The RN will check the integrity of these envelopes as per the randomisation allocation stock. Any discrepancies will be immediately reported to the MCRN CTU.
d. As a back-up, there will also be a 24 hour web accessed central unblinding system. Access will be restricted to password and login. Details will be provided in separate guidance as part of the Investigator Site file.

24 hour unblinding web address: www.catchtrial.org.uk/treatment.aspx

Note that the MCRN CTU is open from 0900 – 1700, Monday – Friday, excluding public holidays
If there are any problems with website, please contact the MCRN CTU helpdesk on:
0845 68 00 951
Or via email on helpdesk@mcrnctu.org.uk

e. The RN will ensure all necessary CRFs are completed and submitted to MCRN CTU (if possible, completed before unblinding is performed). N.B. If unblinding has occurred, the participant will still be followed up as described in section 8.
f. All instances of unblinding should be recorded on the Unblinding CRF and returned to the MCRN CTU within 24 hours including:
    i. Date information needed & date of unblinding
    ii. Detailed explanation of circumstances and reason for unblinding;
    iii. Recipients of the unblinding information;
    iv. If accidental unblinding, action to prevent further occurrence of unblinding.

7.4.3 Trial Closure

The end of the trial will be considered as the date of the final database lock. In the event that the trial is closed prematurely by the Trial Steering Committee, on the recommendation of the Data and Safety Monitoring Committee, for reasons such as clear differences between

safety of trial interventions, the end of the trial will still be considered as the date of the final database lock.

MCRN CTU will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the investigator site file

7.5 Accountability Procedures for Trial Interventions

As the CVCs used in the trial will be sourced via usual NHS procurement arrangements from Cook Medical, the RN will liaise with the local procurement department to ensure that the centre has the following in place and will report any problems to the MCRN CTU:

- A record of deliveries and administration of device/s;
- A system in place that allows for the retrieval of defective products;
- Ensure that there are enough devices within their shelf life assigned to be used in the trial and that they are given to the participants free of charge;
- Ensure devices are used in compliance with the protocol requirements and accountability records are maintained as per local policy;
- Ensure that the CVCs are stored where they are readily accessible to the clinician responsible for randomisation and line insertion;

Once the trial has closed at a centre, Cook Medical will be informed indicating the end of the CVC pricing structure detailed in section 15.1.2. All CVC supplies already procured will remain the property of the procuring institution.

7.6 Assessment of Compliance with Trial Interventions

Allocated trial CVCs will be inserted by the attending clinician. The details of all insertions will be recorded in the eligibility and randomisation CRF. The allocation type (standard, heparin or antibiotic) must NOT be recorded in the medical records during the patient's participation in the trial. The RN and MCRN CTU will monitor that trial allocated CVCs are being used within their shelf life. The MCRN CTU will monitor compliance of centres sending the randomisation envelopes to the MCRN CTU and will check the returned randomisation envelopes to assess the level of compliance of the CVC with the randomisation allocation. See section 13 for further details on monitoring.

7.7 Concomitant Medications/Interventions and Dose Modifications

Antibiotic (including antifungal) medication and anti-coagulant prophylaxis/treatment including start and stop dates for each type of treatment, and route of administration will be recorded at baseline for 72 hours before randomisation and documented throughout trial participation until:

- 48 hours after randomisation if CVC insertion was not attempted within 12 hours from randomisation;
- 48 hours after attempted insertion if a CVC insertion was not successful within 12 hours from randomisation;
- 48 hours after CVC removal if CVC insertion was successful within 12 hours from randomisation (see section 8 for details).

If a patient has a known allergy or hypersensitivity to tetracyclines (including minocycline), rifampicin or heparin, or a history of heparin induced thrombocytopenia, they should be excluded from the trial. Patients known to be pregnant should also be excluded from the trial.

When reporting an Adverse Event all concomitant medication/interventions will be recorded as per section 10.

The trial CVC will be removed when clinically indicated. The time, date and reasons for removal will be recorded on the CVC insertion follow-up CRF by the RN (see section 8).

If a trial participant requires an additional CVC(s) in parallel to the trial CVC, the default CVC used at that centre will be used. If a trial participant requires a subsequent CVC(s) after the trial CVC has been removed (i.e. in series), the default CVC used at that centre will be used.

7.8 Co-enrolment Guidelines

To avoid potential confounding issues, ideally patients should not be recruited into other trials using CVCs as the trial intervention. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the CATCH trial this must first be discussed with the MCRN CTU who will contact the Chief Investigator.

8 ASSESSMENTS AND PROCEDURES

Trial centres will be initiated once all global (e.g. local R&D approval) and trial-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the MCRN CTU. Training in the protocol requirements and the requirements outlined in CTRC SOPs TM017 and TM018 will be disseminated to PICU personnel at a trial launch meeting and continually on site for new staff. Personnel with responsibility for ensuring all staff follow the standardised blood sampling procedures will be so trained prior to commencing the trial. Adherence to the protocol procedures will be monitored throughout the trial by the Trial Coordinator/Data Manager. Participating centres will be expected to each maintain a file of essential trial documentation (Investigator Site File), which will be provided by the MCRN CTU, and keep copies of all completed CRFs for the trial. Data collection will use a combination of paper CRFs (with no carbon copies) and electronic data collected retrospectively from the hospital episodes statistics database, office of national statistics and from PICANet data (see section 13.2 for details on the data capture methods).

All paper CRFs should be completed as described in section 13.2.1 by personnel named on the delegation log as authorised to do so, usually the RN, and returned to the MCRN CTU within 7 days of final clinical follow-up at the centre, unless stated otherwise.

Eligibility, randomisation details including administration of the CVC and consent details will be collected as described in section 6 and 7.3. Patient details including initials date of birth, postcode, NHS number and PICANet ID will be reported on the consent form, separate to clinical data. Once written informed consent has been obtained from the parent or legally acceptable representative, the RN will collect admission characteristics using the admission characteristics CRF and the patient will be followed-up in the trial.

8.1 Schedule of Assessments for Elective Surgical Patients

					Follow-Up Schedule					
						CVC Insertion only				
Procedures		Screening	Consent[1]	Randomisation[2]	Admission Characteristics	Clinically indicated follow-up[3]	CVC Removal	48 Hours After CVC Removal	End of Final follow-up at centre[4]	6 months	Transfer / Discharge
Screening of surgical lists to identify potentially eligible patients		X									
Signed Consent Form			X[1]								
Assessment of Eligibility Criteria		X	X[1]								
Demographics					X						
Review of Medical/Surgical History					X						
Review of Concomitant Antibiotics (including Antifungals)					X	X[3]		X			
Review of Concomitant Anticoagulants					X		X		X[4]		
Review of Co-morbidities					X				X[4]		
Trial Intervention (allocation & administration of CVC)				X[2]							
Details of CVC Use				X[2]			X	X			
Details of Other Devices Inserted					X						
Clinical Indices of Infection						X[3]	X				
Assessment of Adverse Events						X[3]	X	X			
Clinical Laboratory Cultures & Resistance Profiles	Blood Culture					X[3]	X				
	Blood for PCR Bacterial DNA analysis					X[3]	X				
	CVC Tip Culture						X				
Resource Use	RN completed CRF				X						X
	Data from finance, IT and admission departments									X	
	PICANet Database									X	
	Hospital Episodes Statistics Database									X	
	Office of National Statistics									X	

Procedures/assessments where patient/parent contact time is required over and above clinical practice is highlighted by shading.

[1] Consent at pre-admission clinic, admission clinic or ward.

[2] Conducted by the randomising clinician when CVC required. Intervention allocation (CVC type) will be securely sealed with two envelopes, one will be returned to MRCN CTU and one will be securely stored on site.

[3] The Research Nurse will review and complete a progress log daily where possible and a minimum of every 2 days(except at weekends when it will be completed retrospectively), from time of randomisation to the relevant time point(see section 8.4).

[4] See section 8.4 for relevant time point

8.2 Schedule of Assessments for Emergency Admission Patients

Procedures		Randomisatio[1]	Consent[2]	Admission Characteristics	Follow-Up Schedule					
					Clinically indicated follow-up[3]	CVC Insertion only		End of Final follow-up at centre[4]	6 months	Transfer / Discharge
						CVC Removal	48 Hours After CVC Removal			
Screening of surgical lists to identify potentially eligible patients										
Signed Consent Form			X[2]							
Assessment of Eligibility Criteria			X[2]							
Demographics				X						
Review of Medical/Surgical History				X						
Review of Concomitant Antibiotics (including Antifungals)				X	X[3]		X			
Review of Concomitant Anticoagulants				X		X		X[4]		
Review of Co-morbidities				X				X[4]		
Trial Intervention (allocation & administration of CVC)		X[1]								
Details of CVC Use		X[1]				X	X			
Details of Other Devices Inserted				X						
Clinical Indices of Infection					X[3]	X				
Assessment of Adverse Events					X[3]	X	X			
Clinical Laboratory Cultures & Resistance Profiles	Blood Culture				X[3]	X				
	Blood for PCR Bacterial DNA analysis				X[3]	X				
	CVC Tip Culture					X				
Resource Use	RN completed CRF			X						X
	Data from finance, IT and admission departments								X	
	PICANet Database								X	
	Hospital Episodes Statistics Database								X	
	Office of National Statistics								X	

Procedures/assessments where patient/parent contact time is required over and above clinical practice is highlighted by shading.

[1]Conducted by the randomising clinician when CVC required. Intervention allocation (CVC type) will be securely sealed with two envelopes, one will be returned to MRCN CTU and one will be securely stored on site.

[2]Deferred consent will be obtained. Typically consent will be ideally within 48 hours of randomisation.

[3] The Research Nurse will review and complete a progress log daily where possible and a minimum of every 2 days(except at weekends when it will be completed retrospectively), from time of randomisation to the relevant time point(see section 8.4).

[4] See section 8.4 for relevant time point

8.3 Schedule for Follow-up

Table1: Schedule for follow-up time points

Situation	Consented participants will be followed-up
CVC (randomised or other) insertion not attempted within 12 hours from randomisation	48 hours after randomisation
Randomised CVC insertion attempted but not successful and no other CVC successfully inserted within 12 hours from randomisation	48 hours after attempted insertion of the randomised CVC
If randomised CVC insertion not attempted but other CVC insertion attempted but not successful within 12 hours from randomisation	48 hours after attempted insertion of the other CVC
Randomised CVC inserted within 12 hours from randomisation	48 hours after removal of randomised CVC
Randomised CVC not successfully inserted but other CVC inserted within 12 hours from randomisation	48 hours after removal of other CVC

- If there are multiple attempts followed by insertion the patient would be followed-up until the latest relevant time point.

- The time points in table 1 will be referred to hereafter as 'final clinical follow-up'.
-
- The RN should also follow-up the patients using the transfer/discharge CRF until they are discharged home from hospital or until death if death occurs within the hospital admission.

- Linkage to routine electronic databases (PICANet, Hospital Episode Statistics and Office of National Statistics databases) will occur at 6 months post-randomisation (see section 8.6.1).

The RN will complete a progress log, daily where possible and a minimum of every 2 days (except at weekends when it will be completed retrospectively) until final clinical follow-up (see table 1)

The progress log will be used to monitor:

- The presence of clinically indicated infection (see section 8.4);
- Sampling for blood cultures (see section 8.4);
- Blood sampling for bacterial DNA detection (see section 8.4);
- Related adverse events (see section 8.5 and 10)
- Thrombosis (see section 8.5 and 10)
- CVC tip culture at CVC removal (see section 8.4)

At the end of final clinical follow-up (see table 1), both the antibiotic (including antifungal) and anticoagulant medication including start and stop dates for each type of treatment, and route of administration will be recorded on the respective CRFs.

8.4 Procedures for Assessing Efficacy

For all patients from the time of randomisation until final clinical follow-up(see table 1 in section 8.3)
Clinically indicated blood samples should be taken from the time of randomisation until final clinical follow-up for all situations listed in table 1 (see section 8.3). The RN will monitor blood culture sampling and ensure that the CVC tip is sent for culture at removal. The RN will need to chase the culture results and resistance profiles, and ensure that the blood samples for bacterial DNA detection were taken.

Clinical signs of infection may include any of the following in the 24 hours prior to sampling:

a. Increased or very low white blood cell count;
b. Increased levels of C-reactive protein;
c. Temperature instability;
d. Cardiovascular instability;
e. Blood sugar instability.

Detailed instructions on taking blood cultures and blood samples for 16s bacterial DNA detection will be provided to centres.

Blood Culture Samples

- Blood for blood cultures is best taken prior to commencing antibiotics. However, it is still worth taking blood cultures even if already on antibiotics.
- A minimum of 0.5ml should be taken from each lumen.
- If possible ALL lumens should be sampled (using a separate syringe in each case) and inoculated into separate culture bottles for each lumen. Sampling from multiple lumens will be used because sampling from one lumen reduces sensitivity for catheter related bloodstream infection.
- The sample site and lumen sampled should be clearly recorded on the blood culture form, bedside log and in the sampling CRF.
- The primary outcome will be based on any positive blood culture (see definitions in section 4), which may include samples from peripheral blood culture samples, where these are clinically indicated, taken between 48 hours after CVC insertion to 48 hours after CVC removal.

Although the infection is objectively measured in the laboratory, the decision to take a sample requires clinical judgement. The more samples taken, the greater the chances of detecting a positive result, particularly due to skin organisms. Also, sampling technique, sample volume, and whether samples are taken from all catheter lumens, affect the likelihood of obtaining a positive result. Each patient will have a bedside log and an accompanying flowchart showing the process for taking blood samples. The bedside log should be used by all staff to record the details of the sampling procedure. These details should then be transposed into a sampling CRF by the RN. Certain personnel named on the delegation log will be responsible for ensuring all staff at a centre, who may take the patient's blood, are aware of the bedside log, flowchart and the sampling procedures for the trial.

All cultures will be undertaken using standard culture methods by Clinical Pathology Accredited microbiology laboratories (www.cpa-uk.co.uk) supporting the PICUs involved in the trial. Clear criteria for defining a positive blood culture is provided in section 4.

The laboratories will also use E strips (provided by the trial) to test for minocycline or rifampicin resistance in any isolates from blood cultures or CVC tips (see CVC removal below).

Blood samples for bacterial DNA detection
A minimum sample of 0.2ml (preferably 0.5mls) from each CVC lumen if possible should be taken at the same time as EVERY blood culture sample, placed in separate EDTA bottles for each lumen, and frozen at -20ºC as soon as possible and no later than 24 hours after taking the sample.

These samples will be analysed centrally for bacterial DNA using quantitative PCR measures. The RN is responsible for freezing, batching and sending the blood samples for bacterial DNA detection every 3 months or when the box is full to the central microbiology laboratory. Detailed instructions on sampling, storage and transfer to the central laboratory for analysis will be provided to the centres see section 8.6.2 for further details on the analysis and data collection).

Please ensure that the lumen from which blood has been collected is recorded on *both* the blood culture bottle, bedside log and on the bacterial DNA sample tube.

For all patients who have a CVC inserted within 12 hours from randomisation

At CVC removal, the attending clinician/RN will routinely take:

a. A blood culture sample as described above;
b. A blood sample for bacterial DNA detection as described above;
c. A CVC tip culture.

If a patient dies, cultures should NOT be taken from the CVC if the CVC is removed after death. However, every effort should be made to take cultures before death if infection is likely to have contributed to the patient's deterioration. If possible a CVC tip culture should be taken as soon as possible after death.

Detailed instructions on preparing and analysing a CVC tip culture will be provided to the centres.

The blood culture will allow comparison of the isolate with the CVC tip culture. These cultures will be counted as 'clinically indicated' if the line was removed for suspected infection.

At 48 hours after CVC removal the RN will record the details of any additional CVC(s) inserted from the time of insertion until 48 hours after removal.

8.5 Procedures for Assessing Safety

Adverse events whose causal relationship to the trial intervention (CVC) is assessed and judged by the investigator to be possibly, probably, or almost certainly related to the intervention, which occur from the time of CVC insertion until 48 hours after trial removal or from time of attempt of CVC insertion until 48 hours afterwards if CVC insertion was unsuccessful, will be reported as they arise as described in section 10. The RN will use the progress log to prompt review any adverse events. An independent Data and Safety Monitoring Committee (IDSMC) will be convened to monitor safety data (see section 16.3 for further details).

8.6 Other Assessments

8.6.1 Health Economics

The economic analysis will adopt the perspective of the NHS and will be based on the primary trial endpoint of blood stream infections.

Routine Data Collection

- The trial RN will complete the transfer/discharge CRF for each transfer until the patient is discharged home.
- The trial health economist will contact the Finance departments, Information Technology and Patient Administration departments of each recruiting centre to inform them of CATCH, and that a future request will be made for data on trial participants' healthcare resource use.
- Six months after randomising the last patient at each recruiting centre, the trial health economist will contact the Finance departments of each centre, and submit a request (via the CTU, to maintain patient anonymity) for: Ward name; ward speciality (e.g. paediatric, paediatric ICU, special care baby unit etc.); the average cost per bed day on the ward; and the financial year the costs refer to. The health economist will also contact the Information Technology or Patient Administration Departments of each centre and submit a request (via the CTU, to maintain patient anonymity), for: Patient NHS No (or some other means of linking the patient to the trial); ward name; ward speciality (if possible); start date on the ward; end date on the ward; number of occupied bed days on the ward.
- Paediatric Intensive Care Audit Network (PICANet) data will be used to obtain the PIM2 scores and data relating to patients' stay in PICU to six months follow-up (see Appendix C for PICANet data collection forms).
- Data on Hospital Episode Statistics (HES) from the beginning of the financial year prior to baseline, to six months follow-up will be accessed centrally via the NHS Information Centre.
- Death data will be collected from the Office of National Statistics (ONS) up to six months follow-up.

Collection of PICANet, HES and ONS data will be administered by the MCRN CTU and will follow a standard procedure described in section 13.2.2.

Analysis

The economic analysis will entail the valuing of healthcare resource use by calculating the sum-product of each item with the corresponding unit cost, derived from a variety of sources, including routine hospital data (NHS reference costs) and nationally published data.(16) Given that the economic question under consideration is one of technical efficiency (i.e. which of the three CVCs is most cost-effective), the economic analysis will be based on the primary outcome in order to calculate the incremental cost per bloodstream infection

averted. Costs and benefits will not be discounted, as the time horizon of analysis does not exceed 1 year.

Incremental cost-effectiveness ratios (ICERs) will be estimated, with uncertainty in parameter estimates being addressed through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves. (17) Regression analyses of cost primary outcome measure, with age, baseline PIM2 score, baseline costs (1-month prior to baseline) and other covariates as deemed appropriate, will be conducted to minimise bias in the estimate of cost effectiveness. Estimates of ICERs will be compared with published estimates, and a range of uni-variate and multi-variate sensitivity analyses will be conducted to assess the robustness of the analysis.

8.6.2 Special Assays or Procedures

16s Bacterial DNA Detection Using Quantitative PCR
Dr Michael Millar will lead the 16s bacterial DNA analysis using quantitative PCR methods at the Microbiology Laboratories at Barts and the London NHS Trust as described in (12). Blood samples for this analysis will be obtained, stored and transferred to his laboratory using the methods described in section 8.4. The PCR results will be securely transferred to the MCRN (encrypted) with the trial randomisation number, sample date/time and lumen number for collation with the main trial database for the final analysis.

The PCR results will also be used as a secondary outcome to determine if antibiotic impregnated or heparin coated CVCs compared with standard CVCs reduce bacterial load measured by PCR. We will also compare PCR results with culture positive blood stream infections (according to type of organism), culture negative sepsis and no evidence of blood stream infection.

8.7 Loss to Follow-up

Trial follow-up is by the trial RN until the time points specified in section 8.3and from routine medical databases at 6 months. If any of the trial patients are lost to follow up before the relevant timepoint (e.g. lost due to transfer to another hospital), contact will initially be attempted through the trial RNs and the lead investigator at each centre. If the lead investigator at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. PICANet data, Hospital Episode Statistics and Office of National Statistics will still be accessed.

8.8 Trial Closure

The end of the trial will be considered as the date of the final database lock, however the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the independent Data Safety and Monitoring Committee, for reasons such as clear differences between efficacy or safety of trial interventions.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan will be developed prior to the final analysis of the trial. The statistical analysis plan will be agreed by the Trial Steering Committee before being sent to the independent Data and Safety Monitoring Committee for comment and approval. The main features of these planned statistical analyses are included here in the main protocol.

9.2 Method of Randomisation

The randomisation code list will be generated by a statistician (who is not involved with the CATCH trial) at the MCRN CTU. Patients will be randomised to standard, antibiotic impregnated, or heparin bonded CVCs in a ratio of 1:1:1. This ratio reflects uncertainty about which of these three types is best in terms of the risk of bloodstream infection and cost effectiveness. Randomisation will be stratified by centre, location within the centre and emergency/elective patients. Separate series of randomisation envelopes will be provided for each location and for emergency and elective patients.

9.3 Outcome Measures

The primary and secondary outcomes, as well as the precise definitions of the outcomes and details of minimum quantities for blood samples are provided in section 4.

9.4 Sample Size

The primary comparison will be between impregnated and standard CVCs.

9.4.1 Evidence for the Baseline Risk of Blood Stream Infection

Prevalence rates of bloodstream infection have been reported for all patients admitted to PICU, based on audits reported by four units participating in the trial, where standard CVCs only are used. The rates reported by these units are as follows: unit A - 5% per patient with a CVC; unit B - 6-7/1000 CVC days and estimated to be 5% per patient with a CVC based on mean of 8 CVC days; unit C – 5% overall per patient with a CVC and 50% if CVC in situ for >7 days, unit D – 17/233 7.3% per patient with a CVC, 11.8% (15/127) per patient with CVC for > 2 days. Note data are excluded for 3 units using impregnated CVCs for some children.

Similar baseline rates of infection have been reported in the literature. Trials of CVCs in children report baseline rates of 9% to 26% for standard CVCs.(6) A meta-analysis of data from PICUs mostly in the USA reported a pooled estimate of 8/1000 CVC days.(18) A recent USA trial reported a reduction from 9.7 to 6.4/1000 catheter days in catheter related blood stream infections in standard CVCs after introduction of improved practices for CVC care.(19)

These infection rates are likely to underestimate the baseline event rate in the trial. Firstly, they reflect all admissions with a CVC for any length of time whereas the trial will include only patients expected to require a CVC for more than 2 days (as shown by audit results for unit D above). Infection risk increases with time of insertion, hence the large number of patients staying for just 2 days or less (39% in the 10 participating units – data supplied by PICANet) dilutes the overall rate of blood stream infection. Secondly, most studies measure catheter related blood stream infection rather than any blood stream infection, which is the primary outcome for this trial. A previous trial of 200 PICU patients at Great Ormond Street Hospital recorded catheter related blood stream infection in 18% of children given a standard

CVC but any positive blood culture in 33% (mean duration of CVC insertion was 8 days).(20) For these reasons, we have assumed a rate of blood stream infection of 10% in patients with a CVC for more than 2 days. This rate is consistent with the rate of infection observed in the current US trial of children undergoing elective surgery which has been as high as 13% (personal communication, Elaine Cox, see figure 1 in Appendix B).

9.4.2 Expected Losses to Follow-Up

Loss to follow up is likely to be due to patients approached for deferred consent who refuse to participate in the trial. We anticipate this number will be very small as the risks associated with the different options are very small and expected to be similar hence equipoise exists. Furthermore, the additional data collection required over and above routine clinical data is minimal. Loss to follow up for the primary outcome is unlikely. Blood culture results used for the primary outcome will be routinely recorded by the laboratory and retrievable retrospectively. Anticipated losses are therefore estimated at 5%

9.4.3 Sample Size Estimation

Based on the evidence discussed above, the best point estimate for the baseline rate for the primary outcome of blood stream infection is 10%, with a possible range from 5% to 15%. If we were to power the trial to detect the smallest clinically important difference, the sample size would be huge. This is because blood stream infection has such major consequences for the patient and health care resources that even a 1% absolute reduction in infection (e.g. from 10% to 9%, or relative risk of 0.9) would be likely cost effective. We have therefore adopted a pragmatic approach by assuming that detection of a relative risk of 0.5 in patients with a baseline risk of 10% would likely change purchasing policy. Moreover, we have assumed that the relative risk to change purchasing policy would remain relatively constant across the expected range of baseline risks from 5% to 15% while the absolute risk difference would be more variable. This assumption is based on clinical reasoning, the lack of heterogeneity detected in meta-analyses of the relative risks for impregnated CVCs, (1;6) and empirical analyses of 551 systematic reviews that showed that relative effect measures are more stable than absolute risk differences.(21)

Table 2 shows the relative risks and absolute risk differences that would be detectable at 70%, 80% and 90% power given baseline risks ranging from 5% to 15% and a sample size of 1200 (400 per group, allowing for 5% loss to follow up). Figure 1 (Appendix B) shows curves for the absolute risk reduction in relation to baseline risk. At a sample size of 1200, we would have 80% power to detect a relative risk of 0.5 at a 5% level of significance given a baseline risk of 10%, using a Fisher's exact test (Table 2). At the lower expected baseline event rate of 5%, there would be 80% power to detect a relative risk of 0.32 (absolute risk difference 3.4%) whereas at a baseline event rate of 15% there would be 80% power to detect a relative risk of 0.6 (absolute risk difference of 6%). The power to detect these effects would be similar for survival analyses. Explicit power calculations have not been given for the survival analysis to avoid making potentially erroneous assumptions about the distribution of infection times in the standard arm based on the limited information available at present. This sample size is achievable during 2 years recruitment involving the 11 centres that have indicated their willingness to be involved in the trial (see Table 4 in Appendix B).

Table 2: Relative risk (absolute risk difference) that can be detected with specified power and sample size of 1200 for different baseline risks of blood stream infection in the standard arm. Primary comparison is between standard arm and antibiotic and heparin impregnated CVC arms combined (400 patients in each of 3 treatment groups, assuming 5% loss to follow up).

Baseline risk of blood stream infection in standard arm (%)	POWER		
	70%	80%	90%
5	.37 (3.2)	.32 (3.4)	.24 (3.8)
10	.55 (4.5)	.51 (4.9)	.45 (5.5)
15	.64 (5.4)	.60 (6.0)	.55 (6.8)

9.4.4 Recruitment Rate

Table 4 (Appendix B) shows the number of admissions in 2007 to 11 PICUs who have expressed interest in the trial. The shaded area shows children staying more than 2 days admitted after elective surgery at the participating centre or as emergency admissions from the same or another unit (n=4010/year). 60% of these will be less than 1 year old. A majority will require a CVC but the precise proportion is not yet known. Assuming all require a CVC and allowing for a relatively low rate of 20% recruitment of those eligible (n=802), we would be able to recruit more than the 600 needed each year to meet our sample target of 1200.

9.5 Interim Monitoring and Analyses

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial-specific IDSMC charter according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

The trial statistician at the MCRN CTU will prepare the report for the IDSMC, the contents of which will be agreed by the IDSMC . The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

The estimate of the infection rate in the standard arm used in the sample size calculation will be checked after the first 200 participants have been randomised and completed follow-up (approximately 65 randomised to standard arm). The results will be reviewed by the IDSMC who will inform the TSC of the implications for continuing the trial as planned. The consent rates and reasons for refusal will be monitored for each centre. Data on adverse events will be sent to the IDSMC on a monthly basis. There will be an interim analysis of the primary outcome mid-way (approx half patients randomised) through the trial, using Peto-Haybittle stopping rules. A full statistical analysis plan will be written prior to any comparison of the treatment groups.

The trial may be ended at this point, or recommended to continue by the TSC, on recommendation from the IDSMC. Importantly, statistical considerations alone are not adequate for data monitoring due to the over-emphasis placed on the p-value resulting from hypothesis tests. Clinical judgment is essential to the process to account for unexpected adverse events and balance issues of safety and efficacy in light of any new external

information. The decision to stop recruitment will depend on whether the results will be convincing to the medical community.

9.6 Analysis Plan

The trial will be analysed and reported using the 'Consolidated Standard of Reporting Trials' (CONSORT) and the International Conference on Harmonisation E9 guidelines. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included here.

A p-value of 0.05 or less will be used to declare statistical significance for all analyses. Rather than adjust for multiplicity relevant results from other studies already reported in the literature will be taken into account in the interpretation of results.

The primary analysis will be by intention to treat, comparing those randomised to antibiotic impregnated CVCs with standard CVC and those randomised to receive heparin versus standard CVC. A secondary analysis will combine the impregnated CVCs and compare any impregnated CVC against standard CVC. Kaplan-Meier survival curves and log rank tests will be used for the primary outcome 'time to first blood stream infection'. Fishers exact test will be used to compare proportions and relative risks will be presented with n95% confidence intervals. Length of stay and duration data will be compared using 2 sample t-tests or Mann Whitney U tests as appropriate. Results will be presented with 95% confidence intervals throughout. Secondary 3-way analyses comparing heparin bonded, antibiotic impregnated, and standard CVCs will follow a similar analysis plan.

Regression models will be used to further investigate the outcomes between the groups, including an assessment of the potential modifying effect of type of surgery (emergency or elective). Cox proportional hazard models will be used to compare times to event outcomes. Since the hazard of infection may not be constant post cvc insertion (22) non-proportional hazards survival models will also be investigated (23). Missing data will be monitored and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data.

10 SAFETY REPORTING

10.1 Terms and Definitions

10.1.1 National Research Ethics Service (NRES) Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a participant to whom a research procedure has been administered, including occurrences which are not necessarily caused by or related to that procedure.

In medical devices research the National Research Ethics Service (NRES) defines a **Serious Adverse Event (SAE)** as an untoward occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The National Research Ethics Service defines related and unexpected SAEs as follows:

- **'related'** – that is, it resulted from administration of the medical device or any of the research procedures;
- **'unexpected'** – that is, the type of event is not listed in the protocol as an expected occurrence.

NRES require that a SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is related and unexpected, is be reported to the main Research Ethics Committee (REC).

10.1.2 Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Incident Centre (AIC) Definitions

As the trial involves the use of CE-marked medical devices employed for their intended purpose, adverse incidents are also reportable to the Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Incident Centre (AIC) under the User Devices Vigilance requirement.

The MHRA AIC define an **Adverse Incident (AI)** as:

- An event that causes, or has the potential to cause, **unexpected or unwanted effects** involving the safety of device users (including patients) or other persons.

Causes of AIs involving devices may include:

- Design or manufacturing problems;
- Inadequate servicing and maintenance;
- Inappropriate local modifications;
- Unsuitable storage and use conditions;
- Selection of the incorrect device for the purpose;
- Inappropriate management procedures;
- Poor user instructions or training (which may result in incorrect user practice).

Conditions of use e.g. environmental conditions or location may also give rise to adverse incidents.

Any adverse incident involving a device or its instructions for use should be reported to the MHRA AIC, especially if the incident has led to or, were it to occur again, could lead to all occurrences listed under SAEs in section 10.1.1, as well as:

- Unreliable test results and associated risk of mis-diagnosis or inappropriate treatment;
- Ongoing faults that successive service/maintenance visits have failed to rectify.

By these definitions AIs are the same as related and unexpected AEs. As the trial intervention (CVC) is neither a test nor requires ongoing service/maintenance, AIs that should be reported to the MHRA AIC for this trial are the same as unexpected and related serious adverse events.

The MHRA AIC also request that minor safety or quality problems with the device should also be reported as these can help demonstrate trends or highlight inadequate manufacturing or supply systems. Reports of adverse incidents (i.e. related and unexpected AEs) as that appear to be caused by human error should also be reported because:

- The error may be partly (or wholly) due to deficiencies in the design of the device or instructions for use;
- They may prompt promulgation of advice or device design improvements that will help prevent repetition of mistakes.

10.2 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious AE.

10.3 Relationship to Trial Intervention (CVC)

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 3.

If any doubt about the causality exists, the local investigator should inform the MCRN CTU who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, NRES and the MHRA AIC will be informed of both points of view.

Table 3: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. There is an alternative cause for the AE.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after insertion of the CVC). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after insertion of the CVC). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant interventions).
Probably*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*Possibly, probably, or almost certainly related will be referred to throughout the protocol as 'related'.

10.4 Reporting Procedures

AEs and SAEs will only be reported for patients where consent has been obtained and the causal relationship to the trial intervention (CVC) has been assessed and judged by the investigator to be related to the CVC (see section 10.3), which occurs:

- From the time of CVC insertion until 48 hours after CVC removal or;
- From the time of attempted insertion of the CVC until 48 hours afterwards if the insertion was not successful.

All the events listed in table 4 are expected within the trial population and can be related to the trial intervention (CVC).

Table 4: Expected adverse events

Expected event	AE/SAE	Event recorded using.....
Blood stream infections	AE/SAE	Sampling CRF Microbiology CRF
CVC thrombosis	AE/SAE	Sampling CRF Thrombosis CRF
Antibiotic resistance detected to minocycline or rifampicin using standard E tests on isolates from blood or the CVC tip	AE	Microbiology CRF
Hypersensitive reaction to CVC (minocyline, rifampicin, or heparin)	AE/SAE	CVC Insertion Follow-up CRF Related Adverse Event CRF
Unexplained thrombocytopenia defined as a low platelet count (<100,000 per mm^3)	AE	Related Adverse Event CRF
Haematoma at insertion or attempted insertion site (including bruising)	AE	Related Adverse Event CRF
Pneumothorax	AE/SAE	Related Adverse Event CRF
*Erosion or perforation of the central venous system caused by incorrect tip position	AE/SAE	Related Adverse Event CRF
*Vascular injury caused by excessive force when advancing dilators	AE/SAE	Related Adverse Event CRF
*CVC rupture caused by power injecting contrast medium	AE	Related Adverse Event CRF
*CVC tip displacement	AE	Related Adverse Event CRF
*Perforations or erosions of the vessels	AE/SAE	Related Adverse Event CRF
*Breakage of guide wire through needle	AE	Related Adverse Event CRF

**Expected with CVC use according to Cook Medical Uncoated and Heparin-Coated Central Venous Catheters Instructions for Use (August 2007) and Spectrum® and Spectrum Glide™ Central Venous Catheters Instructions for Use (September 2007).*

All AEs/SAEs in table 4 should be reported by the RN using the cited CRFs and returned to the MCRN CTU within 7 days of final clinical follow-up.

If the event is not listed in table 4, it will be graded as unexpected and related, and the CVC should be quarantined (see section 10.6). If the event is an AE, it should be reported by the

RN using the related adverse event CRF with the expectedness code of 'Other' and the CRF returned to the MCRN CTU within 7 days of final clinical follow-up.

If the event is graded as serious (see section 10.1), it should also be reported by the RN using the **related serious adverse event CRF**, and the CRF **returned to the MCRN CTU within 24 hours** of the clinical research team becoming aware of the event.

Do Not Include

- Any AEs whose causal relationship to the trial intervention (CVC) is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial intervention (randomised CVC)
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

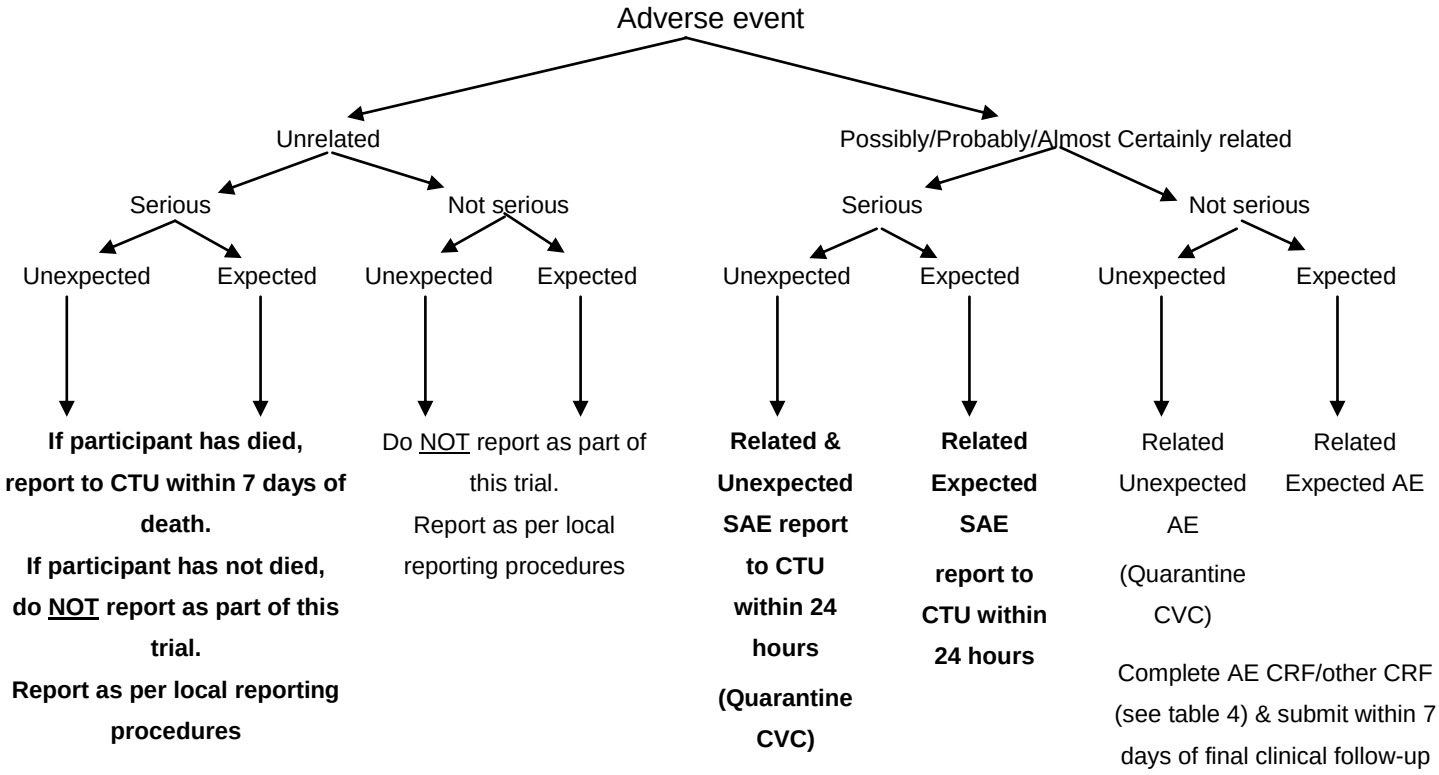
Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after the insertion of the trial intervention (CVC)
- Continuous persistent disease or symptoms present at baseline that worsens following the insertion of the trial CVC
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event or as part of routine follow-up).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents that are not expected.

All hospital re-admissions will be reported as part of the 6 month follow-up using electronic databases. Only report hospital re-admissions using the related SAE CRF if they occur in the specified time frame and are judged to be related to the CVC.

All deaths between the time of randomisation and either consent is declined (for emergency admission patients) or the patient is discharged from hospital should be reported to the MCRN CTU using the death CRF **within 7 days** of the clinical research team becoming aware of the event. If a patient's death has been assessed and judged by the investigator to be related to the intervention (see section 10.3) and consent has been obtained, a related SAE CRF should also be completed. Where consent has been obtained, deaths will be reported as part of the 6 month follow-up using electronic databases.

A flowchart is given below to aid in determining reporting requirements.



The initial report of an event should contain as much relevant detail as is immediately available, but should not be delayed for the sake of gathering additional information. The patient **must** be identified by trial randomisation number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

The SAE CRF should be faxed to the MCRN CTU and the Trial Coordinator/Data Manager notified by telephone that a SAE report has been submitted.

Fax Number: 0151 282 4721

Telephone Number:0151 282 4716

Any questions concerning adverse event reporting should be directed to the MCRN CTU in the first instance.

The data reported will include:

- Centre;
- Trial number;
- Details and location of the device;
- Injury details;
- Nature of the defect/details of the event;
- Severity/grading of the event;
- Relationship of the event to the trial intervention (CVC);
- Expectedness of the event;
- Whether trial intervention was discontinued;
- Any other action taken.

All events listed in table 4 are expected and will not be subject to expedited reporting to the main REC. Neither do they fall within the definition of an Adverse Incident (i.e. unexpected and related AE) and will therefore not be reported to the MHRA AIC as part of this trial.

All device-related unexpected AEs (Adverse Incidents) will be reported to the MHRA AIC as part of user device vigilance reporting.

The MCRN CTU will notify the main REC and MHRA AIC of any related and unexpected SAEs within 15 days of the MCRN CTU/Chief Investigator becoming aware of the event. They will be reported by the fastest means available, for the MHRA AIC preferably online, or by fax or e-mail and will be confirmed with a telephone call. Where the first report is by telephone, a written report will follow as soon as possible.

All investigators will be informed of all related and unexpected SAEs occurring throughout the trial.

As part of the MCRN CTU centre initiation green light process, participating centres should provide the MCRN CTU with the contact details of their local medical device liaison officer(s), patient safety manager(s) and risk manager(s) as appropriate. These personnel will be informed of all adverse incidents (i.e. related and unexpected AEs/SAEs) arising at that centre that are reported to the MHRA AIC by the MCRN CTU. All adverse incidents should be reported by investigators to their NHS organisation according with local incidence reporting procedures.

10.4.1 Procedures to be Followed in the Event of an Abnormal Laboratory Test or Abnormal Clinical Findings

Patients on PICU will be subject to laboratory tests necessary to the clinical management of the patient. However, documentation of laboratory data for the purpose of the trial will be limited to those laboratory parameters that are relevant to safety, trial outcome measures and/or clinical outcome. These measurements are specifically listed in Section 8. Responses to any abnormal laboratory values or clinical findings that are out with the expectations of the primary disease or other concomitant treatments should be discussed by the local team (research nurse and clinician). If they cannot be fully explained by the primary clinical condition or the concomitant treatments then they should be reported as a potential adverse event (AE/ SAE).

10.5 Follow-up After Adverse Events

All AEs should be followed up until satisfactory resolution (clinical recovery is complete and laboratory results have returned to normal) or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. Follow-up may continue after removal of the trial CVC if necessary.

Follow-up information is noted on another AE/SAE form by ticking the box marked ‘follow-up’ and faxing to the MCRN CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

When reporting AEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.6 Quarantine, Labelling & Storage of Devices Involved in an Adverse Incident (i.e. Related Unexpected AE/SAE)

Medical devices that have been involved in an adverse incident (i.e. related and unexpected AE), whether serious or not, should be quarantined.

Until the MHRA has been given the opportunity to carry out an investigation, they should not be discarded, repaired or returned to the manufacturer. All material evidence, i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- Clearly identified and labelled;
- Stored securely.

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions, together with any photographic evidence and eyewitness reports.

If it is thought that an urgent examination of the device (and/or related items) may be required, upon notification of the incident an MHRA device specialist will decide whether to inspect the item urgently on site (or at other appropriate facilities), or may request that the device is sent to the MHRA. If required, the MHRA will contact the manufacturer (Cook Medical) and, if accompanied by an appropriate person, they may be allowed to inspect the items. To facilitate an investigation, it may be possible to provide the manufacturer with a sample of unused stock from a large batch. However, until advised to the contrary by the MHRA, the manufacturer must not be allowed to exchange, interfere with, or remove any part of the product implicated in the incident as this might prejudice MHRA investigations, or those of other official bodies.

10.7 Responsibilities – Investigator

- The Investigator is responsible for reporting all AEs that are observed as possibly, probably, or almost certainly related to the intervention.
- The SAEs forms should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions, and submitted to the MCRN CTU within the timelines specified in section 1**Error! Reference source not found.**. The investigator should assess the SAE for the likelihood that it is a response to the intervention. In the absence of the designated investigator, the form should be completed and signed by an alternative member of the research centre trial team and submitted to the MCRN CTU. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the MCRN CTU. The initial report shall be followed by detailed reports as appropriate.
- For all SAEs, follow-up the patient as described in section 10.5.
- For medical devices that have been involved in an adverse incident (related unexpected AE), whether classed as serious or not, ensure that they have been quarantined as described in section 10.6.
- The responsible investigator must **notify** their R&D department of the event as per standard local governance procedures.
- Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.7.1 Maintenance of Blinding

Systems for AE reporting should, as far as possible, maintain blinding of individual clinicians involved in the day-to-day running of the trial.

If simply removing the CVC is a viable option for the patient's care, it should not be necessary for unblinding to occur.

Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial interventions unless criteria have been fulfilled (section 7.4.2) and unblinding has taken place.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial interventions would have to be unblinded at the MCRN CTU prior to reporting to the regulator.

10.8 Responsibilities – MCRN CTU

The MCRN CTU is undertaking duties delegated by the trial sponsor and is responsible for the reporting of AEs to the main REC and MHRA AIC as follows:

- Related unexpected SAEs must be reported to the main REC and MHRA AIC within 15 days of the MCRN CTU first becoming aware of the event;
- All investigators will be informed, in a timely manner, of all related unexpected SAEs occurring throughout the trial;
- All related unexpected SAEs will also be reported to the Sponsor.
- A list of all SAEs (expected and unexpected) will be reported annually to the main REC;
- All device-related unexpected AEs (Adverse Incidents) will be reported to the MHRA AIC as part of user device vigilance reporting.
- Copies of the reports will be sent to the Principal Investigator at all institutions participating in the trial.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- New events related to the conduct of the trial or the development of the devices and likely to affect the safety of the subjects. For example, a SAE which could be associated with the trial procedures and which could modify the conduct of the trial.
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

10.9 Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of AE reporting rates across centres. The CTU will send annual safety reports containing a list of all SAEs to the Main REC. Any concerns raised by the IDSMC or inconsistencies noted at a given centre may prompt additional training at centres, with the potential for the MCRN CTU to carry out centre visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. All

NHS organisations will receive copies of safety and progress reports that are provided to the main REC.

10.10 Reporting of Pregnancy

No pregnancy testing is planned as part of the trial procedures. Patients who are known to be pregnant will be excluded from the trial.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The relevant approvals will be obtained as described in section 11.2. The specific ethical issues are:

a. Informed consent in a paediatric population

Admission to PICU is a time of enormous anxiety for children and their family. To minimise additional stress due to enrolment in the trial, recruiting investigators (such as consultant intensivists and research nurses) will be experienced at imparting information to families with sick children. Parents or a legal representative of the child will be made aware that the CVCs under investigation are those that are routinely used in PICUs. They will be informed of the potential risks and benefits associated with trial participation and their right to withdraw the child from the trial at any time without the child or family being subject to any resulting detriment. They will be provided with written information and contact details of the trial personnel, who will also be readily available in the PICU, from whom further information about the trial may be obtained.

b. Informed consent in emergency situations

Nearly two thirds of the patients expected to be consented will have their CVC inserted when they are in a very critical condition, when any delay in insertion could be detrimental. We therefore propose using two different approaches to the consenting process:

i. **For elective surgical patients**, prospective consent for trial participation will be obtained as described in section 11.3. Informed written consent will be obtained prior to any trial procedures.

ii. **For emergency admissions patients**, a deferred consent process will be used.

The lead clinical investigator (Dr Quen Mok) successfully used a deferred consent process for her previous trial of impregnated CVCs (20) and we intend to employ a similar practice for CATCH. The planned procedure (see section 6.2.2 and section 11.3 for the randomisation, consent and recruitment process) has been proposed following extensive discussion amongst the project team, including the parent representative.

A deferred approach will be used for all emergency admissions, even though in a few cases, time to CVC insertion may be less critical and there may be time to discuss the trial. When notified of an impending emergency transfer it is not possible to accurately predict those patients for whom a prospective approach would be possible, so allowing variation in the consent process (deferred or prospective) could lead to confusion and potentially jeopardise time to insertion for some children considered for enrolment in the trial. As a result of these concerns we made the decision to adopt a consistent, standardised, approach to recruitment across all centres, with clearly defined responsibilities for recruiters with regard to provision of valid consent.

c. Assent from critically ill patients

Due to the physical status of the target population it will not be possible to involve critically ill children in the consenting process. The ethics application will be supported by parent and child information sheets and parent and child consent/assent forms. Assent of trial participants, if appropriate, will be obtained as soon as their condition allows.

11.2 Ethical Approval

The trial protocol, including the Parent/Patient Information Sheets and Consent/Assent forms and all other relevant trial documentation will be submitted for review by the South West Research Ethics Committee (REC). All participating centres must be granted NHS permission by their Local Research & Development (R&D) department prior to commencing recruitment. A copy of local R & D approval and the Parent/Patient Information and Consent/Assent form on local headed paper should be forwarded to MCRN CTU before the centre is initiated and patients recruited.

11.3 Informed Consent Process

Prospective consent/assent will be sought for elective surgery patients as described in sections 6.2.1 and 11.1. Deferred consent/assent will be sought for emergency admission patients as described in sections 6.2.2 and 11.1. For both prospective and deferred consent, the same process described below will be followed when providing information and discussing the trial, answering any questions and obtaining written informed consent/assent.

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in MCRN CTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience with minors. Age-and-stage-of-development appropriate Patient Information and Consent forms, describing in detail the trial interventions, trial procedures and potential risks/benefits will be approved by an independent research ethics committee (REC) and the patient and their parent/legal representative will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research trial to the patient and their parent/legal representative. This information will emphasise that participation in the trial is voluntary and that the patient and parent/legal representative may withdraw from the trial at any time and for any reason. The patient and their parent/legal representative will be given the opportunity to ask any questions that may arise, the opportunity to discuss the trial with their surrogates and as long as they need to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

Both the person taking consent and the parent or legal representative of the minor must personally sign and date the informed consent document. If capable, and under appropriate circumstances, the patient should assent and sign and personally date a separate REC-approved assent form, describing (in simplified terms) the details of the trial intervention, trial procedures and potential risks/benefits may be used. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative.

The consent form will request permission for personnel involved in the research or from regulatory authorities to have access to the individual's medical records. The original copy of the informed consent/assent document will be filed in the participant's notes, a copy will be given to the participant and their legally acceptable representative, one further copy will be filed in the investigator site file and one final copy of the consent form should be sent to the CTU.

The parent or legal representative may, without the minor being subject to any resulting detriment, withdraw the minor from the trial follow-up at any time by revoking the informed

consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this trial.

After the patient has entered the trial, the clinician must remain free to give an alternative intervention to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the CVC type they have been allocated.

11.4 Trial Discontinuation

In the event that the trial is discontinued, children will be reverted to default care usually provided by the PICU (PICU policy)..

12 REGULATORY APPROVAL

The trial involves the use of CE-marked medical devices employed for their intended purpose, therefore this trial is not considered to be a clinical investigation under the Medical Devices Regulations 2002, nor does it fall within the remit of the Medicines for Human Use (Clinical Trials) Regulations 2004.

13 TRIAL MONITORING

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

Trial monitoring will be informed by the CATCH risk assessment and will be conducted as per the CATCH Trial Monitoring Plan to ensure that the rights and well-being of human participants are protected during the course of the clinical trial and that the data are credible and accurate.

13.1 Source Documents

Each participating centre should maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation – E6- Good Clinical Practice guidelines Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data will be identified and documented in the CATCH Trial Monitoring Plan.

13.2 Data Capture Methods

13.2.1 Case Report Forms

The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". Or if the data item is un-known, write "NK". If a data item has not been recorded on source data then write 'NR'. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

13.2.2 Data from electronic routine administrative databases

Data on Hospital Episode Statistics (HES) from the beginning of the financial year prior to baseline, to six-months of follow-up will be accessed centrally via the NHS Information Centre. Death data will be collected centrally from the Office of National Statistics (ONS) at six months follow-up. A database of patient NHS numbers, postcode and date of birth generated six months after the last patient is recruited will be used to request HES and ONS data within the specified date ranges from the NHS Information Centre and the ONS office.

The Paediatric Intensive Care Audit Network (PICANet) ID number (and if required, the identifiers listed above) will be used to electronically link the CVC allocation and other relevant information collected during the trial with the child's records on the PICANet dataset at six months follow-up (see Appendix E for PICANet data collection forms).

Collection of these data will follow a standard procedure. Any transfer of data (requests for data and the return of the full dataset) will be transferred securely (encrypted) (see section 8.6.1 for further details on using this data). Data will be stored at the MCRN CTU as described in section 13.5. Consent to data linkage will be sought.

13.3 Monitoring at CTU

Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the centre in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Centres will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. CTU will send reminders for any overdue and missing data.

13.4 Clinical Centre Monitoring

In order to perform their role effectively, the trial coordinator and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.5 Confidentiality

All individual participant information collected for the trial about will be confidential, and will be handled, stored and destroyed in accordance with the Data Protection Act 1998. No names will be used in any publications or reports.

Case report forms containing clinical data will be labelled with patient initials, date of birth and a unique trial randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Blood samples transferred to the laboratory at Barts and the London NHS Trust to test for bacterial DNA will be identified by initials, trial randomisation number, date of birth and date/time will only be used for this trial.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the MCRN CTU by recruiting centres. This requires that name data will be transferred to the MCRN CTU, which is disclosed in the information sheet and consent form. Only the consent form will contain identifiable personal data of name, NHS number, intensive care number (PICANet ID), postcode and date of birth. The assent forms will also contain name data.

Trial data collected on paper will be sent to the MCRN CTU and filed in locked filing cabinets. Paper copies of the consent/assent form will be kept separately to the clinical data. The MCRN CTU servers will be used to store electronic data related to the trial. These servers are located in an access controlled server room and are connected to the main university network, located behind a firewall. Physical access to these servers is limited to members of the Universities computing services department; CTU IS staff have access to the server consoles. Trial data will be stored in a SQL server database with access limited to CTU staff with permission to access the trial data held on the MACRO (Infermed) system and CTU IS staff with database access privileges. CTU staff accounts on the MACRO system have different credentials to that required by the University computing systems (which must be accessed prior to logging into MACRO). Access to MACRO is limited to staff using the Universities network. The SQL Server database can only be accessed by computers with a University IP address.

Name data will not be stored electronically. The following personal data will be stored on the CTU servers: NHS Number, PICANetID, postcode, date of birth, participant initials and

participant trial randomisation number. The NHS number, PICANetID, postcode, date of birth and trial randomisation number will be stored in a separate encrypted database with controlled access. The participant's initials, date of birth and trial number will be stored in the unencrypted MACRO database. Transfer of NHS Number, PICANet ID, date of birth and postcode to obtain resource use and death data from electronic routine administrative databases will be encrypted.

Members of the research team outside the MCRN CTU will have access to data generated by the trial, which is relevant to their role, but this will be anonymised.

The MCRN CTU will preserve the confidentiality of participants taking part in the trial and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.6 Quality Assurance and Quality Control of Data

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, centre visits will be conducted and source data verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The Principal Investigator and Research Nurse from each centre will attend the trial launch meeting, coordinated by CTU in conjunction with the Chief investigator, Professor Ruth Gilbert, which will incorporate elements of trial- specific training necessary to fulfil the requirements of the protocol;

- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended trial specific training;

- The Trial Coordinator is to check safety reporting rates between centres;

- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between centres;

- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries;

- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.7 Records Retention

The investigator at each investigational centre must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the MCRN CTU informs the investigator that the documents are no longer to be retained or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The MCRN CTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational centre, which are kept by the investigator only. The MCRN CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INSURANCE AND INDEMNITY

CATCH is sponsored by UCL-Institute of Child Health and co-ordinated by the MCRN CTU in the University of Liverpool. The UCL-Institute of Child Health insurance policy covers for non-negligent harm to trial participants, that is, compensation to participants where negligence cannot be, or is not, proved.

However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This trial is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating centres that will incorporate financial arrangements.

15.1 Financial Support to Collaborating Centres

15.1.1 Research Nurse

0.5 FTE Research nurses will be employed at each of the 11 PICUs which initially expressed interest in the trial.

15.1.2 CVC Supplies from Cook Medical

The devices listed in Appendix A will be supplied by Cook Medical to the participating centres for use in the trial as per the following pricing structure for the duration of the individual centre's participation in CATCH. The Trial Coordinator will be responsible for informing Cook Medical of a centre's participation and closure to CATCH. Centres will only be able to source the CVCs at the discounted price once all required approvals are in place and the centres have been initiated into the trial.

- standard CVCs at list price
- heparin-bonded CVCs at 20% discount from list price
- antibiotic-impregnated CVCs at 20% discount from list price

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MCRN CTU. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately three times a year. The members of the TMG include all the people listed at the front of the protocol and Professor Elizabeth Draper, who will provide expertise in PICANet.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, Dr Robert Tasker (Paediatrics), three independent experts in the fields of Interventional Radiology (Dr Derek Roebuck), Microbiology (Dr Jim Gray) and Biostatistics (Mr Andy Vail), a parent representative (Hazel Greig-Midline) and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, Professor Paul Ewing, an expert in medical statistics, plus two independent members: Professor Mike Sharland who is an expert in the field of Paediatric Infectious Diseases and Professor Neena Modi who is an expert in the field of Neonatal Medicine.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to trial initiation and will then define frequency of subsequent meetings (at least annually).

Details of the interim analysis and monitoring are provided in section 9.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the trial.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group (TMG) will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications arising from the trial trial population shall include a list of contributors to the CATCH trial. For publications reporting the main trial results named authors, or authors listed in the writing committee (if group authorship is used), should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial. The members of the TSC and IDSMC should be listed in the contributor list in the Acknowledgements/Appendix of the main publication.

Additional publications utilising the data collected by the CATCH trial will be discussed by the TMG and authorship agreed.

18 PROTOCOL AMENDMENTS

18.1 Version 1 (23/Nov/2009)

Original Approved Version.

18.2 First substantial amendment Version 2.0 20/09/2010

Page No	Section	Amendment
Throughout		Updated version and date
Throughout		Change of wording from 'Site' to 'Centre'
Throughout		Change of wording from 'Study' to 'Trial'
Throughout		The wording 'polyurethane' has been deleted
Throughout		Change of wording from 'enrolled' to followed-up'
Throughout		Change of wording from 'registration' to 'randomisation'
Throughout		The word 'investigator' has been added to distinguish what the site file is
Throughout		The following time points for data collection: • 48 hours after randomisation if CVC insertion was not attempted within 12 hours from randomisation; • 48 hours after attempted insertion if a CVC insertion was not successful within 12 hours from randomisation; • 48 hours after CVC removal if CVC insertion was successful within 12 hours from randomisation
Throughout		The time points above will be referred to as 'the relevant timepoint'
1		Added ISRCTN number ISRCTN34884569 Added Clinicaltrials.gov Identifier: NCT01029717 Added website www.catchtrial.org.uk
3		Email address change for sponsor from j.southern@ich.ucl.ac.uk to g.lambert@ich.ucl.ac.uk
4		Contact details changed from Jo Southern to Gillian Lambert Addition of Katie Harron and her contact details as Research Fellow UCL-ICH Change of title for Kerry Dwan from 'Ms' to 'Dr' Typo in the word microbiologist details
6-7		Table of contents updated
8		Addition of text "attempted insertion of CVC and needle through skin" Addition of text "although the protocol refers to a RN it may be anyone who have been delegated the relevant duties on the delegation log"
9		Population has changed and the wording "and who weigh more than 3kg" has being deleted Addition of the word 'ideally' Addition of the wording 'or as soon as possible ideally' Trial Duration has changed and the addition of the wording 'based on routinely recorded clinical data collated'
10-11		The order of the flowcharts has been changed and the word 'ideally' added before 48 hours post randomisation

15	2.3.1	Deleted 'Body weight below 3kg' Changed the wording 'accept' to except' Changed the wording 'all three' to 'both' Addition of the wording "There is a very small possibility that a patient may become sensitised to the antibiotics and develop an acute allergic reaction, but this is very rare and there are currently no known cases reported".
19	5.1	Inclusion criteria deleted 'weighing >3kg' as there is no restriction on the weight
	5.2	The wording "Patients expected to require a CVC for 2 days or less (for example, fast-track patients undergoing cardiac surgery); The wording 'currently involved in a study which overlaps with CATCH (listed in the excluded studies list)' has been replaced with "in a randomised controlled trial that excludes participation in CATCH?"
20	6.1	To reflect the collection of information on a screening log the following text was added "A screening log of elective patients who are approached but not consented will be completed by the RN. Screening information on emergency patients who are randomised whether or not they consent will be collected by way of eligibility, randomisation and consent CRF (see section 6.6.2 for further details on CRF content)." The wording "Screening data including the number and reasons not eligible will also be monitored retrospectively using PICANet data." has been deleted.
	6.2.1	The wording 'enrolled' has been replaced with 'eligible to be randomised' The wording 'enrolment form and baseline assessments' has been replaced with 'eligibility and randomisation CRF' The wording 'their allocated CVC type at the time of CVC insertion for their operation' has been replaced with 'and select the appropriate size and length of CVC to be inserted'
	6.2.2	The wording "the patient and choose a device of the type allocated. The selected device will accompany the retrieval team to the patient (either to another hospital or within hospital)" has been replaced with "take the randomisation pack and all three types of CVC in the appropriate length and size with them to the retrieval. At the patient's bedside, if the patient is still eligible for the trial, they will be randomised and insertion of the CVC will be attempted". Addition of the word 'ideally' and 'or as soon as possible ideally'. The wording 'the enrolment form and baseline data will be collected' has been replaced with 'the admission details' Addition of the wording 'and bereavement councillor as appropriate' Addition of the wording 'given to the parents/guardians'
21	6.3	The process for the unblinding envelopes has been reworded. The wording 'to insert' has been replaced with 'but the RN will also stick a trial label containing a space for the randomisation number and patient initials onto the CVC set cover'

		Under note the timings for randomisation and CVC insertion has been reworded.
22	6.4	Addition of wording "The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs patient remains the responsibility of the original centre."
	6.5	The wording changed to reflect the process for patient withdrawal
23	6.6, 6.6.1 & 6.6.2	The wording changed to reflect the process for consent not provided.
24	7.2	The wording 'boxes' has been replaced with 'sets'. The wording 'destruction' has been replaced with 'disposal'.
25	7.3	The wording changed to reflect the process for Administration of Trial Interventions.
25-27	7.4 & 7.4.2	The wording changed to reflect the unblinding process
27	7.4.3	Addition of wording 'and Safety'
28	7.5	Addition of the wording 'as per local policy.'
29	7.6	The wording 'patients' medical records with the exception that' has been replaced with 'eligibility and randomisation CRF'
	7.7	Addition of wording 'CVC insertion' The wording ' the same type of CVC as the randomised allocation should be used. This would require staff to deliberately unblind the CVC allocation as described in section 7.4.2' has been replaced with 'the default CVC used at that centre will be used.'
	7.8	Deleted the wording 'any trials were co enrolment is prohibited will be listed in the excluded studies list.'
30	8	The wording 'the time specified for completion' has been replaced with final clinical follow-up at the.' Addition of the wording 'Eligibility, randomisation details including administration of the CVC and consent details will be collected as described in section 6 and 7.3. Patient details including initials date of birth, postcode, NHS number and PICANet ID will be reported on the consent form, separate to clinical data. Once written informed consent has been obtained from the parent or legally acceptable representative, the RN will collect admission characteristics using the admission characteristics CRF and the patient will be followed-up in the trial.'
31	8.1	Table Schedule of Assessments for Elective Surgical Patients has been updated to so show the schedule of assessments
32	8.2	Table Schedule of Assessments for Emergency Admission Patients has been updated to so show the schedule of assessments
33	8.3	Data collection has been replaced with Schedule for follow-up
34	8.4	Procedures for assessing Efficacy has been updated to reflect the process
36	8.5	Procedures for assessing safety has been updated to reflect the process.
	8.6.1	Addition of the wording 'The trial RN will complete the transfer/discharge CRF for each transfer until the patient is discharged home.

37	8.7	The wording ’48 hours after the CVC is removed, 48 hours after randomisation or 48 hours after attempt of CVC insertion’ has been replaced with ‘the time points specified in section 8.3.’
38	9.2	Addition of the wording ‘location within the centre’ and ‘each location and for’
	9.4.1	The wording ‘days’ has been replaced with ‘for any length of time’
39 & 40	9.4.3	Table 1 has been replaced with Table 2
43	10.1.2	The wording ‘above’ has been replaced with in section 10.1.1
44	10.3	Table 2 has been replaced with Table 3 Table 3 has been updated
45-48	10.4 &10.4.1	Reporting procedures have been updated to reflect the process.
54	11.4	The wording ‘Patients withdrawing early from the trial intervention will also be reverted to normal default care (PICU policy) but will not be unblinded unless protocol criteria are fulfilled (see Section 7.4.2.’ has been deleted.
56	13.2.2	The wording ‘at enrolment’ has been deleted.
57	13.5	Addition of ‘date of birth’.
Appendix C		Instructions for standardised sampling for blood cultures for PCR testing has been deleted as information is already in the protocol. The instruction sheet and form will become part of the investigator site file.
Appendix D		Instructions for CVC Tip Culture has been deleted as the instruction sheet will become part of the investigator site file.
74		PICANet Data Collection form has now become Appendix C

19 REFERENCES

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Ref Type: Pamphlet

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20 APPENDICES

Appendix A: Table 5: CVCs supplied by Cook for use in the trial

Order Code	Catheter Type	French Size	Catheter Design (Lumen)	Length (cm)
C-UDLM-401J-PED	Standard	4.0Fr	Double	5
C-UDLM-401J	Standard	4.0Fr	Double	8
C-UDLM-401J-RSC	Standard	4.0Fr	Double	12
C-UDLM-401J-LSC)	Standard	4.0Fr	Double	15
C-UDLM-401J-PED-WCE-BH	Heparin-bonded	4.0Fr	Double	5
C-UDLM-401J-WCE-BH	Heparin-bonded	4.0Fr	Double	8
C-UDLM-401J-RSC-WCE-BH	Heparin-bonded	4.0Fr	Double	12
C-UDLM-401J-LSC-WCE-BH	Heparin-bonded	4.0Fr	Double	15
C-UDLM-401J-PED-WCE-ABRM	Antibiotic-impregnated	4.0Fr	Double	5
C-UDLM-401J-WCE-ABRM	Antibiotic-impregnated	4.0Fr	Double	8
C-UDLM-401J-RSC-WCE-ABRM	Antibiotic-impregnated	4.0Fr	Double	12
C-UDLM-401J-LSC-WCE-ABRM	Antibiotic-impregnated	4.0Fr	Double	15
C-UTLM-501J-PED	Standard	5.0Fr	Triple	5
C-UTLM-501J	Standard	5.0Fr	Triple	8
C-UTLM-501J-RSC	Standard	5.0Fr	Triple	12
C-UTLM-501J-LSC	Standard	5.0Fr	Triple	15
C-UTLM-501J-PED-WCE-BH	Heparin-bonded	5.0Fr	Triple	5
C-UTLM-501J-WCE-BH	Heparin-bonded	5.0Fr	Triple	8
C-UTLM-501J-RSC-WCE-BH	Heparin-bonded	5.0Fr	Triple	12
C-UTLM-501J-LSC-WCE-BH	Heparin-bonded	5.0Fr	Triple	15
C-UTLM-501J-PED-WCE-ABRM	Antibiotic-impregnated	5.0Fr	Triple	5
C-UTLM-501J-WCE-ABRM	Antibiotic-impregnated	5.0Fr	Triple	8
C-UTLM-501J-RSC-WCE-ABRM	Antibiotic-impregnated	5.0Fr	Triple	12
C-UTLM-501J-LSC-WCE-ABRM	Antibiotic-impregnated	5.0Fr	Triple	15
C-UTLM-701J	Standard	7.0Fr	Triple	15
C-UTLM-701J-RSC	Standard	7.0Fr	Triple	20
C-UTLM-701J-LSC	Standard	7.0Fr	Triple	25
C-UTLM-701J-WCE-BH	Heparin-bonded	7.0Fr	Triple	15
C-UTLM-701J-RSC-WCE-BH	Heparin-bonded	7.0Fr	Triple	20
C-UTLM-701J-LSC-WCE-BH	Heparin-bonded	7.0Fr	Triple	25
C-UTLM-701J-WCE-ABRM-HC*	Antibiotic-impregnated	7.0Fr	Triple	15
C-UTLM-701J-RSC-WCE-ABRM-HC*	Antibiotic-impregnated	7.0Fr	Triple	20
C-UTLM-701J-LSC-WCE-ABRM-HC*	Antibiotic-impregnated	7.0Fr	Triple	25

*Catheter supplied with a hydrophilic coating

Appendix B: Information to Support the Sample Size Calculation

Figure 1: Absolute risk reduction detected with specified power and sample size of 1200 for different baseline risks of blood stream infection in the standard arm. Primary comparison is between standard arm and antibiotic and heparin impregnated CVC arms combined (400 patients in each of 3 treatment groups, assuming 5% loss to follow up).

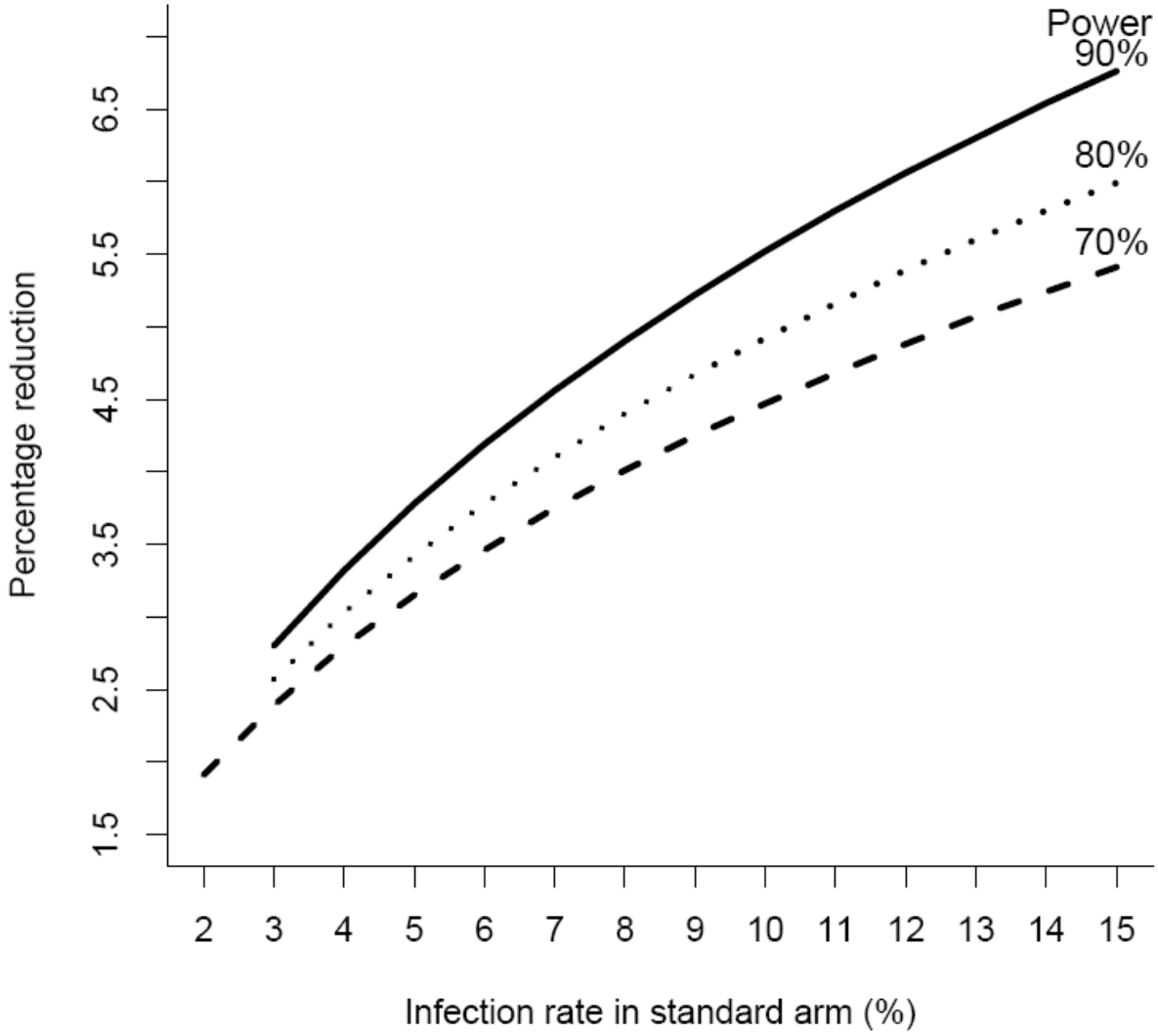
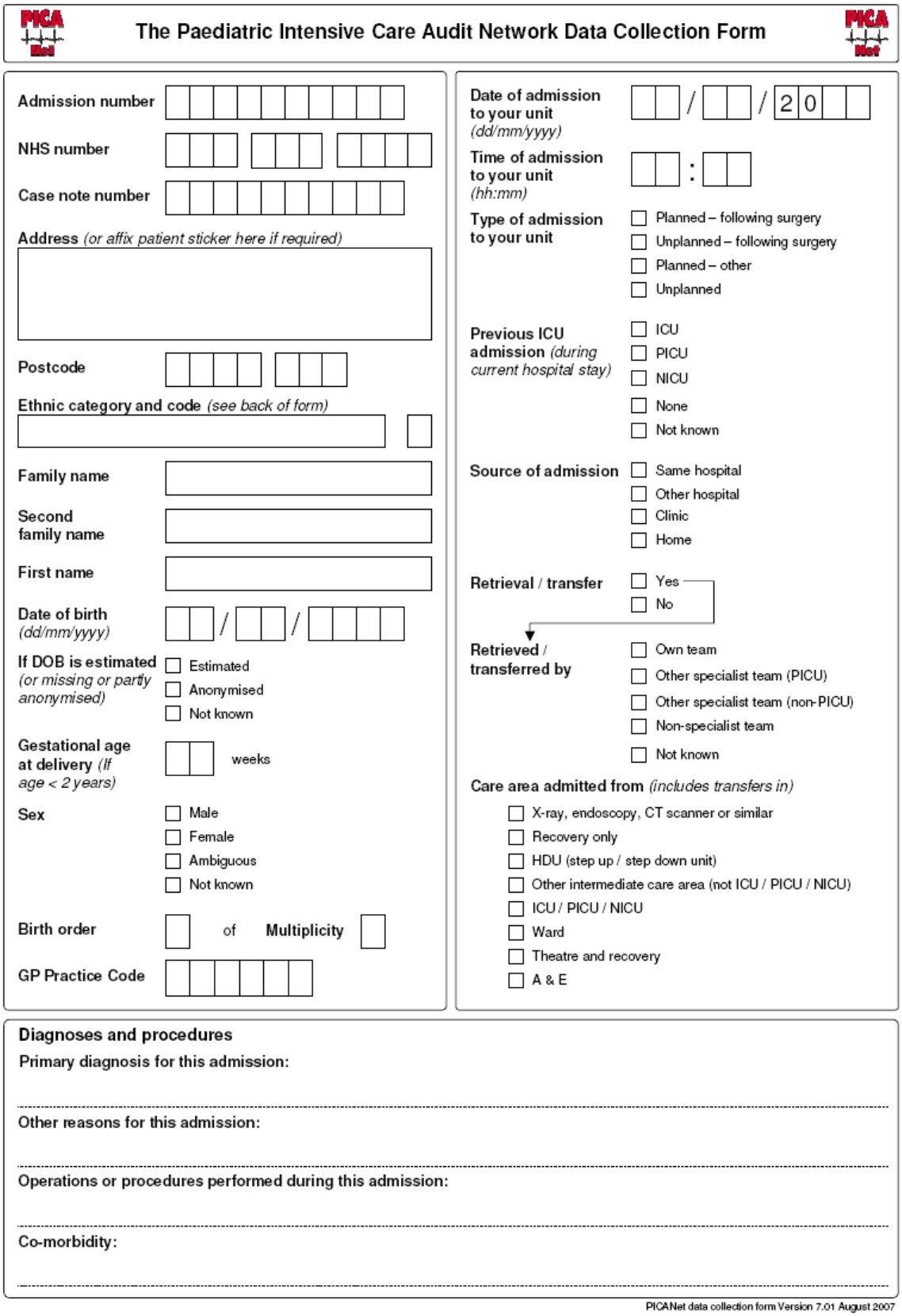


Table 4: Number of potentially eligible patients for CATCH in 2007 and 2008 – best and worst case scenario.
Excludes neonates and admissions other than 3 categories below, and assumes all admissions require a CVC (blue shading = single CATCH centre)

		2007		Predicted for CATCH per year		2008		Predicted for CATCH per year		REQUIRED
		< 3 days	3 +	best	worst*	< 3 days	3 +	best	worst*	
Birmingham	planned surgery-same hospital	170	155			175	163			
	emergency-same hospital	151	241	606	321	144	227	569	319	50
	emergency-different hospital	65	210			71	179			
Bristol	planned surgery-same hospital	100	145			121	139			
	emergency-same hospital	60	105	449	160	69	149	463	190	50
	emergency-different hospital	44	199			46	175			
Leeds	planned surgery-same hospital	201	203			163	191			
	emergency-same hospital	80	123	474	281	57	115	459	220	50
	emergency-different hospital	51	148			45	153			
Leicester Glenfield	planned surgery-same hospital	94	72			75	64			
	emergency-same hospital	20	17	179	114	21	14	167	96	
	emergency-different hospital	27	90			31	89			
Leicester Royal	planned surgery-same hospital	26	24			23	18			50
	emergency-same hospital	68	86	222	94	82	67	200	105	
	emergency-different hospital	42	112			39	115			
Liverpool	planned surgery-same hospital	271	213			260	199			
	emergency-same hospital	103	178	594	374	120	192	629	380	50
	emergency-different hospital	75	203			83	238			
London GOS	planned surgery-same hospital	215	370			268	322			

	emergency-same hospital	63	186	999	278	53	140	984	321	100
	emergency-different hospital	113	443			168	522			
London Guys	planned surgery-same hospital	180	258			207	241			
	emergency-same hospital	39	90	729	219	44	93	667	251	50
	emergency-different hospital	181	381			135	333			
London Brompton	planned surgery-same hospital	135	216			141	220			
	emergency-same hospital	7	28	301	142	27	30	294	168	50
	emergency-different hospital	21	57			28	44			
London St Marys	planned surgery-same hospital	11	6			12	4			
	emergency-same hospital	23	34	257	34	27	30	200	39	50
	emergency-different hospital	58	217			46	166			
Newcastle General	planned surgery-same hospital	46	7			30	4			
	emergency-same hospital	35	39	156	81	46	43	142	76	
	emergency-different hospital	40	110			57	95			
Newcastle Freeman	planned surgery-same hospital	64	133			48	132			
	emergency-same hospital	16	36	194	80	9	41	202	57	50
	emergency-different hospital	3	25			8	29			
Newcastle Royal Victoria	planned surgery-same hospital	37	25			41	42			
	emergency-same hospital	21	50	99	58	30	39	128	71	
	emergency-different hospital	13	24			15	47			
Southampton	planned surgery-same hospital	191	74			185	95			
	emergency-same hospital	58	69	307	249	57	81	329	242	50
	emergency-different hospital	85	164			61	153			
TOTAL				**5566**	**2485**	**3368**	**5433**	**5433**	**2535**	**600**

Appendix C: PICANet Data Collection Forms



The Paediatric Intensive Care Audit Network Data Collection Form

Admission number

NHS number

Case note number

Address *(or affix patient sticker here if required)*

Postcode

Ethnic category and code *(see back of form)*

Family name

Second family name

First name

Date of birth *(dd/mm/yyyy)*

If DOB is estimated *(or missing or partly anonymised)*
- ☐ Estimated
- ☐ Anonymised
- ☐ Not known

Gestational age at delivery *(If age < 2 years)* ☐☐ weeks

Sex
- ☐ Male
- ☐ Female
- ☐ Ambiguous
- ☐ Not known

Birth order ☐ of Multiplicity ☐

GP Practice Code

Date of admission to your unit *(dd/mm/yyyy)* ☐☐/☐☐/20☐☐

Time of admission to your unit *(hh:mm)* ☐☐:☐☐

Type of admission to your unit
- ☐ Planned – following surgery
- ☐ Unplanned – following surgery
- ☐ Planned – other
- ☐ Unplanned

Previous ICU admission *(during current hospital stay)*
- ☐ ICU
- ☐ PICU
- ☐ NICU
- ☐ None
- ☐ Not known

Source of admission
- ☐ Same hospital
- ☐ Other hospital
- ☐ Clinic
- ☐ Home

Retrieval / transfer
- ☐ Yes
- ☐ No

Retrieved / transferred by
- ☐ Own team
- ☐ Other specialist team (PICU)
- ☐ Other specialist team (non-PICU)
- ☐ Non-specialist team
- ☐ Not known

Care area admitted from *(includes transfers in)*
- ☐ X-ray, endoscopy, CT scanner or similar
- ☐ Recovery only
- ☐ HDU (step up / step down unit)
- ☐ Other intermediate care area (not ICU / PICU / NICU)
- ☐ ICU / PICU / NICU
- ☐ Ward
- ☐ Theatre and recovery
- ☐ A & E

Diagnoses and procedures

Primary diagnosis for this admission:

Other reasons for this admission:

Operations or procedures performed during this admission:

Co-morbidity:

PICANet data collection form Version 7.01 August 2007

Daily Interventions

Admission date: .....

Please record all interventions given on each day of admission using a cross ☒.
If no interventions given, choose 'No defined critical care activity'.

			Day 0	1	2	3	4	5	6	7	8	9	10	11	12	13
Basic	No defined critical care activity	Code 99														
	Continuous ECG monitoring	50														
	Continuous pulse oximetry	73														
Airway and ventilatory	Invasive ventilation via endotracheal tube	51														
	Invasive ventilation via tracheostomy tube	52														
	Non-invasive ventilatory support	53														
	Advanced ventilatory support (jet ventilation)	56														
	Advanced ventilatory support (oscillatory ventilation)	56														
	Nasopharyngeal airway	55														
	Tracheostomy cared for by nursing staff	13														
	Supplemental oxygen therapy (irrespective of ventilatory state)	09														
	Upper airway obstruction requiring nebulised adrenaline (epinephrine)	57														
	Apnoea requiring intervention (>3 in 24 hours or need for bag-mask ventilation)	58														
	Acute severe asthma requiring IV bronchodilator therapy or continuous nebuliser	59														
Cardio-vascular	Arterial line monitoring	60														
	External pacing	61														
	Central venous pressure monitoring	62														
	Continuous infusion of inotrope, vasodilator or prostaglandin	06														
	Bolus IV fluids (>80 ml/kg/day) in addition to maintenance IV fluids	63														
	Cardio-pulmonary resuscitation	64														
	Extracorporeal membrane oxygenation (ECMO)	65														
	Ventricular assist device (VAD)	65														
	Aortic balloon pump	65														
Renal	Peritoneal dialysis	05														
	Haemofiltration	16														
	Haemodialysis	66														
	Plasma filtration	67														
	Plasma exchange	67														
Neuro-logical	ICP-intracranial pressure monitoring	68														
	Intraventricular catheter or external ventricular drain	69														
Metabolic	Diabetic ketoacidosis (DKA) requiring continuous infusion of insulin	70														
Other	Exchange transfusion	04														
	Intravenous thrombolysis	71														
	Extracorporeal liver support using molecular absorbent recirculating system (MARS)	72														
	Patient nursed in single occupancy cubicle *(state reason for isolation below†)*	†74														
High cost drugs	Medical gases Band 1 - nitric oxide	X841														
	Surfactant	TBC														

†For patients nursed in a single occupancy cubicle, please state reason for isolation

Reason for isolation:

PIM/PIM2 – Reason for admission

Tick if this is an elective admission

☐

Main reason for this PICU admission

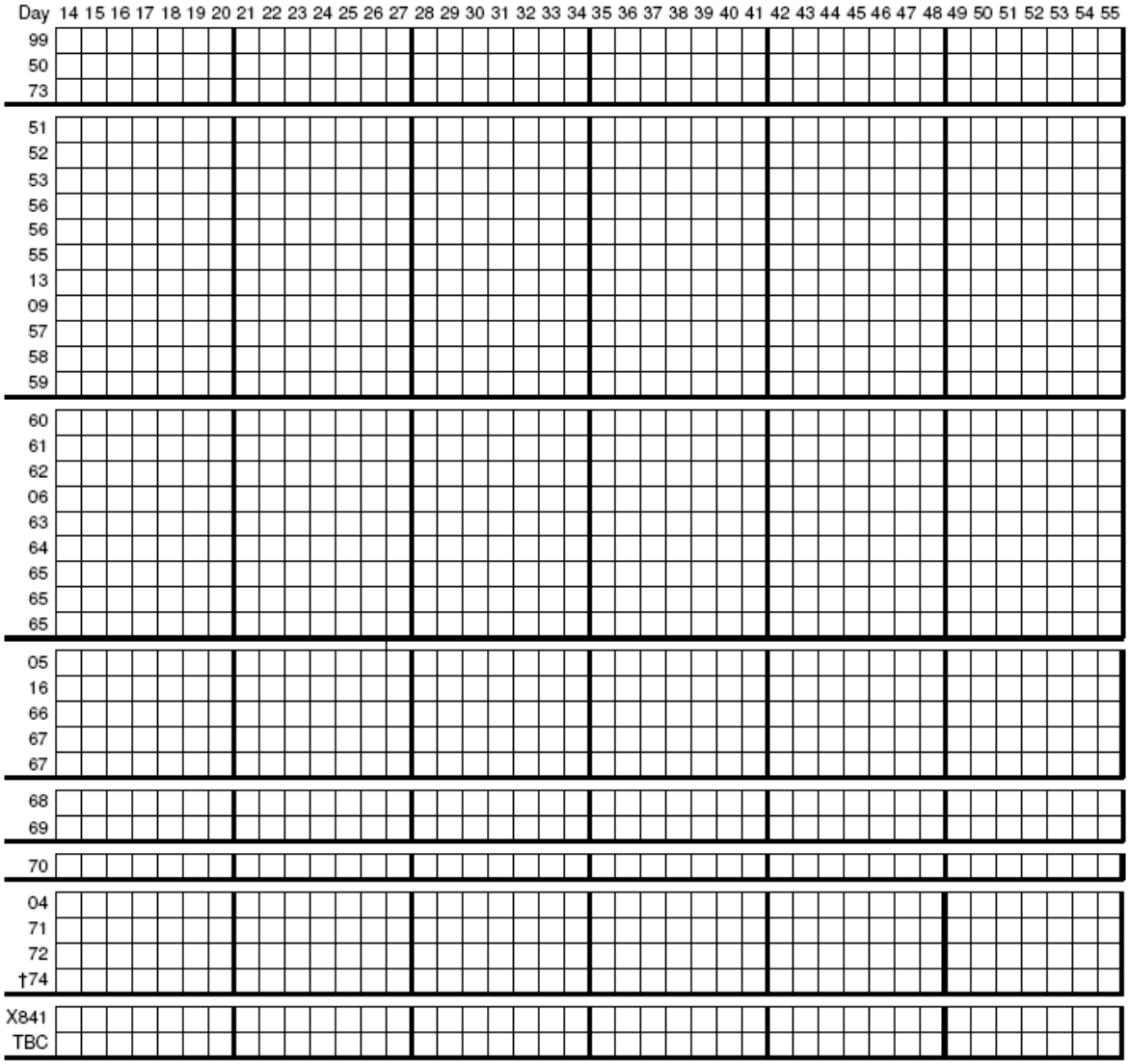
- ☐ None of those below
- ☐ Asthma
- ☐ Bronchiolitis
- ☐ Croup
- ☐ Obstructive sleep apnoea
- ☐ Recovery from surgery
- ☐ Diabetic ketoacidosis

PIM/PIM2 – Medical History

Is evidence available to assess past medical history?
(If Yes, tick all that apply)

- ☐ Yes
- ☐ No

- ☐ Cardiac arrest before ICU admission
  - ☐ Cardiac arrest OUT of hospital
- ☐ Cardiomyopathy or myocarditis
- ☐ Severe combined immune deficiency
- ☐ Hypoplastic left heart syndrome
- ☐ Leukaemia / lymphoma after 1st induction
- ☐ Liver failure (main reason for PICU admission)
- ☐ Admitted following cardiac bypass
- ☐ Spontaneous cerebral haemorrhage
- ☐ Neurodegenerative disorder
- ☐ Severe developmental delay
- ☐ Human Immunodeficiency Virus (HIV)



Did the child have a tracheostomy performed during this admission?

☐ Yes ☐ No

Is the child on a clinical trial? ☐ Yes ☐ No

Name of clinical trial:

PIM/PIM2 – Physiology

This section applies to measurements recorded between the first face-to-face contact with your unit doctor until one hour after admission to your unit

Blood gas in first hour? ☐ Yes ☐ No

Arterial PaO_2 ☐☐ . ☐☐ kPa OR ☐☐☐ mmHg

FiO_2* ☐ . ☐☐

Intubation* ☐ Yes ☐ No

Headbox* ☐ Yes ☐ No

** As recorded at the time of the above PaO_2 sample*

State first measurement recorded in defined time period

Systolic blood pressure ☐☐☐ mmHg

±

Base excess *(arterial/capillary)* ☐ ☐☐ . ☐

Pupil reaction

☐ Both fixed and dilated
☐ Other reaction
☐ Not known

Did the child receive any of the following during the first hour after admission to your unit?

Mechanical ventilation ☐ Yes ☐ No ☐ N/K

CPAP *(include mask, nasal, negative pressure)* ☐ Yes ☐ No ☐ N/K

Discharge information

Status at discharge from your unit

☐ Alive ☐ Dead ☐ Discharged for palliative care

Date of discharge *(dd/mm/yyyy)* ☐☐ / ☐☐ / 20☐☐

Time of discharge *(hh:mm)* ☐☐ : ☐☐

Date of death *(dd/mm/yyyy)* ☐☐ / ☐☐ / 20☐☐

Time of death *(hh:mm)* ☐☐ : ☐☐

Destination following discharge from your unit

- ☐ Normal residence
- ☐ Hospice
- ☐ Same hospital
- ☐ Other hospital

→

- ☐ ICU
- ☐ PICU
- ☐ NICU
- ☐ HDU
- ☐ SCBU
- ☐ Ward
- ☐ Other

Follow-up 30 days post-discharge from your unit

Status ☐ Alive ☐ Dead ☐ Not known

Date of death *(dd/mm/yyyy)* ☐☐ / ☐☐ / 20☐☐

Location

- ☐ Normal residence
- ☐ Hospice
- ☐ Same hospital
- ☐ Other hospital

→

- ☐ ICU
- ☐ PICU
- ☐ NICU
- ☐ HDU
- ☐ SCBU
- ☐ Ward
- ☐ Other

Growth measurements *(if required by unit)*

Height ☐☐☐ . ☐ cm

Weight ☐☐☐ . ☐☐☐ kg

Abdominal circumference ☐☐☐ . ☐ cm

Form completed by

Custom or user-defined fields

Field name	Value

Comments

Standard NHS ethnic categories

Ethnic category		Code
White	British	A
	Irish	B
	Any other White background	C
Mixed	White & Black Caribbean	D
	White & Black African	E
	White & Asian	F
	Any other mixed background	G
Asian & Asian British	Indian	H
	Pakistani	J
	Bangladeshi	K
	Any other Asian background	L
Black or black British	Caribbean	M
	African	N
	Any other Black background	P
Other ethnic groups	Chinese	R
	Any other ethnic group	S
Not stated	Not stated	Z

Queries

An emailed query to **picanet@leeds.ac.uk** *will reach every PICANet team member, or you can contact us individually:*

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