CATCH

CATheter Infections in CHildren

Statistical Analysis Plan

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Change Control

Updated SAP version no.	Section number changed	Description of change	Date changed	Initials
1.1	13 and 14	Comments from Paul Ewings addressed	06/12/2013	KD
1.2	Appendix D	Organisms added to the appendix	21/02/2014	KD
1.3	Section 5.2	Data for 'primary reason for admission based on ICD 10 code, categorised as Infection, Renal, Cancer, Respiratory, Neurological, Circulatory, Other' will now be obtained from PICANET data.	15/05/2014	KD
	Section 5.2	PIMS2 score has been added using PICANET data.		
	Section 7.1, 13	Clarification on timepoint for primary outcome. Date of randomisation and date of insertion are used interchangeably. Version 1 of the SAP does state that the time to event analysis will be calculated from date of randomisation. This has been clarified in the SAP in all relevant sections.		
	Section 11	Per protocol analyses have been removed as this was never stated in the protocol. Clarification has been made on the definition of elective and emergency patients.		
	Section 12	Protocol deviations will not be signed off as a per protocol analysis is not being undertaken Adverse events will be grouped into fewer groups. Clarification has been made to reporting of the two outcomes thrombosis and unexplained thrombocytopenia: 'to avoid double counting of unexplained thrombocytopenia will be presented as an adverse event and thrombosis will be presented as a secondary outcome as the outcome is time to event.		
	Section 14.10	Clarification has been added to the secondary outcome 'length of time in PICU' that this is for the first stay in PICU only as stated in appendix E. Also, CICU and NICU will be treated as PICU		
	Section	For the secondary outcome 'Time to a composite		

	14.3 Appendix E	measure of clinically indicated blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria', antibiotics need to be grouped as they are included on CRFs as free text so often misspelt. This grouping has been added to the appendix. Clarification has been added to the appendix for the time between the two events of flushing or difficulty drawing back blood, this should be up to 5 days.		
1.4	Section 13 Section 14.2 Appendix F	Clarification has been added regarding the process when times are not available and details on censoring. Clarification has been added regarding the process when times are not available and details on censoring. Antibiotics were grouped by a clinical member of the TMG	12/08/2014	KD

1 Table of Contents

Change Control 68

1 Table of Contents 70

2 Introduction 72

3 Study design and objectives 72

3.1 Sample size calculations 73

3.2 Interim analysis 73

4 Inclusion / Exclusion Criteria 74

4.1 Inclusion Criteria 74

4.2 Exclusion Criteria 74

5 Description of study population 74

5.1 Representativeness of study sample and patient throughput 74

5.2 Baseline comparability of randomised groups 74

5.3 Loss to follow-up 75

6 Follow up assessments 76

6.1 Blood culture samples 76

6.2 Clinically indicated 76

6.3 Positive blood culture 77

6.4 High bacterial DNA load indicative of blood stream infection 77

6.5 Culture negative infection 78

6.6 Antibiotic resistance 78

6.7 Positive CVC tip culture 78

6.8 Exit site infection 78

7 Study Outcomes 79

8 Description of compliance with treatment 81

9 Trial monitoring 81

10 Unblinding of randomised treatments 81

11 Patient groups for analysis 81

12 Protocol deviations 82

12.1 Adverse reactions/events 82

13 Analysis of primary efficacy outcome 82

13.1 Analyses of missing data 84

13.2 Sampling frequency 85

14 Analysis of secondary efficacy outcomes 85

14.1 Rate of blood stream infection during CVC insertion per 1000 CVC days 85

14.2 Time to CVC thrombosis 85

14.3 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 86

14.4 A CVC related blood stream infection 86

14.5 Mortality by 30 days 87

14.6 Type of bacteria and fungi isolated from positive blood cultures 87

14.7 Resistance to minocycline or rifampicin of blood culture or CVC tip isolates 87

14.8 Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring 87

14.9 Time to randomised CVC removal 87

14.10 Length of stay requiring PICU 88

14.11 Total length of hospital stay for current episode (for up to 6 month post randomisation) 88

14.12 Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVCs 88

15 Setting results in context of previous research 88

16 References 89

Approval and agreement 90

SAP APPENDIX A: CONSORT DIAGRAM 91

SAP APPENDIX B: PROTOCOL DEVIATIONS 92

SAP APPENDIX C: OUTCOME DEFINITION TABLE 93

SAP APPENDIX D: SKIN AND NONSKIN ORGANISMS 98

SAP APPENDIX E: STEPS TAKEN TO OBTAIN OUTCOME DATA 103

SAP APPENDIX F: ANTIBIOTIC GROUPING 108

SAP APPENDIX G: CLINICAL ENDPOINT REVIEW 117

2 Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final full analysis for the study “CATCH”.

This study is 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 (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These analyses will be performed by the trial statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan specified within the study protocol.

All analyses will be performed with standard statistical software (SAS version 9 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP IS006 Study Closedown and Archiving. The testing and validation of the statistical analysis programs will be performed following SOP ST001: Statistical Analysis and Reporting - v.2.0.

3 Study design and objectives

This study is designed as a prospective, parallel, controlled, multicentre, randomised clinical trial comparing the effectiveness of heparin bonded or antibiotic impregnated CVCs with standard CVCs for preventing hospital acquired blood stream infection in children (aged less than 16 years) admitted to PICU, who require insertion of a CVC for at least 3 days.
The primary objective of this trial is to determine the effectiveness of heparin bonded or antibiotic impregnated CVCs (combined) compared with standard CVCs for preventing hospital acquired blood stream infection

Secondary objectives are:

a. 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.
b. 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.
c. 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).

d. To determine the effect of type of CVC on mortality at 30 days.
e. To identify adverse effects of CVC type on pathogen selection, antibiotic resistance, clinical evidence of CVC thrombosis and thrombocytopenia.

The null hypothesis is that there is no difference in time to first blood stream infection between the standard and impregnated (antibiotic and heparin combined) groups. The alternative hypothesis is that there is a difference between the two groups.

Randomisation

Randomisation lists were generated in STATA using simple block randomisation with random variable block length and a 1:1:1 ratio of treatment allocation.
Randomisation was stratified by elective and emergency participants and centre with further stratification within centre to permit multiple cvc allocation/storage sites.

The randomisation numbers are 9 digits long.

Digits 1 to 4 indicate the UK CRN number;
Digit 5 indicates whether a participant is elective (0) or emergency (1);
Digit 6 indicates the place where the cvc is stored and
Digits 7 to 9 are sequential numbers within place and site.
Treatment allocation could not be blinded to the clinician responsible for randomising a patient and inserting the CVC but was concealed from patients, their parents and PICU personnel responsible for their care.

There was an interim analysis of the primary outcome mid-way (650 patients randomised and consented and entered onto the database) through the trial, using Peto-Haybittle stopping rules.

3.1 Sample size calculations

Sample size calculations were undertaken using NQuery Advisor software.
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. 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.

3.2 Interim analysis

The interim analysis of the primary outcome was completed mid-way (approximately half of the patients randomised and consented and entered onto the database), through the trial, using Peto-Haybittle stopping rules. This was completed under version 2.0 of the SOP as version 3.0 of the SOP was released later (30/06/2012). Details can be found in the IDSMC report dated 22/05/2012.

4 Inclusion / Exclusion Criteria

4.1 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;
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).

4.2 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

5 Description of study population

5.1 Representativeness of study sample and patient throughput

Details will be presented on:

- the number of patients, both elective and emergency who were randomised,
- those emergency patients who were randomised but did not provide deferred consent,
- those who received the randomised allocation,
- those who did not receive the randomised allocation,
- those randomised but where CVC insertion was not attempted,
- those where CVC insertion was attempted but the CVC was not inserted,
- those who withdrew from the study after randomisation and
- those who were lost to follow-up

will be summarised in a CONSORT flow diagram (Appendix A) (1). Due to the nature of the trial, information could not be collected regarding eligible emergency participants who were not randomised. Therefore, this information is not presented for elective patients.

5.2 Baseline comparability of randomised groups

Baseline characteristics will be descriptively summarised (numbers and percentages). Table columns will be: Standard; impregnated (heparin or antibiotic); antibiotic; heparin; and total. This table will be produced across all sites and by site. Variable to be included in the table are:

Descriptor	Form
Baseline characteristics	
Number of patients randomised	1, 2 and 3
Elective/ emergency	1 and 3
Age, categorised as <3 months, 3 months-<1 year, 1-10 years and 11+ years. A median and interquartile range will also be calculated.	
Gender (male/female)	4
Weight, categorised as <3kgs, 3-10kgs, >10kgs. A median and interquartile range will also be calculated.	4
Electives - Type of surgery, categorised as cardiac/other.	4
Source of admission to PICU, categorised as: Elective, same hospital or Emergency, Same hospital or Other hospital – retrieved by: Specialist retrieval team, Other	4
Disease characteristics	
Pre-existing CVC at time of randomisation or within 72 hours prior to time of randomisation (Yes/ No)	1 or 3 and 4
Health status BEFORE the acute problem precipitated PICU admission: (Healthy/ Not Healthy).	4
Anticoagulant medication within 72 prior to randomisation: (yes/no).	4
Antibiotics 72 hours prior to randomisation: (yes/no).	4
Primary reason for admission based on ICD 10 code, categorised as Infection, Renal, Cancer, Respiratory, Neurological, Circulatory, Other.	PICANET data
PIMS2 score (<1%, 1-5%, 5-15%, 15-30%, 30%+)	PICANET data
Positive blood culture within 72 hours prior to time of randomisation (yes/no).	4
Suspected infection at time of randomisation (yes/no).	4
Immune compromised (yes/no).	4
Description of interventions	
Where the CVC was inserted, stratified by elective and emergency and then same hospital and other hospital and then: ICU (PICU/NICU/CICU); other ward (HDU or other ward); theatre; other /A&E	1 or 3
Size of line: (4, 5 or 7)	1 or 3
Number of lumens (triple or double lumen)	1 or 3
Site: (femoral or other)	1 or 3
Sterile procedures used split by elective and emergency: yes/no	1 or 3

Descriptor	Form
48 hours post randomisation	
Other devices in situ in addition to CVC: Less than 4 Greater than or equal to 4	4

5.3 Loss to follow-up

The number lost to follow up within each treatment group will be reported and the reasons where known will be provided.

Reasons for loss to follow up are: transferred to a site not participating in CATCH; deferred consent not obtained. For deaths – see follow up assessments (section 6).

6 Follow up assessments

Where CVC insertion was successful, patients will be followed up to 48 hours after CVC removal. For those where insertion was attempted but not successful, patients will be followed up to 48 hours after attempted insertion.

6.1 Blood culture samples

Blood culture samples may be taken from CVC lumens, peripheral veins, or if necessary, from the arterial line (although this is discouraged). To differentiate potential contaminants or line infection from blood stream infection the best approach to sampling is in the following diminishing order of preference

a. take both a peripheral blood sample and a CVC culture at the same time
b. Take a peripheral blood culture;
c. Take a CVC culture – from all available lumens of the randomised CVC;
d. Take a CVC culture – from all available lumens of any other CVC;
e. Take an arterial line culture (high risk of contamination).

A minimum of 0.5ml of blood should be taken for any blood culture. For CVC cultures, a minimum of 0.5ml of blood will be taken from each lumen and inoculated into separate culture bottles (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.

Blood culture contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.2.1)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)
- A CVC related blood stream infection (7.2.4)
- Type of bacteria and fungi isolated from positive blood cultures (7.2.6)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.2 Clinically indicated

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), or removal of the CVC line due to suspected infection, 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 of signs of infection. 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 or if there were signs of infection at the CVC exit site .

Clinically indicated contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.3.2)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

6.3 Positive blood culture

Positive blood culture will be defined as:

a. one or more positive blood cultures with a non-skin organism from a sample taken from any vascular site; or

b. the same skin organism isolated from 2 or more positive blood cultures (from any vascular site) within 48 hours of each other. One or more of the samples must be taken 48 hrs after CVC insertion or within 48 hours after removal. A review committee will independently classify multiple cultures according to same or different organisms based on species and antibiogram as to whether it is the same BSI or not.

Positive blood culture contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.2.1)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)
- A CVC related blood stream infection (7.2.4)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.4 High bacterial DNA load indicative of blood stream infection

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 sites 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. Note that this may be influenced in advances in methodology since the protocol was approved). 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.

High bacterial DNA load indicative of blood stream infection contributes to the definition of:

- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

6.5 Culture negative infection

Culture negative infection will be defined by a change in antibiotic treatment on the same or subsequent day after a blood culture sample more than 48 hours after CVC insertion or up until 48 hr after CVC removal in the presence of negative blood cultures, and 1 or more clinical signs of infection and at least one other sign (clinical or laboratory). The signs of infection include the following: clinical signs – temperature >38oC 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).

Culture negative infection contributes to definitions of:

- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

6.6 Antibiotic resistance

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. 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.

Antibiotic resistance contributes to the definition of:

- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (07.2.7)

6.7 Positive CVC tip culture

Positive CVC tip culture will be based on any sized tip of the catheter, removed using a sterile procedure, and cultured according to standard methods. 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.

Positive CVC tip culture contributes to definitions of:

- A CVC related blood stream infection (7.2.4)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.8 Exit site infection

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.

Exit site infection is listed within the Adverse Events (Section 12.1) and also contributes to the definition of:

- Time to first blood stream infection (7.1)
- A CVC related blood stream infection (7.2.4)

7 Study Outcomes

7.1 Primary Outcome

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 randomisation and up to 48 hours after CVC removal.

7.2 Secondary Outcomes

7.2.1 Rate of blood stream infection during CVC insertion per 1000 CVC days.

Where blood stream infection is defined as per primary outcome but without any criteria around the timing of the sample and the CVC must be in situ.
Second episode of blood stream infection (defined as per primary outcome) will be defined by a positive blood culture (see definition above) of a different isolate (in terms of species and antibiogram) from a sample taken whilst the cvc is in situ. Any positive blood cultures of the same isolate will be regarded as the same episode regardless of time since the first sample.

7.2.2 Time to CVC thrombosis - defined clinically by (any one or more of the following):

a. 2 records of difficulty drawing back blood from one or more lumen;
b. 2 or more episodes of flushing to unblock;
c. an episode of swollen limb;
d. positive ultrasound;
e. removal of CVC because of clinical evidence of a blocked CVC.

7.2.3 Time to a composite measure of clinically indicated blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria defined as :

a. Primary outcome as defined above
b. Any of the clinical indicators of infection (Section 6.2) and blood culture taken and
    i. High bacterial DNA load from a PCR positive result or
    ii. change in antibiotic on same day or next day or
    iii. CVC removal for infection

7.2.4 A CVC related blood stream infection will be defined by:

a. the same isolate (species and antibiogram) from the CVC tip and from a blood culture sample taken from any site more than 48 hours after CVC insertion and within 48 hours following CVC removal;

b. differential positivity of the same isolate in blood cultures taken from multiple CVC 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).
c. OR positive BSI AND CVC removed for infection
d. OR positive BSI AND CVC exit site infection

7.2.5 Mortality by 30 days

7.2.6 Type of bacteria and fungi isolated from positive blood cultures

7.2.7 Resistance to minocycline or rifampicin of blood culture or CVC tip isolates

7.2.8 Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring

7.2.9 Time to randomised CVC removal

7.2.10 Length of stay requiring PICU

7.2.11 Total length of hospital stay for current episode (for up to 6 month postrandomisation)

7.2.12 Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVC

8 Description of compliance with treatment

The number of patients where CVC insertion was attempted but was not successful, where insertion was not attempted after randomisation and for those that received a CVC other than the randomised CVC will be reported in the CONSORT flow diagram (Appendix A).

9 Trial monitoring

There have been two IDSMC meetings, one in February 2012 to investigate the control group event rate and the other in June 2012 for the interim analysis of the primary outcome for 650 patients randomised, consented and entered onto the database. The recommendation from both of these meetings was to continue recruitment.

10 Unblinding of randomised treatments

The number of patients who were unblinded prior to database lock will be reported for each treatment group along with the reasons as to why they were unblinded.

Checks were made on the order of patients being randomised and records were kept of any unblinding requests that were made by sites.

11 Patient groups for analysis

The principle of intention-to-treat, as far as is practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all patients randomised to the treatment groups, regardless of whether CVC insertion was attempted or not.

The membership of the analysis set for each outcome will be determined and documented. Reasons for participant exclusion will be given prior to blinding being broken and the randomisation lists being requested. Reasons may include missing data or loss to follow up.

The safety analysis data set will contain all participants that were randomised and had CVC insertion attempted. Patients will be included in the treatment group that they actually received (the CVC that was actually inserted or the CVC that was attempted if no CVC was inserted).

Patients to be excluded from populations will be defined in template ST001TEM04 (Protocol deviations and population exclusions template) and will be agreed and approved prior to any release of randomisation codes.

Patients will be classified as elective/emergency based on consent given i.e. deferred/prospective.

12 Protocol deviations

Any protocol deviations will be tabulated and the frequency of these deviations presented by site and in total, and by treatment group.

Protocol deviations have been defined in the draft monitoring plan (Appendix B). The monitoring plan also defines whether each deviation is considered major or minor.

Description of safety outcomes

12.1 Adverse reactions/events

All related adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) reported by the clinical investigator (as in Section 10.4 of the protocol) will be presented, identified by treatment group. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Any adverse events entered in free text will be assessed by a team of clinical professionals and summarised as below.

- Thrombosis
- Exit site infection
- Antibiotic resistance
- Low platelets/hypersensitivity
- Line displacement (falling out/tip displaced)
- Trauma from line insertion
- Line breakage/mechanical problem
- Mortality

To avoid double counting of unexplained thrombocytopenia will be presented as an adverse event and thrombosis will be presented as a secondary outcome as the outcome is time to event.

13 Analysis of primary efficacy outcome

The primary efficacy outcome is 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 (see section 7.1 and Appendix C, D, E).

- If an organism is cultured it is identified on the microbiology form. Organisms cultured will be discussed with the microbiologist to identify whether they are skin or non skin organisms (Appendix D). If a non skin organism is identified

then this is automatically a positive blood stream infection. If a skin organism is identified then the microbiology form will be checked to identify whether the same skin organism has occurred again from any site within 48 hours (only one sample has to be within the correct timeframe for the primary outcome). This will be checked with the microbiologist and clinician endpoint review committee (Appendix G) to ensure the skin organisms are in fact the same. If this is confirmed then this will be a positive blood stream infection. Date and time of the samples are included on the microbiology form.

- Timings will then be checked to ensure the sample was taken 48 hours post randomisation (insertion also used in a sensitivity analysis) and up to 48 hours after removal of the CVC. These timings are included on form 1 section B (date and time of randomisation and date and time of successful insertion) and form 5 (date and time of CVC removal). The sample times are indicated on forms 9 and 10 (date and time sample taken). If no CVC removal date was recorded, date of transfer was used. For those with no time for removal but when the date is the same as randomisation, the time was set to 23.59.
- Clinically indicated: defined in section 6.2. The sampling form will then be checked to determine whether there were one or more clinical indices within 48 hours of the sample being taken. Clinical indication of infection is recorded on form 9 (sampling form: section A question 4 and section B question 1), 6 (progress log) and on form 5 (CVC insertion follow up form: section A question 1 and section B question 3. Note that there may be two reasons for removal) if the reason for removal is 'CVC associated infection suspected'. Raised CRP and white blood cell counts alone will not be regarded as clinical indicators of infection.

The number of positive blood stream infections taken more than 48 hours after randomisation and up to 48 hours after CVC removal will be presented split by treatment, the site of the sample (i.e. lumen, arterial, peripheral) and whether the organisms cultured were skin or non-skin.

Kaplan-Meier survival curves stratified by CVC will be presented. A survival analysis will be performed using the Log rank test and Cox proportional hazard regression models if appropriate for heparin bonded or antibiotic impregnated CVCs (combined) compared with standard CVCs and adjusted for one the variables used for stratifying randomisation (elective and emergency participants). In the design, the stratification of CATCH between emergency and elective was due to prognostic importance but centre and storage site were logistical. ICH E9 states that "In some trials there may be no reason to expect the centres to have any influence on the primary or secondary variables because they are unlikely to represent influences of clinical importance. In other trials the limited number of subjects per centre will make it impracticable to include centre effects in the statistical model" (3). Heterogeneity of treatment effects by centre will be considered in a graphical display.

Since the hazard of infection may not be constant post CVC insertion, non-proportional hazards survival models will also be investigated. Results will be presented using Hazard Ratios and 95% confidence intervals. Survival times will be measured from the date and time of randomisation to the date and time of positive

blood stream infection as identified above. For those not experiencing the primary outcome, they will be censored at death, 48 hours after CVC removal or for those with no CVC inserted, 48 hours after randomisation/attempted insertion.

Differences between date and time of randomisation and date and time of insertion will be summarised using medians and IQR.

A secondary analysis will compare each impregnated CVC against standard CVC i.e. i) heparin bonded versus standard and ii) antibiotic impregnated versus standard.

Regression models will be used to further investigate the outcomes between the groups, including: type of admission (emergency clean, emergency dirty or elective); Immune compromised (yes/no); infection at admission (yes/no) and other devices in situ (4 or more in addition to CVC), age (as categorised within the baseline table), site (femoral vs other). An interaction of elective and emergency will also be considered.

A p-value of 0.05 or less will be used to declare statistical significance for all analyses.

The number needed to treat (NNT) and 95% confidence intervals will be calculated (4).

13.1 Analyses of missing data

As much information as possible will be collected about the reasons for missing outcome data and this will be used to inform sensitivity analyses.

If there are clinical indicators of infection but no microbiology report of blood cultures then no blood stream infection will be assumed, a sensitivity analysis will assess whether the conclusion differs if we assume there is an infection. Clinical indicators of infection will not be included where the clinical indicator that was on the sampling form was only for raised CRP or white blood cell counts or both. The ICD-10 code reason for admission will also be considered.

If the patients without microbiology reports are included in the denominator of the primary outcome then this assumes that there was no clinically indicated blood stream infection. The following classifications (Table 1) make use of all data available for each case and present reasonable assumptions on their primary outcome classification. Where there is uncertainty these cases are highlighted for sensitivity analysis.

TABLE 1: ASSUMPTIONS FOR SENSITIVITY ANALYSIS

Clinically indicated and samples taken	Include in numerator for sensitivity analysis
Clinically indicated but no samples taken (taking into account ICD-10 code)	Include in numerator for sensitivity analysis
Not clinically indicated and no samples at removal	Included in denominator only

Inserted for less than 48 hours/ attempted after 12 hours after randomisation/not successfully inserted	Included in denominator only
'None' was not ticked for organisms and there were no other organisms noted.	Included in denominator only

13.2 Sampling frequency

Samples will be descriptively summarised (numbers and percentages) for samples taken 48 hours after insertion and within 48 hours after removal that are clinically indicated. Table columns will be: Standard; impregnated (heparin or antibiotic); antibiotic; heparin; and total. These tables will be produced across all sites and by site.

a) Type of sample – arterial, peripheral or CVC

b) Number with multiple samples from same cvc and different lumens

c) Site (femoral, other)

d) CVC tip sampled and paired CVC tip and blood culture within 48 hours

e) PCR sampled

14 Analysis of secondary efficacy outcomes

The null hypothesis for each secondary outcome (in which statistical tests are being performed) will be that there is no difference in outcome between the standard and impregnated (antibiotic and heparin) groups. The alternative hypothesis is that there is a difference between the two groups. The stratification variable elective/emergency participants will be included as a covariate. The outcomes will also be analysed with the groups separately. (Appendix C, D, E, F)

14.1 Rate of blood stream infection during CVC insertion per 1000 CVC days

Data obtained as per the primary outcome although the CVC must be in situ. For a second infection the isolate needs to be a different strain (review conducted blind to allocation by a team of clinical professionals) and not within 48 hours to that identified in the primary outcome otherwise considered same infection.

The analysis will involve the number of infections and the number of days the CVC is in situ. This will be standardised to 1000 CVC days and the rate ratio and 95% confidence intervals will be presented based on poisson regression.

14.2 Time to CVC thrombosis

Data will be obtained from form 1 or 3 (Section B question 2: date and time of randomisation), 11 (difficulty withdrawing blood, episodes of flushing, swollen limb, ultrasound done – positive results obtained from sites), form 9 (section A, question 2: date and time sample taken and question 3: difficulty withdrawing blood), form 6

(thrombosis indicated, not bleeding back as a reason for no sample taken – to confirm unclear text with clinical team), form 5 (Section B, question 1: date and time of CVC removal and question 3: reason for removal 'CVC blocked').

This will also be checked against the related adverse events form (form 12) to ensure all thrombosis events have been recorded on the thrombosis form and reviewed by a team of clinical professionals. There was no time on the progress log (form 6) or thrombosis form (form 11) therefore the time was set at 23.59. Patients with no event were censored at 48 hours after removal.

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented. Survival times will be measured from the date and time of randomisation to the date and time of CVC thrombosis.

14.3 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

Data used will include forms 1, 3 (date and time of randomisation), 5 (removal due to CVC infection), 6 (as per primary outcome), 7 (change in antibiotics), 9 (clinical signs of infection),10 and downloads (microbiology – culture negative and high DNA load, Appendix D). A blood culture must have been taken.

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of a composite measure of clinically indicated blood stream infection will be used to calculate the time to a composite measure of clinically indicated blood stream infection.

Antibiotics will be grouped by a clinical professional (Appendix F). Data will be reviewed by a team of clinical professionals (Appendix G).

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented. Survival times will be measured from the date and time of randomisation to the date and time of the blood stream infection.

14.4 A CVC related blood stream infection

Data will be obtained as per the primary outcome although CVC tip is included and exit site infection (forms 5 and 12). Differential positivity will be reviewed by a team of clinical professionals (Appendix G).

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.5 Mortality by 30 days

At the time of clinical analysis death will be taken as that recorded prior to discharge (form 16). ONS data will be obtained and reconciled with that held on form 16 and final analysis completed upon the reconciled data set.

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.6 Type of bacteria and fungi isolated from positive blood cultures

The data will be taken from the microbiology form (form 10) and also obtained from a microbiology download from each site. Line listings will be given to the microbiologist to specify the groupings (Appendix D and F).

14.7 Resistance to minocycline or rifampicin of blood culture or CVC tip isolates

The data will be obtained from a microbiology download from each site from positive blood cultures for the primary outcome and repeat bloodstream infections identified in Outcome 14.1 and CVC tip**Error! Reference source not found.** and provided to the microbiologist to determine resistance (Appendix G).

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.8 Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring.

The data will be obtained from the adverse event form (form 12 number 2 and 13). This will be measured from randomisation up to 48 hours after removal.

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.9 Time to randomised CVC removal

The date and time of randomisation will be taken from form 1 and 3, section B, question 2. The date and time of CVC removal will be taken from form 5, section B, question 1. Note this does not have to be the randomised CVC, but rather the CVC inserted following randomisation.

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Survival times will be measured from the date and time of randomisation to the date and time of CVC removal. Results will be

presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented.

14.10 Length of stay requiring PICU

The length of stay will be measured from the date of randomisation to the date of transfer/discharge from PICU for the first stay in PICU (NICU and CICU will also be treated as PICU). Date of randomisation (form 1 and 3 section B) or, date admitted to PICU (form 4) will be used as the start date and details of the ward will be used (form 1 and 3 section B question 7). Date and time of transfer/discharge from PICU is included on form 14 section A. A small number will need data from HES (those randomised at end of recruitment period)

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

14.11 Total length of hospital stay for current episode (for up to 6 month post randomisation)

The date/time of randomisation (form 1 and 3) and the date/time of transfer/ discharge (form 14) will be used. A small number will need data from HES (those randomised at end of recruitment period).

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

14.12 Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVCs

The analysis will be undertaken by health economics using data downloaded from HES. Please see health economics analysis plan.

15 Setting results in context of previous research

Once the trial has been completed the results of the trial will be set in context of the existing evidence base**.** This will compare the results of the trial with those reported within relevant systematic reviews.

Generalisability of results

Once the trial has been completed the results will be used in analyses that take into account trends in blood stream infection across all PICUs in the UK, in order to estimate the absolute risk difference associated with purchasing impregnated vs standard CVCs. The analysis will be undertaken by the team at UCL-ICH. Please see the generalizability study analysis plan.

16 References

1. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010;152. Epub 24 March.
2. ICH E3 chapter 12.
3. ICH E9 chapter 3.
4. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319:1492–5.

Approval and agreement

Two versions of the SAP should be approved.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: _____

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician or Head of Statistics

Name _____

Signed _____ Date _____

Chief Investigator

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

Chair of Trial Steering Committee

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

OR TSC not reviewing SAP (ensure agreement is documented) ☐

Chair of Data Monitoring Committee

Name _____

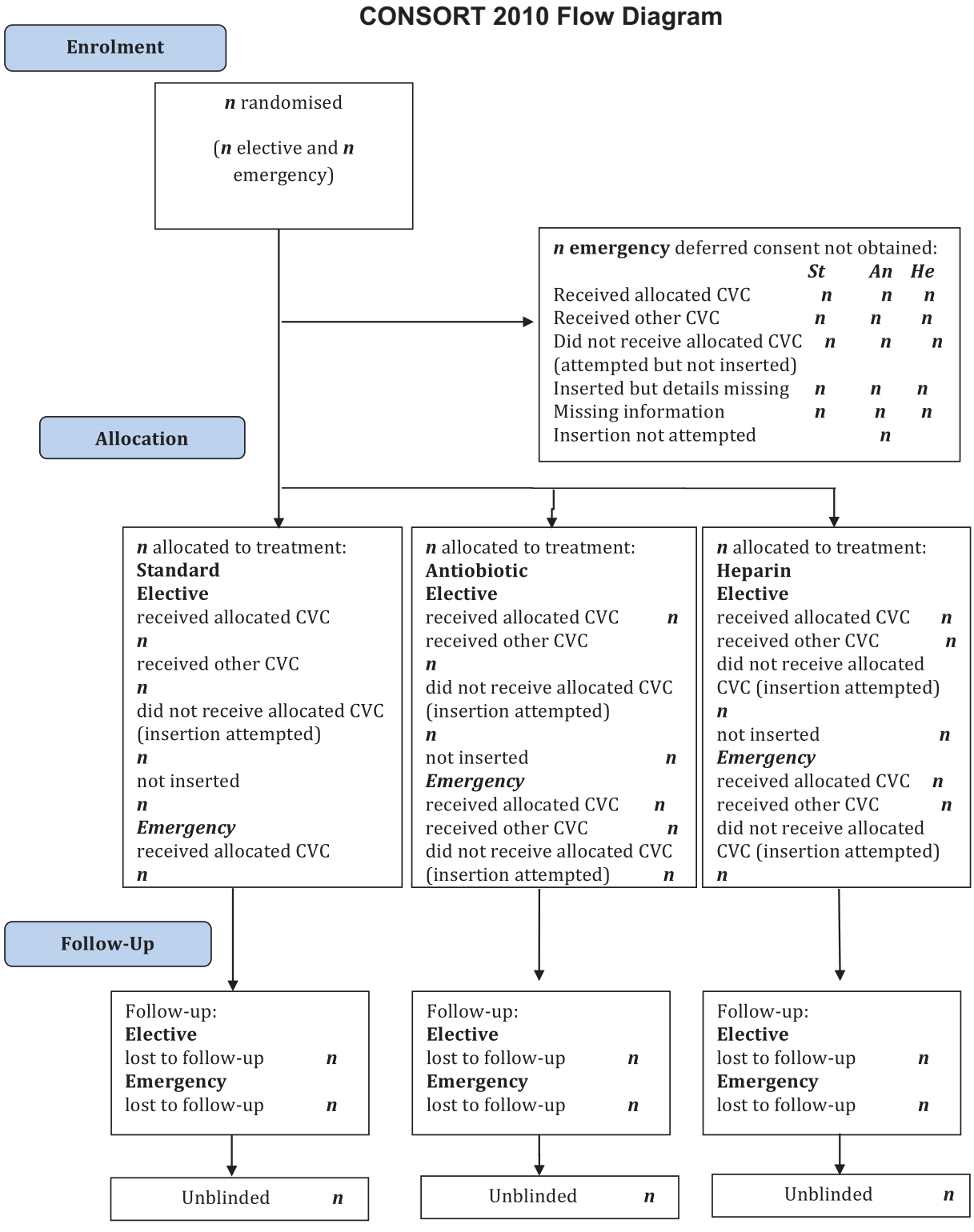
Signed _____ Date _____

OR Electronic approval attached ☐

OR IDSMC not reviewing SAP (ensure agreement is documented) ☐

Form prepared: 06/12/2013 v1.1 for CATCH Study

SAP APPENDIX A: CONSORT DIAGRAM



Form prepared: 06/12/2013 v1.1 for CATCH Study

SAP APPENDIX B: PROTOCOL DEVIATIONS

Eligibility	**Major/minor**
Child over 16	Minor
Randomised multiple times	Major
Trial Procedures	
Patient not followed up for full trial duration from randomisation to 48 hours after follow up	Major
CVC was not needed for 48 hours and removed	Major
CVC inserted more than 12 hours after randomisation	Major
Samples not taken within 48 hours of clinical indication	Major
Line not required following randomisation (post 12hrs) randomisation pack returned to CTU	Minor
Randomisation and sequence	
Incorrect randomisation envelope used - elective randomising envelope for an emergency line insertion or emergency randomising envelope for an elective line insertion	Minor

SAP APPENDIX C: OUTCOME DEFINITION TABLE

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
Primary Endpoint										
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	Y	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y But need at least 2 positive blood culture samples with matching isolate taken within 48 hrs of each other. Only one sample needs to be in time window.	N	N	A P C	Arterial, peripheral and CVC apply. a 'skin' BSI *always* requires at least two blood samples with an indistinguishable (by ID and antibiotic suseptibility) strain within defined period. **Assessed by team of clinical professionals**
Secondary Endpoint										
Rate of blood stream infection during CVC insertion per 1000 CVC days	Y As per primary outcome (PO)	Y	Y	N	PO For a second infection the isolate needs to be different strain and AB resistance profile to that identified in the PO and taken from a second sample more than 48 hours after first positive BSI otherwise considered same infection.	PO	PO	PO	A P C	Arterial, peripheral and CVC apply **Assessed by team of clinical professionals**

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
Time to CVC thrombosis - defined clinically • 2 records of difficulty drawing back blood from one or more lumen; • 2 or more episodes of flushing; • an episode of swollen limb; • positive ultrasound (up to 5 days after removal); • removal of CVC because of clinical evidence of a blocked CVC	NA.	Y	Y	Y	NA	NA	NA	NA	NA	**Assessed by team of clinical professionals**
Time to a composite measure of a clinically indicated blood stream infection (any one of below) • primary outcome	Y	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y But need at least 2 blood samples with matching isolate taken within 48 hrs of each other. Only one sample needs to be in time window.	N	N	A P C	

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
• high bacterial DNA load	Y	N	Y	Y	NA	NA	NA	NA	NA	
• culture negative bloodstream infection based on clinical criteria defined by: • a change in antibiotic treatment on the same or subsequent day after a blood culture sample more than 48 hours after CVC insertion **and** • 1 or more clinical signs of infection. clinical signs - temperature >38°C or temperature instability, - haemodynamic instability (hypotension, mottled, poor perfusion, capillary refill>3s); - OR CVC removed for infection	Y	N	Y	Y	NA	NA	NA	NA	NA	Laboratory signs only counted if one other clinical sign present – excluding crp or wcc Blood culture sample had to have been taken And no other sources of infection except clinical signs **Culture negative infections assessed by team of clinical professionals**
CVC related blood stream infection a) the same isolate (species and antibiogram) from the CVC tip and from a blood culture	N	N – blood Y-tip	Y	Y	Y	Y	Y If positive BSI in time window	Y If positive BSI (one skin)	A P C T	Positive BSI AND same organism and antibiogram for tip. If positive BSI>48

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
										hours, tip can be anytime.
b) differential positivity of the same isolate in blood cultures taken from multiple CVC 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).	N	N	Y	Y	Y	Y	N	N	MC	when the primary outcome definition for a BSI has been fulfilled, and where there are multiple CVC lumens, and blood cultures have been collected from multiple lumens at the same sampling time, but not all give a positive result.
c) OR positive BSI AND CVC removed for infection	N	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y any positive BSI, two BSI needed	N	N	A P C	
d) OR positive BSI AND CVC exit site infection	N	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y any positive BSI one BSI only needed	N	N	A P C E	

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	**48 hours after insertion to removal**	**Up to 48 hours after removal**	**Non-Skin**	**Skin**	**Non Skin**	**Skin**	**A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site**	
Mortality by 30 days	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Type of bacteria and fungi isolated from positive blood cultures	List of all isolates to be sent to a team of clinical professionals to classify									
Resistance to minocycline or rifampicin of blood culture or CVC tip isolates >15 isolates e-test will be performed	NA	Y	Y	Y	Y	Y	Y	Y	A P C	Data from download from individual sites. Report separately for BSI and tip **Assessed by team of clinical professionals**
Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring	NA	NA	NA	NA	NA	NA	NA	NA	NA	

* Note: Raised WBC and/or CRP are not sufficient criteria alone for clinically indicated blood stream infection. Other additional criteria are required. Must be clinically indicated within 48 hours of the sample taken.

SAP APPENDIX D: SKIN AND NONSKIN ORGANISMS

The contents of this table have been developed over the data monitoring committee reports by the statisticians and microbiologist. These organisms will be reconciled with the microbiology downloads. This table is based on the line listings as entered into the clinical trials database. No correction has been made to spelling mistakes or abbreviations, so each has been classified as it appears on the database. For production of a table summarizing the different types of organisms self evident corrections agreed by the clinical team will be utilized.

Organism as stated in the CRF	Corrected organism name	Skin/nonskin	Minocycline/ Rifampicin active/inactive
Coagulase-negative staphylococcus	Many possible names – *Staphylococcus epidermidis, Staphylococcus spp.*, Anything with *Staphylococcus* which does not include *aureus*.	skin	Active
Staph.aureus	*Staphylococcus aureus*	Non skin	M and R Active
Klebsiella spp.	*Klebsiella spp.* (or a species name – *oxytoca, pneumonia* etc.)	Non skin	Inactive
Enterobacter spp.	*Enterobacter spp.* (or a species name – for example *cloacae*)	Non skin	Inactive
E.coli	*Escherichia coli*	Non skin	Inactive
Enterococcus spp.	*Enterococcus spp.* (or a species name such as *faecalis*)	Non skin	MR and R variable
Candida spp.	*Candida spp.* (or a species name such as *albicans*)	Non skin	Inactive
Acinetobacter spp.	*Acinetobacter spp.* (or a species name such as *baumanii*)	Non skin	Inactive
Haemophilus influenzae	Haemophilus influenza	Non skin	A
gram negative coccus	Gram negative coccus	Non skin	A
viridans streptococcus	Streptococcus spp.	Non skin	A
Yeast or yeasts	Yeast	Non skin	I
germ tube negative	Yeast	Non skin	I
gram Positive cocci	*Staphylococcus spp.*	Skin	A
Gram +ve cocci query staph	*Staphylococcus spp.*	Skin	A
Escherichia coli or Escherichia Coli or escherichia coli	Escherichia coli	Non skin	I
E.coli	Escherichia coli	Non skin	I
staphylococcus epidermis	Staphylococcus epidermis	Skin	A
Coliform Strain 1 coliform strain 2	Enterobacteriaceae	Non skin	I
Staph.aureus	Staphylococcus aureus	Non skin	A
Serratia Marcescens or SERRATIA MARCESCENS	Serratia marcescens	Non skin	I
Pseudomonas aeruginosa or Pseudomonas Aeruginosa or pseudomonas aeruginosa or PSEUDOMONAS AERUGINOSA or Pseudomonas Aeruginose or Pseudomonas	Pseudomonas aeruginosa	Non skin	I

aeruignosa or Pseudomonas Aerginosa or Pseudomonas Aerugonsa or pseudomonas aeruguosa or			
Pseudomonas or pseudomonas	Pseudomonas spp.	Non skin	I
Viridans Streptococcus	Streptococcus spp.	Non skin	A
Enterococcus spp.	Enterococcus spp.	Non skin	A
Serraha soecies coliform	Serratia species	Non skin	I
Candida spp.	Candida spp.	Non skin	I
MRSA	Meticillin-resistant Staphylococcus aureus	Non skin	A
Staph.aureus	Staphylococcus aureus	Non skin	A
Coliform or Coliforms	Enterobacteriaceae	Non skin	I
Enterobacter spp.	Enterobacter spp.	Non skin	I
Mixed growth including viridans streptococcus	Streptococcus spp.	Non skin	A
Enterococcus spp	Enterococcus spp	Non skin	A
Klebsiella pneumoniae	Klebsiella pneumoniae	Non skin	I
Klebsiella spp.	Klebsiella spp.	Non skin	I
Cellulomas	Cellulomas spp.	Non skin	I
Acinetobacter spp.,	Acinetobacter spp.,	Skin	I
Micrococcus luteus	Micrococcus luteus	Skin	A
88 >15 colonies staphylococcus epidermus (STAEP)	Staphylococcus epidermus	Skin	A
Gram negative bacilli	Gram negative bacillus	Non skin	I
Gram negative Bacilli	Gram negative bacillus	Non skin	I
Scanty Growth	Scanty growth	Non skin	NA
+ PCR Influenza A	Virus	Non skin	NA (exclude from analysis as viral)
99 Aerobic spore bearing bacillus	Bacillus spp.	Non skin	A
Viridans Streptococcus	Streptococcus spp.	Non skin	A
Streptococcus	Streptococcus spp.	Non skin	A
Uepidermidis	Staphylococcus epidermidis	Skin	A
Staphylococcus or staphylococcus	Staphylococcus spp.	Skin	A
Staphyloccus epidermidis or Staphyloccus epidemidis or STAPHYLOCOCCUS EPIDERMIDIS	Staphylococcus epidermidis	Skin	A
staphylococcus epidermidis	Staphylococcus epidermidis	Skin	A
Staca Staep Eccf	Staphylococococcus capitis, Staphylococcus epidermidis (skin) Enterococcus faecalis (non-skin)	Skin Non –skin	A
Menigococcal -ve pneumococcal -ve	Negative result	Non skin	NA (exclude from analysis as negative result)
Serraha soecies coliform	*Serratia spp.*	Non skin	I
Rothia Sp	Rothia spp.	Skin	A
Neisseria Meningitidis or Neisseria meningitides or n meningitidis	Neisseria meningitidis	Non skin	A
Meningoccocus or Meningococcus	Neisseria meningitidis	Non skin	A
N:Meningitis Group B (PCR)	Neisseria meningitidis	Non skin	A
Micrococcus SP	Micrococcus spp.	Skin	A

Beta haem streptococcus group B	Streptococcus agalactiae	Non skin	A
Diphtheroid Species or Diphtheroid species	Corynebacterium spp.	Skin	A
Group B Streptococcus or group b streptococcus	Streptococcus agalactiae	Non skin	A
Coliform and coliform strain 2	Coliform	Non-Skin (NS)	I
Serratia Macsecens	Serratia marcescens	NS	I
scanty mixed flora	(Mixture)	?	?
Scanty Respiratory flora	(Mixture)	?	?
streptococcus pneumoniae	Streptococcus pneumonia	NS	A
raoultella planticola	Raoultella panticola	NS	I
Rothia Mucilginosis	Rothia mucilaginosis	Skin (S)	A
s.capitis	Staphylococcus capitis	S	A
s epidermidis or S Epidermidis	Staphylococcus epidemidis	S	A
streptococcus mitis	Streptococcus mitis	NS	A
s.oralis	Streptococcus oralis	NS	A
Staoh Hacomolyticus	Staphylococcus haemolyticus	S	A
S Hominis	Staphylococcus hominis	S	A
S EPI	Staphylococcus epidermidis	S	A
s. parasanguis, s salivarius	Streptococcus parasanguis & Streptococcus salivarius	NS	A
s. warneri	Staphylococcus warnerii	S	A
staph scuiri	Staphylococcus scuiri	S	A
Fungi	Fungi	NS	I
lactococcus lacis	Lactococcus lactis	NS	A
group b strep	Streptococcus agalactiae	NS	A
less than colonies staca	Staphylococcus capitis	S	A
gramulicatella adiacens	Gramulicatella adjacens	NS	A
<15 colonies staphylococcus epidermidis	Staphylococcus epidermidis	S	A
Staphylococcus Uepidermidis	Staphylococcus epidermidis	S	A
Micrococcus luteus	Micrococcus luteus	S	A
staphylococcus warnen STAWA) and staphlococcus hominis (STAHO)	Staphylococcus warneri & Staphylococcus hominis	S	A
ENTEROCOCCUS FAECIUM or enterococcus faecium	Enterococcus faecium	NS	I
STAEP	Staphylococcus epidermidis	S	A
Staphyloccus SP (STA)	Staphylococcus spp.	S	A
<15 rothia	Rothia spp.	S	A
Micrococcus SP	Micrococcus spp.	S	A
Beta heam streptococcus group B	Streptococcus agalactiae	NS	A
Staphyloccus epidermis	Staphylococcus epidermidis	S	A
Escherichia Col staphylococcus epidermidis yeast	Escherichia coli Staphylococcus epidermidis& yeast	NS & S	I & A
Gram Negative bacilli	Gram negative bacilli	NS	I
Staca Staep Eccf	Staphylococcus capitis & Staphylococcus epidermidis & Enterococcus faecalis	S & NS	I & A
Staep	Staphylococcus epidermidis	S	A
Staca less than 15 colonies	Staphylococcus capitis	S	A

> 15 colonies staphylococcus hominis	Staphylococcus hominis	S	A
Mixed	(Mixture)	?	?
Small amount of mixed organisms	(Mixture)	?	?
mixed organisms	(Mixture)	?	?
candida albicans	Candida albicans	NS	I
coliform bacilli or Coliform baolli	Coliform	NS	I
strep mitis	Streptococcus mitis	NS	A
aspergillis niger	Aspergillus niger	NS	I
>100 colonies of candida aubicans	Candida albicans	NS	I
gram +ve stapylococci	Staphylococcus spp.	S	A
propionibacterium	Propionibacterium spp.	S	A
gram positive staph	Staphylococcus spp.	S	A
Group B Strep	Streptococcus agalactiae	NS	A
mixed skin flora	(Mixture)	S	A
coagulase negative staphyloccus #2 or coagulase-negative staphylococcus #2	Staphylococcus spp.	S	A
micrococcus	Micrococcus spp.	S	A
streptococcus porincus	Streptococcus porcinus	NS	A
k pneumoniae ssp pneumoniae	Klebsiella pneumoniae	NS	I
alpha haemolytic streptococcus streptococcus mitis	Streptococcus mitis	NS	A
serratia liquifaciens & lactococcus lactis	Serratia liquifaciens & Lactococcus lactis	NS	I & A
lactococcus lactis	Lactococcus lactis	NS	A
serratia liquifaciens & lactococcus lactis	Lactococcus lactis & Serratia liqifaciens	NS	A & I
k pneumoniae	Klebsiella pneumoniae	NS	I
methicillin resistant staph aureus	Methicillin resistant Staphylococcus aureus (MRSA)	NS	A
neisseria meningitidis	Neisseria menigitidis	NS	A
N.Meningitiois	Neisseria menigitidis	NS	A
88 Group B Streptococus	Streptococcus agalactiae	NS	A
candida albicans	Candida albicans	NS	I
Positive Cocci	Gram positive cocci	?S	?A
Micrococcus species Enterococcus faecium	Micrococcus spp.& Enterococcus faecium	S & NS	A & I
esbl e.coli	Escherichia coli (ESBL)	NS	I
escherichia coli	Escherichia coli	NS	I
Gram positive cpcco	Gram positive cocci	?S	?A
Pseudomonas (High resistance strain)	Pseudomonas spp.	NS	I
Scant growth of stpaph epidermin	Staphylococcus epidermidis	S	A
heavy Growtyh Staphyloccous epidermis	Staphylococcus epidermidis	S	A
88 scanty growth capitis	Staphylococcus capitis	S	A
Scanty Growth Staph Epidermin	Staphylococcus epidermidis	S	A
Neisseria Meningitis	Neisseria meningitidis	NS	A
Betahaemolytic Streptococcus	Streptococcus spp.	NS	A
Scanty Growth Staphepidermis and capitis	Staphylococcus epidermidis & capitis	S	A

Nesseira meningitiolis	Neisseria meningitidis	NS	A
staph epidermis	Staphylococcus epidermidis	S	A
Staphyloccous hominis	Staphylococcus hominis	S	A
Staph Heminis	Staphylococcus hominis	S	A
Staphylococus Heminis	Staphylococcus hominis	S	A
Entrococcus Faecalis	Enterococcus faecalis	NS	I
gram positive bacilli	Gram positive bacilli	NS	A
Meningococcal Type B	Neisseria meningitidis group B	NS	A
group b streplococcus	Streptococcus agalactiae	NS	A
adenovirus & parainfluenza 3	Virus	Not relevant	Not relevant
neisseria meningitidis type b	Neisseria meningitidis group B	NS	A
scanty bacillus	Bacillus spp.	NS	A
(at local) group A strep	Streptococcus pyogenes	NS	A
Gram + Cocci	Gram positive cocci	S	A
enterococcus faecalis	Enterococcus faecalis	NS	I
strepsobinue	Streptococcus spp.	NS	A

The A indicates that minocycline and rifampicin would be expected to be Active against the bug. The I indicates that the micocycline and rifampicin are less likely to be active. NA indicates that this is not applicable.

Neisseria meningitidis and Group B streptococci are very unlikely to be CVC associated infections.

staphylococcus epidermis Staphylococococcus capitis, Staphylococcus epidermidis (skin)
Staphylococcus spp. Gram +ve coccus = *Staphylococcus spp*. (coagulase –ve)

SAP APPENDIX E: STEPS TAKEN TO OBTAIN OUTCOME DATA

<u>Primary outcome:</u> 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.

Step 1

Identify those with microbiology blood sample taken (CVC tip is excluded)

a. Results with no organisms cultured are classed as negative
b. Those with organisms (bacteria or fungi) are categorised as either skin/non-skin by microbiologist and a new variable created to indicate skin/non-skin classification.
    i. Non skin= positive blood culture
    ii. Skin
        1. If a skin organism is identified, check whether any other skin organisms have been identified
        2. If so, check whether they are within 48 hours of each other.
        3. If so, check to see if this is the same organism based on clinician endpoint review
        4. If 1-3 = yes then this results in a positive blood culture all others are negative

Note that this assumes those with missing microbiology are negative cultures. However, the microbiology downloads will be checked if there is no microbiology CRF for a participant or if one skin organism within the time frame has been detected.

Step 2

Timepoints.

For those with a positive blood culture identified from step 1 we check whether the sample was taken 48 hours after randomisation and within 48 hours after removal (This is done at this point as there are implications for skin organisms). For positive blood culture based on skin organisms at least one of the samples has to be within the above timeframe but not both. If timeframe is not that specified here then the result is coded as a negative blood culture.

Positive blood cultures outside of the timeframe will be tabulated along with the time of occurrence.

Step 3

For each remaining positive blood culture need to determine whether this was clinically indicated based on <u>one</u> of the criteria a to c below:

a. check whether the CVC was removed because a CVC associated infection was suspected (form 5 section B question 3, note that some participants have two reasons for removal) or whether there were signs of exit site infection (form 5, section A, question 1)
b. check progress log (form 6) to see whether clinically indicated was marked as 'yes'

c. check sampling form (form 9 section A question 4) to see whether one or more of the clinical indicators were present (WBC and/or CRP are not sufficient to clinically indicate infection) or whether there were signs of CVC infection prior to sampling (form 9 section B question 1)
d. check that a clinical indicator (from step a-c) is present within 48 hours either side of the positive blood culture. For positive cultures from a skin organism, the clinical indication has to be within 48 hours of the sample taken in the time window in step 2.
e. If the positive blood culture is clinically indicated, this results in a positive blood stream infection.

The time of randomisation and the time the sample of the positive blood culture was taken is used to calculate the time to first blood stream infection. For positive blood cultures from two skin organisms, the first skin organism to occur in the specified time frame will be the organism used for first positive blood culture.

Secondary outcomes:

1. **Rate of blood stream infection during CVC insertion per 1000 CVC days.**

Second episode of blood stream infection (defined as per primary outcome) will be defined by a positive blood culture of a different isolate (in terms of species) from a sample taken whilst the CVC is in situ. Any positive blood cultures of the same isolate will be regarded as the same episode regardless of time since the first sample.

- Same as PO but not after removal
- Data to be presented to the clinician endpoint review: first infection, second infection and the time between these who will decide how many separate blood stream infection each participant had.

2. **Time to CVC thrombosis - defined clinically by:**
   a. 2 records of difficulty drawing back blood from one or more lumen (within 5 days);
   b. 2 or more episodes of flushing to unblock (within 5 days);
   c. an episode of swollen limb;
   d. positive ultrasound;
   e. removal of CVC because of clinical evidence of a blocked CVC.

- To check thrombosis form (form 11) and AE form (form 12), sampling form (form 9) and progress log (form 6), follow up form (form 5)
  1. Create an indicator if there are 2 or more occasions of difficulty drawing back blood (form 9 and 11)
  2. Create an indicator if there are 2 or more occasions of an episode of flushing to unblock (form 11)
  3. Create an indicator if there was a swollen limb (form 11, form 12)
  4. Create an indicator if there was a positive ultrasound (form 11 and separate data received from sites)
  5. Note if removal of CVC was because of clinical evidence of a blocked CVC (form 5, note that there may be two reasons for removal)
- If any of these (i to v) then a thrombosis has occurred.

- Check whether thrombosis was indicated on the progress log (form 6)

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of thrombosis will be used to calculate the time to CVC thrombosis.

Extra information to check for thrombosis

1) If indicated on the progress log that they have the corresponding entry on the thrombosis form (And vice versa);
2) If indicated as text on the progress log i.e. not bleeding back , not sampling back – that there is a relevant entry on the progress log and thrombosis form (possibly form 9
depending on the interpretation);
3) On form 5 (not sampling back/ Not bleeding back) thrombosis event recorded on the progress log, thrombosis form and possibly form 9 depending on the interpretation;
4) CVC blocked/ not sampling back as reason for removal – corresponding thrombosis event on progress log, Thrombosis form and Sampling Form (form 9 depending on the interpretation)
5) Any lumens on Form 9 not bleeding back – check entry on Thrombosis Form, Progress log and Sampling form ;
6) Thrombosis events are on the AE form and ensuring the corresponding events are on the thrombosis form – therefore the AE's can be ignored;
7) Progress log - the same event can continue during the trial however only one row of data would be indicated on the thrombosis form – check that each day with an event has a corresponding row of data.

3. Time to a composite measure of clinically indicated blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria defined as:

a. Primary outcome as defined above
b. Any of the clinical indicators of infection and (negative) blood culture taken and
    i. High bacterial DNA load from a PCR positive result or
    ii. change in antibiotic on same day or next day or
    iii. CVC removal for infection

- As primary outcome
- High bacterial DNA load from a PCR positive or negative result initially taken from microbiology downloads. A positive will fulfil the high bacterial load criterion.
- change in antibiotics (form 7 and Appendix F)
- check form 5 as to whether removal of CVC was for infection (note that there may be two reasons for removal).

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of a composite measure of clinically indicated blood stream infection will be used to calculate the time to a composite measure of clinically indicated blood stream infection.

4. A CVC related blood stream infection will be defined by:

a. the same isolate (species) from the CVC tip and from a blood culture sample (one skin or one non skin) taken from any site more than 48 hours after CVC insertion and within 48 hours following CVC removal;

b. differential positivity of the same isolate in blood cultures taken from multiple CVC 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).
    i. Non-skin and both negative =No
    ii. Non-skin and both positive =No
    iii. Non-skin and one negative and one positive =Yes
    iv. Skin and one negative and one positive on two occasions (otherwise, as primary outcome criteria) =Yes
c. OR positive BSI AND CVC removed for infection (and two skin organisms)
d. OR positive BSI AND CVC exit site infection (and two skin organisms)

- Organisms cultured sent to clinical review team to decide if they are the same isolate.
- Note positivity of isolates
- Positive BSI as noted for primary outcome and reason for removal is infection (form 5)
- Positive BSI and reason for removal is exit site infection (form 5)
- If a-d is yes then CVC related BSI

5. Mortality by 30 days

- Check death form (form 16)
- Date/time of death (form 16)
- Date/time of randomisation (form 1 and 3)
- Data will also come from HES

6. Type of bacteria and fungi isolated from positive blood cultures

- Line listings will be given to the microbiologist to specify what the groupings for each are. (CRF 10 and downloads)

7. Resistance to minocycline or rifampicin of blood culture or CVC tip isolates

- Microbiologist to classify based on organisms listed (CRF 10) for positive blood cultures only (see primary outcome (main analysis) and secondary outcome 1) between 48 hours after insertion and within 48 hours after removal.

8. Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring

- AE form (12 number 2 and 13)
- From randomisation up to 48 hours after removal.

9. Time to randomised CVC removal

- Date/ time of randomisation (form 1 and 3)
- Date/ time of removal (form 5)
- Note this does not have to be the randomised CVC, but rather the CVC inserted following randomisation.

10. Length of stay requiring PICU (for first episode)

- Date/time admitted to PICU (form 1, 3 and 4)
- Date/ time discharged from PICU/ transferred (form 14)

- A small number will need data from HES (those randomised at end of recruitment period)

11. Total length of hospital stay for current episode (for up to 6 month post randomisation)

- Date/ time admitted (form 1 and 3)
- Date/ time discharged (form 14)
- Data will come from HES

12. Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVC

- see health economics plan

SAP APPENDIX F: ANTIBIOTIC GROUPING

Antibiotic name	Group
1% chloramphenical ointment	0
1% clotrimazole	0
Aciclofvir	0
aciclovi	0
Aciclovir	0
ACICLOVIR	0
aciclovir	0
Aciclovir 3% ointment	0
aclclovir	0
Acliclovir	0
Aclovir	0
Acyclovir	0
ACYCLOVIR	0
acyclovir	0
Acylivir	0
ACYLOVIR	0
Acylovir	0
Amakacin	1
Ambisome	3
ambisome	3
Ambisone	3
ambisone	3
amicacin	1
Amikacin	1
Amikacin	1
AMikacin	1
AMIKACIN	1
amikacin	1
Amikazin	1
Amixicillin	2
Amkacin	1
Amoxacillin	2
amoxacillin	2
amoxcicillin	2
Amoxcycillin	2
Amoxicilin	2
amoxicillan	2
Amoxicillin	2
AMOXICILLIN	2
amoxicillin	2
Amoxiclin	2
amoxiclin	2
Amoxtcillin	2
Amoxycillin	2
amoxycillin	2
Amoxyclillin	2
Ampcillin	2
Amperotericin	3
amphiotericin	3
Amphoitericin	3
Amphoteracin	3
AMPHOTERACIN	3
amphotercin	3
Amphotericin	3
AMphotericin	3
amphotericin	3
AMPHOTERICIN	3
amphotericin B	3
amphotericin b	3
Amphotericin Liposomal	3
amphotericin liposomal	3
Amphotericin Liposome	3
Amphotericin Liposoml	3
Amphotericin Lipsomal (Ambisone)	3
Amphotericin/Liposome	3
amphoteritinlipsoml	3
ampiccillin	2
ampicilin	2
Ampicilin	2
Ampicillin	2
AMPICILLIN	2
ampicillin	2
Ampicilllin	2
Ampiclillin	2
Ampiicillin	2
anoxycillin	2
Augmentin	2
augmentin	2

augmentin duo	2
Ayciclovir	0
Azithromicin	4
azithromicin	4
Azithromycin	4
AZITHROMYCIN	4
azithromycin	4
Azithromycin1	4
Azithromycn	4
Aztreonam	5
aztreonam	5
Baclofen	0
Bacroban	0
bactoban	0
bactrobam	0
Bactroban	0
bactroban	0
BACTROBAN 2%	0
Bactron	0
Basiliximab	0
Benpencillin	6
benpenicillin	6
Benzlpenecillin	6
benzlpenicillin	6
Benzlypenicillin	6
benzy penicillin	6
benzyl pencillin	6
Benzyl pencillin	6
Benzyl Penicillin	6
benzyl penicillin	6
Benzylepenicillin	6
Benzylpencillin	6
Benzyl-pencillin	6
benzylpencillin	6
benzylpenecillin	6
Benzylpenecillin	6
benzylpenicilin	6
Benzylpenicilin	6
Benzylpenicillin	6
benzyl-penicillin	6
BENZYLPENICILLIN	6

benzylpenicillin	6
Benzyl-Penicillin	6
Benzyl-penicillin	6
Benzylpenicllin	6
BENZYLPENILLIN	6
Benzylpenillin	6
benzypenicillin	6
Benzypenicillin	6
biopatch	0
BIOPATCH	0
Biopatch	0
Cafotaxime	7
Caftazidime	7
Canesten 1%	0
casfungin	9
Casofungin	9
Caspofungin	9
caspofungin	9
Cefalexin	7
cefataxime	7
Ceferiaxone	7
cefhazidine	7
Ceflacor	7
Ceflazidime	7
ceflazidime	7
Ceflazidine	7
ceflazidine	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefohaxime	7

Cefolaxime	7	Cefuromxime	7
cefolaxime	7	cefuroxim	7
Ceforoxime	7	Cefuroxime	7
Cefotamime	7	CEFUROXIME	7
Cefotamine	7	cefuroxime	7
Cefotaxim	7	Cefuroxime2	7
CEFOTAXIME	7	Cefuroxine	7
Cefotaxime	7	Cefurozime	7
cefotaxime	7	Cefurxime	7
Cefotaximine	7	Cephalexin	7
cefotaxine	7	cephalexin	7
Cefotaxinme	7	ceptriaxone	7
Cefotaxiome	7	cetotaxime	7
Cefotaxome	7	Cetotaxime	7
Cefotriaxone	7	Chloramphenical	0
Cefriaxone	7	Chloramphenical eye drops	0
Cefroxime	7	chloramphenicol	0
Cefrtiaxone	7	Chloramphenicol	0
Cefruxime	7	Chloramphenicol 0.5%	0
Ceftaidime	7	Chloramphenicol 1%	0
Ceftaoxime	7	chloramphenicol 1% eye ointment	0
ceftaxidime	7	Chloramphenicol 1% ointment	0
Ceftaxime	7	Chloramphenicol 1.1%	0
ceftazidime	7	chloraphenical eye drop 1%	0
Ceftazidime	7	chloraphenicol	0
ceftazidine	7	Chloraphenicol	0
Ceftdazadime	7	chlorhexidine	0
Ceftiaxone	7	chlorhexidine biopatch	0
Ceftlazidime	7	chlorhexidine mouth gel	0
Ceftoaxime	7	Chrolamphenicol	0
Ceftqazidime	7	Ciclosporin	0
Ceftraxone	7	Cidofavir	0
Ceftriaxone	7	cidofivir	0
CEFTRIAXONE	7	Cidofovir	0
ceftriaxone	7	Ciproflaxacin	13
Ceftriazone	7	Ciproflaxin	13
Ceftrioxone	7	Ciprofloxacillin	13
Ceftrixone	7	ciprofloxacillin	13
Ceftruaxone	7	Ciprofloxacin	13
Cefuoxime	7	CIPROFLOXACIN	13
Cefuroime	7	ciprofloxacin	13

ciprofloxacine	13
ciprofloxcain	13
ciprofloxican	13
Ciproflxacillin	13
Ciproflxacin	13
ciproloxacin	13
Ciprolxacin	13
Clariithromycin	4
Clarithomicin	4
Clarithomycin	4
Clarithromycin	4
clarithromycin	4
Clarithromyin	4
clarithromyrin	4
Clarithroycin	4
Clarithroymcin	4
Clarithroymicin	4
clarithyromycin	4
Clarithyromycin	4
clarothromycin	4
clarythromycin	4
Clindamycin	15
CLINDAMYCIN	15
CLindamycin	15
clindamycin	15
CLINDOMYCIN	15
CLOTIMAZOLE CREAM 1%	0
CLOTRAMAZOLE	0
Clotrimazole	0
clotrimazole	0
clotrimazole 1%	0
clotrimazole 1% cream	0
Clotrimazole Cream	0
CLOTRIMAZOLE CREAM 1%	0
clotrimazole cream 1%	0
Co Amoxiclav	2
co- amoxiclav	2
co amoxiclav	2
Co amoxiclav 125/31	2
co amoxiclav 250/62	2
Co Amoxiclav Suspension	2
Coamixoclav	2
Co-Amixoclav	2
co-amixoclav	2
Co-amixoclav	2
Co-Amoixiclav	2
co-amoxacillin	2
Co-amoxcillin	2
Co-Amoxicillin	2
Co-amoxiclan	2
coamoxiclav	2
Co-amoxiclav	2
CoAmoxiclav	2
CO-AMOXICLAV	2
Co-Amoxiclav	2
co-amoxiclav	2
Coamoxiclav	2
Co-Amoxiclav (125 mg + 31mg/5mls)	2
co-amoxiclav (250/62)	2
Co-amoxiclav (Augmentin)	2
co-amoxiclav 125/31	2
Co-amoxiclav 125/31	2
co-amoxiclav 250/62.5	2
Co-Amoxiclav 250mg + 31 mg/5ml suspension	2
co-amoxiclav 400/51	2
co-amoxiclav 400/57	2
Coamoxyclav	2
co-amoxyclav	2
Co-amoxyclav	2
Co-Aoxiclav	2
Co-aoxiclav	2
colistimethate	0
Colistimethate	0
colistin	17
COLISTIN	0
Colistin	17
colistin cream	0
Coliston	0
colomycin	17
Colomycin	17
Contrimaxazole	16
Corsodyl Gel	0

cotriamoxazole	16
cotrimaxazole	16
Co-Trimaxazole	16
Co-trimaxazole	16
Cotrimaxole	16
Co-trimaxozole	16
Co-trimazole	16
Cotrimazole 1% Cream	0
Co-trimexazole	16
Cotrimoxaole	16
Cotrimoxazole	16
Co-Trimoxazole	16
co-trimoxazole	16
cotrimoxazole	16
Co-trimoxazole	16
Co-Trimoxazole 1%	0
co-trimoxozole	16
Co-Trimozaole	16
Cotrimozazole	16
Co-trinoxazole	16
co-trinoxazole	16
Cufuroxime	7
daktarin cream	0
dermol	0
doxycycline	17
erithromycin	4
Erthomycin	4
Erthromicin	4
Erthromycin	4
erthyromycin (prokinetic dose)	0
Erythomycin	4
Erythormycin	4
erythromicin	4
Erythromicin	4
Erythromycin	4
ERYTHROMYCIN	4
erythromycin	4
Erythromycin (for prokinetic)	0
Erythromycin (Gastric motility)	0
erythromyln	4
Erytromycin	4

Ethambutol	20
ethambutol	20
Eyrthromycin	4
Flagyl	27
flagyl	27
Flocloxacillin	21
Flocoxacillin	21
Flucanazole	22
fluccoxacilin	21
fluccoxicillin	21
Flucloaxacillin	21
fluclonazole	22
Flucloxacill,in	21
Flucloxacillin	21
FLUCLOXACILLIN	21
FLucloxacillin	21
flucloxacillin	21
Flucloxacilllin	21
Flucloxaillin	21
FLUCLOXAXILLIN	21
Flucloxaxillin	21
Flucloxazillin	21
flucloxicillin	21
Flucloxicillin	21
flucloxzcillin	21
Fluconazole	22
FLUCONAZOLE	22
fluconazole	22
FLuconazole	22
Fluconzale	22
Fluconzaole	22
Fluconzole	22
Flucoxacilin	21
Flucoxacillin	21
flucoxacillin	21
Fluonazole	22
Foscarnet	0
g.levofloxacin	21
Ganciclovir	0
GANCICLOVIR	0
ganciclovir	0

ganciclovire	0
Gantamicin	1
GCSF Leuograstin	0
Gentamicin	1
GENTAMICIN	1
gentamicin	1
Gentamin	1
gentamin	1
gentamiycin	1
Gentammicin	1
Gentamycin	1
gentamycin	1
gentaycin	1
gentaycinn	1
gentomicin	1
Gentomycin	1
gentomycin	1
Getamicin	1
Getamycin	1
Grentamicin	1
Heparin	0
Isoniazid	24
isoniazid	24
Itraconazole	25
itraconazole	25
Linezolid	26
LINEZOLID	26
linezolid	26
liposomal amphotercin	3
liposomal amphotericin	3
Liposomal aphotericin	3
lymecycline	17
maxitrol ointment	0
Melonidazole	27
Menepenem	27
Menopanem	27
Menopenem	27
Merepenum	27
Meroopenan	27
Meropenam	27
meropenam	27
Meropene	27
Meropenem	27
MEROPENEM	27
meropenem	27
Meropenen	27
Meropenim	27
Meropenom	27
Meropenum	27
MEROPENUM	27
meropenum	27
Meroperem	27
meroprenem	27
Metopenem	27
metrinidazole	27
Metrondazole	27
Metrondiazole	27
Metronidazole	27
METRONIDAZOLE	27
metronidazole	27
metronidzole	27
metronirazole	27
metronizadole	27
metroridazole	27
Micafongin	29
MICAFUNGIN	29
Micafungin	29
micafungin	29
miconazole	0
Miconazole	0
Miconazole gel	0
miconozole	0
MNetronidazole	27
mupirocin	0
naseptin	0
neomycin	0
NEOMYCIN	0
Neomycin	0
nitrofurantoin	30
Nstatin	0
Nsystatin	0
Nysatin	0

Nystain	0
Nystatin	0
nystatin	0
NYSTATIN	0
Nystatin Cream	0
nystatin suspension	0
nystol	0
Octenilin Wound Gel 0.05%	0
octenisan	0
OCTENISAN 0.3%	0
ofloxacin	0
Omeprazole	0
omeprazole	0
Oselhamivir	0
Oseltamavir	0
Oseltamir	0
oseltamirir	0
Oseltamive	0
Oseltamivir	0
oseltamivir	0
OSELTAMIVIR	0
osomal amphotericin	3
Osteltamive	0
Osteltamivir	0
PENCILLIN V	0
Penicillin	0
penicillin	0
Penicillin V	0
PENICILLIN V	0
penicillin v	0
phenoxymethyl penicillin	0
Phenoxy-methyl penicillin	0
PHENOXYMETHYL/PENICILLIN	0
phenoxymethylpenicillin	0
Phenoxymethyl-penicillin	0
Pifampicin	31
pip tazobactam	32
pip/tazobactam	32
pipazobactam	32
Pipazobactam	32
Pipeicillin/Tazobactam	32
Piperacilin/Tazobactam	32
Piperacillin	32
piperacillin	32
PIPERACILLIN & TAZOBACTAM	32
Piperacillin & Tazobactam	32
piperacillin & tazobactam	32
piperacillin & tazobactum	32
Piperacillin / Tazoabactam	32
Piperacillin / Tazobactam	32
Piperacillin / Tazobactan	32
Piperacillin + Tazobactam	32
Piperacillin + tazobactam	32
piperacillin + tazobactam	32
Piperacillin 2g/Tazobactam 250 mg	32
Piperacillin 2g/tazobactam 250mg	32
Piperacillin 4g/Tazobactam 500g	32
Piperacillin 4g/Tazobactam 500mg	32
Piperacillin and Tazobactam	32
piperacillin and tazobactam	32
Piperacillin and tazobactam	32
Piperacillin and Tazobactem	32
piperacillin tazobachim	32
Piperacillin Tazobactam	32
piperacillin tazobactam	32
Piperacillin tazobactam	32
piperacillin tazobactan	32
Piperacillin Tazobactum	32
piperacillin tazobactum	32
Piperacillin w/Tazobactam	32
Piperacillin W/Tazobactam	32
Piperacillin with tazobactam	32
Piperacillin with Tazobactam	32
piperacillin with tazobactam	32
PIPERACILLIN/ TAZOBACTAM/TAZOCIN	32
PIPERACILLIN/TAZOBACTAM	32
Piperacillin/Tazobactam	32
Piperacillin/tazobactam	32
piperacillin/tazobactam	32
Piperacillin/Tazobactan	32
piperacillin/tazobactum	32
Piperacillin/Tazobactum	32

Piperacillin/Tazobatam	32
piperacillin-tazobactam	32
pipercillin + tazobactam	32
Pipercillin and Tazobactam	32
Pipercillin Tazobactam	32
Pipercillin/Tazobacran	32
Pipercillin/Tazobactam	32
Pipercillin/tazobactam	32
pipercillin/tazobactom	32
PIPERCILLIN/TAZOBACTUM	32
Pipertazobactam	32
Piptazbactam	32
PIPTAZOBACAM	32
Piptazobactam	32
piptazobactam	32
Piptazobactern	32
piptazobactum	32
piptazocin	32
Pitazobactam	32
Pyrazinamide	33
Pyridoxine	0
rasburicase	0
Ribavirin	0
rifabutin	31
rifampacin	31
Rifampicin	31
rifampicin	31
SDD gel	0
SDD GEL	0
SDD Gel	0
sdd gel	0
sdd gell	0
SDD paste	0
SDD Paster	0
Septin	16
septrin	16
Septrin	16
Tabromycin Base	0
tarocin	34
taurolock	0
tazobactam/piperacillin	32

Tazocin	32
TAZOCIN	32
tazocin	32
Tazocin (Pipercillin and Tazobactam)	32
tazocin/piperacillin tazobactam	32
tazolin	32
teicloplanin	35
Teicloplanin	35
Teicopanin	35
Teicoplanim	35
Teicoplanin	35
teicoplanin	35
TEICOPLANIN	35
Teicoplaning	35
Teicopleinin	35
teicopleinin	35
Teicoplnanin	35
Teicplanin	35
Telcoplanin	35
Tiecoplanin	35
Tobramycin	34
TOBRAMYCIN	34
tobramycin	34
Tobramycin base	0
TOBRAMYCIN BASE	0
Tobramycin Base	0
tobramycin base	0
Tobtamycin	34
Tqazocin	32
Trimethoprim	36
TRIMETHOPRIM	36
trimethoprim	36
trimethroprim	36
trimetroprim	36
Trimpethoprim	36
Vacomycin	37
valganciclovir	0
Vancomycin	37
VANCOMYCIN	37
vancomycin	37
Vancomyin	37

Vancoycin	37
vanomycin	37
Vanomycin	37
Vaoncymycin	37
Variconazole	37
Vencomycin	37
Voncomycin	37
Voriconazole	37
voriconazole	37
Warfarin	0
Zanamavir	0
Zanamivir	0

SAP APPENDIX G: CLINICAL ENDPOINT REVIEW

TABLE 2: PATIENT IDENTIFIER

Randomisation number	Date of birth	Age (years)	Initials	Date/time of randomisation	Date/time of removal	Time from randomisation to removal (hours)

TABLE 3: SKIN ORGANISMS IN THE TIME FRAME FOR THE PRIMARY OUTCOME

Date/time of sample	Time from randomisation (hours)	Time from removal (hours)	Blood/ CVC tip	Isolate (skin)	ICD-10 code for primary reason for admission*	Committee decision (same isolate/not the same isolate)

*This has been inserted to determine the status of those with no microbiology for the sensitivity analyses

TABLE 4: NUMBER OF SEPARATE BLOODSTREAM INFECTIONS (RATE OF BLOOD STREAM INFECTION DURING CVC INSERTION PER 1000 CVC DAYS)

Date/time of sample	Time from randomisation (hours)	Blood/ CVC tip	Isolate	Skin/ non-skin	Committee decision: number of separate bloodstream infections

Note microbiology profile comes from patient uploads: sensitive/ resistant/ intermediate

TABLE 5: COMMITTEE DECISION: CVC RELATED BLOOD STREAM INFECTION

Date/time of sample	Time from randomisation (hours)	Time from removal (hours)	Blood/ CVC tip	Isolate	Positivity of isolates	Positive BSI (as in primary outcome)	CVC removed for infection	CVC exit site infection	Committee decision: CVC related blood stream infection (Yes/No)

TABLE 6: A COMPOSITE MEASURE OF CLINICALLY INDICATED BLOOD STREAM INFECTION

Date/time of sample	Time between randomisation and sample (hours)	Time between removal and sample (hours)	Date/time of antibiotic change	Time between blood culture and antibiotic change (hours)	Blood/ CVC tip	PCR result (positive/negative)	Primary Outcome Positive BSI (Yes/No)	CVC removed for infection	CVC exit site infection	Committee decision: Composite measure of clinically indicated blood stream infection (Yes/No)

TABLE 7: THROMBOSIS

Date/time	Difficulty drawing back blood	Flushing	Swollen limb	Positive ultrasound	Comment from ultrasound (if available)	Removal of CVC because of clinical evidence of a blocked CVC	Committee decision: thrombosis (yes/no: if yes give date and time of thrombosis)

TABLE 8: RESISTANCE TO MINOCYCLINE OR RIFAMPICIN OF BLOOD CULTURE OR CVC TIP ISOLATES

Date/time of sample	isolate	Blood sample/ CVC tip	e-test result	Committee decision: (Resistant/ Not resistant)

NOTE THAT THERE MAY BE A PROBLEM MATCHING E-TEST RESULTS WITH SAMPLES AS THERE IS NO TIME AVAILABLE FOR E-TEST RESULTS

Type of bacteria and fungi isolated from positive blood cultures: CRF

a. Line listings presented to microbiologist (separately for i-iii)
    i. For primary outcome
    ii. For rate of blood stream infection (those not in primary outcome and between 0 and 48 hours)
    iii. For CVC related bloodstream infection (those not in primary outcome and skin organisms only)

This will be presented as in Appendix D of the SAP