Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection (The BATCH Trial)

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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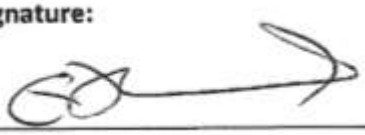
Chief Investigator		
Name:	**Signature:**	**Date:**
Professor Enitan Carrol		5/12/18

General Information This protocol describes the BATCH clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The BATCH trial is being coordinated by is being coordinated by South East Wales Trials Unit (SEWTU), a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit which is part of the Cardiff University Centre for Trials Research (CTR).

This protocol has been developed by the BATCH Trial Management Group (TMG).

For **all queries** please contact the BATCH trial team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigator.

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Randomisations:

Randomisation

To randomise a participant visit the BATCH trial database www. Batch.sewtudb.cf.ac.uk
or call 02920 687822 from Monday to Friday between 9am-5pm

(See section 9.5 for more details).

Clinical queries:

Clinical queries

BATCH@cardiff.ac.uk

All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to BATCH@cardiff.ac.uk

within 24 hours of becoming aware of the event (See section 16 for more details).

Contact details:

BATCH Trial Manager: 02920 687609

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Table of Contents

Glossary of abbreviations

AE	Adverse Event
AMR	Anti-Microbial Resistance
AMS	Anti-Microbial Stewardship
CACE	Complier Average Causal Effect
CEAC	Cost-effectiveness Acceptability Curves
CF	Consent Form
CI	Chief Investigator
CLABSI	Central line-associated bloodstream infection
CRF	Case Report Form
CRP	C-Reactive Protein
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
ED	Emergency Department
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HAI	Hospital Acquired Infection
HB	Health Board
HE	Health Economics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute of Health Research
PCT	Procalcitonin
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
PID	Participant identification number
PIS	Participant Information Sheet
PSA	Probabilistic sensitivity analysis
PT	Project Team
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SAP	Statisitical Analysis Plan
SBI	Severe Bacterial Infection
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKECA	United Kingdom Ethics Committee Authority
USM	Urgent Safety Measure
YPAG	Young Person Advisory Group

Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
Substantial	2.0	25.06.2018	• Contact details table updated (p.2-3). • Glossary of abbreviation updated (p.7). • Inclusion criteria clarified – i.e. conditions include 'but not limited to…..'(p.10 & 22). • CHU9D - removed 'for children aged 5 and above' (p.11, 20 &47). • Number of hospitals changed to 'around 10' (p.13). • Primary objective - duration of IV antiobitics corrected by removing '(IV and Oral)' (p.19). • Lead centres changed to six and hospital names corrected (p.20). • Gillick competent children added to informed consent section (p.24). • Trial Intervention section amended to include blood samples taken at a separate time point to routine blood samples if needed, and salvaged samples from admission to be used for comparision of PCT levels (p.25-26). • Adherence of lab by reports and printout corrected to 'where possible' (p.26). • Figure 2 Sample Flow diagram revised (p.27). • Table 2 Schedule of enrolement, interventions and assessments amended to reflect data captured on CRF (p.29-31). • CHU9D - Child version corrected to be completed 'where appropriate' and proxy version of CHU9D to be completed by parents added (p.32). • Archiving period changed to 10 years (p.55).

			• Data Protection Act changed to General Data Protection Regulation (p.56 and 57). • Funding section amended for High Street shopping vouchers to be given to participaints completing the parental qulaitaitve interviews only (p.57). • Cost Effectiveness analysis updated to remove one way sensitivity analysis, probabilistic sensitivity analysis and cost effectiveness acceptability curves (p.52).
Substantial	3.0	28.11.2018	• Qualiative Researcher added to trial team (p.4) • Remaining on IV antibiotics for more than 48 hours clarified (p.11, p.23); • New age criterion of children older than 72 hours (p.11, p.21, p.22); • Children with chronic comorbiididites exclusion crirerion amended to where there is already a predefined length of course of anitbiotics (p.10, p.23). • Removal of typo- (IV and Oral) from Duration of IV antibiotics objective (p.12). • Particiapnt flow diagram amended (p.15, p.67) • Algortihm formatting revised (p.16, p.66). • Clarification around when PCT tests are taken i.e. every 1-3 days whilst on IV antibiotics (p.21, p.26). • Names of lead sites amended (p.21). • Table 1 removed (p.26). • Clarifiaction that the VIDAS platform is semi-automated (p.27). • Biochemistry laboratory changed to 'laboratory where VIDAS machine is located' (p.27). • Sample flow amended (p.28). • Progression criteria for adherence to algorithm revised (p.36). • Quali sampe size for HCP interviews changed to 'up to 5' lead sites and 10-20 HCPs depending on data saturation and breadth of views (p.39).

			• Seeking additional participation in the think aloud observations based on satuation of data (p.40).

1 Synopsis

Short title	Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection
Acronym	BATCH
Internal ref. no.	
Clinical phase	Phase IV
Funder and ref.	NIHR Health Technology Assessment (HTA) 15/188/42
Trial design	Prospective two-arm individually randomised controlled trial (RCT)
Trial participants	Children aged between 72 hours old and up to 18 years old admitted to hospital, and being treated with IV antibiotics for suspected or confirmed bacterial infection
Planned sample size	1942
Inclusion criteria	• All children aged between 72 hours old and up to 18 years old admitted to hospital for confirmed or suspected bacterial infection or sepsis, in whom IV antibiotics are commenced, and expected to remain on IV antibiotics for more than 48 hours. • Conditions include but not limited to: bacteraemia, central line-associated bloodstream infections (CLABSIs), bone and joint infections, discitis, empyema, pneumonia, pyelonephritis, sinusitis, retropharyngeal abscess, pyomyositis, uncomplicated culture-negative meningitis, intra-abdominal infections, lymphadenitis, cellulitis. • First time in the BATCH trial.
Exclusion criteria	• Preterm infant age <37 weeks corrected gestational age, under 72 hours old or ≥18 years of age. • Children admitted moribund and not expected to survive more than 24 hours. • Children with a predicted duration of IV antibiotics of less than 48 hours. • Children not expected to survive at least 28 days because of pre-existing condition. • Bacterial meningitis, bacterial endocarditis, brain abscess. • Children receiving antibiotics for surgical prophylaxis. • Chronic co-morbidities, such as cystic fibrosis, chronic lung disease, bronchiectasis where there is already a pre-defined length of course of antibiotics. • Severe immunocompromised (e.g. chemotherapy, stem cell transplant, biological therapy for inflammatory or rheumatological conditions), • Children who in the opinion of the local investigator, are unsuitable for randomisation due to high probability of requiring long term IV therapy. • Presence of existing directive to withhold life-sustaining treatment.
Treatment duration	As determined by treating clinician

Follow-up duration	28 days
Planned trial period	1st Sept 2017 – 31st August 2020
Primary objective	To determine if the addition of Procalcitonin (PCT) testing to current best practice based on the NICE Antimicrobial Stewardship (AMS) guidelines can safely allow a reduction in duration of antibiotic therapy in hospitalised children with suspected or confirmed bacterial infection compared to current best practice alone. To meet this objective specifically, we will assess; 1. Duration of IV antibiotics 2. Unscheduled admissions/readmissions (admitted/re-admitted to PICU, or unplanned readmission to hospital within 7 days of stopping intravenous (IV) antibiotics) 3. Re-starting IV antibiotic therapy (for any reason within 7 days of stopping IV therapy) 4. Mortality (death for any reason in the 28 days following randomisation)
Secondary objectives	To assess the effect of additional PCT testing in AMS best practice on: 1. Total duration of antibiotics (oral and IV) 2. Time to switch from broad spectrum to narrow spectrum antibiotics 3. Time to discharge from hospital 4. Suspected Adverse Drug Reactions (ADR) (defined using the Liverpool Causality Assessment Tool), 5. Cost of hospital episode 6. Hospital acquired infection up to Day 28 7. Health utility (CHU9D) baseline and up to Day 28 8. To provide detailed understanding of parent and health professionals attitudes to, and experiences of, participating in the BATCH RCT.
Primary outcomes	The trial will use a co-primary outcome of antibiotic use and safety. 1) Antibiotic usage is defined as the number of days IV antibiotics used. 2) Safety is defined as the number of patients experiencing one of: 1) Unscheduled admissions/re-admissions (to include readmission rate within 7 days of discharge with infective diagnosis, unscheduled readmission to PICU with infective diagnosis, or admission to PICU with infective diagnosis, 2) Re-treatment for same condition within 7 days of stopping IV antibiotics (re-starting IV antibiotics which have been stopped), 3) Mortality.
Secondary outcomes	• Total duration of antibiotics (IV and oral) • Unscheduled admissions/re-admissions (to include readmission rate within 7 days of discharge with infective diagnosis, unscheduled readmission to PICU with infective diagnosis, or admission to PICU with infective diagnosis. • Re-treatment for same condition within 7 days of stopping IV antibiotics (re-starting IV antibiotics which have been stopped). • Time to switch from broad spectrum to narrow spectrum antibiotics. • Time to discharge from hospital. • Suspected Adverse Drug Reactions (ADR) (defined using the Liverpool Causality Assessment Tool). • Cost of hospital episode. • Hospital Acquired Infection (HAI) up to Day 28.

	• Health utility (CHU9D) up to Day 28. • Mortality. • Qualitative process evaluation of RCT with guidance to improve trial conduct.
Intervention	Procalcitonin (PCT) test

3. Trial summary & schema

Sepsis is defined as the body's response to infection, which can often be indistinguishable from the response to other insults like burns or surgery. On one hand, giving antibiotics promptly saves lives, but on the other hand, giving antibiotics to people who don't need them, leads to overuse of antibiotics and antimicrobial resistance. The Department of Health recommends that antibiotics should be given for as short a course as is safe, to prevent antimicrobial resistance.

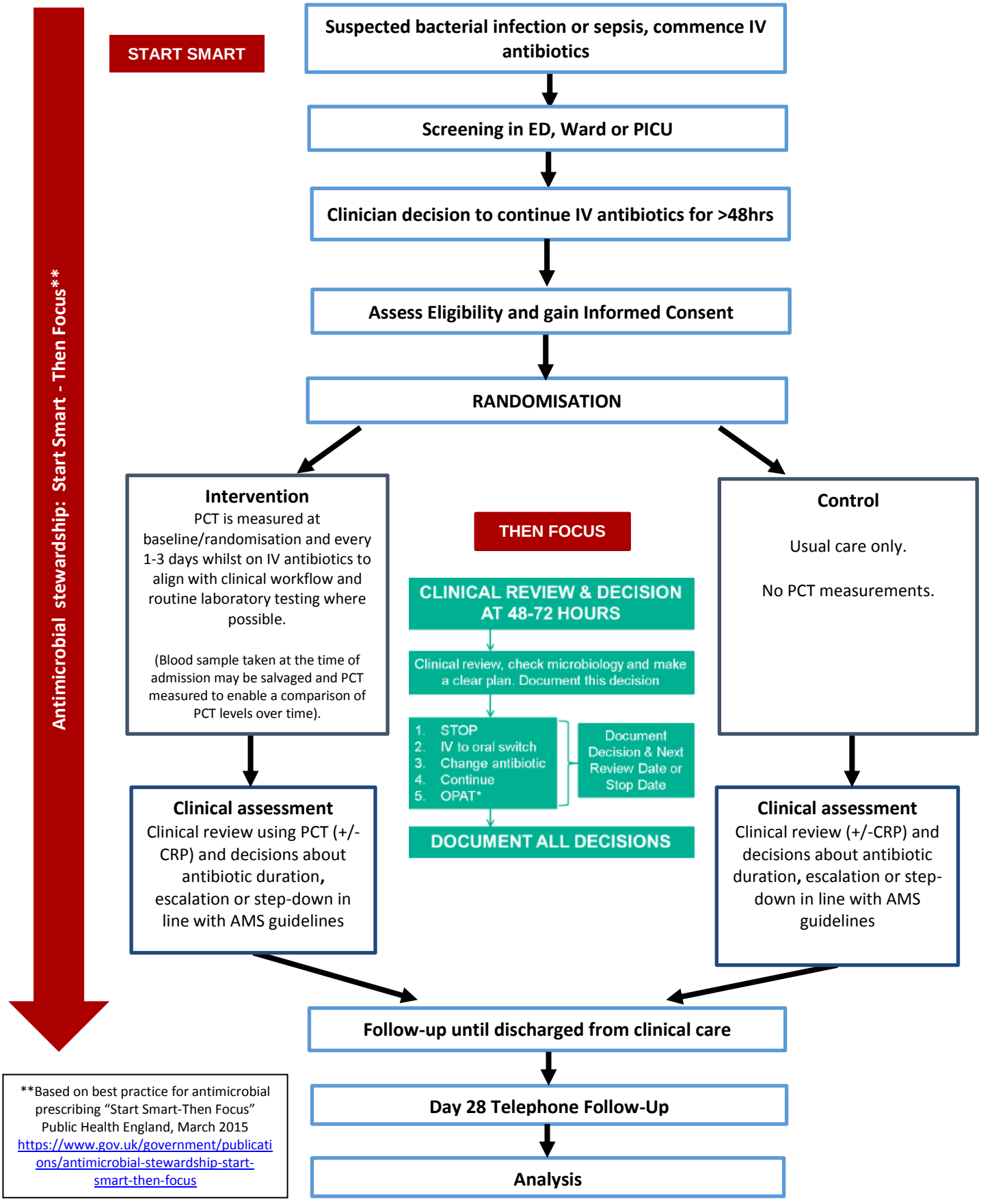
Most hospitals in the NHS use a blood test called C-Reactive Protein (CRP) to monitor response to infection, but it is not specific for bacterial infection and shows a delayed response to infection. Procalcitonin (PCT) is a blood test which is specific for bacterial infection and responds more quickly than CRP, but is not routinely used in the NHS. Studies done mainly in adults shows that using procalcitonin to guide clinicians may reduce the amount of antibiotics used, reduce hospital stay, and is not associated with adverse effects such as hospital re-admission, incomplete treatment of infections, relapse or death. A recent guideline from the National Institute for Health and Care Excellence (NICE) recommends further research on procalcitonin testing to guide antibiotic use in children.

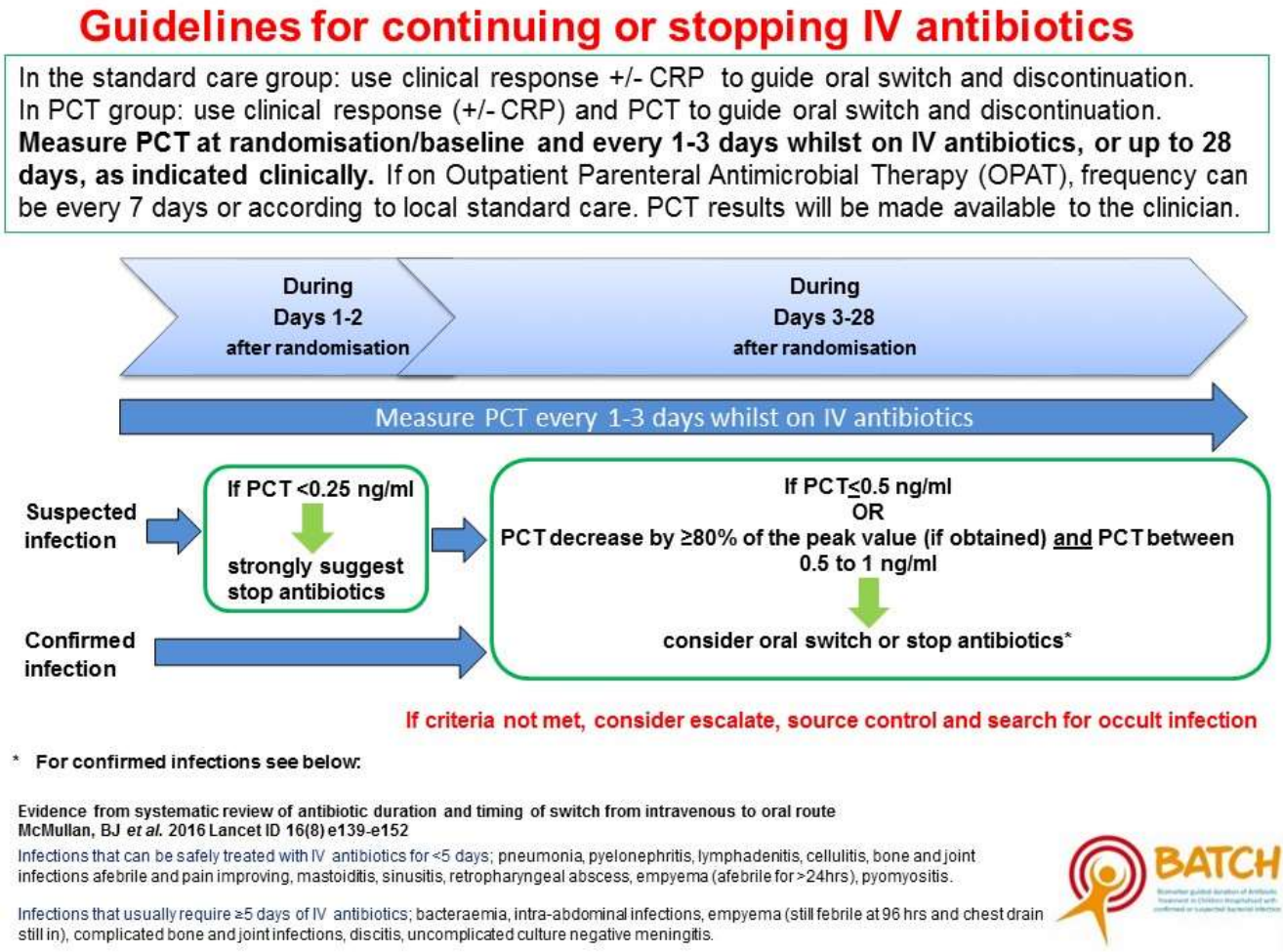
In this study, we will conduct a randomised controlled trial which will compare current management of severe bacterial infection (SBI) in children (doctors use clinical judgement and may also use CRP to decide on duration of intravenous antibiotics) with procalcitonin-guided management, where the management is identical to current practice, except that doctors have an additional procalcitonin test with advice on how to interpret the result.

We will use qualitative methods to capture parents' and health professionals' perspectives on participating in the BATCH trial, and to explore the experiences and understanding of parents about their child's condition and treatment of infection.

Around ten hospitals across the UK will participate in the study. Children admitted to hospital with bacterial infection and receiving intravenous antibiotics for more than 48 hours will be considered for inclusion. Parents will be given information about the trial and invited to take part. All included children will be randomly assigned to either procalcitonin-guided clinical management or to standard clinical management. See Figure 1 for participant flow diagram.

Figure 1: Participant Flow Diagram and Algorithm





4 Background

Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (2). Sepsis causes many non-specific symptoms and signs that can also be caused by a large number of conditions that may or may not be due to infection, and that may or may not require immediate or urgent treatment. Sepsis is usually caused by bacteria, although viral and fungal causes do occur. The problem for clinicians is the difficulty in distinguishing bacterial sepsis from other conditions presenting with non-specific signs and symptoms. Prompt administration of antibiotics reduces mortality by half (3), but indiscriminate antibiotic use increases antimicrobial Resistance (AMR), resulting in increased costs in hospitalised patients (4, 5). Severe sepsis accounts for approximately 45% of ICU bed-days and 33% of hospital bed-days, representing a significant resource burden in the NHS. Not all children admitted with bacterial infection will meet the criteria for sepsis, but they could still have serious infection, requiring IV antibiotics for several days. In this proposal, we will focus on children presenting with suspected or confimed bacterial infections, including sepsis.

Suspected or confirmed bacterial infections requiring hospitalisation will be referred to as Serious Bacterial Infection (SBI), and it will be this group of patients being studied in the BATCH trial.

Blood tests currently used in the NHS, such as CRP do not reliably differentiate beween SBI and inflammation, and show a delayed response (12-24 hours) to bacterial infection. Procalcitonin (PCT) is a biomarker released in response to inflammatory stimuli including bacterial infections, with very high levels produced in SBI (6). In contrast to CRP, PCT rises early (within 6-12 hours) and peaks early, falling rapidly in response to effective antimicrobial therapy. This makes blood PCT potentially a better biomarker for monitoring progression of SBI and response to antimicrobial therapy, and for informing initiation, change or discontinuation of antimicrobial therapy. There are no evidence-based biomarker-guided algorithms to support AMS in adults or children, and a RCT is needed to determine if PCT can help deliver the shortest, safe duration of antibiotics to treat SBI in children.

AMR is an increasing threat to the NHS quality and safety agenda. The lack of significant new antimicrobials in the development pipeline has led to increased pressure on existing antibiotics and greater challenges in treating patients with infections. Inappropriate use of antimicrobials increases the risk to patients of acquiring resistant organisms and subsequent transmission to other patients. The term 'antimicrobial stewardship' is defined as 'an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness'. AMS is a fundamental component of the UK Five Year Antimicrobial Resistance Strategy (7). A ***Start Smart - then Focus*** approach is recommended for antibiotic prescribing in order to reduce AMR and improve patient safety (8). NICE guidance on AMS (https://www.nice.org.uk/guidance/ng15) recommends reviewing IV antimicrobial prescriptions at 48–72 hours including response to treatment and microbiological results, in order to determine if the antimicrobial needs to be continued and, if so, whether it can be switched to an oral antimicrobial. The Department of Health Five Year Antimicrobial Resistance Strategy 2013-2018, aims to conserve and steward the effectiveness of existing antimicrobials by ensuring that antibiotics are used responsibly and less often (7). PCT is a reliable biomarker that (a) changes early in the course of bacterial infection, and (b) correlates with clinical progression to enable real–time monitoring and facilitate clinical decision making. In critically ill adults with SBI, PCT kinetics in the first 24 hours after commencing empirical antimicrobial therapy could be used to specifically tailor therapy to PCT response (9). In this group of patients, dynamic changes in PCT over 48 and 96 hours were predictive of survival (10).

A systematic review and cost-effectiveness analysis funded by the HTA, evaluated PCT testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial

infection in emergency department (ED) settings in adults and children (11). The review was conducted on behalf of NICE (https://www.nice.org.uk/guidance/dg18). It concluded that addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults in ICU settings and in the ED without any adverse consequences. The use of a PCT algorithm may also be associated with reductions in hospital and ICU stay in adults. In children, very limited data suggest that similar effects may apply for children presenting to the ED with community acquired pneumonia, but no evidence was identified on the effectiveness using a PCT algorithm to guide antibiotic treatment for children with suspected or confirmed SBI admitted from emergency care. None of the identified studies were conducted in the UK, and it was not clear whether the control arms of these studies were representative of standard practice in the UK.

The report recommended further studies to adequately assess the effectiveness of adding PCT algorithms to the information used to guide antibiotic treatment in adults and children with suspected or confirmed SBI in ICU settings and in adults and children with suspected bacterial infection in ED settings. High-quality studies, in which the control arm is similar to the intervention arm in all respects other than the use of PCT testing, are needed to inform the question of whether any observed effects are attributable to PCT testing or may be due to the effects of introducing protocolised care. It states that further studies are needed particularly for children, where data are currently lacking, and research examining (short-term) health-state utility values in the UK for adults and children with confirmed or suspected SBI in the ICU and ED.

NICE guidance on AMS (https://www.nice.org.uk/guidance/ng15) recommends decision support systems as an AMS intervention. The use of PCT to guide antibiotic stopping or escalation is one such decision support system which can be used. The AMS guidelines made the following research recommendations: 1) RCT to determine whether short or long courses reduce AMR, and 2) RCT to determine if using point-of-care tests is clinically and cost effective when prescribing antimicrobials in children with respiratory infection. Our proposed study is aligned with these recommendations in seeking to evaluate if PCT-guided management can result in shorter courses of antibiotics.

A recent systematic review and meta-analysis of antibiotic duration for bacterial infections in children, demonstrated that IV to oral switch can occur earlier than previously recommended. The authors produced recommendations for antibiotic duration and IV to oral switch to support clinical decision making, and recommend prospective research on optimal antibiotic durations (1). The lack of good evidence on recommended duration of antibiotic therapy leads to an overuse of antibiotics,

contributing to the development of AMR, a national and global priority. Shorter courses of antibiotic therapy would be associated with reductions in adverse effects for patients, and reductions in healthcare resource utilisation. Results from this research will inform recommendations relating to the duration of antibiotic use in future guideline updates including NICE sepsis guidelines.

The NICE guideline on *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use* recommends that randomised controlled trials should be undertaken to determine whether using point-of-care tests in decision-making is clinically and cost effective when prescribing antimicrobials in children, young people and adults presenting with respiratory tract infections http://www.nice.org.uk/guidance/ng15 . Results from this research will inform recommendations relating to the duration of antibiotic use in future guideline updates including NICE sepsis and AMS guidelines.

We have supporting data in an observational study of 639 children admitted to PICU, with PCT measured longitudinally, which suggests that serial measurement of PCT could be used to reduce duration of antibiotic therapy and hospital stay. Differential profiles between children with and without sepsis at admission, suggest that in many children antibiotics could have been confidently discontinued at 48 hours (in the group with no SBI) or on Day 5 (in the group with SBI) using thresholds and percentage reduction in PCT value (Figure 1). This suggests that antibiotics could be stopped at 48 hours if PCT values remain in the normal un-infected range. RCTs in adults, but not children, in ICU have reported on the effectiveness of adding PCT testing to guide antibiotic therapy. The HTA meta-analysis demonstrates that the summary effect estimate indicates that the addition of a PCT algorithm to clinical decision making was associated with a significant reduction in duration of antibiotic therapy (WMD-1.2 days, 95% CI 1.33 – 1.07) (11). No such studies have been conducted in hospitalised children (11).

This study has the potential to impact the clinical care of hospitalised children with confirmed or suspected SBI, which currently accounts for a large proportion of antibiotic use in hospitalised children. It will lead to the development of PCT-guided antibiotic management guidelines of childhood infections in hospitalised children, and will address the safety of shorter antibiotic courses. If shorter duration of PCT-guided antimicrobial therapy is shown to be safe and effective, this will have major implications for direct and indirect costs of childhood hospitalisations from infection. This will lead to significant reductions in duration of hospitalisation and reduced antibiotic exposure, resulting in a positive impact on healthcare services and societal costs. Reduced exposure to antibiotics will, in turn reduce AMR. This trial is timely as it aligns with the current Department of Health Five Year Strategy,

and is a response to research recommendations from two recently published NICE guidance documents (DG18 and NG15).

5 Trial objectives

The primary research question is whether addition of PCT testing to current best practice based on the NICE AMS guidelines can safely allow a reduction in duration of antibiotic therapy in hospitalised children with suspected or confirmed bacterial infection compared to current best practice alone. The aim of the intervention is to reduce prescribing with no effect on safety.

5.1 Primary objectives

To determine if the addition of PCT testing to current best practice based on the NICE AMS guidelines can safely allow a reduction in duration of antibiotic therapy in hospitalised children with suspected or confirmed bacterial infection compared to current best practice alone.

To meet this objective specifically, we will assess;

- Duration of IV antibiotics
- Unscheduled admissions/readmissions (admitted/re-admitted to PICU, or unplanned readmission to hospital within 7 days of stopping intravenous (IV) antibiotics)
- Re-starting IV antibiotic therapy (for any reason within 7 days of stopping IV therapy)
- Mortality (death for any reason in the 28 days following randomisation)

5.2 Secondary objectives

To assess the effect of additional PCT testing in AMS best practice on:

- Total duration of antibiotics (oral and IV)
- Time to switch from broad spectrum to narrow spectrum antibiotics
- Time to discharge from hospital
- Suspected Adverse Drug Reactions (ADR) (defined using the Liverpool Causality Assessment Tool),
- Cost of hospital episode
- Hospital acquired infection up to Day 28
- Health related quality of life (CHU9D) baseline and up to Day 28

- To provide detailed understanding of parent and health professionals attitudes to, and experiences of, participating in the BATCH RCT.

6 Trial design and setting

6.1 Design

A multi-centre, prospective, individually randomised, two-arm RCT with internal pilot study. The trial will assess the use of an additional PCT test in children (aged 72 hours up to 18 years) hospitalised with suspected or confirmed bacterial infection to guide antimicrobial prescribing decisions.
In children randomised to the intervention arm, a PCT test will be performed in the hospital laboratory at baseline/randomisation and every 1-3 days whilst on IV antibiotics,. Children in the control arm will not have the PCT test performed.

6.2 Setting

Paediatric wards or Paediatric Intensive Care Units (PICUs) within Children's hospitals and General hospitals in the United Kingdom (approximately n=10) which have implemented AMS best practice guidelines. There are 6 lead centres (Alder Hey Children's Hospital, Liverpool; Noah's Ark Children's Hospital for Wales, Cardiff; Bristol Royal Hospital for Children; Children's Hospital, Southampton General Hospital; Sheffield Children's Hospital and Children's Hospital, John Radcliffe Hospital, Oxford). Further additional sites will be opened as required. If further sites are needed, those who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial. This will be facilitated by the site's local Research Network.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the BATCH Trial: BATCH@cardiff.ac.uk

- Favourable opinion of host care organisation/PI from Main Ethics committee and Health Research Authority (HRA)
- Statement of activities and Schedule of events
- A signed Trial Agreement (PI, sponsor and site signatures),
- Completed Signature List and Roles and Responsibilities document,
- Completed contacts list of all site personnel working on the trial,
- Consent form and PIS on Trial site letter headed paper,
- Site initiation training,
- CPA accrediation certificate of laboratory in host care organisation for NHS approved tests including CRP,
- Evidence of laboratory training in the Instrument to be used for PCT measurement and QA logs for QA of instrument , including laboratory normal ranges,
- Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the site is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial packs and trial manuals holding all the documents required to recruit into the trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by attendance at a BATCH launch meeting or by teleconference if attendance of key personnel is unfeasible.

8 Participant selection

All children admitted to hospital with suspected or confirmed SBI and commenced on IV antibiotics, in whom antibiotics are likely to be continued for more than 48 hours. Children will be only be randomised once it is clear that the clinician expects IV antibiotics will be prescribed for longer than 48 hours.

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

- All children aged between 72 hours old and up to 18 years old admitted to hospital for confirmed or suspected SBI, in whom IV antibiotics are commenced, and expected to remain on IV antibiotics for more than 48 hours.

  Conditions include (but not limted to): bacteraemia, central line-associated bloodstream infections (CLABSIs), bone and joint infections, discitis, empyema, pneumonia, pyelonephritis, sinusitis, retropharyngeal abscess, pyomyositis, uncomplicated culture-negative meningitis, intra-abdominal infections, lymphadenitis, cellulitis.
- First time in the BATCH trial.

8.2 Exclusion criteria

- Preterm infant age <37 weeks corrected gestational age, under 72 hours old or ≥18 years of age.
- Children admitted moribund and not expected to survive more than 24 hours.
- Children with a predicted duration of intravenous (IV) antibiotics of less than 48 hours.
- Children not expected to survive at least 28 days because of pre-existing condition.
- Children with bacterial meningitis, bacterial endocarditis, or brain abscess.
- Children receiving antibiotics for surgical prophylaxis.
- Children with chronic co-morbidities, such as cystic fibrosis, chronic lung disease, bronchiectasis where there is already a pre-defined length of course of antibiotics.
- Children who are severely immunocompromised (e.g. chemotherapy, stem cell transplant, biological therapy for inflammatory or rheumatological conditions).
- Children who in the opinion of the local investigator, are unsuitable for randomisation due to high probability of requiring sustained IV therapy.
- Children with a presence of existing directive to withhold life-sustaining treatment.

9 Recruitment, screening and registration

9.1 Participant identification

This protocol will use the term 'parent' to refer to the person with legal responsibility for the child, therefore, as applied in this protocol the term also encompasses carers (parents and carers designated as legal guardians).

Identification of potential participants will be by the clinical care team, or the clinical members of the research team involved in care of children on the ward or the general paediatric or infectious diseases teams involved in care of children on the ward. In some sites it may be possible for screening of eligible patients to take place once a day between 0800 and 1200, when a member of the research team will vist the wards where children with SBI are admitted, to assess eligibility.

The parent(s) of children admitted to hospital with suspected or confirmed bacterial infection and commenced on IV antibiotics will be approached by the normal clinical care team and research team and will be given a patient information sheet (PIS) about the study. The parent(s) will be told that their child may be eligible for the study if IV antibiotics are expected to be continued for more than 48 hours, and they are being given time to think about it, should they be approached later.

Children in whom antibiotics are likely to be continued for more than 48 hours are potentially eligible for the trial. The clinician or designated research nurse will explain the trial to the child's parent and will ensure that the parent has had enough time to consider participation and answer any questions that the parent may have. Eligibility will be confirmed by a member the clinical care team, or delegated members of the research team, who may be medical or nursing practitioners. Age appropriate information sheets will also be provided for children who are old enough to use them.

Participants may also be recruited through posters and leaflets displayed in the Emergency Department (ED) , Paediatric Intensive Care Unit (PICU) and on the wards. Adverts and study website will also be used to publicise the study if needed.

9.2 Screening logs

A screening log of all eligible and potentially eligible patients but not consented/not approached will be kept at each site to inform adjustment of recruitment strategies and trial processes. The logs will

also be used to assess any biases from differential recruitment will be detected. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the study specific email address (BATCH@cardiff.ac.uk) every month (see section 24 for further detail on data monitoring/quality assurance).

9.3 Informed consent

Parents of eligible children (or the child if over the age of 16 or Gillick competent) will be given as much time as they need (upto the 48 hours of the study inclusion window) after the initial invitation to participate before being asked to sign the consent form. Parents will be notified that they can withdraw consent for their child's participation in the trial at any time during the trial period. Parents will also be informed that they have the right to refuse their child's entry to the trial without giving a reason and that this will not affect the care their child receives in any way.

Informed consent will be sought by suitably qualified, experienced and trained personnel in accordance with the GCP directive on taking consent and before any study related procedures are undertaken. Written informed consent will be obtained from the child's parent or legal guardian. One copy will be given to the parent and the original copy will be kept in the Site File. A further scanned copy will be kept in the child's medical record.

For all children, the person taking consent will assess the child's capacity to understand the nature of the trial. Age appropriate information sheets will be supplied where appropriate and the views of children capable of expressing an opinion will be taken into account. Children who are deemed to have capacity will be asked to sign an age appropriate assent form.

Only when written informed consent has been obtained from the child's parent (or the child if over 16 years or Gillick competent) and they have been enrolled into the study can they be considered a study participant. Once consented, participants will be allocated a unique study number (participant ID), which will be the primary identifier for all participants in the study.

The participant will remain free to withdraw at any time from the protocol without giving reasons and without prejudicing their further treatment.

Participant consent is requested to collect NHS Numbers to utilise NHS Digitial data for future research.

We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

9.4 Registration

Eligible participants who have consented to take part in the study will be registered by recording key information including; contact details, past medical and medication history, as well as demographics.

9.5 Randomisation process

Children will be only be randomised if the clinician expects IV antibiotics will be prescribed for longer than 48 hours. This will typically be between 20-48 hours after admission, to fit in with clinical work flows of ward rounds and phlebotomy times for routine blood tests. Patients will be randomised (1:1 ratio of allocation) using minimisation using a secure (24-hour) web based randomisation programme controlled centrally by the CTR. At weekends, screening and recruitment will take place depending on availability of research team and GCP trained clinical care team members on the wards.

10 Trial Intervention

In children randomised to the intervention arm, a PCT test will be performed in the hospital laboratory at baseline/randomisationand every 1-3 days whilst still on IV antibiotics.
We will aim to collect the sample at the time as routine bloods are taken, however an additional sample may need to be collected at separate time point if routine blood tests are not due, or there is not enough rountine blood left over to perform the PCT test.

In addition, for the patients in the intervention arm, if there is no PCT level taken close to randomisation, then the blood sample taken at the time of admission may be salvaged (these samples are normally discarded after a few days once the routine tests have been performed, so we would only be using samples that are about to be discarded) and PCT test performed, to enable a comparison of changes in the levels of procalcitonin over time.

Children in the control arm will not have the PCT test performed.

In the BATCH trial, we will use the **bioMérieux** VIDAS® platform, a semiautomated immunoassay system based on Enzyme Linked Fluorescent Assay (ELFA) principles. It is simple and flexible to use and gives results in 20 minutes. The VIDAS® instrument requires 200µl of plasma or serum, and can be run on a sample sent for routine biochemistry after the routine tests (typically urea and electrolytes and CRP) have been performed.

PCT results feed into an algorithm where thresholds have been defined by previous data. The algorithm provides both definitive guidelines, e.g. stop antibiotics if PCT <0.25 ng/mL, and advisory guidelines, e.g. consider oral switch if PCT decreased by ≥80%. The algorithm, patient and sample flow are described in detailed in Figure 1 and in Appendix 1 .

10.1 Adherence

Adherence to the algorithm will be recorded on the CRF and will capture instances where the treating clinican overrules the algorithm if they feel it is appropriate to do so.

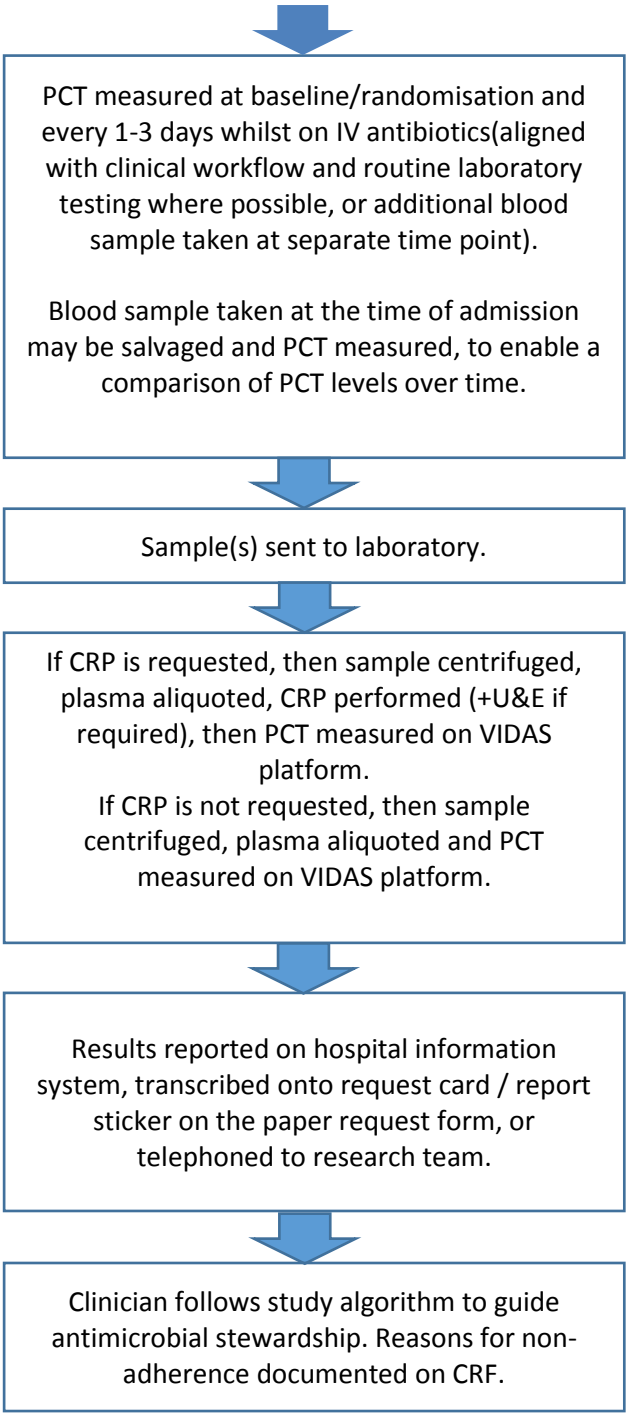
Adherence at Laboratory sites will be assessed during the pilot phase by asking them to send a report/ print-out of the tests performed by the bioMérieux VIDAS® platform where possible. This is to monitor compliance and ensure the machine has performed the appropriate tests i.e. for patients randomised to the PCT arm only.

10.2 Samples

PCT should only be performed on children in the intervention arm. The site will complete a request form and send to the laboratory where the VIDAS machine is located.
An Additional 1ml (minimum 0.5 ml) lithium heparin sample will be collected for PCT analysis. The minimum volume of plasma needed for the PCT test is 200ul. The sample flow is shown in figure 2.

Surplus blood will be stored for future research. At the end of the study plasma samples will be collected and transferred to University of Liverpool, Ronald Ross building for storage in in batches. Further detail can be found in the Standard Operating Procedure for Procalcitonin sample ordering and Storage and the BATCH Laboratory manual.

Figure 2 Sample Flow Diagram



11 Trial procedures

All participants will be enrolled in the trial from the date of randomisation until the Day 28 follow up. Participants will be assessed until they are discharged from clinical care. Assessments include PCT measurement as per algorithm and outcome at Day 28, unscheduled admissions/readmissions (admitted/re-admitted to PICU, or unplanned readmission to hospital within 7 days of stopping intravenous (IV) antibiotics), re-starting IV antibiotic therapy (for any reason within 7 days of stopping

IV therapy), mortality (death for any reason in the 28 days following randomisation) and adverse drug reactions. All clinical management decisions will be recorded at all time points.

For children who are discharged home with Out-patient Parenteral antimicrobial therapy (OPAT), local procedures will be followed. The OPAT nursing team will document the doses received and will scan or send electronically to the Research team. Participants will only be identified by their PID number, date of birth and initials only.

At Day 28, there will be a follow up by telephone or email with the parent to ask about the healthcare utilisation and quality of life of the child. If unsucssessful a questionnaire booklet will be posted to the parent for them to complete and return with a pre-paid envelope.

11.1 Assessments

Outcome data will be recorded daily by the research nurse for all recruited participants (up to and including Day 28, or until discharge). Research nurses will review observation and medication charts, and medical notes for all recruited participants to collect the data described in Table 2 below:

Table 2: Schedule of enrolement, interventions and assessments

Data Type		Source Data	Data type	Screening	Baseline	Post randomisation until discharged home	Follow up (Day 28)	Frequency	By whom
1	Informed Consent	Consent form	-	X				Once	Site Clinical/Research team
2	Eligibility Assessment	Eligibility CRF	-	X				Once	Site research team
3	Demographics	CRF			X			Once	RN
4	Admission data	CRF	Comorbidities, preadmission antibiotic use, initial working diagnosis		X			Once	RN
5	Health-related Quality of Life	QRF	CHU9D		X		X	Twice	Patient/parent reported (over telephone or post at Day 28)
6	Randomisation	CRF	-		X			Once	Site Research team
7	Antibiotic (ABx) use (IV/Oral)	Observation (Obs) charts/ Medical notes	ABx type, dose, duration, including			X		Daily	RN
8	Blood tests including PCT	CRF/Medical notes	Routine blood tests PCT results (for those in intervention arm)			X			
9	Clinical review	CRF/Medical notes	Clinical decision made and whether the			X		As required when a clinical	

Data Type		Source Data	Data type	Screening	Baseline	Post randomisation until discharged home	Follow up (Day 28)	Frequency	By whom
			algorithm was complied with					decions has been made	
10	Cerebrospinal fluid metrics, radiology and microbiology	CRF/Medical notes	White cell count, biochemistry. Microbiology results, radiology resutls			X			
11	Re-commencing of ABx (IV and oral	Obs charts/ Medical notes	ABx type, dose, duration, time recommenced			X		Daily	RN
12	Unscheduled Admissions	Medical notes	PICU readmissions post discharge			X		Daily	RN
13	Mortality	Medical notes	Date, description			X		If before Day 28	RN
14	Discharge	Medical notes	Date, description			X		If before Day 28	RN
15	Adverse events	Obs charts/ Medical notes	Date, type			X		Daily	RN
16	Suspected Adverse Drug Reactions (ADR)	Liverpool Causality Assessment tool	Date, description			X		Daily	RN
17	Resource Use	QRF	Direct Medical costs (inc. medication and ventilation and vasosuppressor)				X	Once	Patient/parent reported (over telephone or post)

Data Type		Source Data	Data type	Screening	Baseline	Post randomisation until discharged home	Follow up (Day 28)	Frequency	By whom
			and Resource Use						
18	SAE	SAE form			←----------As Required----------→				RN
19	Withdrawals	Withdrawal form			←----------As Required----------→				RN / CTR

11.2 Follow-up

Day 28 follow-up (+ 2 week time window) will be via telephone or email, with both utilised where possible to maximise response. Around 3-5 attempts will be made and if unsucssessful, a questionnaire booklet will be posted to the parent for them to complete and return with a pre-paid envelope. Patient outcomes (readmission, re-treatment, hospital acquired infection) and use of health care resource (hospital admissions, outpatient parenteral antimicrobial therapy, other prescribed medicines, privately purchased over-the-counter medicines, GP and hospital outpatient attendance) will be captured. Furthermore direct non-medical costs borne by parents and carers as a result of attending hospital with the child (travel costs, child care costs, expenses incurred while in hospital, self-reported lost earnings and other direct non-medical expenses) will be collected. Parents will be asked to support their child to complete the CHU9D questionnaire (where appropriate) and complete the parent proxy verison of the CHU9D questionnaire.

12 Withdrawal & lost to follow-up

12.1 Withdrawal

Parents may withdraw consent for their child to participate in any aspect of the trial, at any time. Declining to participate or withdrawing from the trial will not affect the care of the child.

Parents who wish to withdraw their child from the trial will be asked to decide whether they wish to withdraw their child from:

- further treatment/trial intervention but participate in all further data collection,
- active follow-up but allow existing data and their child's medical records to be used,
- sample storage for future studies
- data linkage for future studies
- from completing questionnaires,
- all aspects of the trial and require all data collected to date to be excluded from analysis.

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the parent withdraws on behalf of their child because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a parent wishes their child to stop taking part in the trial completely, the child may need to be seen one last time for an assessment.

A participant may be withdrawn from the trial intervention for the following reasons:

- withdrawal of consent for intervention by the parent,
- any alteration in the participant's condition, which, in the opinion of the patient's treating clinician, justifies the discontinuation of the treatment.

In all instances for those participants who consent and subsequently withdraw, the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant's parent. The PI in each site should ensure that the withdrawal form is completed as fully as possible and sent to the Trial Manager at CTR. Any queries relating to potential withdrawal of a participant should be forwarded to the Trial Manager.

12.2 Lost to follow up

It is essential for the trial that every participant complies with the data collection regime. We will ensure that all data collected can be obtained from the medical notes (where possible). At enrolment we will ask parents of those children recruited to provide contact details for members of the research team to contact while attempting to make follow-up interviews. To minimise loss to follow up, parents who have given permission to be contacted by SMS text messaging will be sent a reminder of their follow up interview. Participants will also consent to the research team communicating with their GP.

- Participants will be identified as lost to follow-up if it is not possible to contact them directly or via their GP for 6 weeks post randomisation.

13 Internal pilot and recruitment rates

We will conduct an internal pilot phase over the first eight months of the recruitment phase (study months 4 – 12).

The internal pilot phase will assess the site and patient absolute recruitment and consent rate, proportion of patients undergoing PCT assessments and the ability to collect the primary outcome data. The progression criteria have been designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes. We will discuss the results with our Trial Steering Committee, before reporting to the NIHR HTA Programme at Month 12, for permission to proceed.

In accordance with the HTA guidance on internal pilot studies, we will exclude the first two months of recruitment from our calculation of the recruitment rate as we anticipate a 'lag phase' during which the first 5 sites are still being registered and participating clinicians develop confidence and competence in identifying and recruiting patients. We will constantly be assessing the criteria during the internal phase. We will also conduct a qualitative evaluation of the acceptability of the algorithm with clinicians and identify any problems with contamination/changes to usual care in the control arm. Feedback from these interviews will assist with any refinement in processes during the pilot phase.

To progress from the internal pilot to the full trial, we would be looking to utilise the following criteria in Table 3 below:

Table 3: Progression Criteria

Criteria	Level	Action
Absolute number of recruited patients*	>350 200-350 <200	GO Discuss potential mitigating strategies STOP
Eligible patients identified	>50% >30%, <50% <30%	GO Discuss potential mitigating strategies STOP
Consent rate	>50% 30-50% <30%	GO Discuss potential mitigating strategies STOP

Consideration of the PCT result and algorithm during clinical decision making at each PCT test (in intervention group)	>60% 40-60% <40%	GO Discuss potential mitigating strategies STOP
Contamination/changes to usual care in control arm	Qualitative interviews	
Ability to collect primary outcome information	>90% 80-90% <80%	GO Discuss potential mitigating strategies STOP
Ability to collect Day 28 follow-up information	>75% 60-75% <60%	GO Discuss potential mitigating strategies STOP

Will include all participants recruited during pilot.

13.1 Recruitment rates

Recruitment rates were estimated based on a feasibility questionnaire sent to all 10 participating sites. The following numbers of children fulfilling inclusion criteria per year were reported: 500 for four of the lead centres, Liverpool, Southampton, Bristol, Sheffield; 200 for Cardiff, and 100 for the additonal sites. Total: 2700/year. If only 50% of eligible children are recruited, then the sample size of 1942 is easily achievable over 24 months. We anticipate that once all processes of screening and data collection are embedded at each site, we anticipate between 90 -120 participants per month. In our projections we have also taken seasonality into account, as the rate of infections is likely to be higher in the winter months.

14 Qualitative process evaluation

The UK MRC recommends an early feasibility and pilot phase prior to a full evaluation to identify and address problems which might undermine the successful delivery of an intervention (12). Increasingly, qualitative methods are being used within pilot studies to provide an insight into recruitment, acceptability, and adherence. Qualitative methods are particularly important when a trial is to be undertaken with a complex patient group or within a complex environment (13).

More specifically this qualitative evaluation will aim:

1. To explore the experiences and understanding of parents of children in the BATCH trial children about their child's condition and treatment of confirmed or suspected bacterial infection.

2. To explore the views and experiences of parents of children in the BATCH trial, in both intervention and control arms, about participating in a RCT, in particular focusing on: information required in order to provide informed consent; views about and acceptability of intervention; willingness to be randomised to either arm (i.e. treatment or control); influences on these factors.

3. To explore the views and experiences of health professionals involved in the BATCH trial about participating in a RCT, in particular focusing on acceptability of trial, clinical equipoise, taking informed consent, and support needs of trial involvement.

14.1 Semi-structured interviews

We will use semi-structured qualitative interviews to encourage participants to initiate and elaborate on topics most important to them which we may not have pre-empted if using survey type closed questions. Semi-structured interviews will be conducted with health professionals and parents. Parent interviews will be undertaken face-to-face, or via telephone if this is not possible, and professional interviews will be a combination of face to face and telephone. See Appendix 2 for the timeline of qualitative evaluation components.

The length of the interviews will vary, but we expect them to take about 30-60 minutes. Brief demographic details will be taken by the interviewer (interviewee age, gender, etc.). Field notes will be made by the interviewer following the interview which will include reflections on the interview process, overall observations, and any relevant contextual details.

Health professional interviews

Interviews with health professionals will be conducted at different time points which will enable us to capture whether there are any changes in attitudes towards the PCT test; **I1** will explore initial perceptions of possible facilitators and barriers to the test. This will take place before the intervention begins or at the very beginning of the intervention; **I2** will explore actual experiences of using the test

once the process has been better established and reflections back across the whole trial process and will take place after the individual health professional has finished delivering the intervention.

Parent interviews

Parent interviews will be conducted as soon as possible after day 28 follow-up (with sensitivity shown to the child patient's current state of health). The interviews will take place at a time and location convenient to the parent. This might be at the parent's home. Participants will be able to choose whether they want to be interviewed alone or with other family members present e.g. mother and father together.

Topic guide

The semi-structured interview topic guide will be developed from a review of previous research with input from the multi-disciplinary research team to avoid bias in wording of questions. The topic guide will be piloted and refined as necessary. The direction of questions may be led by the participants themselves and therefore the interview topic guide will remain flexible, in keeping with the method of semi-structured interviewing. Interviews will be recorded and transcribed verbatim. References to identifiable personal details such as name, address, and date of birth, will be removed from the transcript.

The main aims of the qualitative interviews will be:

- to explore how delivery of the intervention was achieved and what was delivered (qualitative measure of fidelity); how the intervention components and delivery processes worked in the real healthcare setting (covers feasibility, implementation, practicality of intervention), and acceptability of the trial to patients and intervention deliverers (e.g. how did the consent models work, how was randomisation understood, was trial information understood, to what extent was there equipoise amongst stakeholders).
- To explore the experiences and understanding of parents of children in the BATCH trial about the child's condition and treatment of confirmed or suspected bacterial infection.

Sample size

Sample size is based on guidance on using qualitative methods within feasibility studies for trials (13). A purposive sample of health professionals who are involved in delivering the BATCH Trial will be identified from the five lead sites. The sample strategy will be developed to address representation

from up to 5 of the different lead sites and variation in health professional role (e.g. ward nurse, consultant, research nurse etc.) We anticipate that interviews with around 10-20 professionals based on saturation and breadth of views expressed should be sufficient.

A purposive sample of parents of child patients' participating in the BATCH trial will be identified. We anticipate that a sample size of 10-15 parents will be sufficient. The sample strategy will be developed to include parents from both the intervention and control arm, and inclusion of different sites. By sampling along these lines we envisage there will be a range in terms of child age and gender, parent age and gender, carer role (i.e. mother, father etc.), range and severity of child patient condition, to ensure maximum variation.

With regards to the sample size for both health professinals and parents, the qualitative researcher(s) will make pragmatic decisions along with research team regarding when enough is known about certain themes (i.e. data saturation has occurred).

14.2 Non-participant observation

Non-participant observation of episodes of patient care and trial delivery will be carried out in up to 5 centres. The observations and field notes of trained qualitative researchers will enable us to understand how the individual intervention components and delivery processes work in the real healthcare setting, and the complex environment in which consent must be taken. This will allow us to address adherence, feasibility, implementation, and practicality of intervention. More specifically, we will ask: is there adherence to the protocol; is delivery of the intervention adapted according to local context; which bits of the intervention must be rigid or can be flexible; are there problems with the delivery of the intervention; what are the contextual threats to the trial? We will similarly observe usual care, in order to ensure we can capture what occurs in that group of patients, and assess if it changes with the introduction of the alternative management pathway.

The qualitative researcher(s) will work with the trial team and trial deliverers at individual sites to develop a detailed non-participant observation strategy. This will include the sample size (how many sites to observe e.g. detailed observation of one site vs less intensive observation of three sites), unit of observation (i.e. the people to be observed e.g. trial coordinator, research nurse etc.) and the observation period (e.g. half day for two consecutive days).

14.3 'Think aloud' interviews with professionals

As a result of non-participant observation at the site, we will identify a smaller sample of key health professionals (expected to be 1-2 health professionals per site where non-participant observation is carried out, but we may seek additional participation based on saturation of data) involved in carrying out the BATCH trial at the lead centres e.g. nurses responsible for taking informed consent etc. We will ask these key health professionals to be involved in 'think aloud' interviews to talk about the challenges of the intervention as they follow the trial process in real time. This will provide us with a greater understanding of the process of clinical reasoning and decision making and how it is influenced by involvement in the trial. More specifically we will explore; how professionals 'use' the results given in the intervention arm to make decisions; how PCT is combined with the CRP results to inform clinical judgement in actual real life cases; what is 'treatment as usual' and how is CRP routinely used to inform clinical judgement; whether there is learned behaviour from professionals as they alter their 'treatment as usual' behaviour in the light of the information they gain on specific patient groups, due to their delivery of the intervention; what influence the introduction of protocolised behaviour has on clinical behaviour and decision making regardless of the PCT test result.

14.5 Qualitative analysis

The data will be analysed using thematic analysis and will draw on the principles of qualitative framework analysis (14). The framework approach involves a systematic five-stage method which is increasingly being used in health care research (15). It will allow us to compare themes across different data sources (interviews, observations, case notes), and centres. We will identify contradictory data, as points of contrast, as well as similarities in order to understand challenges to intervention delivery. The method is well defined and allows for greater transparency. We will adopt a dynamic approach (13) to not only identify problems in intervention delivery and trial process, but to also work with stakeholders to resolve difficulties in real time, with the possibility of making changes to the pilot study itself and assess impact of changes. Vital measures will be put into place to ensure validity and reliability. More than one person will be involved in the analysis, and double coding will be carried out until consensus is reached.

15 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR unless the SAE is specified as not requiring immediate reporting (see section 15.2).

For the purposes of this trial, SAEs will need reporting if the event:

- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

The trial population comprises very sick children, and hospitalisation is normal in this population. Events such as prolongation of existing hospitalisation, life threatening events and death are primary outcomes of the trial, and are recorded as part of routine data collection and therefore are not subject to expedited reporting on an SAE form.

15.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Serious Adverse Event (SAE)	Any adverse event that - • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect

15.2 Trial Specific SAE Reporting requirements

As stated above, prolongation of existing hospitalisation, life threatening events and death are primary outcomes of the trial, and are recorded as part of routine data collection and therefore are not subject to expedited reporting on an SAE form.

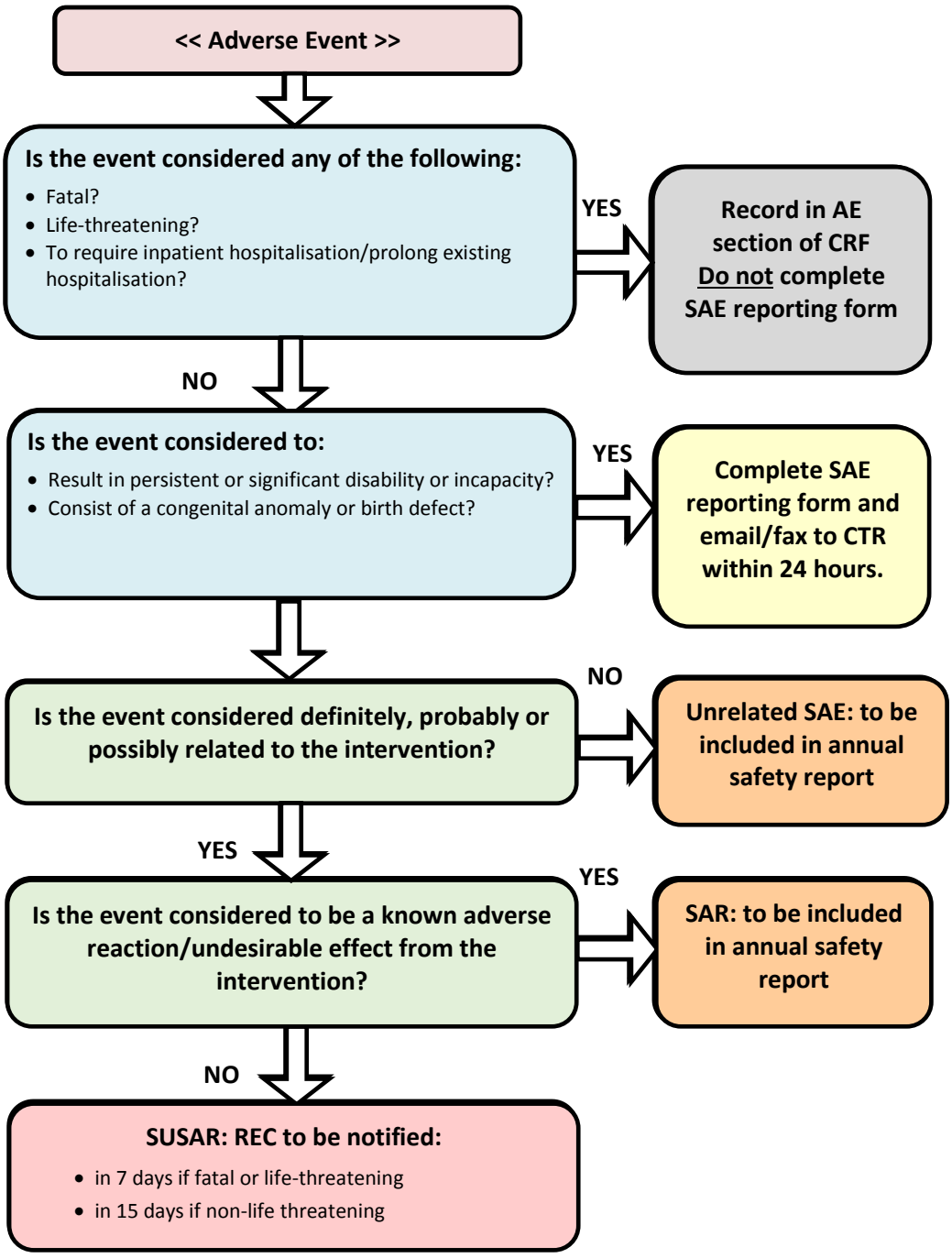
For the purposes of this trial the following events will **not** require reporting as SAEs:

- Death
- Life threatening event
- Hospitalisation or prolongation of hospitalisation

- Non serious AEs potentially attributable to PCT test and step down approach will be collected as part of routine follow up at 28 days.
- Suspected drug reactions defined by the Liverpool Causality Assessment Tool will be collected as part of routine follow up at 28 days.
- Other non serious AEs will not be collected.

These events should be recorded in the participant's notes and on the relevant CRF and forwarded to the CTR in the normal timeframes for CRF completion. A flowchart (Figure 3) is given below to illustrate reporting procedures.

Figure 3: SAE reporting procedures flow diagram



15.3 Causality

Causal relationship will be assessed for the clinical and data collection procedures. For SAEs this assignment should be made by the PI or delegated research nurse and the assessment confirmed by the Chief Investigator or a delegated Clinical Reviewer.

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

15.4 Expectedness

The Chief Investigator(s) (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness. Expectedness decisions should not be guided by factors such as the participant population and participant history. Expectedness is not related to what is an anticipated event within a particular disease. SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events.

15.5 Reporting procedures

15.5.1 Participating Site Responsibilities

The PI (or delegated research nurse from the study team registered on the delegation log) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or NHS trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR BATCH Trial Team within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

BATCH@Cardiff.ac.uk

BATCH Fax number:

02030 095405

Serious adverse events should be reported from randomisation, throughout the treatment period up to, and including 28 days after the participant is randomised.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or delegated research nurse from the study team registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 18.

15.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form. The CTR should continue reporting SAEs until 28 days after the participant is randomised. Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator(s) (or their delegate) for an assessment of expectedness.

CTR will notify the main REC of all related and unexpected SAEs (i.e. all unexpected SARs) occurring during the study within **15** calendar days of the CI becoming aware of the event. All SAEs and SARs will be reported to the monitoring committees (TMG and TSC/IDMC) as required by the relevant committee/party. All unrelated SAEs will be reported to the TMG and TSC/IDMC, and any arising safety concerns will also be reported to the main REC as part of the annual progress report.

The CTR will not be reporting hospitalisation, prolonged hospitalisation, life threatening events or death to REC as they do not meet the criteria of an SAE in this trial. These will be reported to the IDMC for monitoring.

15.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a study against any immediate hazard to their health or safety. Any urgent safety measure relating to this study must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

16 Statistical considerations

16.1 Randomisation

Participants will be randomised in a 1:1 ratio to receive either current clinical management alone (control) or clinical management with the addition of PCT test guidance (intervention). Randomisation will take place centrally in the CTR. Details on the generation of the randomisation sequence will be documented in a seperate Randomisation protocol and this will be concealed from the treating teams.

16.2 Primary outcomes measure

The study will use a co- primary outcome of antibiotic use and safety.

1) Antibiotic usage is defined as the number of days IV antibiotics used.
2) Safety is defined as the number of patients experiencing one of:
    - Unscheduled admissions/re-admissions (to include readmission rate within 7 days of discharge with infective diagnosis, unscheduled readmission to PICU with infective diagnosis, or admission to PICU with infective diagnosis),
    - Re-treatment for same condition within 7 days of stopping IV antibiotics (re-starting IV antibiotics which have been stopped),
    - Mortality.

16.3 Secondary outcomes measures

- Total duration of antibiotics (IV and oral)
- Unscheduled admissions/re-admissions (to include readmission rate within 7 days of discharge with infective diagnosis, unscheduled readmission to PICU with infective diagnosis, or admission to PICU with infective diagnosis).
- Re-treatment for same condition within 7 days of stopping IV antibiotics (re-starting IV antibiotics which have been stopped).
- Time to switch from broad spectrum to narrow spectrum antibiotics.
- Time to discharge from hospital.
- Mortality
- Suspected Adverse Drug Reactions (ADR) (defined using the Liverpool Causality Assessment Tool).

- Cost of hospital episode.
- Hospital Acquired Infection (HAI) up to Day 28.
- Health utility (CHU9D) up to Day 28.

16.4 Sample size

Two co-primary outcomes (IV antibiotics duration in days and a composite safety outcome) are defined in this study and the overall sample size is determined by both. Composite safety measures are common in conditions where individual event rates are low. They are however subject to criticism and challenge and therefore need to be considered with care to ensure that events do not 'trade off' each other (for example more children die quickly, so there is less opportunity for other events to occur). It is important that composite measures are specific to the intervention being tested and are anticipated to be unidirectional (all component parts are expected to change in the same direction) (16, 17).

The focus for the intervention is on moving the step down from IV to oral therapy earlier, and therefore the time until this step down is our primary outcome on antibiotic usage (overall usage across both oral and IV is a secondary outcome), and the study is powered to detect if PCT-directed care is *superior* to standard care on time until switch from IV antibiotics. The size of potential shortening of time to detect an effect has been taken from the recently published, HTA-funded systematic review (11). The safety co-primary is a composite measure reflecting various outcomes which represent deterioration or lack of clinical response in the child, and would be expected to increase if IV antibiotics were being withdrawn inappropriately early (described in detail above).
For the composite safety outcome proposed here we have selected the following elements (see table 4):

Table 4: Composite Safety Outcomes

Composite element	Definition	Reason for inclusion	Expected prevalence in usual care	Potential direction of change with intervention
Unscheduled admissions/ readmissions	Admitted/readmitted to PICU or unplanned readmission to hospital within 7 days of stopping IV antibiotics	Indicators of a deterioration and need for increased level of care	Our observation study showed 8.8% patients have admissions/re-admissions.	increase
Reinstating IV antibiotic therapy	Restarting IV antibiotic (for any reason) therapy within 7 days of stopping IV therapy	Indicator of potentially inappropriate withdrawal of IV antibiotics and deterioration	De Jong study 2.9% in control arm re-started IV antibiotic [3]falgor.	increase
Mortality	Death for any reason in the 28 days following randomisation		PICANet Annual report 2015: deaths on PICUs ~4% in 2012-2014 [4].	increase

In terms of IV antibiotic duration, one day reduction (11) in antibiotics from an estimated median of 5 days in the control arm (from our observation data) demonstrates a hazard ratio of 1.25. At 5% significance level with 90% power, 844 participants with observed IV antibiotics duration are needed. In terms of the event rates of safety elements, our observational study data showed an admission/re-admission rate of 8.8%. In critically ill patients, up to 3% reinstating IV antibiotic therapy rate, and 4% mortality were reported (2, 11). With some overlaps considered, we estimate around 15% overall rate of our composite safety outcome. The recent SAPS trial in adults used a non-inferiority margin of 8% for mortality (11). Given the lower expected rate of safety outcomes in this population we have chosen a similar relative non-inferiority bound of 5%. This means increases in the composite safety measure of less than 5% (from 15 to 20%) using PCT guided therapy would be considered not inferior. With a one-sided significance level of 0.05 and 90% power we would need 1748 participants to test non-inferiority. Overall, with 1748 effectively recruited participants, we would have 99% power to detect antibiotic duration decrease and 90% power to test non-inferiority in safety separately. Assuming that these two co-primary outcomes are independent, this would give us at least 89% power for the combined analysis (18). By considering 10% loss to follow-up for the primary outcomes, our final targeted sample size is inflated to 1942, for which our feasibility questionnaire has demonstrated its achievability.

16.5 Missing, unused & spurious data

Missing primary outcome data is likely to be minimal, so complete case analysis will be used. However, if this exceedes more than 20% of participants we will employ multiple imputation and report the impact on the treatment effect alongside the complete case analysis. Further detail is provided in the BATCH Statistical Analysis Plan (SAP).

16.6 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

16.7 Termination of the trial

Progression criteria for the internal pilot phase is described in section 13. There is potential for the study to terminate early if our funder assesses the trial as not being feasible following an assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

16.8 Inclusion in analysis

All randomised particpants will be included in the intention to treat analysis as primary analysis. The ineligible/inevaluable participants need to be excluded in secondary analyses (per protocol, CACE etc.).

17 Analysis

17.1 Main analysis

Our two co-primary outcomes will each be evaluated using the intention to treat principle, and then combined using the criteria specified in the table 5 below:

Table 5: Combined Primary Outcome

	Antibiotic duration different (reduction in PCT group) (H1)	Antibiotic duration no different (H0)
Safety composite not worse in PCT group (H1)	✔	✖
Safety composite worse in PCT group (H0)	✖	✖

✔ - Intervention successful; ✖ - Intervention unsuccessful

Our primary analysis of co-primary outcomes will be intention to treat and will a) compare the duration of days of IV antibiotics following randomisation, in each trial arm, using cox' regression; and b) compare the rate of adverse events between each trial arm using logistic regression, with a one-sided 95% confidence interval constructed to assess non-inferiority. This analysis will control for balancing factors in the randomisation. A positive conclusion will be made if both a decrease in IV antibiotic duration AND non-inferiority in safety. We will assess if the heterogeneity among centres exists and fit it by a two-level model if confirmed. A Complier Average Causal Effect (CACE) analyses will also be undertaken to test the treatment effects to patients with fully utilised PCT algorithm (see table 6 below).

Table 6: Summary of analyses of co-primary outcomes

	Co-primary outcomes	Analysis approach	Covariates in the model
Primary analysis	Duration of days of IV antibiotics (Intervention effect)	Cox regression (superiority test)	Trial arm and factors for randomization (site, age group etc.)
	Adverse events (composite safety outcome)	Logistic regression (non-inferiority test)	Trial arm and factors for randomization (site, age group etc.)
Secondary analyses	Duration of days of IV antibiotics (Intervention effect)	Kaplan Meier plot	Trial arm
		Log rank test	Trial arm
		Cox regression (assessments of suspected baseline confounders)	Covariates in the primary analysis, plus suspected baseline confounders (gender etc.)
		Complier Average Causal Effect (CACE)	Covariates in the primary analysis, plus intervention adherence
	Adverse events (composite safety outcome)	Logistic regression (assessments of suspected baseline confounders)	Covariates in the primary analysis, plus suspected baseline confounders (gender etc.)

For secondary outcomes, differences in the proportion of ADR, unscheduled readmission, re-commencing IV antibiotics, re-commencing IV antibiotics and mortality will be assessed separately by logistic regression models. We will also compare the total duration of antibiotics (IV and oral) and time to discharge from hospital between treatment groups via Kaplan Meier plots and Cox's regression. Average utility will be compared between the two groups at 28 days using linear regression. (see table 7 below).

Table 7: Summary of analyses of secondary outcomes

Secondary outcomes	Analysis approach	Covariates in the model
Proportion of ADR	Logistic regression	Trial arm and factors for randomization (site, age group etc.)
Proportion of unscheduled readmission		
Proportion of re-commencing IV antibiotics		
Proportion of mortality		
Duration of antibiotics (IV and oral)	Cox's regression	Trial arm and factors for randomization (site, age group etc.)
Time to discharge from hospital		
Average utility	Linear regression	Trial arm and factors for randomization (site, age group etc.)

17.2 Sub group analysis

Analysis will be split by the organ system of the infection (i.e. lower urinary tract, lower respiratory, intra-abdominal, bacteraemia, skin and soft tissue etc).

17.3 Cost effectiveness analysis

Health economic analysis will include direct and indirect costs associated with unscheduled admissions (to ward or PICU), re-admissions, re-starting IV antibiotics, hospital-acquired infections. Descriptive and regression analysis will be used to identify key elements of service use and cost and to explore the potential impact of baseline participant characteristics on the costs and outcomes measures. Average cost per participant will be estimated at end of treatment and end of follow-up and average cost per sub-groups of patients may be explored for the same time points. Bootstrapping and missing data imputation will be done if justified. Differences in each arm will be assessed and used for the computation of an incremental cost-effectiveness ratio (ICER). We will calculate ICERs for a

clinically effective outcome (less days on IV antibiotics with increased or equal safety) and the cost per IV antibiotic day avoided.

A cost-effectiveness analysis is deemed appropriate to assess possible efficiency gains. An NHS perspective will be used and relevant direct medical costs will be collected. Patients will be recruited prospectively. Information on resource use will include data on inpatient bed days, antibiotic consumption, nursing and medical resources, other medicines including over the counter medicines, diagnostic and monitoring laboratory tests, OPAT, GP visits, emergency visits, and treatment of side effects. Direct hospital costs will be calculated by multiplying resource use with the accompanying unit costs collected from patient level data in the participating hospitals, routine NHS sources (e.g. NHS reference costs and *British National Formulary* (BNF), and from the manufacturer of the PCT test, as appropriate. Time horizon will be 28 days, therefore there is no need to consider a discount rate. Patients' health related quality of life will be measured in patients ≥ 5 years old using CHU9D. Descriptive and regression analysis will be used to identify key elements of service use and cost and to explore the potential impact of baseline participant characteristics on the costs and outcomes measures. Differences in each arm will be assessed and used for the computation of an incremental cost-effectiveness ratio (ICER). One way sensitivity analysis will be carried out in key model parameters. Probabilistic sensitivity analysis (PSA) and cost-effectiveness acceptability curves (CEACs) will be constructed. Information on direct non-medical costs, like travelling to and from the hospitals, and indirect costs, like parents' productivity losses, will also be collected.

In a sub-sample of children, we will use time-motion techniques to measure the additional parental time, resource use and costs incurred during the child's hospital stay.

18 Data Management

The source data for BATCH trial will be from a variety of sources. Data will be collected using an electronic system with paper CRF back up. There will also be data collected from participant's medical notes and patient reported questionnaires. Source data from the VIDAS machine and laboratory data will recorded, downloaded and stored electronically in individual patient folders within the Trial Master File (TMF). Derived data from this source will be entered into the trial database.

Training for completion of study CRFs will be provided to the appropriate trial staff prior to trial commencement at site initiation.

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

18.1 Completion of CRFs

All assessments and data collection will be completed using web-based CRFs. This is a secure encrypted system accessed by username and password, and complies with Data Protection Act standards. In the event that the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted into the web-based system once it is accessible. A full data management plan will accompany this protocol and will be stored in the TMF.

18.1.1 Electronic CRFs

We intend to develop data recording for this trial as a web-based system. This is a secure encrypted system accessed by an institutional password, and complies with Data Protection Act standards.
A user password will be supplied to investigators upon completion of all processes required prior to opening.

18.1.2 Paper CRFs

If the electronic database is not available, paper CRFs will be used and data will be entered on to the database at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.
CRF pages and data received by the CTR from participating study sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.
If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participants' CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in

timely manner. Further details of data management procedures will be specified in the Data Management Plan.

18.2 Qualitative study data management

All the information, including any personal information (e.g. patient name), will be kept completely confidential. Recordings will not be labelled with patient name. Any written report of the research will have the patient's name removed. Written quotes of what the patient says in the interview may be used word for word, but quotes will be anonymised. Patient names will not appear on any publications. All study related records will be stored until the youngest participant has reached the age of 21. The results are likely to be published in medical journals over the next few years. The patient will not be personally identified in any report or publication. Full details of data management will be specified in the Data Management Plan.

19 Protocol/GCP non-compliance

The PI / local researcher should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOPs.

20 End of Trial definition

The end of the study is defined as the date of final data capture to meet the trial endpoints. Sponsor must notify REC of the end of a clinical trial within 90 days of its completion or within 15 days if the study is terminated early.

21 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for 10 years. The CTR will send the TMF and TSFs to Sponsor for achiving. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

22 Regulatory Considerations

22.1 Ethical and governance approval

This Study Protocol has been submitted to a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures (including recruitment of participants).

This Study Protocol will be submitted through the relevant permission system for global governance via Health Research Authority (HRA).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS Research and Development (R&D). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

22.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data

Protection Regulation (GDPR) (EU2016/679). The data custodian and the translational sample custodian for this study is the Chief Investigator.

Participants will always be identified using their unique study identification number and any additional identifiers. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with NHS Digitial.

22.3 Indemnity

BATCH is sponsored by The University of Liverpool and will be co-ordinated by the CTR at Cardiff University. The Sponsor does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. 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. Compensation is therefore available in the event of clinical negligence being proven. The Sponsor does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

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".

The Sponsor has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

22.4 Trial sponsorship

University of Liverpool will act as Sponsor for study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The GDPR (EU2016/679).
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to CTR, the CI, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

22.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 15/188/42) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

High street vouchers to a maximum value of £20 will be offered to participants taking part in the parental qualitative intervews as a token of appreciation for their time in taking part in the study.

The study will be adopted on the NIHR portfolio.

23 Trial management

23.1 Project Team (PT)

The Project Team (PT) will meet fortnightly and will include the Chief Investigators Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

23.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the study. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

23.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), consisting of an independent chair, and three other independent members including a patient representative, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the study and provide advice through its independent chair. The ultimate decision for the continuation of the study lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

23.4 Independent Data Monitoring Committee (IDMC)

In order to monitor accumulating data on safety and any trial intervention benefit, an IDMC will be established. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the trial commences in order to review the Protocol and agree on timelines for interim analyses to take place. The main role of the IDMC is to review the data periodically and makes recommendations to the TSC.

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

23.5 Public and Patient Involvement (PPI)

In developing the design of this research study, we actively sought the input of Liverpool GenerationR Young Person's Advisory Group (YPAG). The group consists of 19 young people aged between 12 to 17 year olds. The group have worked with several researchers exploring the topic of developing tests to rapidly detect or diagnose serious bacterial infection in children, including the development of a rapid salivary test to detect serious bacterial infection in children presenting to the Emergency

Department (ED) (SPICED study), and a study looking at the diagnostic biomarkers in children on PICU (DISTINCTIVE study). The YPAG are well aware of the problems associated with diagnosing and treating sepsis and when approached by the research team to discuss this study they expressed a preference for a shorter course of IV antibiotics, if it was safe to do so. The group have discussed at length the issues associated with AMR and the need to educate young people and families about the misuse of antibiotics and felt that findings from this study could be developed into educational materials for patients and families.

A parent advisory group consisting of approximately 4-6 parents/carers will be set up and supported by our PPI liaison officer. Their role will be to advise on: the design of parent information leaflets, design of interview schedules and the data generation templates for the qualitative work in the pilot phase, qualitative data analysis, and dissemination strategies. Members of the group will be invited to attend steering group meetings on a rotational basis. We will also involve the Liverpool GenerationR YPAG, throughout the duration of the trial. The group will advise on young peoples' information sheets for research ethics; interview schedules and the production of educational materials for young people and families on the most appropriate use of antibiotics. Educational materials will be made available in hospitals, GP practices, and schools, distributed to teachers, parents and young people, and posted on the GenerationR website. We will invite parents and young people to contribute actively to dissemination events, including presenting parents/young peoples' views/stories. Members of the YPAG and parents will be supported and trained and supported by our PPI liaison officer.

The parent and YPAG will seek to partner with Antibiotic Action, a charity promoting public awareness about antibiotics and AMR, and utilise their resources. They will be encouraged to register as Antibiotic Champions providing information to peers, schools and other contacts about the importance of antibiotics, how to use them, and the need for new treatments for infections.

24 Quality Control and Assurance

24.1 Risk Assessment

A Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as Low + risk, where the level of risk is slightly higher than the risk of standard medical care. A copy of the study risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 24.2).

24.2 Monitoring

The risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the BATCH study. Low+ monitoring levels will be employed and are fully documented in the study monitoring plan. Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

24.3 Audits & inspections

The study is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The study may also be participant to inspection and audit by Liverpool University under their remit as Sponsor.

25 Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the required final report and monograph

for the HTA Programme, we will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. At the local level, we will interact with and promote the research findings through wider NHS Trusts (Health Boards in Wales), the NIHR Clinical Research Network: North West Coast, North West Coast CLAHRC, North West Coast AHSN (Innovation Agency). The Innovation Agency is the national lead within AHSNs for sepsis through the Patient Safety Collaborative.

Nationally, we will engage with NICE, the Royal College of Paediatrics and Child Health, The British Society for Antimicrobial Chemotherapy, British Infection Society, and the British Paediatric Allergy, Immunity and Infection Group.

Through the Liverpool GenerationR YPAG, we will produce educational materials for young people and families on the most appropriate use of antibiotics. Educational materials will be made available in hospitals, GP practices, and schools. Materials will also posted on the GenerationR website www.generationr.org.uk to be distributed to teachers, parents and young people. With the help of the YPAG, we will develop the website content for a lay audience, and produce an annual newsletter for children, young people and families. The study findings will be disseminated to children, families and schools through the YPAG.

26 Milestones

Month 1-3: Study and site set-up (at least 5 sites to be open for month 1 of recruitment)

Month 4-12: Internal pilot phase (assessed by progression criteria). Assess acceptability of the PCT results in clinical management, and finalise study management algorithm, based on feedback. Training materials will be developed for clinical staff.

Month 13-30: Continuation of RCT recruitment and data collection to determine effectiveness and cost effectiveness of the intervention**.**

Month 30-36: Data cleaning, statistical analysis, prepare for HTA report.

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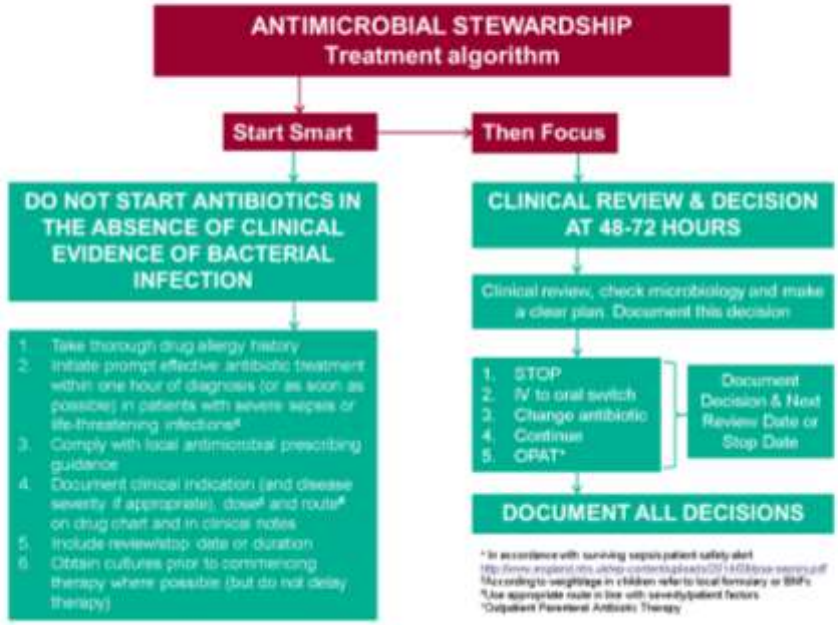
28 Appendices

Appendix 1 – Antimicrobial Stewardship – Antibiotic Treatment algorithm

Start Smart Then Focus tools

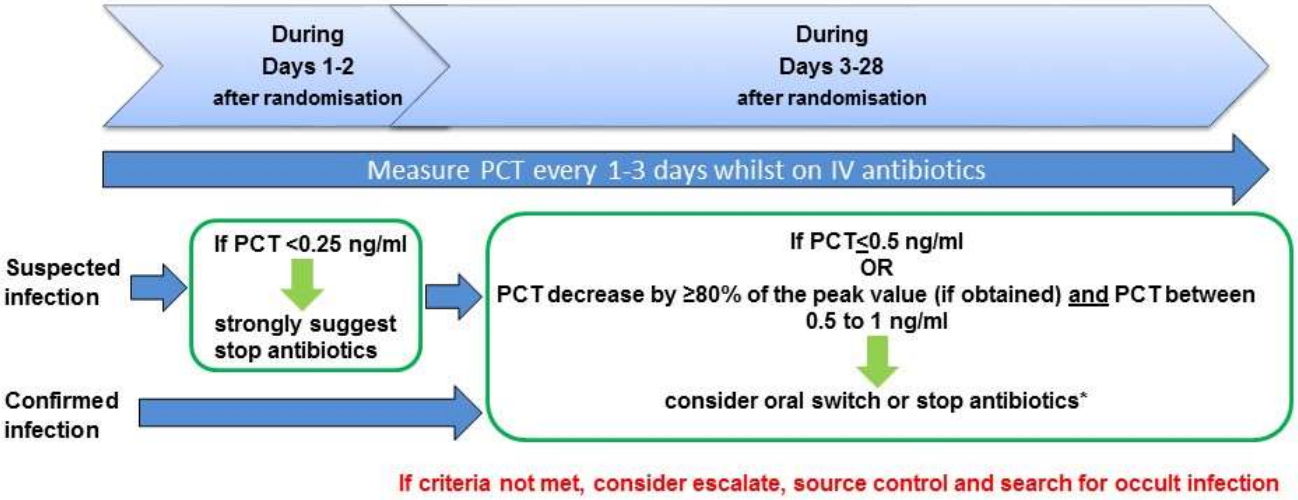
Antimicrobial Stewardship – Antibiotic Treatment Algorithm



Advocating patient safety and auditing of antimicrobial stewardship in hospitals should be based around the principles stated in this algorithm. Examples of audit tools are shared in the following pages

Guidelines for continuing or stopping IV antibiotics

In the standard care group: use clinical response +/- CRP to guide oral switch and discontinuation.
In PCT group: use clinical response (+/- CRP) and PCT to guide oral switch and discontinuation.
Measure PCT at randomisation/baseline and every 1-3 days whilst on IV antibiotics, or up to 28 days, as indicated clinically. If on Outpatient Parenteral Antimicrobial Therapy (OPAT), frequency can be every 7 days or according to local standard care. PCT results will be made available to the clinician.



If criteria not met, consider escalate, source control and search for occult infection

* **For confirmed infections see below:**

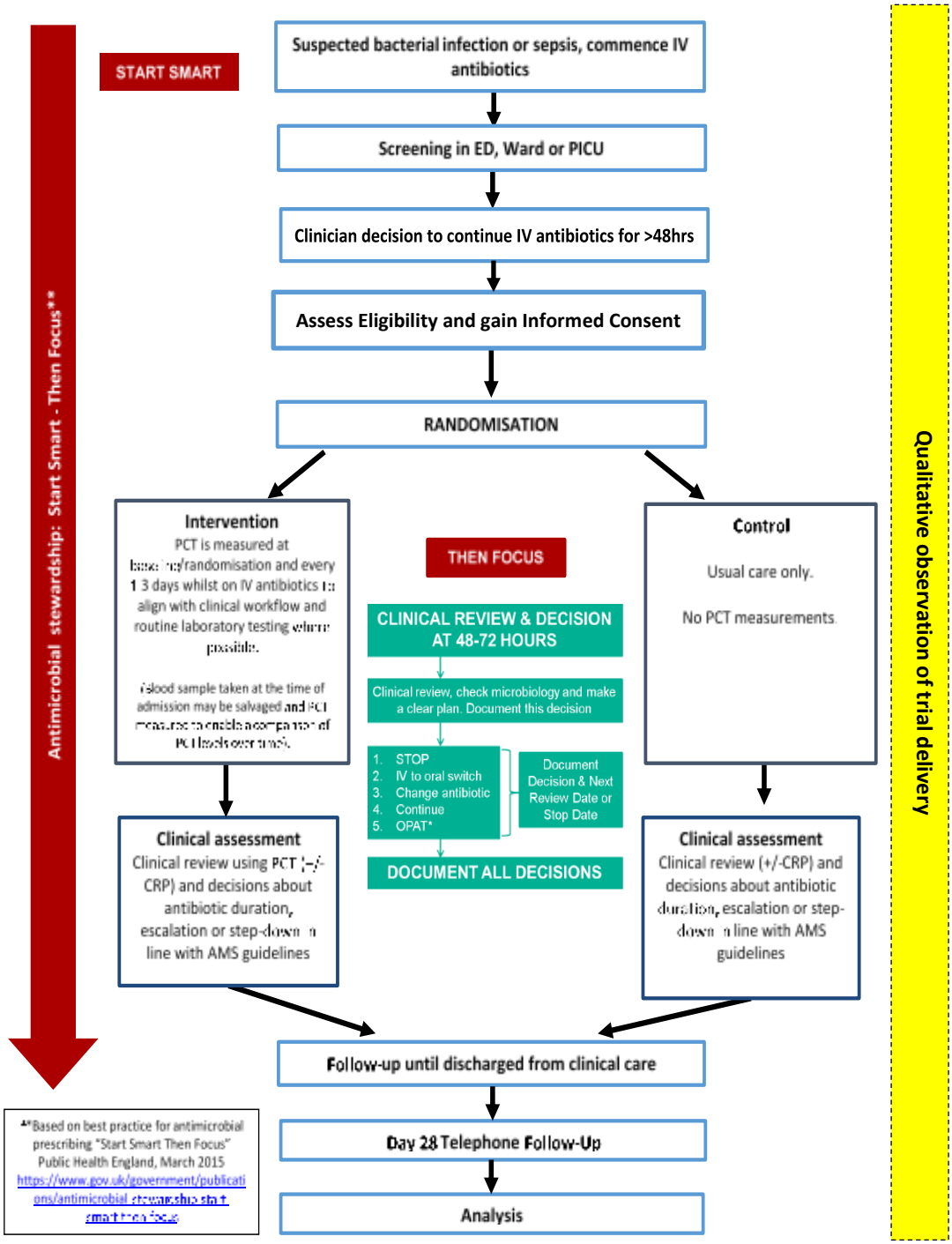
Evidence from systematic review of antibiotic duration and timing of switch from intravenous to oral route
McMullan, BJ *et al.* 2016 Lancet ID 16(8) e139-e152

Infections that can be safely treated with IV antibiotics for <5 days; pneumonia, pyelonephritis, lymphadenitis, cellulitis, bone and joint infections afebrile and pain improving, mastoiditis, sinusitis, retropharyngeal abscess, empyema (afebrile for >24hrs), pyomyositis.

Infections that usually require ≥5 days of IV antibiotics; bacteraemia, intra-abdominal infections, empyema (still febrile at 96 hrs and chest drain still in), complicated bone and joint infections, discitis, uncomplicated culture negative meningitis.

Appendix 2 – Timeline of Qualitative Evaluation Components

Health professional qualitative interview 1 (Prior to intervention)



Parent qualitative interview after day 28 follow-up

Health professional qualitative interview 2 (After intervention)