Empirical oral AntibioticS for possible UTI in well appearing Young febrile infants (EASY)

A multicentre, randomised controlled, open-label, non-inferiority trial, comparing parenteral antibiotics with oral antibiotics for the management of suspected UTI in low risk infants.

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PROTOCOL AUTHORISATION

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A review of the protocol has been completed and is understood and approved by the following:

Tom Waterfield		21 / 03 / 2024
Chief Investigator	Signature	Date
Christina Campbell	C Campbell	20 / 03 / 2024
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
AR	Adverse Reaction
BHSCT	Belfast Health and Social Care Trust
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EASY	Empirical oral AntibioticS for possible UTI in well appearing Young febrile infants
ED	Emergency Department
FIDO	Febrile Infants Diagnostic assessment and Outcome study
GAPRUKI	General and Adolescent Paediatric Research in the United Kingdom & Ireland
GCP	Good Clinical Practice
GLM	Generalised Linear Models
GP	General Practitioner
HTA	Health Technology Assessment
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
IBI	Invasive Bacterial Infection
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
MHRA	Medicine and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
PedsQL	Paediatric Quality of Life
PERUKI	Paediatric Emergency Research in the UK and Ireland
PI	Principal Investigator
PIS	Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
RCT	Randomised Controlled Trial
RD	Risk Difference
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAR	Serious Adverse Reaction
SEAR	Screened, Eligible, Approached, Randomised
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within a Trial
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UTI	Urinary tract infection

1 STUDY SUMMARY

Scientific title	A multicentre, randomised controlled, open-label, non-inferiority trial, comparing parenteral antibiotics with oral antibiotics for the management of suspected UTI in low risk infants.
Public title	Empirical oral AntibioticS for possible UTI in well appearing Young febrile infants (EASY)
Health condition(s) or problem(s) studied	Urinary Tract Infections (UTI)
Study Design	A multicentre, randomised controlled, open-label, non-inferiority trial, comparing parenteral antibiotics with oral antibiotics for the management of suspected UTI in low risk infants.
Study Aim and Objectives	**Aim** To assess the clinical effectiveness and cost-consequence of early oral antibiotics in infants presenting to hospital with suspected UTI who appear well and are at low risk of complications. **Objectives** 1. To determine if the clinical effectiveness of oral antibiotics pending urine culture results is non-inferior to parenteral antibiotics pending urine culture results in terms of treatment failure (i.e. the requirement for additional parenteral antibiotics) and a range of secondary outcomes. 2. To evaluate the impact of oral antibiotics on healthcare resource use, costs and selected outcomes via a cost-consequence analysis.
Study Intervention and Comparator	Participants will be randomised in a 1:1 ratio to one of two treatment groups. <u>Intervention:</u> Oral antibiotics (the choice of oral antibiotic prescribed is at the discretion of the clinical team and should reflect locally agreed prescribing protocols). <u>Comparator:</u> Parenteral antibiotics (the choice of parenteral antibiotic prescribed is at the discretion of the clinical team and should reflect locally agreed prescribing protocols).
Primary Outcome	Treatment failure (i.e. additional parenteral antibiotics) within seven days of randomisation

Secondary Outcomes	1. Treatment failure (i.e. additional parenteral antibiotics) assessed at day 28 2. Escalation in care defined as, escalation in the level of care (i.e. admission from home, admission to intensive care or a high dependency unit) OR change in antibiotic therapy OR death due to poor response. Assessed at 7 and 28 days. 3. Time to defervescence 4. Time to normal feeding 5. Time to normal activity 6. Length of stay 7. Antibiotic-associated adverse events (including diarrhoea and allergic reaction) 8. Antibiotic adherence (full course taken or no more than two missed doses) 9. Paediatric quality of life (measured using PedsQL acute infant version) 10. Family impact (measured using PedsQL Family Impact Module acute version) 11. Health service use and costs
Key Inclusion and Exclusion Criteria	**Inclusion criteria** 1. 29 to 90 days of age (Infants from their 29th day of life to their 90th day of life inclusive. Day of birth is day 1 of life) 2. Suspected urinary tract infection (UTI) requiring treatment with antibiotics 3. History of fever as defined as temperature ≥38°C measured by any method OR likely fever in last 24 hours including subjective fever reported by caregiver 4. Abnormal urinalysis defined as: (1) abnormal urinary dipstick test (leucocyte esterase ≥1+, or nitrite ≥Trace) OR (2) abnormal urine microscopy (≥5 white cells per high-power field in centrifuged urine or ≥10 white cells per mm3 in un-centrifuged urine or bacteriuria with any bacteria per high power field) 5. Well on global clinical assessment using the paediatric assessment triangle assessed by a consultant grade doctor **Exclusion criteria** 1. Born at <30 weeks gestation 2. Discharged from hospital more than 7 days after birth 3. Required re-admission to hospital after birth for more than 24 hours 4. Known or suspected structural renal abnormality 5. Evidence of sepsis and/or meningitis (appear unwell, shock, hypotension, altered mental state, bulging

	fontanelle, lumbar puncture suggestive of bacterial meningitis) 6. Received vaccination within 48 hours of attendance 7. Sodium < 128mmol/l on lab or blood gas sample 8. Potassium > 6.5 mmol/l on lab sample 9. Plasma creatinine > 50 micromol/l 10. Inability to tolerate oral medication 11. Urine sample was not sent for culture 12. Received additional antibiotics (with the exception of the parenteral antibiotic administered within 24 hours of hospital attendance) 13. Declined consent for participation
Countries of Recruitment	England, Northern Ireland, Scotland, Wales
Study Setting	Paediatric emergency departments (ED)
Target Sample Size	584
Study Duration	42 months

Funder Statement

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Project Reference NIHR 152733). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

2 STUDY TEAM

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3 ROLES AND RESPONSIBILITIES

3.1 Funder

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme is providing the research costs to the EASY study (Reference NIHR152733), as the result of a commissioned call (HTA 22/1). Further details can be found at www.fundingawards.nihr.ac.uk/award/NIHR152733 and the formal Funder Statement can be found in Section 1, Study Summary. The funder has no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2 Sponsor

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation undertaking Sponsor-delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

3.3 Trial Oversight Committees

3.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. It will comprise the CI and representatives from the Clinical Trials Unit (CTU), and any other co-investigators who provide trial specific expertise as required at the time. The TMG will meet face to face or by teleconference on a monthly basis, and will communicate between times via telephone and email as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All day-to-day activity will be managed by the Trial Manager, in consultation with the CI as needed, providing a streamlined approach for handling enquiries regarding the trial and disseminating communications.

3.3.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened to provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. An independent chair will lead the TSC, with at least 75% independent membership. The TSC will include the CI, a Patient and Public Involvement and Engagement (PPIE) representative, an independent statistician and a group of experienced paediatric emergency consultants and trialists. The membership, the role of the TSC and the frequency of meetings will be listed in the TSC Charter. The TSC, in the development of this protocol and throughout the trial, will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants. Meetings will be formally minuted and stored in the TMF. On occasion, observers may be invited and in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

3.3.3 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising two independent clinicians with experience in undertaking clinical trials in paediatric emergency medicine and an independent statistician. The DMEC's overarching responsibility is to safeguard the interests of trial participants, in particular with regard to safety, and assist and advise the TSC so as to protect

the validity and credibility of the trial. The membership, the role of the DMEC and the frequency of meetings will be listed in the DMEC Charter. The DMEC will meet to agree conduct and remit, which will be detailed in the DMEC Charter and include: monitoring the data and making recommendations to the TSC on whether there are any ethical, safety, or other reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies; and making recommendations to stop the trial for benefit on the basis of an effect estimate that is likely to influence decisions about the use of the relevant therapy by clinicians outside of the trial. Meetings will be formally minuted and stored in the TMF. Following recommendations from the DMEC, the TSC will decide what actions, if any, are required. It will be the responsibility of the TSC to inform the Sponsor if concerns exist about participant safety, following which the Sponsor will take appropriate action.

If a trial extension and/or funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

3.3.4 User Involvement or Any Other Relevant Committees

The PPIE co-applicant will attend TMG meetings when possible and there will be an independent PPIE member on the TSC to ensure appropriate representation of, and sensitivity to, the views of parents/guardians. Parent/guardian experience of paediatric emergency care will be taken into consideration when preparing participant information leaflets and consent forms. In addition a PPIE Advisory Group will be convened and actively contribute to the design and content of all participant-facing materials throughout the course of the study.

4 BACKGROUND AND RATIONALE

4.1 Background Information

Dogma states that because young febrile infants, under three months of age are at higher risk, than older children, of bacterial infections such as bacterial meningitis, bacteraemia and urinary tract infection (UTI) they should all be treated with broad-spectrum parenteral antibiotics [1-5]. Over the last two decades, this “just in case” approach has been challenged as research from the UK, Europe and the USA has shown that it is possible to identify a lower risk group of infants who do not require parenteral antibiotics [1-5]. In this lower risk cohort, the rates of the most serious bacterial infections (meningitis, bacterial sepsis) are extremely low and similar to those of older febrile children (0.2% - 0.7%) [6,7]. However, concern remains that the febrile infant who appears well may have an evolving UTI. UTIs are the most common serious bacterial infection (SBI) observed in febrile infants, accounting for over 90% of all SBIs in this age group [1-4]. Diagnosing UTIs in young infants is difficult for a number of reasons. The clinical features of UTI are non-specific (poor feeding, unsettled, fever, vomiting), and non-invasive urine collection is challenging because young infants cannot provide an on demand midstream urine sample; instead, urine samples have to either be “caught” in a dish by a parent or collected in a urine pad placed inside the nappy. This means that many of these urine samples are low volume and contaminated with faecal matter making urine microscopy unreliable [8-12]. These challenges lead to a necessarily cautious approach, with UK national guidelines advising broad-spectrum parenteral antibiotics for all febrile infants under three months of age with suspected UTI pending culture results [13,14]. Conversely, UK national guidelines advise that infants over three months of age are suitable for oral antibiotic therapy pending culture results [15,16]. The discrepancy in prescribing practices is due to uncertainty around the absorption of oral antibiotics in younger infants [17]. The overwhelming evidence however, shows that outside of the neonatal period (<28 days), oral antibiotics are well absorbed, well tolerated and effective at treating UTI [17- 25]. Faced

with concerns over the theoretical risk of missed SBI and the challenges of diagnosing UTI in young infants many clinicians simply admit all febrile infants and treat them with parenteral antibiotics "just in case". This "just in case" approach explains why febrile infants under three months of age incur significantly higher healthcare resource use than any other febrile age group [26]. It has been reported that amongst the lowest risk infants where parenteral antibiotics could have been avoided, the cost of admission and parenteral antibiotic therapy is ten times higher than that of those discharged (£1352/child) [26]. Avoiding "just in case" parenteral antibiotics has the potential to significantly reduce healthcare costs, reduce the demand for paediatric inpatient beds and improve the patient and family experience through shorter hospital stays and fewer painful procedures.

In preparation for this protocol we conducted a Medline literature search (updated 15/03/2023). The search terms were "urinary tract infection" AND "oral antibiotics" limited to include children under 23 months of age. The initial search returned 37 studies of which 29 were either not relevant or were editorials, narrative reviews and correspondence. There were eight relevant manuscripts including four clinical trials (summarised in Table 1), a Cochrane review and three systematic literature reviews combined with consensus guidelines [18-25]. The clinical trials summarised in table 1 all demonstrated that oral antibiotics and early switch from parenteral to oral antibiotics were non-inferior to parenteral antibiotics alone in terms of duration of fever and complications [19-22]. These findings were supported by the Cochrane review that found no difference in the duration of fever or renal damage between parenteral and oral antibiotic treatment strategies for suspected UTI [18].

Of the four clinical studies two were clinical trials directly comparing oral antibiotics with parenteral antibiotics for UTI. The first (published in 1999) was by Hoberman et al and was conducted in the USA [20]. They performed a randomised controlled trial involving infants with febrile UTI. They randomised 306 (144 under six months of age) infants to receive either oral or parenteral antibiotics. They found no difference between treatment groups for time to defervescence, microbiological cure and complications such as recurrent UTI and renal scarring [20]. They did however, report a significant difference in treatment costs with the parenteral treatment arm costing over double that of the oral treatment arm ($3577 vs $1473) [21]. Similarly in 2007 Montini et al published a randomised controlled non-inferiority trial of oral versus parenteral antibiotics for febrile UTI conducted in Italy [21]. This included 186 infants under six months of age. They too found no difference in time to defervescence, rates of microbiological cure, normalisation of infection markers and complications such as renal scarring [21].

Several international consensus guidelines have been published that recommend oral antibiotics as first-line treatment for infants with suspected UTI [23-25]. The Swiss consensus guidelines published in 2021 recommend oral antibiotics as first-line for all young infants if they are able to tolerate oral medication and are clinically well [23]. Canadian guidance from 2014 recommends oral antibiotics for infants over 28 days of age but with additional monitoring and most recently (2021) the American Academy of Paediatrics have advised that well appearing infants over 28 days of age with suspected UTI should be treated with oral antibiotics as first line therapy [24,25]. Prior to preparing this application we searched www.clinicaltrials.gov for potentially similar clinical trials. This search was repeated on the 15/03/23. There are currently 122 trials relating to UTI in children. None of them were similar or demonstrated overlap to EASY.

Table 1. Studies comparing oral versus intravenous antibiotic therapy for UTIs in febrile infants

Author	*Year*	*Country*	*N*	*Antibiotic Intervention*	*Design*	*Outcome*	*Comments*
Hoberman	1999	USA	306	Oral Vs IV	RCT	Duration of fever, microbiological cure, recurrence, renal scarring	No difference between groups.
Montini	2007	Italy	502	Oral Vs IV	RCT	Duration of fever, microbiological cure, Renal scarring	No difference between groups
Bocquet	2011	France	171	Early switch to oral Vs Prolonged IV	RCT	Duration of fever Renal scarring	No difference between groups
Olson	2022	USA	174	Early switch to oral Vs Prolonged IV	Cohort	Length of stay	Shorter length of stay in oral group

4.2 Rationale for the Study

In the UK, the diagnosis and management of febrile young infants is primarily guided by the National Institute for Health and Care Excellence (NICE). Clinical guidelines CG54, NG143 and NG111 recommend that all febrile infants, 90 days and younger, with a suspected UTI are admitted to hospital and treated with parenteral antibiotics [13-15]. However, this guidance is not always followed. In preparation for this project, we conducted the Febrile Infants Diagnostic assessment and Outcome study (FIDO) study [1] as an observational cohort study in six Paediatric Emergency Research in the UK and Ireland (PERUKI) sites between 31 August 2018 and 01 September 2019 [1]. The aims were to report the aetiology of infections amongst young febrile infants, validate clinical practice guidelines and assess current UK practices. That pilot work demonstrated that the average Paediatric Emergency Department in the UK and Ireland sees approximately one infant per day with a history of fever (based on 1942 cases). Of those with fever on arrival to hospital (n=555), 500 (90%) were admitted to hospital and 423 (76%) received parenteral antibiotics [1]. However, of these 555 infants febrile on arrival to hospital, only 11 (2%) had bacterial meningitis or bacterial sepsis and (67) 12% had a UTI [1].

Of the 555 febrile infants in the study, 114 (21%) met the American Academy of Paediatrics definition of "low risk" [>28 days of age, appear well, CRP of <20mg/l, absolute neutrophil count (ANC) < 5,200/mm3] and had abnormal urinalysis [2]. According to NICE guidance, all these infants should have been admitted to hospital and been given parenteral antibiotics [13-15] but only 81 (71% of the 114) were admitted to hospital and 33 (29%) were discharged home from ED with no oral antibiotic therapy. Amongst these 114 lower risk infants, 4 (4%) were diagnosed with a confirmed UTI and there were no cases of meningitis or bacterial sepsis. There was one case of treatment failure occurring in an infant who was not given parenteral antibiotics.

This pilot work demonstrates that clinicians do not routinely follow NICE guidance and that there appears to be considerable uncertainty regarding the management of well appearing febrile infants with abnormal urinalysis.

To resolve this uncertainty, the EASY study will determine if treating with oral antibiotics pending urine culture results, has the potential to safely reduce length of stay and reduce hospital costs, without requiring additional parenteral antibiotics within seven days of randomisation.

5 STUDY AIM AND OBJECTIVES

5.1 Research Hypothesis

Oral antibiotics are non-inferior to parenteral antibiotics for the treatment of suspected UTI in well appearing febrile infants at low risk of meningitis and bacterial sepsis.

5.2 Study Aim

To assess the clinical effectiveness and cost-consequence of early oral antibiotics in infants presenting to hospital with suspected UTI who appear well and are at low risk of complications.

5.3 Study Objectives

1. To determine if the clinical effectiveness of oral antibiotics pending urine culture results is non-inferior to parenteral antibiotics pending urine culture results in terms of treatment failure (i.e. the requirement for additional parenteral antibiotics) and a range of secondary outcomes.
2. To evaluate the impact of oral antibiotics on healthcare resource use, costs and selected outcomes via a cost-consequence analysis.

6 STUDY DESIGN

6.1 Study Design

A multicentre, randomised controlled, open-label, non-inferiority trial, comparing parenteral antibiotics with oral antibiotics for the management of suspected UTI in low risk infants.

6.2 Internal Pilot

An internal pilot study will run for the first 6 months of the trial to assess the feasibility of recruiting eligible participants and will inform the decision to progress to the main trial. This pilot will run from months 13-18 and will follow the processes described in the main study section below. Once a site is opened, defined by recruitment of their first participant, the target recruitment for each site will be 1.5 participants per month. With staggered opening of sites it is anticipated that pilot data will come from approximately 14 sites who will be set up during this period (out of the minimum of 18 in total for the full trial), and 17% of the total recruitment will be met. Therefore, the internal pilot recruitment target is 99. The pilot will be used to confirm screening, consent procedures, recruitment rates, and randomisation processes. Full details of the criteria for progression from the pilot to the full trial are given below.

If recruitment of 99 participants occurs more quickly than anticipated, progression to the full trial may occur earlier than 6 months at the discretion of the funder. The main parameter of interest to guide the progress of the trial and inform the procedures to be used in its delivery, is recruitment rates. Participants enrolled in the pilot will be included in the analysis of the main study.

The recommended traffic light system will guide progression [27] with appropriate actions according to observed performance:

Green: Progress to main trial.

Amber: Discuss feasibility with the TSC and NIHR, and develop improvement plans. Aspects evaluated to guide improving recruitment will include: number of eligible participants identified, percentage of participants randomised and reasons for non-randomisation, recruitment site performance, and review of recruitment procedures.

Red: Discuss cessation of the trial with the TSC and NIHR.

Table 2 presents a detailed breakdown of the internal pilot recruitment outcomes. The total number of participants recruited is based on the recruitment rate and the number of sites open during the pilot period.

Table 2. Detail of internal pilot phase during the first 6 months of recruitment

	Red	Amber	Green
% Threshold	<50%	50-99%	100%
Recruitment rate/site/month	<0.75	0.75-1.4	1.5
Number of sites opened	<7	7-13	14
Total number of participants recruited	<49	49-98	99

6.3 Study Schematic Diagram

The flow diagram depicting an overview of the trial is presented in Figure 1.

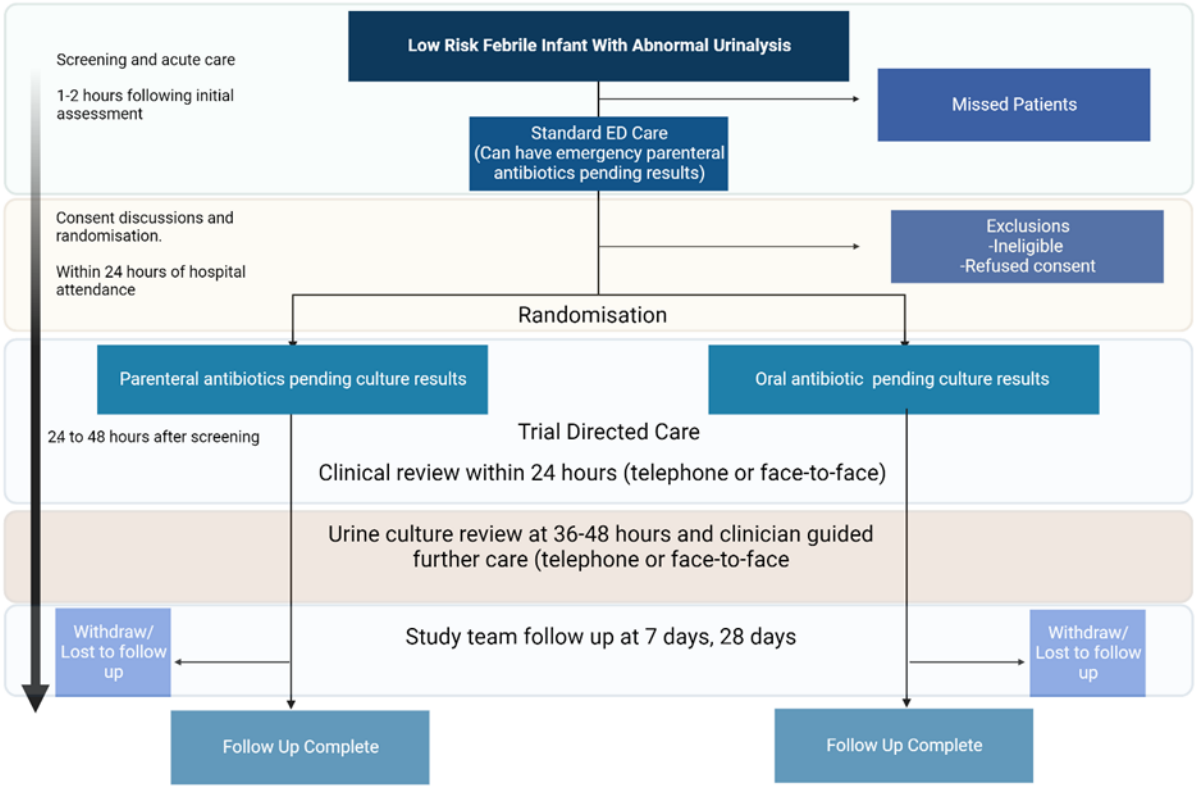

Figure 1. Flow diagram for EASY study

6.4 Study Timelines

The overall duration of the study is 42 months. Details of specific trial tasks and planned timelines are presented in Table 3.

Table 3. Study timeline and key tasks

Phase				PHASE 1									PHASE 2						PHASE 3																										
Milestones	Pre Grant			Set Up									Internal Pilot						Main Trial																				Analysis & Reporting						
Year				Year 1												Year 2												Year 3												Year 4					
Quarter				Q1			Q2			Q3			Q4			Q1			Q2			Q3			Q4			Q1			Q2			Q3			Q4			Q1			Q2		
Project Month	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	33	33	34	35	36	37	38	39	40	41	42
Calendar Month	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Jan-26	Feb-26	Mar-26	Apr-26	May-26	Jun-26	Jul-26	Aug-26	Sep-26	Oct-26
Trial Set Up	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x																														
Trial Staff Recruitment	x	x	x																																										
Protocol Development	x	x	x	x	x	x	x																																						
REC Approval							x	x	x	x	x	x																																	
HRA Approval							x	x	x	x	x	x	x	x	x																														
R&D Approval							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x																								
Site Set Up and Training							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x																								
Internal Pilot Study																x	x	x	x	x	x																								
Main Study																						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x							
Sites Initiated/Open to Recruitment																6	8	10	14	14	14	16	18	20	22	24	24	24	24	24	24	24	24	24	24	24									
Patient Recruitment/Month/Site																1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5									
Patient Recruitment/Month																9	12	15	21	21	21	24	27	30	33	36	36	36	36	36	36	36	36	36	36	36									
Patient Recruitment Cumulative																9	21	36	57	78	99	123	150	180	213	249	285	321	357	393	429	465	501	537	573	609									
Data Collection/Cleaning																x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x							
Internal Pilot Review																						x																							
TMG Meetings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
DMEC Meetings												x										x									x											x			
TSC Meetings												x										x									x											x			
PPIE Advisory Group							x														x									x												x			
Site Closure																																							x	x	x	x	x	x	x
Statistical Analysis																																							x	x	x	x	x	x	x
Health Economics Analysis																																							x	x	x	x	x	x	x
Reporting and Dissemination																																											x	x	x

Abbreviations: REC = Research Ethics Committee; MHRA = Medicines and Healthcare products Regulatory Agency; HRA = Health Research Authority; R&D = Research and Development; TMG = Trial Management Group; TSC = Trial Steering Committee; DMEC = Data Monitoring and Ethics Committee; PPIE = Patient and Public Involvement and Engagement

6.5 End of Study

The trial will end when all participants have completed their 28 day follow-up and database lock occurs. The trial will be stopped early if:

- Mandated by the Research Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency
- Mandated by the Sponsor e.g. following recommendations from the DMEC
- Funding ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the clinical trial authorisation will be notified in writing if the trial has been concluded or stopped early.

7 TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA

7.1 Trial Setting

Recruitment for the trial will take place in at least 18 paediatric emergency departments (EDs) and assessment units from across the UK, from within the Paediatric Research in the UK and Ireland (PERUKI) research network and the General and Adolescent Paediatric Research in the United Kingdom & Ireland (GAPRUKI) research network. Sites will be selected based on a wide geographical spread and they must provide evidence that they have:

- Access to the target population
- Local PI willing to lead the trial at that site and a local trial team
- A proven track record of participating in research
- Availability of either point-of-care urinalysis or laboratory microscopy 24 hours a day
- Access to laboratory testing for full blood count, C-reactive protein, creatinine 24 hours a day
- Ability to dispense trial medications 24 hours a day
- Ability to provide a dedicated phone number that can be accessed by parents/guardians between 8am and 8pm 7 days a week
- Ability to provide a departmental phone number that can be accessed by parents/guardians outside of these times

Staff must also comply with the protocol, standard operating procedures (SOPs), the principles of Good Clinical Practice (GCP), regulatory requirements, and be prepared to participate in appropriate trial training. Training will be provided to sites who participate in the study. A list of study sites will be maintained in the TMF.

7.2 Trial Population

Participants will be screened from attendances to paediatric EDs and assessment units at recruiting sites. All participants who meet the study inclusion criteria will be entered into a screening log. If the participant is not recruited the reason will be recorded. This information is required to ensure the study can be reported in keeping with Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

7.3 Eligibility Criteria

Participants will be assessed using the inclusion and exclusion criteria set out below. Eligibility to participate in the trial will be confirmed by a physician who is named on the Delegation Log. The medical care given to, and medical decisions made on behalf of, trial participants will be the responsibility of an appropriately qualified treating physician. Participants will be eligible to participate in the study in accordance with the following criteria:

7.3.1 Inclusion Criteria

1. 29 to 90 days of age (Infants from their 29th day of life to their 90th day of life inclusive. Day of birth is day 1 of life)
2. Suspected urinary tract infection (UTI) requiring treatment with antibiotics
3. History of fever as defined as temperature ≥38°C measured by any method OR likely fever in last 24 hours including subjective fever reported by caregiver

4. Abnormal urinalysis defined as: (1) abnormal urinary dipstick test (leucocyte esterase ≥1+, or nitrite ≥Trace) OR (2) abnormal urine microscopy (≥5 white cells per high-power field in centrifuged urine or ≥10 white cells per mm3 in un-centrifuged urine or bacteriuria with any bacteria per high power field)
5. Well on global clinical assessment using the paediatric assessment triangle* assessed by a consultant grade doctor. [28]

***Paediatric Assessment Triangle (appendix 1)**:
Normal **Appearance** defined as having a normal cry, good muscle tone and alert. Normal **Circulation** defined as normal colour, heart rate less than 160 beats per minute and a central capillary refill time of less than three seconds. Normal **Work of breathing** defined as regular breathing without excessive respiratory muscle effort and RR<60 breaths per minute.

7.3.2 Exclusion Criteria

1. Born at <30 weeks gestation
2. Discharged from hospital more than 7 days after birth
3. Required re-admission to hospital after birth for more than 24 hours
4. Known or suspected structural renal abnormality
5. Evidence of sepsis and/or meningitis (appear unwell, shock, hypotension, altered mental state, bulging fontanelle, lumbar puncture suggestive of bacterial meningitis)
6. Received vaccination within 48 hours of attendance
7. Sodium < 128mmol/l on lab or blood gas sample
8. Potassium > 6.5 mmol/l on lab sample
9. Plasma creatinine > 50 micromol/l
10. Inability to tolerate oral medication
11. Urine sample was not sent for culture
12. Received additional antibiotics (with the exception of the parenteral antibiotic administered within 24 hours of hospital attendance)
13. Declined consent for participation

7.3.3 Co-enrolment Guidelines

Participants in the EASY study may be eligible for co-enrolment in other studies, and this will be decided on a case-by-case basis by the Trial Management Group. Participants enrolled in other investigational drug studies are not candidates for this study. Participants enrolled in other observational studies are potential candidates for this study. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

8 TRIAL INTERVENTIONS

8.1 Study Intervention and Comparator (standard care)

When a febrile infant (under three months of age) attends hospital they should undergo blood and urine testing and may receive broad-spectrum parenteral antibiotics in the EDs or assessment unit pending laboratory results. This initial hospital assessment will be unaffected by the EASY study.

Clinicians will be free to perform investigations and administer parenteral antibiotics (standard care) during that initial assessment without delay.

Administration of initial parenteral antibiotics, if required based on national clinical guidelines and local policy, should not be delayed pending consent discussions.
Screening should occur once initial laboratory results are known and only eligible "low risk" infants will be invited to participate in the trial.

Randomisation must occur within 24 hours of hospital attendance.

Eligible "low risk" participants will be randomised in a 1:1 ratio to one of two treatment groups.

Intervention: Oral antibiotics and continuation of oral treatment at least until urine culture results are known (typically after 36 to 48 hours).

Comparator: Continuation of parenteral antibiotics (standard care) at least until urine culture results are known (typically after 36 to 48 hours).

Section 9 of the protocol, outlines the oral and parenteral antibiotics to be used in the EASY study.

8.2 Assignment of Intervention

8.2.1 Sequence Generation

Participants will be randomised using an automated web-based or telephone system via randomly permuted blocks in a 1:1 ratio. There will be stratification by recruitment site, sex, age (29-60 days/61-90 days) and antibiotic use.

8.2.2 Allocation Concealment Mechanism

The randomisation sequence will be saved in a restricted section of the TMF, which can only be accessed by the trial statistician and not those who enrol or assign interventions.

8.2.3 Allocation Implementation

After informed consent, participants will be randomised via an automated web-based or telephone system. Sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team. Each participant will be allocated their own unique Participant Study Number during the randomisation process, which will be used throughout the study for participant identification on all data collection forms and questionnaires. An entry will be recorded in the participants' medical notes noting enrolment into the study.

8.2.4 Blinding

This study will be a randomised, open label, unblinded trial. Parents/guardians, those who provide health care to the participants, and outcome assessors, will not be blinded to the allocated intervention in this trial. This reflects the pragmatic design focused on clinical effectiveness; it also permits realistic evaluation of the effect of the intervention on hospital admission to take account of admission for reasons other than parenteral antibiotic administration.

The trial statistician, who has no role in decision-making with regards the conduct of the trial, will be unblinded and this will also facilitate linkage with the DMEC. The remainder of the trial team will also be unblinded for the purposes of managing data collection, reviewing cases to assess protocol deviations, and to undertake pharmacovigilance duties.

9 STUDY INVESTIGATIONAL MEDICINAL PRODUCTS

9.1 Safety Considerations of the Intervention

Parenteral antibiotics are routinely given in standard clinical practice to treat suspected UTI until urine culture results are known. In the EASY study we are investigating the use of oral antibiotics pending urine culture results. The safety profile and efficacy of parenteral and oral antibiotics are well established and as they will be used in accordance with their marketing authorisations, the EASY study has been categorised as a Type A Clinical Trial of an Investigational Medicinal Product (CTIMP) study. As the risks are no higher than standard care, a risk-adapted approach to the management of the parenteral and oral antibiotics as investigational medicinal products has been adopted [29].

9.2 Study Drug

The most commonly prescribed oral antibiotics are cephalexin, co-amoxiclav and trimethoprim as outlined in Table 4 and these will be considered as investigational medicinal products (IMP) in the EASY study. These will be used as per the manufacturer's authorisation and within their licensed range of indications, dosage, and form (according to the Summary of Product Characteristics (SPC).

As in standard clinical practice, if the baby is sick within 30 minutes of administration of any doses of cephalexin, co-amoxiclav or trimethoprim, the dose should be repeated. If this occurs after 30 minutes, the dose should not be repeated and the oral antibiotic should be administered at the next scheduled dosing time. If the baby is sick within 30 minutes for 2 consecutive doses, the clinician should consider whether the oral antibiotic cannot be tolerated.

Table 4. Oral Antibiotics

Oral Antibiotics	
Cefalexin	Licensed oral formulations used in accordance with standard care practice at participating sites
Co-amoxiclav	
Trimethoprim	

The most commonly prescribed parenteral antibiotics are ceftriaxone, cefotaxime, gentamicin, amoxicillin, cefuroxime and co-amoxiclav as outlined in Table 5 and these will be considered as investigational medicinal products (IMP) in the EASY study. These will be used as per the manufacturer's authorisation and within their licensed range of indications, dosage, and form (according to the Summary of Product Characteristics (SPC).

Table 5. Parenteral Antibiotics

Parenteral Antibiotics	
Ceftriaxone	Licensed parenteral formulations used in accordance with standard care practice at participating sites
Cefotaxime	
Gentamicin	
Amoxicillin	
Cefuroxime	
Co-amoxiclav	

9.3 Study Drug Storage

Study drug will be stored in accordance with manufacturer's recommendations and local practice.

9.4 Study Drug Prescribing, Labelling and Dispensing

When a participant is recruited a member of the research team will use the randomisation service to obtain the unique Participant Study Number and the treatment allocation assigned to the participant. Study drug will be prescribed and dispensed in accordance with usual local site prescription practice. There will be no additional labelling outside the usual practice at local sites. Communication will be given between the research and clinical teams as to which arm of the trial a participant has been randomised to, and participant enrolment into the trial and treatment allocation will be recorded in the clinical notes.

9.5 Study Drug Accountability

There will be no additional records of accountability for supply, administration or destruction of study drug outside the standard clinical practice for these products at the local hospital site.

9.6 Study Drug Administration

Oral and parenteral antibiotics will be given as per locally determined scheduled prescription.

9.7 Study Drug Termination Criteria

Antibiotic treatment may be ended or switched based on clinical assessment during admission or at dedicated telephone reviews. The study drug may also be terminated once urine culture results are known and if no longer clinically indicated.

9.8 Study Drug Adherence

Inpatient administration will be recorded in the hospital prescription chart. Post discharge from hospital, parents/guardians will be verbally asked about adherence at the follow up time points. Any omission of study drug will not be recorded as a protocol deviation.

9.9 Concomitant Care

Paracetamol and ibuprofen can be administered as required to control the infants fever and its associated symptoms. These drugs, and any other concomitant medications, will be recorded on the CRF.

10 OUTCOMES and OUTCOME MEASURES

10.1 Primary Outcome

The primary outcome is treatment failure (i.e. additional parenteral antibiotics) within seven days of randomisation.

Additional parenteral antibiotics in the standard care group is defined as:

(i) administration of an additional parenteral antibiotic not prescribed as part of initial empirical treatment
(ii) a change of parenteral antibiotics from standard empirical treatment
(iii) re-commencing parenteral antibiotics after the decision to terminate parenteral antibiotics.

For the intervention group additional parenteral antibiotics are defined as administering parenteral antibiotics for any reason.

10.2 Secondary Outcomes

1. Treatment failure (i.e. additional parenteral antibiotics) assessed at day 28
2. Escalation in care defined as, escalation in the level of care (i.e. admission from home, admission to intensive care or a high dependency unit) OR change in antibiotic therapy OR death due to poor response. Assessed at 7 and 28 days.
3. Time to defervescence
4. Time to normal feeding (as reported by parent/guardian)
5. Time to normal activity (as reported by parent/guardian)
6. Length of stay
7. Antibiotic-associated adverse events (including diarrhoea and allergic reaction)
8. Antibiotic adherence (full course taken or no more than two missed doses)
9. Paediatric quality of life (measured using PedsQL acute infant version) within 24 hours of randomisation, day 7 and day 28
10. Family impact (measured using PedsQL Family Impact Module acute version) at day 7
11. Health service use and costs

11 SCREENING, CONSENT and RECRUITMENT

11.1 Screening Procedure

Participants will be screened from attendances to paediatric EDs and assessment units at recruiting sites. Eligible participants will then be discussed with their clinical team to confirm agreement with trial enrolment. If a participant is initially deemed to be unwell but then becomes well within 24 hours of hospital attendance, they can be reconsidered for participation in the EASY study.

All screening data must be recorded by the Principal Investigator (PI) or designee onto the EASY study screening database. The PI or designee will be required to submit screening data to the CTU each month. Monthly screening data will be used to monitor trial recruitment and provide feedback to sites. The collection of accurate screening data is also required to meet CONSORT 2010 trial reporting guidelines [30].

The outcome of the screening process and reasons for the non-enrolment of potentially eligible participants will be recorded on the EASY study screening database using the Screened, Eligible, Approached, Randomised (SEAR) framework [31]. A minimal dataset will also be recorded for eligible and non-recruited participants which will include age, ethnicity and sex (with the exception of non-recruited participants in Scotland).

Screening: Enter ALL potentially eligible EASY participants who meet the EASY study inclusion criteria onto the screening log:

1. 29 to 90 days of age (Infants from their 29th day of life to their 90th day of life inclusive. Day of birth is day 1 of life)
2. Suspected urinary tract infection (UTI)
3. History of fever as defined as temperature ≥38°C measured by any method OR likely fever in last 24 hours including subjective fever reported by caregiver
4. Abnormal urinalysis defined as: (1) abnormal urinary dipstick test (leucocyte esterase ≥1+, or nitrite ≥Trace) OR (2) abnormal urine microscopy (≥5 white cells per high-power field in centrifuged urine or ≥10 white cells per mm3 in un-centrifuged urine or bacteriuria with any bacteria per high power field)
5. Well on global clinical assessment using the paediatric assessment triangle assessed by a consultant grade doctor

Eligibility Assessment: a physician will confirm the participant's eligibility or reason for exclusion. A participant may be eligible for enrolment assuming the eligibility criteria are met. If the participant is ineligible, the reason will be recorded on the screening log using the following codes:

1. Born at <30 weeks gestation
2. Discharged from hospital more than 7 days after birth
3. Required re-admission to hospital after birth for more than 24 hours
4. Known or suspected structural renal abnormality
5. Evidence of sepsis and/or meningitis (appear unwell, shock, hypotension, altered mental state, bulging fontanelle, lumbar puncture suggestive of bacterial meningitis)
6. Received vaccination within 48 hours of attendance
7. Sodium < 128mmol/l on lab or blood gas sample
8. Potassium > 6.5 mmol/l on lab sample
9. Plasma creatinine > 50 micromol/l
10. Inability to tolerate oral medication
11. Urine sample was not sent for culture
12. Received additional antibiotics (with the exception of the parenteral antibiotic administered within 24 hours of hospital attendance)
13. Declined consent for participation

Approach: the participant's parent/guardian will be provided with information about the study and asked for their consent. If not approached, enter the reason for non-approach onto the screening log.

If **Randomised**: the participant's Participant Study Number will be recorded on the screening log. If the parent/guardian declined, enter the reason they declined consent on the screening log.

11.2 Informed Consent Procedure

A member of the clinical team will initially approach the parent/guardian of the participant. If the family is interested, they will be introduced to a researcher and presented with the participant information leaflet, consent form and provided with a verbal explanation of the trial procedures. If the trial site has been randomised to the Study Within a Trial (SWAT) intervention (section 15), the parent/guardian will also be provided with an infographic about the study. The family will then be given the opportunity to discuss issues related to the trial with the researcher.

The Principal Investigator (PI) (or designee) is responsible for ensuring that informed consent for trial participation is given for each participant by their parent/guardian. An appropriately trained doctor or nurse may take consent. The person taking informed consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty on the delegation log. Appropriate signatures and dates must be obtained on the informed consent documentation prior to randomisation, collection of trial data and administration of the IMP. If no consent is given the participant cannot be enrolled into the trial.

11.3 Withdrawal of Consent

The parent/guardian may withdraw consent from the study at any time without detriment. If consent is withdrawn this will be documented in the participant's medical notes and in the CRF.

If the parent/guardian declines on-going participation, anonymised data recorded up to the point of withdrawal, will be included in the study analysis unless the parent/guardian requests otherwise.

11.4 General practitioner (GP) Contact

Sites will be advised to send a letter to the participants GP to advise them of their participation in the EASY study.

12 SCHEDULE of ASSESSMENTS

12.1 Participant Assessments

The frequency of assessments and follow up are detailed in the schedule of assessments (Table 6). The schedule defines the timing of assessments (with windows) necessary for data collection. Participants should be followed until the final follow-up assessment at day 28, even if antibiotics have been discontinued.

The decision to discharge a participant home is not mandated by the allocation to the oral antibiotic treatment group. The local clinical team should determine when the participant should be discharged and have agreed that it is an appropriate management strategy.

Table 6: Schedule of Assessments

Day/Timepoint	Screening (Day 0)	Baseline (Day 0)	Within 24* Hours of Randomisation	36 – 48* Hours After Randomisation	Follow Up Day 7# (+/- 1 day)	Follow Up Day 28# (+/- 3 days)
At Hospital/Remote	Hospital	Hospital	Hospital/Remote	Hospital/Remote	Remote	Remote
Point of Care Dipstick Urinalysis	x					
Urine sample sent for microscopy and culture	x					
Eligibility	x					
Consent (Trial)		x				
Admission Details		x				
Demographics		x				
Medical History		x				
Symptoms		x	x	x	x	x
Physical Examination		x				
Full Blood Count (including CRP, Creatinine, Electrolytes)		x				
Medications		x	x	x	x	x
Hospital Resource Use			x	x	x	x
Antibiotic Administration (pre randomisation)		x				
Randomisation		x				
Antibiotic Administration (post randomisation) Including Adherence/Tolerability			x	x	x	x
Urine Culture Results			x	x		
Escalation in the level of care/Readmission			x	x	x	x
Adverse Events/ Serious Adverse Events		x	x	x	x	x
$PedsQL Infant (completed by parent/guardian)			x		x	x
$PedsQL Family Impact (completed by parent/guardian)					x	
SWAT Questionnaire on Consent (completed by parent/guardian)				x		
Health Resource Use and Activities Questionnaire (administered by site staff via telephone)						x

*Assessments will be face-to-face (hospital) or may be by telephone (remote) for participants who have been discharged.
Within 24 hours, the parent/guardian should complete the PedsQL Infant Questionnaire.
Within 36-48 hours, site staff should remind the parent/guardian to complete the SWAT Questionnaire.

#Assessments will be by telephone (remote) for both cohorts.
At day 7, site staff should remind the parent/guardian to complete the PedsQL Family Impact Questionnaire.
At day 7 and day 28, site staff should remind the parent/guardian to complete the PedsQL Infant Questionnaire.
At day 28, site staff should administer the Health Resource Use and Activities Questionnaire via telephone.

12.2 Procedures to Support Parents/Guardians and Maintain Participant Safety

In this trial, normal pathways of care will be encouraged. However, there is a responsibility to balance this approach with the need to ensure the safety of all participants, particularly those treated with oral antibiotics who have been discharged prior to the urine culture results. In addition to standard clinical practice, additional measures for trial participants who have been randomised to oral antibiotics will be:

- Parents/guardians will be provided with a dedicated telephone contact number, allowing direct access to the local clinical team between 8am – 8pm Monday to Friday, should they have any questions or concerns.
- Parents/guardians will be provided with a telephone contact number for the paediatric emergency department at the local site, which can be used at all other times, should they have any questions or concerns.
- Parents/guardians will be reassured that they can attend the emergency department at any time, should they have any concerns.
- Follow up assessments will be performed by an appropriately trained member of the clinical team via telephone at 24 hours and 36-48 hours after randomisation, asking the parent/guardian to report if their child has ongoing fever or other symptoms of concern. Symptom data will be monitored remotely during trial follow up by the local clinical team. If there are any concerns parents/guardians will be advised to attend the emergency department so that a medical review can be undertaken.

12.3 Participant Follow-Up at Day 7 and Day 28

Follow up assessments will be performed via telephone at day 7 (+/- 1 day) and day 28 (+/- 3 days). This will include an ongoing review of symptoms, antibiotic administration and adverse events. In addition, site staff should remind parents/guardians to complete the PedsQL Infant Questionnaire (day 7 and day 28) and the PedsQL Family Impact Questionnaire (day 7). At day 28, site staff should also administer the Health Resource Use and Activities Questionnaire via telephone.

12.4 Study Instruments for Participant Follow-Up

12.4.1 Paediatric Quality of Life (PedsQL) Infant Scales 1-12 month Version (Acute).

The PedsQL Infant Scales [32] 1-12 month Version is a 36-item modular, parent/guardian reported, health-related quality of life (HRQOL) instrument encompassing 5 scales: Physical Functioning (6 items), Physical Symptoms (10 items), Emotional Functioning (12 items), Social Functioning (4 items) and Cognitive Functioning (4 items). The Acute version asks the parent/guardian how much of a problem each item has been during the past 7 days. Responses are measured on a 5-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL. The total score is calculated as the sum of all the items divided by the number of items answered. Scale scores are computed as the sum of the items divided by the number of items answered. The PedsQL has previously been shown to be a valid and responsive indicator of HRQOL for short-term febrile illnesses evaluated in the ED [33].

12.4.2 Paediatric Quality of Life (PedsQL) Family Impact Module (Acute)

The PedsQL Family Impact Module [34] is 36-item modular parent/guardian self-reported, HRQOL instrument encompassing 6 scales: Physical Functioning (6 items), Emotional Functioning (5 items), Social Functioning (4 items), Cognitive Functioning (5 items), Communication (3 items), Worry (5 items), and 2 scales measuring parent/guardian reported family functioning: Daily Activities (3 items) and Family Relationships (5 items). The Acute version asks the parent/guardian how much of a problem each item has been during the past 7 days. Responses are measured on a 5-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL. The total score is calculated as the sum of all the items divided by the number of items answered. Scale scores are calculated as the sum of the items divided by the number of items answered. Parent/guardian HRQOL Summary Score (20 items) is calculated as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning Scales. The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and Family Relationships Scales. Only one parent/ guardian needs to complete the instrument and their relationship to the child will be recorded.

12.4.3 Health Service Use and Activities Impact Questionnaire

A study specific questionnaire will measure participants' use of primary care services since discharge as well as the impact of the participants' health condition on the parents'/guardians' ability to work and undertake their usual activities.

13 DATA COLLECTION and MANAGEMENT

13.1 Data Collection

To ensure accurate, complete, and reliable data are collected, the CTU will provide training to site staff. All data for an individual participant will be collected and recorded in source documents and transferred onto a bespoke, web-based, electronic CRF for the study. A data dictionary, record of automatic and manual data queries, and a full audit trail, will ensure data captured are consistent, reliable, and fully compliant with GCP and any other relevant regulatory requirements. For routinely collected clinical data the NHS record will be the source document. Participant identification on the CRF will be through their unique participant study number, allocated at the time of randomisation. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF submission guidelines.

For the economic evaluation paediatric HRQoL will be measured using the PedsQL administered within 24 hours of randomisation, 7 days and 28 days. Hospital resource use data including readmissions and outpatient attendance will be collected via the CRF and primary care use will be collected using a brief questionnaire administered by site staff via telephone at 28 days. The questionnaire will also measure the impact of the participants' health condition on the parents'/guardians' ability to work or perform usual activities (see section 14.3). The PI or designee will provide the parent/guardian with the questionnaires prior to discharge. As part of the telephone follow up at 7 days and 28 days, the site staff will remind the parent/guardian to complete the questionnaires and return these in prepaid envelopes provided to the Trial Co-ordinating Centre.

13.2 Data Quality

The CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Source data verification (SDV) will be completed by the CTU and will check the accuracy of entries on the electronic CRF against the source documents and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control is implemented by the CTU in the form of Standard Operating Procedures (SOPs), which encompass aspects of the clinical data management process, and ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A DMEC will be convened for the study to carry out reviews of the study data at staged intervals during the study.

13.3 Data Management

Following the entry of participant data into the study database, the data will be processed as per the CTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated electronically for site staff to clarify data or provide missing information, with the expectations that these queries will be completed within 14 days of receipt. All queries will be responded and amended within the study database.

14 STATISTICAL CONSIDERATIONS

14.1 Sample Size

With a treatment failure rate (i.e. additional parenteral antibiotics within 7 days of randomisation) of 0.5% and a non-inferiority margin of 2%, 524 participants are required based on 90% power and a 1-sided 97.5% Confidence Interval. Of the required population, it is estimated that up to 10% might not provide 7-day follow up. Therefore, a sample size of 584 is needed to obtain the 524 required for analysis.

14.2 Data Analysis

14.2.1 Analysis Population

Primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat (ITT) analysis. Per-protocol analysis will also be conducted which will involve a comparison of treatment groups that includes only those participants who completed the treatment originally allocated. In view of the risk of bias arising from either analysis alone in a non-inferiority trial, we will conclude that non-inferiority of the intervention has been proven only if it is demonstrated in both analyses.

14.2.2 Statistical Methods

Baseline characteristics, follow-up measurements and safety data will be described using appropriate descriptive summary measures depending on the scale of measurement and distribution.

Analyses for the primary outcome will be 1-sided and at a significance level of 0.025 and investigated using generalised linear models (GLM) to estimate the risk difference (RD). The difference in treatment failure rate (95% CI) will be compared to the non-inferiority margin of 2%. Non-inferiority is established by showing that the upper bound of a one-sided 97.5% confidence interval for the difference in treatment failure rate is <2%.

A secondary comparison of the primary outcome between the two groups will be investigated using GLM, adjusting for site, sex, age, antibiotic use and other covariates

All remaining analyses for secondary outcomes will be two-sided and at a significance level of 0.05.

Binary outcomes between the two groups will be investigated using GLM, adjusting for covariates.

Comparison of continuous outcomes between the two groups will be investigated using independent t-tests or ANCOVA if appropriate or nonparametric equivalents.

We will include sensitivity analyses looking at treatment failure (day 28) and escalation in care (day 7 and day 28) for those children with a confirmed UTI*.

Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed where required.

A detailed statistical analysis plan (SAP) will be written by the trial statistician prior to the final analysis.

14.3 Health Economics Evaluation

A switch from parenteral to oral antibiotics has the potential to reduce healthcare costs by reducing the observation time, facilitating an earlier discharge from hospital. A cost-consequence analysis will evaluate the impact of early discharge with oral antibiotics on healthcare resource use, costs and selected outcomes over a 28-day time horizon. The base-case analysis will be from a health service and personal social service perspective. Resource use data will be measured from randomisation until 28 days and will include length of stay, setting type (e.g. emergency assessment unit, ward, ambulatory care, HDU/ICU), readmissions to ED, outpatient visits and contacts with primary care. Data will be collected using the case report forms, medical records and a parent/guardian completed questionnaire. Costs will be calculated by attaching appropriate unit costs from publicly available sources (e.g. NHS Reference Costs) or hospital finance departments. We anticipate that 28 days will be sufficient to capture any readmissions. HRQoL of the participants will be measured within 24 hours of randomisation, 7 and 28 days using PedsQL Infant Scales 1-12 month Version (Acute) completed by the parent/guardian [32]. The PedsQL Family Impact Module (Acute) [34] will be used to measure the impact of the participants' health condition on the parents/guardians at 7 days. Discounting of costs and outcomes will not be required due to the short timeframe. Current guidelines for conducting [35-37] and reporting [38] economic evaluations will be followed where appropriate. Descriptive statistics (means, 95% confidence intervals) will be used to summarise (by treatment arm); health service use during primary hospital admission and after discharge until 28 days; associated costs; PedsQL Infant Scales and PedsQL Family Impact scores.

Sensitivity analyses will be conducted to explore the impact on the results of the costs-consequence analysis to variations in key assumptions. These will include an analysis from a broader societal perspective encompassing out-of-pocket costs borne by the parent/guardian (specifically due to inability to work/perform usual activities), and the impact of multiply imputing missing health economic data using chained equations and predictive mean matching. A health economic analysis plan will be written prior to analysis of these data.

14.4 Additional Analysis

Exploratory analyses for the primary outcome will be reported using interaction tests (treatment group by subgroup) and 99% confidence intervals for the following subgroups:

I. Age (29-60 days, 61-90 days)
II. Site
III. Sex
IV. Antibiotics pre randomisation
V. Confirmed UTI*

14.5 Missing Data

Every effort will be made to minimise missing baseline and outcome data in this trial. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

*Urinary Tract Infection (UTI) is defined as greater than 100,000 CFU/ml of a single, non-contaminant, organism from a single clean urine (clean catch, suprapubic aspiration, urethral catheter specimen) or greater than 100,000 CFU/ml of the same single organism from two non-clean urines (pads, bags, cotton wool).

15 STUDY WITHIN A TRIAL: Impact on recruitment by using an infographic in addition to the participant information sheet

15.1 Objectives

1. A cluster randomised study within a trial (SWAT) will be embedded within the EASY study to assess the impact on recruitment of using a simple specially developed information graphic (infographic) in addition to the standard PIS to explain the two treatment arms of the EASY Study to parents/guardians of eligible participants.
2. To explore satisfaction with and understanding of the EASY study consent process.

15.2 Background

Recruitment and retention to trials within a paediatric emergency setting is challenging as there is very little or no time for parents/guardians to consider research information and make an informed decision about their baby's involvement in a study. Parents can be distressed and understandably focused on their baby, often prioritising verbal information provided by clinicians over written study information. However, brief verbal information provision by practitioners in the emergency setting has been associated with poor parental understanding and poor recall of any aspect of the study presented [39]. Practitioner views and preferences may influence how they present the study, or be misunderstood by parents, which may impact upon trial recruitment and retention [40, 41].

We will explore ways to improve this in the EASY study, including assessing the effect of an infographic and collecting information on the consent process. Guidance on how to use the infographic will be provided during the site initiation visit (SIV). The infographic is a simple, brief representation of the information provided in the standard PIS about the two treatments and was developed with input from the PPIE group. The intention is to prompt a more structured conversation between the consenting clinician and the parent/guardian of the eligible child about the EASY study and how the randomisation will influence their child's care pathway.

After being provided with the PIS (and infographic if in the SWAT intervention arm) staff will ask each parent/guardian to complete a brief questionnaire within 48 hours post-screening. Staff will be asked to write the participants screening number at the top of the questionnaire. This will include parents who have been approached and declined their child's involvement in the trial. The questionnaire will aim to explore satisfaction with and understanding of the EASY study consent process, factors that may have informed decisions to decline participation in the EASY study and quality of decision making (measured using the validated SURE scale [42]). The questionnaire will be placed in a stamped self-addressed envelope and returned by post to the NICTU.

15.3 Intervention and Comparator (SWAT Objective 1)

EASY study sites allocated to the SWAT intervention arm will provide parents/guardians with an infographic in addition to the standard PIS during the consent process. Sites allocated to the control arm will use the standard PIS.

15.4 Participants

Parents/guardians of participants who are approached to participate in the EASY study.

15.5 Randomisation

The randomisation process will be separate from the main trial randomisation. Sites will be randomised (1:1 using mixed block sizes) to either the SWAT intervention or the SWAT control arm. The EASY study statistician will generate the randomisation sequence using NQuery Advisor.

15.6 Consent

Separate consent will not be required for Objective 1 (standard PIS versus standard PIS and infographic). For Objective 2 (questionnaire), consent will be implied by its completion and return, as it can be completed by all parents/guardians approached about the EASY study and not just those who consented for their child to participate.

15.7 Outcome Measures

Primary: Recruitment rates

Secondary:

- Immediate post-randomisation withdrawal rate (measured up to first dose of antibiotic post-randomisation)
- Retention rate at 28 days post-randomisation
- Cost per participant recruited and participant retained; calculated as the incremental cost of embedding the SWAT divided by the incremental number of participants recruited and the number of participants retained at 28 days.
- Satisfaction with and understanding of the consent process.
- Quality of parental decision making.

15.8 Analysis

Descriptive statistics will be used to summarise the outcomes by SWAT arm (where appropriate) including number (%), means (95% confidence intervals). A separate SWAT analysis plan will written prior to final analysis of the data.

The SWAT is registered on the SWAT repository: SWAT225 Ashley Agus, Kerry Woolfall, Mike Clarke, Tom Waterfield (2022 SEP 1 2328).pdf (qub.ac.uk)

16 PHARMACOVIGILANCE

16.1 Definition of Adverse Events

The European Clinical Trials Directive 2001/20/EC and applicable clinical trial regulations set out the legal requirements for adverse event recording, management and reporting of clinical trials.

The MHRA Good Clinical Practice Guide 2012 provides the definitions given in Table 7.

Table 7: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Suspected unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect 'Important medical events' may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

16.2 Adverse Event Reporting

The AE reporting period for the trial begins upon consent and ends at day 28 (the last follow up assessment).

The PI or designee should record all directly observed AEs and all AEs spontaneously reported by the parent/guardian. In addition, the parent/guardian will be asked about AEs as part of the follow up assessments to be completed.

This paediatric population may experience a range of AEs such as common cold or other common childhood illnesses. Symptoms that are due to an alternative emergent condition (e.g. upper respiratory tract infection or other viral illness) should not be reported as an AE, unless the event is considered by the PI or designee to be associated with the study drug or unexpectedly severe or frequent.

Symptoms known to be associated with UTI (fever, vomiting, and interference with normal activity) will be captured as part of the follow up assessments and should not be reported as an AE. Events that are collected as outcomes for the EASY study do not need to be reported as AEs, including treatment failure, deterioration, hospital readmission and fever.

Laboratory confirmed invasive bacterial infections (IBI) including bacterial meningitis and symptomatic bacteraemia should be reported as AEs. Complications of peripheral venous access such as extravasation injury, tissued lines and line infections should be reported as AEs.

All other events should be reported, including new onset of vomiting, diarrhoea, rashes or oral thrush (or a change in severity or frequency of these) which are common side effects of parenteral and oral antibiotics. See section 16.7 for the recording and reporting of adverse events and serious adverse events.

16.3 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the intervention (Table 8).

Table 8. Categories of causality for adverse events

Category	Definition
Definitely*	Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.
Probably*	Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
Possibly*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
Unlikely	Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
Not Related	Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

16.4 Assessment of Severity

The PI or designee should make an assessment of severity according to the following categories (Table 9).

Table 9. Categories of severity for adverse events

Category	Definition
Mild (Grade 1)	A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
Moderate (Grade 2)	A reaction that is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	A reaction that prevents normal everyday activities.
Life Threatening (Grade 4)	A reaction that has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	A reaction that results in death.

16.5 Assessment of Seriousness

The PI or designee should make an assessment of seriousness on the basis that it:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

16.6 Assessment of Expectedness

The PI or designee is required to make an assessment of expectedness for ARs (the event is possibly, probably or definitely related) based on the reference safety information (RSI).

The reference safety information is the Summary of Product Characteristics (SPC) for the oral or parenteral antibiotic as approved by the MHRA.

As documented in the relevant section of the SPC (section 4.8 undesirable effect) ARs may be classed as either:

- Expected: The AR is consistent with the toxicity of the study drug listed in the SPC
- Unexpected: The AR is not consistent with the toxicity in the SPC.

An AR may be described as ‘unexpected’ if it has occurred with greater frequency or severity that might otherwise have been expected.

16.7 Recording and Reporting of Adverse Events and Serious Adverse Events

AEs and SAEs should be recorded in the medical notes of the participant in accordance with GCP.

AEs are to be recorded on the Adverse Event Form within the CRF and submitted to the CTU as per the CRF submission schedule.

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in section 16.5. SAEs will be evaluated by the PI or designated investigator for causality (i.e. their relationship to the study drug) and expectedness (if the event was deemed to be related).

SAEs are to be recorded on the Serious Adverse Event Form. SAEs should be reported to the CTU within 24 hours of the investigator becoming aware of the event, by email to clinicaltrials@nictu.hscni.net. All SAEs should also be reported on the AE Form within the CRF.

The site should not wait until all information about the event is available before notifying the CTU of the SAE. The CTU will acknowledge receipt of the SAE Form by email to the site. Information not available at the time of the initial report must be sought and submitted to the CTU as it becomes available.

16.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be related to the intervention and are unexpected, i.e. their nature or severity is not consistent with the RSI.

The CTU is responsible for reporting SUSARs to the Sponsor, REC and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to MHRA and REC within 15 days after the knowledge of such an event.

16.9 Recording and Reporting Urgent Safety Measures

The Sponsor and investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The investigator may implement urgent safety measures without prior approval from the REC or MHRA.

When a PI becomes aware of information that necessitates an urgent safety measure, they should phone the MHRA Clinical Trials helpline (020 3080 6456) and discuss the issue with a safety scientist or medical assessor immediately after an urgent safety measure has been implemented.

The PI or designee should report the urgent safety measure to the CTU immediately, by email to clinicaltrials@nictu.hscni.net.

The CTU will report the urgent safety measure to the Chief Investigator and to the Sponsor immediately, using the dedicated email address: clinical.trials@belfasttrust.hscni.net. The CI will notify the MHRA and the REC providing full details of the information they have received and the decision-making process leading to the implementation of the urgent safety measure within 3 days.

The PI or designee should respond to queries from the Sponsor or Chief Investigator immediately to ensure the adherence to reporting requirements to REC and MHRA.

17 DATA MONITORING

17.1 Data Access

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Each participant's confidentiality will be maintained and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

17.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. The frequency and type of monitoring (on site and/or remote) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents) that are required to facilitate the monitoring process. The extent of source data verification (SDV) will be documented in the monitoring plan.

18 REGULATIONS, ETHICS AND GOVERNANCE

18.1 Regulatory and Ethical Approvals

The trial will comply with the principles of GCP, the requirements and standards set out in the UK policy framework for health and social care research and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC) and clinical trial authorisation (CTA) will be obtained from the MHRA under the notification scheme for Type A CTIMPs before the start of the trial.

The trial protocol is prepared in compliance with the SPIRIT 2013 statement [43] and the trial will be registered at https://www.isrctn.com/ before randomisation of the first participant.

18.2 Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the REC and the MHRA. A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented. A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that any potential serious breaches are reported directly to the CTU within one working day using the dedicated email address (clinicaltrials@nictu.hscni.net).

The CTU will notify the CI and Sponsor immediately to ensure adherence to reporting requirements to REC and MHRA where a serious breach has occurred. Protocol compliance will be monitored by the CTU to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs and participant consent forms) is being completed appropriately.

18.3 Protocol Amendments

All protocol amendments will be undertaken in accordance with the regulatory requirements. Substantial changes to the protocol will require REC and MHRA approval prior to implementation, except when modification is needed to eliminate an immediate hazard to participants.

18.4 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

18.5 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to participants through the Clinical Negligence Fund in Northern Ireland. Queen's University Belfast will provide indemnity for negligent and non-negligent harm caused to participants by the design of the research protocol by Queen's University Belfast staff.

18.6 Participant Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the participants by their unique participant study number and initials only. Participant confidentiality will be maintained at every stage and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

18.7 Record Retention

The site PI will be provided with an Investigator Site File (ISF) by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their sites in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.
The TMF will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in a SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and as required by the BHSCT as Sponsor.

18.8 Competing Interests

The research costs are funded by the NIHR Health Technology Assessment Programme. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC and TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC or TSC member reports a conflict of interest, advice will be sought from the Sponsor.

19 DISSEMINATION/PUBLICATIONS

19.1 Publication Policy

The study will be reported in accordance with the CONSORT guideline [30]. If necessary, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) statement [44] will also be applied in the event that the COVID-19 pandemic or any other extenuating circumstances require major modifications to the trial during its course.

We will publish our trial protocol and statistical analysis plan to ensure transparency in our methodology. The study findings will be presented at national and international meetings. Presentation at these meetings will ensure that results and any implications are rapidly disseminated to the wider UK paediatric emergency medicine community.

In accordance with the open access policies proposed by the NIHR we plan to publish the clinical findings of the trial as well as a separate paper describing the cost-consequence analysis in the NHS setting in high quality peer-reviewed open access (e.g. including via Pubmed Central) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists. A final report will also be published in the NIHR HTA journal.

We will actively promote the findings of the study to journal editors and opinion leaders in paediatric emergency medicine to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. Due to limited resources, it will not be possible to provide each parent/guardian with a personal copy of the results of the trial. However, upon request, parents/guardians involved in the trial will be provided with a lay summary of the principal study findings. We will also work with our PPIE Advisory Group, PPI co-applicant, and PPI member of our Trial Steering Committee (should they be willing to contribute) to produce lay summaries, and determine a dissemination strategy of these, for circulation via relevant family support networks.

The most significant results will be communicated to the wider public through media releases. An on-going update of the trial will also be provided on the CTU website.

19.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

19.3 Data Access/Sharing

Following publication of the primary and secondary outcomes there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI via the CTU, who will discuss this with the Sponsor. The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials [45, 46] and data sharing will be undertaken in accordance with the required regulatory requirements. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission.

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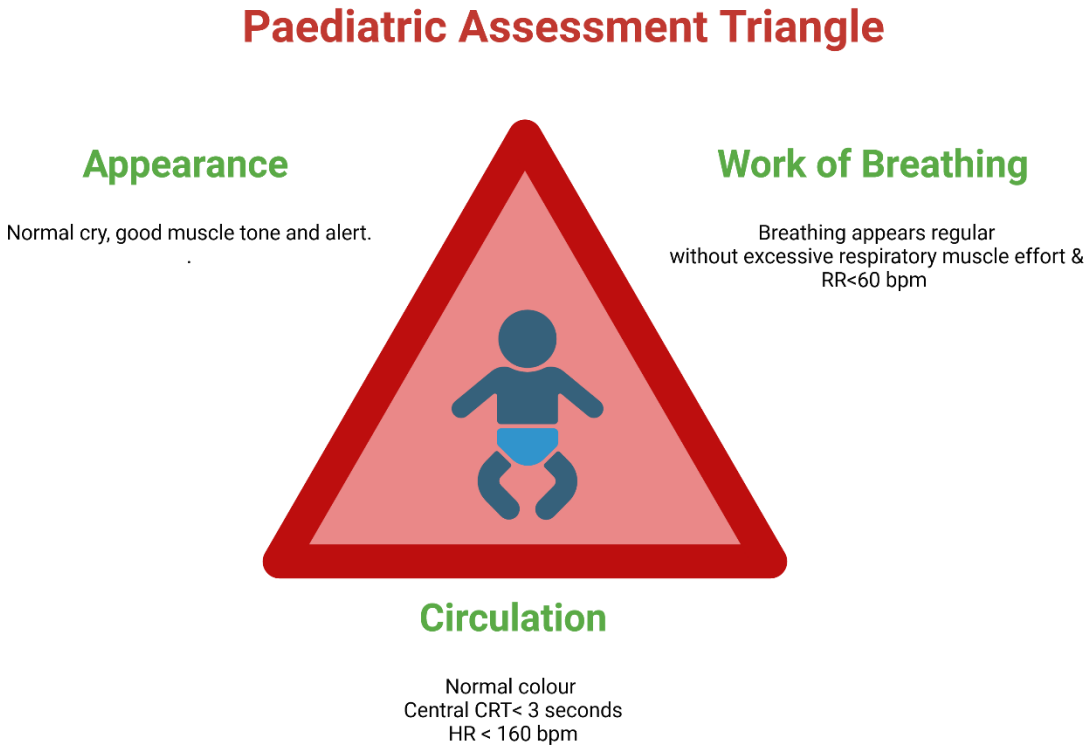
21 APPENDICES

21.1 Appendix 1: Paediatric Assessment Triangle



Normal Appearance defined as having a normal cry, good muscle tone and alert.

Normal Circulation defined as normal colour, heart rate less than 160 beats per minute and a central capillary refill time of less than three seconds.

Normal Work of breathing defined as regular breathing without excessive respiratory muscle effort and RR<60 breaths per minute.