TRIAL PROTOCOL

A multi-centre, randomised trial to determine the optimal duration of cefalexin therapy for the treatment of febrile urinary tract infections in children.

Cefalexin for **U**TIs – **R**ight treatment **L**ength in **Y**oung children

CURLY

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number:	**3.0**
Version Date:	**19th December 2023**

PROTOCOL DEVELOPMENT

Protocol amendments

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

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	19-12-2023	2	Non-substantial	Added progression table (Table 3) Updated original Table number order due to the addition of Table 3 Added ISRCTN number Added further clarification of any cefalexin brand being suitable to despense and that pharmacies will be resuspending the cefalexin suspension on page 29.

Funding and support in kind

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This protocol was written in response to a commissioned call from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (20/109 Shorter vs longer fixed-course antibiotic treatments). The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation.

The views expressed in this document are those of the authors and not necessarily those of the NHS, the National Institute for Health and Care Research, or the Department of Health and Social Care.

PROTOCOL SIGN OFF

Chief Investigator (CI) Signature Page

As Chief Investigator, I confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

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

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

Trial name:	NIHR 134534 – **The CURLY trial**
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
CI name:	Dr Stuart Hartshorn
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor Statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance Statement

This protocol describes the CURLY trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the CURLY trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018, Human Tissue Act 2004 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof[1]. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

[1] Ireland: In compliance with applicable EU and Irish regulations.

Principal Investigator (PI) Signature Page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

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

Trial name:	NIHR 134534 – **The CURLY trial**
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AMR	Antimicrobial resistance
AR	Adverse reaction
BCTU	Birmingham Clinical Trials Unit
BNFC	British National Formulary for Children
BWC	Birmingham Women and Children's NHS Foundation Trust
CAKUT	Congenital anomalies of the kidney and urinary tract
CHU9D	Child Health Utility instrument
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
E. coli	Escherichia coli
eCRF	Electronic Case Report Form
ED	Emergency Department
ESBL	Extended-spectrum beta-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EudraCT	European Union Drug Regulatory Agency Clinical Trials database
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratios
ICF	Informed Consent Form

IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ISF	Investigator Site File
ITT	Intention-to-treat
MALDI-TOF MS	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry
MDR	Multi-drug resistance
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PCR	Polymerase chain reaction
PERUKI	Paediatric Research in the UK and Ireland
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and public involvement
PPIE	Patient and public involvement and engagement
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance team
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File

TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UK	United Kingdom
UKHSA	UK Health Security Agency
UoB	University of Birmingham
UoL	University of Liverpool
UTI	Urinary tract infection
YPAG	Young Person's Advisory Group

TRIAL SUMMARY

Title: Cefalexin for UTIs – Right treatment Length in Young children (the CURLY trial). A multi-centre, randomised trial to determine the optimal duration of cefalexin therapy for the treatment of febrile urinary tract infections in children.

Objectives: This trial aims to determine the optimal duration of oral cefalexin treatment for infants and young children with a clinical diagnosis of febrile urinary tract infection (UTI).

Trial design: A multi-centre, open label, multi-arm randomised controlled trial with internal pilot, using a "DURATIONS design," which will produce a "cefalexin duration vs cure rate" curve to determine the optimal number of treatment days.

Setting: Paediatric emergency departments (EDs) across the UK and Ireland, from the Paediatric Research in the UK and Ireland (PERUKI) research network.

Participant population and sample size: Infants and children with a clinical diagnosis of febrile UTI in whom the decision has been made to treat with oral cefalexin.

For this "DURATIONS" trial design, a total of 500 participants with a microbiological-confirmed UTI are required.

Eligibility criteria:

Inclusion criteria:

(1) Age 3 months to 11 years inclusive

(2) Clinical diagnosis of febrile UTI at presentation to ED as defined by **both** (i) Temperature ≥38°C measured by any method or likely fever in the last 24 hours **AND** (ii) Clinical feature(s) suggestive of UTI at presentation

(3) Early urine testing (urine dipstick or urine microscopy) suggesting likely UTI

(4) Decision to treat with oral cefalexin on discharge from the ED

Exclusion criteria:

(1) Known congenital anomalies of the kidney and urinary tract (CAKUT), reflux nephropathy or indwelling catheter

(2) Known immune deficiency or currently receiving immunosuppression therapy

(3) Systemic antibiotics for any reason (treatment or prophylaxis) in the previous 14 days

(4) Weight > 50kg

(5) Known allergy to cefalexin or previous severe allergic reaction to any beta-lactam antibiotic

Interventions: Patients will be randomised to one of five cefalexin course durations (3, 5, 6, 8 or 10 days). Patients will be allocated to groups using central randomisation in a 1:1:1:1:1 ratio with minimisation to ensure balance for age group, sex and study site. Cefalexin will be administered as a standard proprietary liquid suspension at a dose in line with current recommendations of the British National Formulary for Children (BNFC).

Outcome measures:

Primary outcome: Clinical UTI cure, defined as patients in whom there is (i) fever resolution and (ii) no additional systemic antibiotic prescription by 16 days post-randomisation.

Secondary outcomes:

- UTI recurrence (relapse or reinfection), up to final follow-up, 30 days post-randomisation
- Fever resolution at the primary outcome assessment visit (16 days post-randomisation)
- Producing a sterile urine at the primary outcome assessment visit (16 days post-randomisation)
- No additional systemic antibiotic prescription by the primary outcome assessment visit (16 days post-randomisation)
- Antibiotic-associated adverse events (including diarrhoea, rashes, and candida infections) up to 30-day follow-up
- Adherence to trial medication (no more than 1 missed dose and no additional doses)
- Antimicrobial resistance, determined from a comparison of the antibiotic sensitivities of pre- and post-treatment urine samples along with the identification of extended-spectrum beta-lactamase (ESBL)-producing organisms
- Differences in quality of life (using the Child Health Utility instrument CHU9D) between the different treatment duration arms.

Follow-up: To 30 days post-randomisation.

Health economics: An incremental cost-utility analysis will determine the cost-effectiveness of the different treatment durations over the follow-up period.

Analysis: Duration-response curves will be generated for both the microbiological-confirmed and intention-to-treat (ITT) cohorts using fixed-2 fractional polynomial models. These curves will then be used to estimate the minimum duration of cefalexin, to ensure that at least 90% of the efficacy provided by the maximum length (10 day) course of antibiotics is achieved.

TRIAL SCHEMA

Figure 1: Randomisation, study populations and outcomes

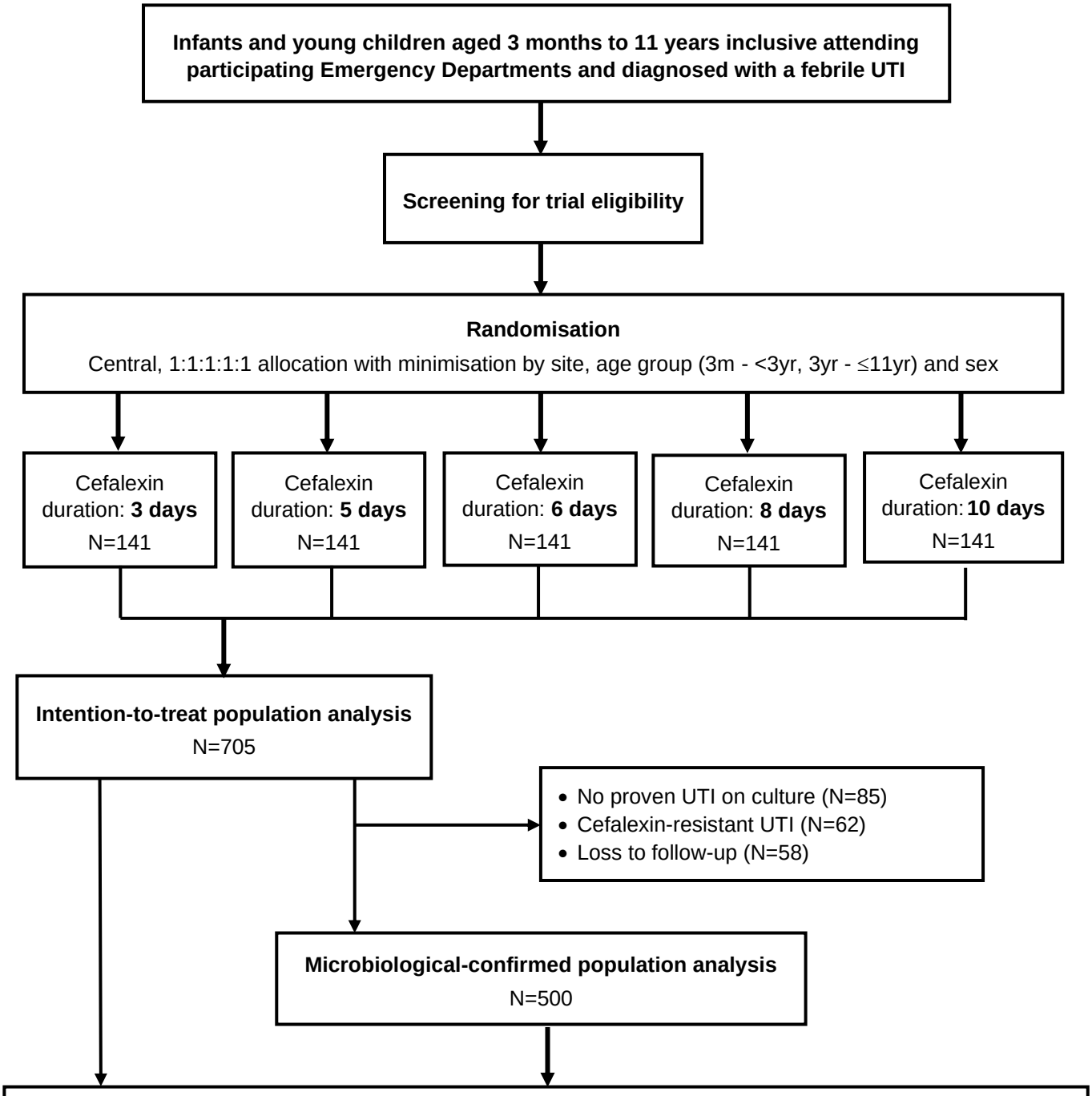
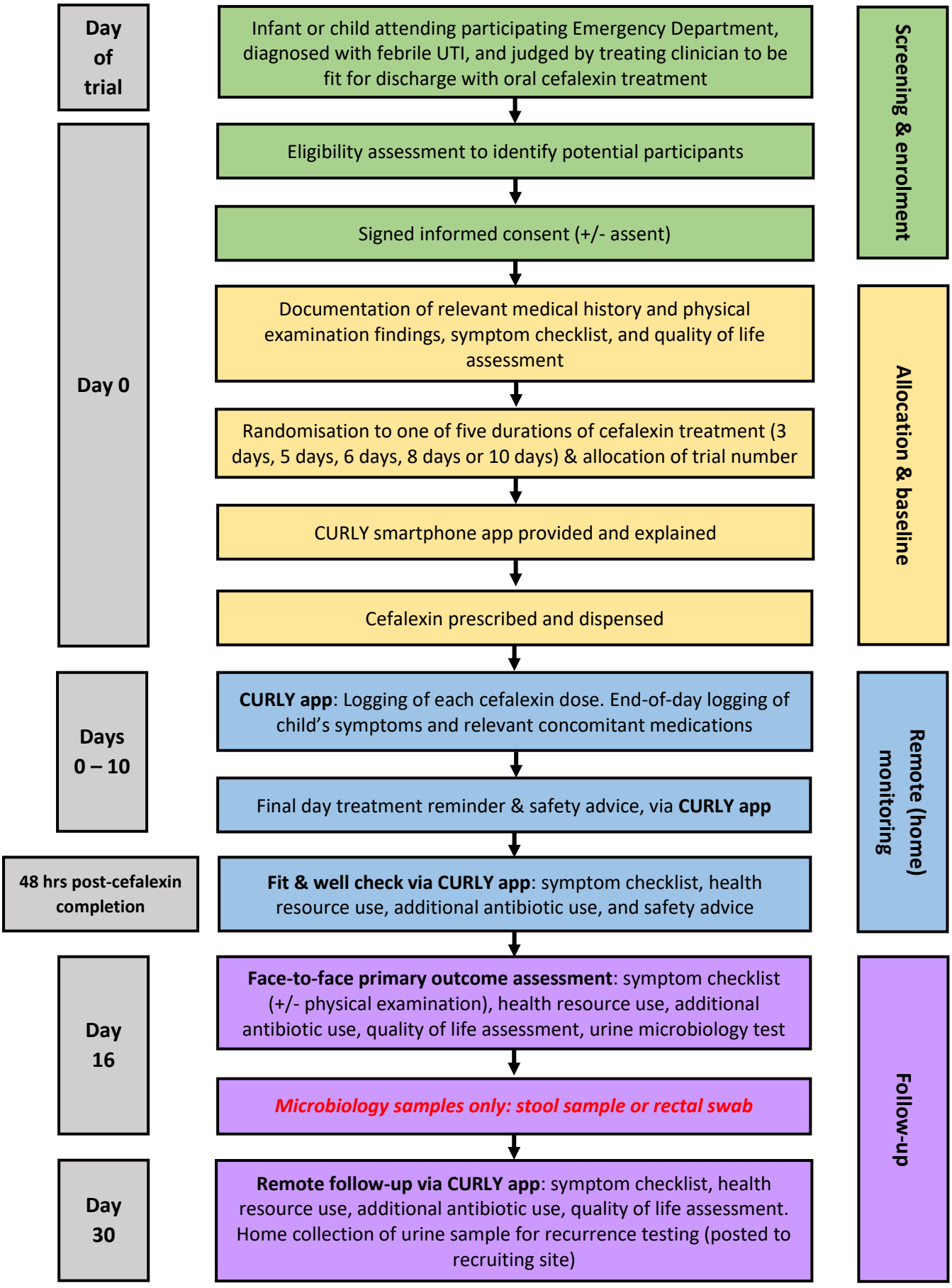


Figure 2: Trial activities



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1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Problem being addressed

Urinary tract infections (UTIs) are the second most common bacterial infection in children (1); 1 in 10 girls and 1 in 30 boys will have had a UTI by the age of 16 years (2). UTIs account for 5-14% of emergency department (ED) visits by children annually (3), as well as numerous presentations to primary care services. The majority of UTIs are caused by Gram-negative bacteria (most commonly Escherichia coli (E. coli)) colonising the perineum, which enter and ascend the urinary tract (4).

Lower UTIs involve the bladder (cystitis), causing symptoms such as lower abdominal pain, painful urination, urinary frequency, and urgency. Upper UTIs involve the kidneys and ureters (acute pyelonephritis) and lead to abdominal pain and loin tenderness with systemic features such as poor feeding (in younger children)/loss of appetite, vomiting, and fever. UTI with fever (febrile UTI) is the most common presentation of acute pyelonephritis in infants and young children (5).

Rarely, major complications may develop after UTIs, such as perinephric abscess formation and urosepsis. Renal injury and scarring can occur in 15% of children following a first febrile UTI (6). UTIs may point to an undiagnosed congenital anomaly of the kidney and urinary tract (CAKUT) (7), such as vesico-ureteric obstruction (8).

1.1.2 Current practice: duration of antibiotic therapy for febrile UTIs

From the age of 3 months, most children with a febrile UTI can be safely treated with oral antibiotics. Intravenous antibiotics are reserved for younger infants, those who cannot tolerate oral antibiotics, or those with systemic sepsis (9, 10).

For bacterial infections in children, there are few studies that investigate short versus long courses of antibiotics (11). More specifically, there is limited evidence for the optimal duration of antibiotic treatment for children with febrile UTIs, and this has been highlighted as a research priority in systematic reviews and national guidelines (12, 13).

This evidence gap has resulted in variations in international guidelines. Guidance from the United States advocates antibiotics for 7 to 14 days (13), whilst The National Institute for Health and Care Excellence (NICE) and national bodies in Canada, Australia and Spain advocate a slightly shorter course of 7 to 10 days (9, 14-16). Clinical practice in the United Kingdom (UK) has further variation, with a survey of 58 UK paediatric EDs (undertaken in August 2020) demonstrating that departmental protocols vary between 3 and 10 days. Similar variation was the case in adult practice, though several randomised controlled trials (RCTs) have demonstrated the safety of shorter courses of antibiotics.

Given the high incidence of UTIs, antibiotic prescribing represents an important opportunity for focused antibiotic stewardship. Treatment course durations have not been reduced for children with febrile UTIs as they have in adults, with some fears that underlying renal tract abnormalities may lead to treatment failure in children. However, there is evidence that reducing the antibiotic duration might similarly be safe in children (17). Despite this, the degree to which treatment duration can be shortened without affecting treatment failure, relapse or complications remains unknown. Caution is required to ensure that any reduction in the duration of therapy does not paradoxically increase the total use of antibiotics because of the need for re-treatment.

1.1.3 Published and ongoing research

For adults with acute pyelonephritis, there is a growing body of evidence to support the benefits of shorter durations of antibiotic therapy (18). However, similar evidence is lacking for children.

A 2014 Cochrane systematic review appraised the evidence for the antibiotic treatment of acute pyelonephritis in children (12). Four RCTs (total participants = 376) compared different durations of antibiotic administration, but none were relevant to our proposed research question. These studies used antibiotics not available in the UK (19), compared a single intravenous antibiotic dose against a longer course of oral antibiotics (20, 21), or only included children with a specific complication of pyelonephritis (22). The Cochrane review concluded that adequate data from RCTs are not available to determine the optimal treatment duration of antibiotic therapy required for acute pyelonephritis. It recommended the need for further RCTs in children.

We performed the same search strategy to identify any more recent evidence (Ovid MEDLINE and Embase, run 4 August 2021). Since the Cochrane review, a large retrospective observational study reported that, for 791 children with acute pyelonephritis in the USA, no difference was found in the odds of treatment failure for children prescribed a short-course of antibiotics (6-9 days) compared with a prolonged-course of antibiotics (≥10 days) (17). This population were treated with a range of antibiotics, including first and third generation cephalosporins, co-trimoxazole, and fluoroquinolones, using intravenous, oral, or sequential routes.

There are several ongoing trials (23-25) that are also seeking to address a similar question to this trial, however the applicability of these to UK clinical practice is uncertain. For these other ongoing trials, arbitrary durations (5 or 7 days) have been applied for the shorter course treatment arm, rather than attempting to identify the optimal duration of therapy. In several cases, the studies are not pragmatic, with eligibility assessments occurring after an initial period of antibiotic treatment and with knowledge of the urine culture results, therefore limiting the applicability to routine practice. In addition, these trials include antibiotics that are not recommended for treating UTIs in the UK, and antibiotic resistance rates are likely to differ between the UK, Poland, Italy and the USA.

1.2 Trial rationale

1.2.1 Justification for participant population

Benefits for patients and the NHS

Antibiotic resistance is a key concern. In England, the resistance rates of E. coli to the previous first-line antibiotics for UTI, amoxicillin (60%) and trimethoprim (30.3%), preclude their use as empiric therapy (10). As such, cefalexin, a first-generation cephalosporin, is now the recommended first-line oral antibiotic for febrile UTIs in England (9, 10). However, resistance to cefalexin, often mediated by extended-spectrum beta-lactamases (ESBLs), is a growing problem (26). ESBL production usually occurs in conjunction with other antibiotic resistance mechanisms, rendering the bacteria multidrug-resistant (MDR), leaving few or no options for oral antibiotic therapy. In England, the resistance of E. coli to cefalexin in urine specimens is now 9.9% (10).

This trial will determine the shortest safe effective course of cefalexin for infants and children with febrile UTIs. Children with known congenital anomalies of the kidney and urinary tract (CAKUT) or reflux nephropathy and those with indwelling catheters will be excluded as they are more prone to cefalexin-resistant uropathogens (27).

Current variation in the duration of antibiotic prescribing will be eliminated by standardising treatment to the shortest safe duration of cefalexin treatment. Overall antibiotic exposure may be reduced, lowering the selection pressure for MDR organisms and preserving cefalexin as a viable first-line therapy for UTI in children (11).

The potential benefits to individual patients include reduced cefalexin-associated adverse effects, such as vomiting, diarrhoea, abdominal discomfort, candidiasis and allergic reactions (28), and less risk of subsequent UTI caused by MDR organisms. For parents/guardians, benefits might include less interference with the feeding of infants and young children and fewer days inconvenienced by antibiotic administration and complications of care arrangements.

This trial will provide evidence that can be incorporated into future national guidelines to ensure that infants and children with febrile UTIs are treated with the shortest effective cefalexin duration.

1.2.2 Justification for design

The standard method of comparing different durations of therapy is using a non-inferiority design in which two arbitrary durations are compared. There are inherent limitations with this forced binary hypothesis testing paradigm, including:

- Incorrect assumptions when selecting a non-inferiority margin (when evidence on the expected active control event rate is limited).
- The arbitrary selection of the duration of the shorter intervention arm.

The major challenge with this approach is that there is no guarantee that either of the two durations chosen for comparison are optimal. In particular, if the shorter duration is inferior to the longer duration, such a trial provides no information about durations between the two, both in terms of positive aspects (cure rate) and negative aspects (antibiotic toxicity, development of antimicrobial resistance (AMR)).

Rather than picking two arbitrary durations, the CURLY trial will randomise children to one of multiple different antibiotic treatment durations, using a methodology known as the "DURATIONS design" (29, 30). The DURATIONS design is specifically devised for trials aiming to identify the minimal effective treatment duration of therapeutic agents, particularly antimicrobial drugs. It will be used to estimate the actual "duration-response" curve for primary and secondary outcomes. This approach will enable a precise estimate of the durations at which specific rates of clinical UTI cure are achieved, and where the duration-response curve flattens off, meaning that additional antibiotic exposure is no longer adding relevant clinical benefit. The DURATIONS design is more efficient than arbitrarily choosing two durations and comparing them in a standard non-inferiority trial (29).

1.2.3 Justification for choice of interventions

Cefalexin, a first-generation cephalosporin, is the recommended first-line oral antibiotic for febrile UTIs in England (9, 10). Children taking part in the CURLY trial will be randomised to one of five cefalexin course durations. The number of arms chosen is in accordance with the employed "DURATIONS design" (29, 30).

Justification for shortest and longest treatment lengths

Evidence on short course efficacy to inform the duration of the shortest treatment is limited. Treatment of **3 days** is standard practice for UTIs in adults (31). This duration has been selected for our shortest treatment arm, following a consultation survey with clinical representatives from 58 paediatric EDs. The survey identified that a small number of EDs currently deviate from national guidance and prescribe 3-day antibiotic courses for children with febrile UTIs. The longest treatment duration of **10 days** is in line with the maximum duration suggested by the NICE guideline (9).

1.2.4 Justification for choice of primary outcome

The primary outcome is clinical UTI cure rate. This will be defined as those patients in whom there is (i) fever resolution and (ii) no additional systemic antibiotic prescription by 16 days post-randomisation. This outcome is informed by a systematic review that identified wide variation in the outcomes reported within paediatric febrile UTI trials, and proposed criteria to harmonise study

design (32), which were endorsed by the European Medicines Agency (33). In addition to fever resolution, the review proposed documentation of urine sterilisation. However, the outcome of urine sterilisation was largely developed for industry-sponsored 'efficacy trials'. The collection of post-treatment urine samples to test for bacterial clearance is not standard clinical practice, with clinicians assessing 'UTI cure' from the resolution of clinical symptoms. The primary outcome in this 'pragmatic trial' will therefore reflect clinical practice by defining 'cure' based on clinical symptoms, with urine sterilisation assessed as a secondary outcome.

Parents and young people in Patient and Public Involvement (PPI) workshops were involved in selecting the outcomes in this study. Parents felt that the primary outcome covered the essential markers that would indicate a child's recovery. It was important that their child was feeling better after antibiotic treatment and eliminating fever was a reassuring sign.

1.2.5 Justification for follow-up duration

Follow-up will be for 30 days post-randomisation. This timing, for the assessment of UTI recurrence, is in accordance with recommendations for harmonised design in studies of paediatric febrile UTIs (32-34).

2. AIMS AND OBJECTIVES

This trial aims to determine the optimal duration of oral cefalexin treatment for infants and young children with a clinical diagnosis of febrile UTI.

2.1 Internal pilot

The internal pilot will be conducted over the first 6 months of recruitment to assess the feasibility of identifying eligible patients and the acceptability of randomisation, and to determine if the pilot phase should continue to a full trial.

2.2 Main trial objectives

2.2.1 Clinical objectives

1. To determine the optimal (shortest effective) cefalexin duration for the treatment of febrile UTIs in children, to achieve clinical cure (**primary objective**).
2. To assess the impact of cefalexin treatment duration on UTI recurrence (relapse or reinfection) up to 30 days post-randomisation.
3. To assess the impact of cefalexin treatment duration on microbiological cure and antimicrobial resistance.
4. To assess the impact of cefalexin treatment duration on antibiotic-associated adverse events, including diarrhoea, rashes, and candida infections.
5. To assess patient adherence to the trial drug across the treatment duration arms.
6. Differences in quality of life (using the Child Health Utility instrument CHU9D) between the different treatment duration arms.

2.2.2 Economic objectives

1. The health economics analysis will assess the cost-effectiveness of different antibiotic treatment durations, to include the effect of treatment duration on the cost of antibiotic resistance. A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, following an agreed Health Economics Analysis Plan, and the methods will adhere to the recommendations of the NICE Reference Case (35).

3. TRIAL DESIGN AND SETTING

3.1 Trial design

A multi-centre, open label, multi-arm RCT using a "DURATIONS design," with an internal pilot and a within-trial cost effectiveness analysis. Participants will be randomised to one of five different durations of cefalexin treatment: 3, 5, 6, 8 and 10 days.

3.2 Trial setting

We will recruit from paediatric EDs from the Paediatric Research in the UK and Ireland (PERUKI) research network (36). Where any participating site streams patients to an alternative co-located acute paediatric unit (e.g. a Paediatric Assessment Unit or Urgent Treatment Centre), the research team may also recruit eligible patients from here. For simplicity of notation within this protocol and other trial documentation, the term "ED" may be assumed to include all such acute paediatric areas.

3.3 Assessment of risk

All clinical trials can be considered to involve an element of risk. In accordance with Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

- Type A = No higher than the risk of standard medical care

4. ELIGIBILITY

Infants and children with a clinical diagnosis of febrile UTI (defined clinical features and early urine testing suggesting a likely UTI) in whom the decision has been made to treat with oral cefalexin.

4.1 Inclusion criteria

1. Age 3 months to 11 years inclusive
2. Clinical diagnosis of febrile UTI (9) at presentation to ED as defined by **both**:
   - Temperature ≥38°C measured by any method **OR** likely fever in last 24 hours
   - **AND** Clinical feature(s) suggestive of UTI at presentation (i.e. one or more of the following):

If <2 years of age	If ≥2 years of age
• Poor feeding • Vomiting • Irritability	• Vomiting • Dysuria • Urinary frequency • Urinary urgency • Abdominal or flank pain • Suprapubic or flank tenderness

3. Early urine test suggesting likely UTI as defined by **either**:
   - Abnormal urine dipstick (both nitrite and leucocyte esterase positive)
   - **OR** Abnormal urine microscopy (bacteriuria by microscopy with Gram stain)
4. Decision to treat with oral cefalexin on discharge from the ED
5. Able to give written informed consent (and assent as appropriate)

4.2 Exclusion criteria

1. Known congenital anomalies of the kidney and urinary tract (CAKUT), reflux nephropathy or indwelling catheter
2. Known immune deficiency (e.g. HIV, malignancy, solid-organ transplant recipients) or currently receiving immunosuppression therapy
3. Systemic antibiotics for any reason (treatment or prophylaxis) in the previous 14 days
4. Weight > 50kg
5. Known allergy to cefalexin or previous severe allergic reaction to any beta-lactam antibiotic*

   * e.g. ampicillin, amoxicillin, cephalosporins, co-amoxiclav, penicillin

4.3 Co-enrolment

Concurrent participation in any other clinical trial of an investigational medicinal product is not permitted. Co-enrolment in other types of studies will be permitted.

5. CONSENT

Informed consent will be obtained by the Principal Investigator (PI) at each site or a delegated member of the local study team. A member of the clinical team will approach the patient and their parent/guardian initially about the study. If the patient/parent/guardian is interested, they will be introduced to a local researcher.

The researcher will present the study 'explainer video' and provide a verbal explanation of the trial, together with the Parent/Legal Guardian Information Sheet and, where appropriate, an age-appropriate Participant Information Sheet (PIS) (all hosted on the CURLY trial website – see Section 5.1.4). The parent/guardian ± patient will be given sufficient time to consider and discuss the trial with members of their family and friends, and ask the researcher any questions they may have about the trial. The researcher will ensure that the parent/guardian has fully understood the aim of the trial, the trial interventions, and the anticipated benefits and potential hazards of their child taking part in the trial. It will be made clear that the parent/guardian of the child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child.

If the parent/guardian expresses an interest in their child participating in the trial, and only once eligibility has been confirmed, they will be asked to sign and date an electronic informed consent form (ICF) (parent/guardian) and sign an assent form (child; see below). The PI (or delegate) will then sign and date the electronic ICF and assent form. This must occur before any trial-specific procedures take place.

Depending on the age and understanding of the child, and at the discretion of the clinician and parent/guardian, the child will be invited to sign an electronic assent form. Whilst we will endeavour to collect assent from all children with the capacity to understand the study, the absence of assent does not exclude the child if consent has been obtained from the parent/guardian. If a child completes the assent form indicating that they do not wish to participate, the child will not be included in the study. It is the responsibility of the PI to obtain written informed consent for each participant prior to performing any trial related procedures.

An electronic copy of the signed ICF, and assent form where relevant, and link to the CURLY website containing the PIS will be sent via email to the parent/guardian. A copy will be filed in the medical

notes, and a copy will also be filed in the Investigator Site File (ISF) and on the trial database held at the BCTU.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the parent/guardian information sheet and child PIS given to participant, version number of ICF (and assent if applicable) signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes of the time consent was obtained and what time procedures started. At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial and completion of data online will imply willingness to continue.

5.1 CURLY and participant information

Materials for the CURLY trial are largely digital, and the use of paper will be kept to a minimum.

The CURLY trial is dependent on high-quality information being presented to families in a clear and efficient way. We have followed lessons learned from several NIHR trials that have recruited from the PERUKI network that effectively used and evaluated multimedia resources to improve decision-making about participation in trials involving children and adolescents (37). CURLY will follow a similar approach, utilising a Research Ethics Committee (REC) approved multimedia website with images and animations to offer an overview of the trial, supported by trial materials presented in an abbreviated paper format.

5.1.1 CURLY animation video

The CURLY animation is designed to provide a clear and efficient method of explaining the CURLY trial to parents/guardians and, where appropriate, children. This video will be presented prior to consent/assent, along with the accompanying Parent/Guardian Information Sheet and age-appropriate PIS (all hosted on the CURLY trial website – see Section 5.1.4).

5.1.2 CURLY eCRF and electronic consent forms

Data for CURLY will be stored on a bespoke database hosted on a secure server at the University of Birmingham, and research team members at each site will have individual accounts to enter their data. An electronic informed consent form and electronic assent form will be used. Following consent/assent, the researcher will ask questions to the parent/guardian and, where appropriate, their child, and will enter the data into the baseline electronic Case Report Form (eCRF).

5.1.3 CURLY mobile/ web app

An app for the CURLY trial will be made available to all parents/guardians participating in the trial. This will be shared at the baseline ED visit, when its use will be demonstrated. For parents/guardians who do not have a smartphone, the same features can be accessed via a web-based platform. The Carnegie Trust have identified that 99% of the UK population with school age children have access to the internet via a desktop computer, laptop, netbook or smartphone (38, 39).

The main purpose of the app is to allow parents/guardians to log cefalexin administration, in a similar way to the many commercially available products. This data will be used to monitor adherence to cefalexin treatment, particularly treatment duration, to ensure validity of the trial results. The app will assist parents/guardians to keep track of the twice daily cefalexin schedule, alongside the administration of any relevant concomitant medications (paracetamol, ibuprofen, and any other non-trial antibiotic). In addition, the app will provide a prompt to parents/guardians about the duration of the allocated cefalexin, and when their child's final antibiotic dose is due.

The app will also be used by parents/guardians to log the presence/absence of key symptoms following discharge from the ED.

5.1.4 CURLY trial website

Families will be able to access the CURLY trial website throughout the duration of the trial. This will contain information to support their participation, including copies of the trial Patient/Parent information sheets, and information reminding them how to collect a non-contaminated urine sample from their child at home.

5.2 Long-term outcomes (optional consent)

Consent will be sought from participants to allow potential future follow-up through efficient means using data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS England and other central UK NHS bodies. This will permit the sharing of personal identifiers (i.e. name, date of birth and NHS number) with the relevant national registry, and for the national registry to link this to their data and transfer of this information to the trial team. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow assessment of the longer-term impact and health service usage of UTIs in children without further contact with the trial participants. Any such work will be funded and reported separately.

5.3 Sample collection (optional consent)

Consent will be sought from participants at selected sites to collect samples for futures studies into the impact of cefalexin duration on antimicrobial resistance. This is briefly described in section 24.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1 Identification

Clinicians within participating EDs will be made aware of the trial. If they are providing clinical care for a patient who is potentially eligible for the study, they will briefly mention the study to the parent/guardian and, if appropriate, their child. If the child, and/or the parent/guardian are interested, they will then be introduced to a local researcher who will further explain the study to them.

6.2 Screening and enrolment

Initial study discussions with the parent/guardian and if appropriate, their child, will be undertaken by the local researcher who has been delegated this duty. However, formal assessment of study eligibility will be performed by the PI or other medically qualified member of the research team who has been delegated this task. Informed consent will then be obtained.

Non-identifiable details of all patients approached about the trial will be recorded on the online CURLY Trial Screening Log.

6.3 Randomisation

Randomisation will be provided by BCTU using a secure online system (available at https://bctu-redcap.bham.ac.uk), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who have been delegated the role of randomising participants

into the trial as detailed on the CURLY Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the rare case of a technical failure within the online randomisation system an emergency paper back up can be used; contact the Trial Office for details.

6.4 Randomisation process

After eligibility for participation in the CURLY trial has been confirmed and informed consent has been given, the participant can be randomised into the trial using the online system. All data items on the online randomisation form must be answered prior to a participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory email will be sent to the local PI, randomiser, and the Trial Office.

The local research team should add the participant to the CURLY Trial Participant Recruitment and Identification Log which links participants with their Trial Number. PIs must maintain this document securely and it must not be submitted to the Trial Office. The CURLY Trial Participant Recruitment and Identification Log should be held in strict confidence.

6.4.1 Randomisation method

Participants will be randomised at the level of the individual in a 1:1:1:1:1 ratio to one of five cefalexin course durations (3, 5, 6, 8 or 10 days).

A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- Age (3 months - <3 years vs 3-11 years)
- Sex (male vs female)
- Participating centre

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5 Blinding

This is a pragmatic, open-label trial. Participants, parents/guardians and investigators will not be blinded to allocation of treatment duration and no placebo will be used. By excluding the placebo we avoid the need for every child to complete a 10-day treatment course. This is more convenient for families and will allow more accurate assessment of the potential health economic impact (e.g. with regard to nursery/school days missed and parental leave from work). It also allows investigators and clinicians to make informed decisions when assessing if additional antibiotics are needed.
Informing the participant's GP

The participant's General Practitioner (GP) (family doctor) and/or community paediatrician will be notified of their patient's participation in the CURLY trial, using the CURLY GP Letter.

7. TRIAL INTERVENTION

7.1 Trial intervention and dosing schedule

All participants in CURLY will receive oral cefalexin (all cefalexin brands suitable in line with each trial site's stock).

7.1.1 Route of cefalexin administration

Cefalexin will be administered as an oral liquid suspension (to be resuspended by the site pharmacies).

7.1.2 Dose of cefalexin

CURLY will apply the British National Formulary for Children (BNFC) weight-based cefalexin dosing schedule, following the target dose of 12.5 mg/kg twice daily. Body weight should be obtained on the day of presentation to the ED by weighing children on an appropriate scale. It will be advised to weigh children in light clothes, without shoes. Body weight reported by parents is not acceptable.

To reduce the risk of dose calculation errors and ensure that the desired volume is easy to draw-up, all sites will prescribe using a study prescription chart which will include the prespecified weight-dose volume table (Table 1).

Table 1: Cefalexin will be dosed according to body weight in kg by using the following dosing table:

Weight band (kg)		mls per dose (twice daily)
Lower limit	Upper limit	
5	5.49	1.4
5.5	5.99	1.5
6	6.49	1.7
6.5	6.99	1.8
7	7.99	2
8	8.99	2.3
9	9.99	2.5
10	11.99	3
12	13.99	3.5
14	15.99	4
16	17.99	4.5
18	19.99	5
20	21.99	5.5
22	23.99	6

Weight band (kg)		mls per dose (twice daily)
Lower limit	Upper limit	
24	25.99	6.5
26	27.99	7
28	29.99	7.5
30	31.99	8
32	33.99	8.5
34	35.99	9
36	37.99	9.5
38	39.99	10
40	41.99	10.5
42	43.99	11
44	45.99	11.5
46	47.99	12
48	50	12.5

7.1.3 Duration of cefalexin

Trial participants will be randomised to either 3 days (6 doses), 5 days (10 doses), 6 days (12 doses), 8 days (16 doses) or 10 days (20 doses) of cefalexin.

7.1.4 Cefalexin preparations

Cefalexin used for the trial will be a standard proprietary oral liquid suspension. After reconstitution, each bottle contains 100ml of suspension at a concentration of 250mg/5ml. Each patient will receive between 1 and 3 bottles, sufficient to cover their weight-based dose volume and assigned number of

treatment days/doses (Table 2). Cefalexin doses should be discussed with parents before they leave the ED.

Table 2: Number of bottles required for full treatment course, according to weight band and course duration.

Weight range (kg)		mls per dose (twice daily)	Total volume (ml) needed for full course				
Lower limit	Upper limit		3 days	5 days	6 days	8 days	10 days
5	5.49	1.4	8.4	14	16.8	22.4	28
5.5	5.99	1.5	9	15	18	24	30
6	6.49	1.7	10.2	17	20.4	27.2	34
6.5	6.99	1.8	10.8	18	21.6	28.8	36
7	7.99	2	12	20	24	32	40
8	8.99	2.3	13.8	23	27.6	36.8	46
9	9.99	2.5	15	25	30	40	50
10	11.99	3	18	30	36	48	60
12	13.99	3.5	21	35	42	56	70
14	15.99	4	24	40	48	64	80
16	17.99	4.5	27	45	54	72	90
18	19.99	5	30	50	60	80	100
20	21.99	5.5	33	55	66	88	110
22	23.99	6	36	60	72	96	120
24	25.99	6.5	39	65	78	104	130
26	27.99	7	42	70	84	112	140
28	29.99	7.5	45	75	90	120	150
30	31.99	8	48	80	96	128	160
32	33.99	8.5	51	85	102	136	170
34	35.99	9	54	90	108	144	180
36	37.99	9.5	57	95	114	152	190
38	39.99	10	60	100	120	160	200
40	41.99	10.5	63	105	126	168	210
42	43.99	11	66	110	132	176	220
44	45.99	11.5	69	115	138	184	230
46	47.99	12	72	120	144	192	240
48	50	12.5	75	125	150	200	250

1 bottle
2 bottles
3 bottles

7.1.5 Drug interaction or contraindications

For this trial, there are no drug interactions or contraindications of note for cefalexin, other than those mentioned in the licensing information. As stated in the exclusion criteria, any child with a known allergy to cefalexin or previous severe allergic reaction to any beta-lactam antibiotic will be excluded from participation in the trial.

7.2 Concomitant medication

Paracetamol and ibuprofen are commonly administered by parents/guardians to control their child's fever and associated symptoms. As per standard clinical practice, both can be administered along with cefalexin in this trial. These drugs, along with any non-trial antibiotic, will be logged on the medicine tracker page of the CURLY app and thereby captured within the eCRF.

7.3 Repeated doses

As in standard clinical practice, any doses of cefalexin that are spat out or vomited (within 10 minutes of administration) should be repeated. Considering the possibility of spillages and doses being spat/vomited, for dose regimes close to the threshold between 1 bottle/2 bottles and 2 bottles/3 bottles, supply of an additional bottle will be provided as stated on the prescription.

7.4 Premature discontinuation of cefalexin

Cefalexin may be discontinued prior to a participant completing the assigned treatment course duration. Reasons for this include:

- The baseline urine culture result demonstrates a UTI caused by a cefalexin-resistant pathogen. As per standard practice, cefalexin will be discontinued and a different antibiotic with proven pathogen susceptibility will be commenced.
- The baseline urine culture result demonstrates no growth or below threshold growth. Sites will be permitted to inform families and advise discontinuation of cefalexin therapy, should this be their standard practice.
- A significant adverse reaction to cefalexin.
- Failure to tolerate oral cefalexin treatment and/or other clinical deterioration.

All such decisions are at the discretion of the treating clinician. The reason for any premature discontinuation of cefalexin will be logged on the Change of Status and Primary Outcome Assessment eCRF by the local study team.

7.5 Extension of cefalexin course duration

After the final day of treatment, parents/guardians will be advised to obtain a medical review if they feel that their child's symptoms have not resolved. If the clinician believes the child requires additional antibiotic treatment, this will be prescribed at the clinician's discretion. Reasons for any additional non-trial antibiotics prior to the primary outcome assessment visit will be documented and logged on the Primary Outcome Assessment eCRF.

7.6 Intervention supply and storage

Standard proprietary oral liquid suspensions of cefalexin at a concentration of 250mg/5ml will be used. This will be supplied, stocked, and dispensed in line with the usual practice at each site. No clinical trial specific pharmacy requirements of the drug intervention including supply, storage, labelling, drug accountability and destruction is needed.

7.7 Adherence

In contrast to trials which investigate medications in tablet form, it will not be possible to dispense a rationed volume of liquid medication appropriate for the allocated duration arm. In paediatric practice, medication suspensions are reconstituted according to the manufacturer's instructions, and any excess volume in the bottle allows for common issues of spillage or doses being spat out by the child. The dispensing of these standard volume bottles creates a potential for non-adherence with allocated cefalexin duration, and it will therefore be necessary to monitor adherence, which will

be defined as no more than one missed dose from the allocated full course, as logged on the medicine tracker page of the CURLY app, and no additional dose(s) beyond the assigned treatment duration. The app will support adherence by providing a visual prompt to parents/guardians about the duration of the allocated cefalexin, and when their child's final antibiotic dose is due.

8. OUTCOME MEASURES

CURLY will have an internal pilot period to determine if it should continue to a full trial. The primary criteria assessed will be recruitment per centre per month. The stop/go criteria, agreed with the funder elsewhere, will be assessed after 6 months of recruitment (Table 3).

Table 3: Traffic light system for progression criteria from internal pilot to main study.

Internal pilot recruitment = 201 participants by 6 months			
	Red	**Amber**	**Green**
Participants recruited per centre per month	<4.5	4.5-7.49	≥7.5
% of target recruitment per centre per month	<60%	60-99%	100
Number of centres opened (out of 8)	<6	6-7	≥8

8.1 Primary outcome

The primary outcome is clinical UTI cure rate, which will be assessed at a face-to-face follow-up assessment at 16 days post-randomisation. Clinical UTI cure is defined as those patients in whom there is (i) fever resolution and (ii) no additional systemic antibiotic prescription by 16 days post-randomisation. This primary outcome is informed by a systematic review that identified wide variation in the outcomes reported within paediatric febrile UTI trials, and proposed criteria to harmonise study design (32), which were endorsed by the European Medicines Agency (33).

8.2 Secondary outcomes

8.2.1 Clinical

UTI recurrence

- Relapse (recurrent infection with the original bacterial strain) up to final follow-up, 30 days post-randomisation.
- Reinfection (recurrent infection with a different bacterial strain) up to final follow-up, 30 days post-randomisation.

Individual components of the primary outcome

- Fever resolution at the primary outcome assessment visit.
- No additional systemic antibiotic prescription by the primary outcome assessment visit

Microbiological cure

- Urine sterilisation at the primary outcome assessment visit.

Antibiotic-associated adverse events

- Antibiotic-associated adverse events, including diarrhoea, rash, and candida infections.

Adherence to trial drug

- No more than one missed dose from the allocated full course, as logged on the medicine tracker page of the CURLY app and no additional dose(s) beyond the assigned treatment duration.

Antimicrobial resistance & ESBL rates

- Overall rates of antibiotic resistance of urinary pathogens within pre- and post-treatment urine samples.
- Regional rates of antibiotic resistance.
- Identification of ESBL-producing organisms within post-treatment urine samples.

Quality of life – CHU9D

- Differences in quality of life (using the Child Health Utility instrument CHU9D) between the different treatment duration arms (40).

8.2.2 Economic

Health economics

- An incremental cost-utility analysis will determine the Cost per Quality Adjusted Life Years of the different treatment durations over the follow-up period.

9. TRIAL PROCEDURES

9.1 Schedule of assessments

The frequency of follow-up visits and assessments are detailed in the **Schedule of Assessments** (Table 4).

Trial visits and contact schedules should be determined and assigned for each child at randomisation, and children should be followed on that schedule, until the final follow-up visit, even if their trial medication is discontinued prematurely. The schedule defines visit dates (with windows) necessary for data collection.

The face-to-face ED follow-up for the primary outcome assessment will be scheduled in advance, ideally at 16 days post-randomisation, but with a window of ±2 days to allow for weekends and public holidays. If the visit is missed without notice, the research team will endeavour to contact the parent/guardian by phone. If the primary outcome follow up can only be conducted by phone, the parent/guardian will be encouraged to provide a sample of their child's urine remotely.

During any unscheduled acute events, the child can be seen face-to-face if attending the randomising centre. Otherwise, a telephone contact can be arranged.

Table 4: Schedule of Assessments

Day of Trial	d0	d0	d0-d10	48-72 hrs post-cefalexin completion	d16 (±2d)	d30 (±2d)	Any
Visit	Screening	Baseline	Monitoring via CURLY app	Fit & well check	Primary outcome assessment	Recurrence follow-up	Any acute event
At site/remote	Site	Site	Remote	Remote	Site	Remote	Either
Point-of-care dipstick urinalysis	X				X		(X)
Urine sample sent for culture, microscopy & antibiotic sensitivity	X				X	X	(X)
Eligibility check	X						
Valid informed consent/assent		X					
Relevant medical history taken		X					
Documentation of relevant physical examination findings		X			(X)	(X)	(X)
Symptom checklist		X	X	X	X	X	(X)
CHU9D questionnaire		X			X	X	
Randomisation		X					
Allocation of trial number		X					
Cefalexin prescription & dispensing		X					
Setup of CURLY app		X					
Education/advice to parent/guardian		X					
Concomitant medications			X		X	X	
Log of administration of cefalexin doses			X				
Adverse event reporting			X	X	X	X	X
Reminder text/email on final day of cefalexin			X				
Health resource use questionnaire				X	X	X	X
Stool sample or rectal swab					(X)*		

(X) = Optional sample collection participants only (after optional consent)*

9.1.1 Routine ED care prior to consent

- History and physical examination as part of routine ED assessment.
- Patient weight.
- Urine sample: point-of-care dipstick urinalysis.
- Urine sample: sent to lab for routine microscopy, culture, and antibiotic sensitivity.

9.1.2 Trial procedures at baseline ED visit

- Confirmation of inclusion and exclusion criteria.
- Informed consent/assent.
- The following baseline information will be obtained:
    - Demographic information including sex, ethnicity, and home postcode (for subsequent determination of indices of deprivation), to ensure results are generalisable.
    - Medical history and documentation of relevant medical diseases.
    - Documentation of usual urinary continence status of child.
    - Documentation of relevant physical examination findings from this ED attendance, including weight, temperature, and heart rate.
    - Standardised symptom checklist including those commonly associated with UTIs.
- Quality of life assessment (using CHU9D questionnaire).
- Randomisation and allocation of trial number.
- Cefalexin prescription and dispensing.
- Set-up of CURLY trial app and documentation of parent/guardian preferred contact details (email address and/or mobile phone number).
- Education and advice to parent/guardian (± child): routine clinical discharge safety netting advice.
- Education and advice to parent/guardian (± child): trial-specific instructions.

9.1.3 Remote data collection during cefalexin course (using CURLY trial app)

- Log of administration of cefalexin doses.
- Log of administration of relevant concomitant medicines (paracetamol, ibuprofen, and any non-trial antibiotic).
- Standardised symptom checklist including those commonly associated with UTIs, and those associated with side effects of cefalexin.
- Text/email alert will be sent to the parent/guardian on the final day of treatment, reminding them that the cefalexin is due to finish that day, but recommending medical review if their child's symptoms are not resolving.

9.1.4 Remote data collection 48 – 72 hours after end of treatment (via text/online questionnaire)

- Standardised symptom checklist including those commonly associated with UTIs, and those associated with side effects of cefalexin for "fit and well" check.
- Any acute illnesses requiring assessment by a healthcare provider since baseline ED visit, including whether any antibiotics were issued.
- Adherence review by site research team monitoring the app data.
- Health Resource Usage questionnaire.

9.1.5 Face-to-face ED primary outcome assessment at 16 days post-randomisation

- Standardised symptom checklist including those commonly associated with UTIs, and those associated with side effects of cefalexin.
- Any acute illnesses requiring assessment by a healthcare provider since last protocol contact, including whether any antibiotics were issued.
- Antibiotic treatment since last protocol contact, including, as appropriate, adherence to CURLY treatment and whether any additional/new antibiotic prescriptions were issued.
- Quality of life assessment (using CHU9D questionnaire).
- Urine sample for (i) point-of-care urinalysis and (ii) urine microscopy, culture and antibiotic sensitivity.
- Health Resource Usage questionnaire.

Should the child have any signs or symptoms of a UTI, the following will also be recorded:

- Relevant physical examination findings including vital parameters (temperature and heart rate).

The following will be obtained from children enrolled at sites participating in optional sample collection (and where additional consent/assent is given):

- Stool sample or rectal swab (see Section 24.1)

9.1.6 Remote follow-up for recurrence at 30 days post-randomisation (via text/online questionnaire)

- Standardised symptom checklist including those commonly associated with UTIs, and those associated with side effects of cefalexin.
- Any acute illnesses requiring assessment by a healthcare provider since last appointment with the CURLY research team, including whether any antibiotics were issued.
- Any additional/new antibiotic treatment since last appointment with the CURLY research team.
- Quality of life assessment (using CHU9D questionnaire).
- Health Resource Usage questionnaire.

9.1.7 Remote follow-up for recurrence at 30 days post-randomisation (urine sample collection at home)

- Urine sample collected at home and posted to lab.
- On receipt of urine sample at the local NHS lab, testing for urine microscopy, culture and antibiotic sensitivity.

9.2 Urine microbiological tests

9.2.1 Time points for urine sample collection

Urine samples will be collected at the following time points:

- Baseline ED visit as part of standard clinical assessment, following consent.
- Primary outcome assessment visit, 16 days post-randomisation.
- Follow-up for recurrence, 30 days post-randomisation.
- At any face-to-face review that takes place as a result of any acute event, if deemed to be clinically indicated.

9.2.2 Minimisation of urine contamination

As with standard clinical practice, it is essential to reduce contamination of urine samples during collection as this complicates the interpretation of culture results. Contamination occurs when urine flushes the vulva or glans and foreskin on voiding and becomes polluted with bacteria from normal skin bacteria (flora). This typically results in a mixed growth of multiple bacterial species.

Cleaning before collection can reduce the burden of incidental skin flora. To ensure that this cleaning is optimised, participating sites will be provided with standardised cleaning instructions which will be used for the clinical care of all participants throughout the duration of the trial. In addition, bag collection of urine will be avoided, as this is known to result in very high contamination rates and is not reliable for culture (41).

9.2.3 Urine sample collection in the ED

Collection within the ED will follow standard clinical practice:

(a) Infants and pre-continent children:

- Clean catch collection
- In-out-catheterisation (this is an alternative collection method which is commonly used in EDs for infants <1 year of age)

(b) Continent children:

- Midstream urine collection

For clean catch and midstream urine collections, parents/guardians will receive standardised instructions for cleaning and collection, along with support from the ED nursing staff, as is standard practice.

Each urine specimen will be collected in a sterile universal container and, following early urine testing (see Section 9.2.5) will be processed at each site laboratory following the standard pathway at each site. Where the delay between specimen collection and laboratory processing exceeds 4 hours, refrigeration of the urine sample is essential. Samples may be refrigerated for up to 48 hours before processing, in line with UK Standards for Microbiological Investigations (42).

9.2.4 Urine sample collection at home

A final urine sample for microscopy, culture and antibiotic susceptibility testing will be collected at home at 30 days post-randomisation, and posted to the local site laboratories via Royal Mail Safebox delivery[2]. This home collection of urine samples will follow the standard clinical practice that is commonly utilised for children who are susceptible to recurrent infections. Universal containers containing boric acid, a preservative which increases the maximum permissible time for transport to the laboratory to up to 96 hours, will be used, in line with UK Standards for Microbiological Investigations (42). These containers will be supplied to parents/guardians at the preceding face-to-face assessment visit. The importance of filling the containers with the correct volume of urine will be explained.

9.2.5 Early urine testing

In line with standard practice, screening urine samples collected as part of clinical assessment will undergo point-of-care testing within the ED. Reading of urinalysis reagent strips may be performed manually or by using a machine analyser, in accordance with standard practice at each participating centre. As part of the inclusion criteria for CURLY, point-of-care urinalysis must demonstrate positive

[2] Ireland: An equivalent service will be used.

results for both nitrites and leucocyte esterase. Where urgent urine microscopy analysis is requested by the treating clinician, the presence of bacteriuria on microscopy with Gram stain is an acceptable alternative marker of likely UTI for inclusion in the CURLY trial.

9.2.6 Culture-positive UTI definition

As in clinical practice, a culture-positive UTI will be defined using these thresholds (32):

Either:

(i) Pure growth of a single organism recognised as pathogenic for UTI with the following colony count:

- ≥100,000/ml (clean catch urine or midstream urine)
- ≥10,000/ml (catheter urine or suprapubic aspirate)

or

(ii) Growth of no more than 2 organisms. One predominant organism recognised as pathogenic for UTI with the following colony count:

- ≥100,000/ml (clean catch urine or midstream urine)
- ≥10,000/ml (catheter urine or suprapubic aspirate)

9.2.7 Testing for antimicrobial resistance and ESBL rates

We expect the majority of participants will be microbiologically cured after treatment (i.e. their post-treatment urine cultures will be negative). However, some participants may have significant post-treatment bacteriuria; possible reasons are persistence or recurrence of the original infection, or secondary infection with a different (and likely more antibiotic-resistant) bacterium. Different treatment durations may be associated with different risks of, and reasons for, failure to achieve microbiological cure.

We will investigate this first by comparing the species and antibiotic sensitivities of bacterial isolates from pre- and post-treatment urine samples. Species identification and antibiotic susceptibility testing will be performed by the local laboratories, following their routine standard operating procedures. Antibiotic susceptibilities will be reported following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (https://www.eucast.org/clinical_breakpoints; v13.0; date accessed: 03/05/2023).

We expect the great majority of Gram-negative urinary isolates in the study population to be E. coli or Klebsiella species. Cefalexin resistance in these bacteria is mainly conferred by production of ESBL. Primary outcome visit (post-treatment) isolates of Gram-negative bacteria will undergo testing for ESBL-production. All Enterobacterales isolated will be speciated using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and screened phenotypically for ESBL production by subculture onto a selective indicator medium (such as CHROMagar™ ESBL, or similar). Isolates of phenotypic ESBL producers will then be stored on nutrient agar slopes and transferred to the UoB Microbiology laboratory for future studies of ESBL gene subtype.

9.3 Costs and measures of quality of life

Information on missed days of day care/nursery/school, and additional costs from a family member's time off work and/or additional paid childcare will be collected at the primary outcome assessment at 16 days post-randomisation, and at the follow-up for recurrence at 30 days post-randomisation. Data on all events and resources used among CURLY participants will be prospectively captured and will cover the use of medication and laboratory tests as well as hospital, primary care and community health services. Similarly, health outcomes in terms of duration of

illness, any subsequent hospital admission (and length of stay), relapse and mortality will be collected. This will be captured on the Primary Outcome Assessment eCRF and as required on the Change of Status and SAE eCRFs.

With the exception of the youngest children in the trial (those below 2 years of age), quality of life questionnaires (CHU9D) will be completed at baseline, at the primary outcome assessment at 16 days post-randomisation, and at the follow-up for recurrence at 30 days post-randomisation. Where appropriate, this will be self-completed (typically by children over 7 years of age). A proxy version of the CHU9D will be used for younger children and for those lacking understanding. The proxy version can also be used for children over 7 years of age if they require parental assistance. The resulting descriptive profiles will be converted into utility values using the UK tariff (40).

9.4 Acute events

Additional healthcare attendances may be necessary, for example if the child gets worse or develops potential adverse drug reactions or other clinical events. Parents/guardians will be advised to seek immediate emergency assessment with a qualified healthcare provider, preferably at the recruiting centre ED, whenever they feel this is required. Any unscheduled events will be captured retrospectively *via* the CURLY app at the "fit and well" check (48 hours after completion of the antibiotic course) and on the Day 16 primary outcome assessment eCRF and on the Day 30 questionnaire on the CURLY app.

Urinalysis and laboratory processing for culture, microscopy & antibiotic sensitivity will be performed if felt necessary by the treating clinician (i.e. where there is suspicion of clinical deterioration from the UTI, or failure of treatment). Medical judgement will be exercised in determining whether an event is an important medical event and might require special treatment or hospitalisation.

Following any acute unscheduled medical assessment, symptoms, health services utilisation and adherence (if appropriate) will be reviewed in the same way as during regular remote monitoring *via* the CURLY app. Face-to-face visits will be arranged, if necessary, with the clinical team at the recruiting centre.

9.5 Procedures to support participants and maintain patient 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 for shorter durations than the current recommended practice.

Compared with standard clinical practice, additional measures for trial participants will be:

- The medicine tracker feature within the CURLY app will help parents/guardians to track medicine administration.
- Parents/guardians will be provided with a telephone contact number at their local site for any questions or concerns.
- A text/email alert will be sent to the parent/guardian on the final day of treatment, reminding them that the cefalexin is due to finish, but recommending medical review if their child's symptoms are not resolving.
- A text/email "fit and well" check will be performed 48-72 hours after the end of treatment, asking the parent/guardian to report if their child has ongoing fever or other symptoms of concern. They will be advised to seek medical advice and/or medical review if there are ongoing concerns.
- Parents/guardians will have access to the CURLY trial website throughout the duration of the trial which will suggest contacting the medical team if they have any concerns about their child.

- If at any point the parent/guardian fails to respond to the text/email questionnaires, or if they do not attend the primary outcome visit, the local study team will attempt to telephone the parent/guardian to ensure that all is well with their child and, if necessary, to provide support and advice.

9.5.1 Procedures for assessing safety

The CURLY app symptom checklist will explicitly prompt for known clinical adverse effects of cefalexin, which are primarily diarrhoea, rashes, and candida infections.

Additional investigations may be performed to investigate symptoms as clinically indicated. Symptom data will be monitored remotely during trial follow-up by the local clinical team.

Pre-specified clinical adverse events will be recorded on the eCRF. Serious adverse events will be defined according to Section 10.

9.6 Missing data

Every attempt will be made to collect full follow-up data on all study participants. Guidance for the following situations is given:

Participant does not attend primary outcome assessment visit:

Where the assessment visit is missed, the local research assistant will make three attempts to contact the parent/legal guardian by telephone. If contact is made, the family will be encouraged to return for their assessment. Should the family decline, they will be asked to provide information over the telephone about the child's current symptoms, use of any additional health care provider in the preceding days, and receipt of any non-trial antibiotics which will be recorded on the Change of Status eCRF. If no contact can be made with the family, the patient's GP will be contacted (after sufficient time for notification from other healthcare providers) to enquire about any consultations ± antibiotic prescriptions in the preceding days.

Post-treatment urine culture sample not provided (day 16 visit):

This would occur for the participants discussed in the previous paragraph. In addition, children will occasionally fail to provide a urine sample within an acceptable period of time. As in clinical practice, some families may choose to leave and collect the sample at home, before returning it to the hospital.

The approach to missing data analysis is discussed in Section 14.7.

9.7 Withdrawal and changes in participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants and/or parents/guardians should be made aware that they can freely withdraw (discontinue participation) from the trial (or part of the trial) at any time, without giving a reason and that the medical care of the child will not be affected in any way.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in participation within the trial are categorised in the following ways (participant and parent/guardian are used interchangeably):

No remote data collection:

The participant does not wish to complete remote data collection. They may be willing to be followed up at face to face follow up visits, or at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No face-to-face follow-up:

The participant does not wish to attend trial visits in accordance with the schedule of assessments. They may be willing to be followed up *via* the CURLY app or at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection:

The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (only data collected prior to the change in participation can be used in the trial analysis).

The details of changes in participation (date, reason, and category of status change) should be clearly documented in the source documents.

9.8 Contingency plan for follow-up visits

Visits throughout the informed consent process and beyond will take place in person at clinic, or at the participant's home, by telephone, or by video call as per local practice where patient and/or public health circumstances dictate. Where visits are in the participant's home or by telephone or video call, due care will be paid to ensure the participant is in a suitably safe and confidential environment before proceeding.

10.ADVERSE EVENT REPORTING

10.1 Definitions

Table 5: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this intervention. Comment:

		An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2 Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA), and The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof[3]. Definitions for adverse event reporting are listed in **Table 5: Adverse event reporting definitions** in Section 10.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention in accordance with the protocol.

10.3 Adverse event reporting in the CURLY trial

The AE reporting period in CURLY will be from the day of consent until the end of trial follow-up.

The safety profile for this trial population and interventions are well characterised so a strategy of targeted reporting of AEs will not affect the safety of participants. Only some AEs (as detailed below) will be reported.

- Symptoms known to be associated with UTIs (fever, vomiting, dysuria, frequency, urgency, incontinence, abdominal pain, loin/flank pain, reduced oral intake, irritability, lethargy, interference with normal activity). These will be captured *via* the symptom checklist at regular points in the trial.
- Known common side effects of cefalexin - diarrhoea, rash, and candida infections. These will be captured via the symptom checklist at regular points in the trial.

10.4 Serious Adverse Advents (SAE) reporting in the CURLY trial

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the Trial Office as per Section 10.4.1 Serious Adverse Events not requiring reporting to the Trial Office.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office.

3. **Report SAEs to the trial office in an expedited manner**. All SAEs not covered by the above 2 categories must be reported within 24 hours of the site research team becoming aware of the event, as per Section 10.5 SAE Reporting process.

[3] Ireland: In compliance with applicable EU and Irish regulations.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1 Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, from consent to end of participant follow-up, the following are not considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation
- Admission to any short-stay ward in which a participant remains under the care of an ED clinician (e.g. ED Observation Ward/Unit).

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting. Such events are "safety reporting exempt."

10.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE may be known. That is, such events are protocol-defined as "expected" (see Section 10.5.2 Assessment of expectedness of an SAE by the CI).

For the CURLY trial, expected SAEs requiring non-expedited reporting to the Trial Office will be any hospital admission for one of the following recognised complications of UTI or its treatment:

- Intolerance of oral antibiotic treatment (failed administration, vomiting)
- Need for nasogastric/orogastric or parenteral fluid therapy
- Switch to intravenous antibiotic therapy
- Febrile seizure
- Sepsis
- Suspected anaphylaxis or significant allergic reaction to cefalexin

Such events should still be recorded by the local trial team in the participant's notes and reported to the Trial Office on the SAE form within four weeks of becoming aware of the event. These events do not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined.

10.4.3 Serious Adverse Events requiring expedited reporting to the Trial Office

All SAEs not listed in Sections 10.4.1 and 10.4.2 must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

10.5 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the BCTU trials office, the PI or delegate must complete, date and electronically sign the trial specific SAE form. The completed form together with any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below in accordance with the timelines given in Section 10.4.2 and 10.4.3.

To report an SAE, submit the SAE Form via the trial database

Where an SAE Form has been initially completed by someone other than the PI, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within one working day of reporting, the site should contact the Trial Office.

10.5.1 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 6: Categories of causality) of the event.

In defining the causality, the PI or delegate, must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 6: Categories of causality, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 6: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per Table 6: Categories of causality) with the intervention will be regarded as a related SAE. The severity and

causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

10.5.2 Assessment of expectedness of an SAE by the CI

The CI or delegate will also assess all related SAEs for expectedness with reference to the criteria in Table 7: Categories of expectedness.

Table 7: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the reference safety information (RSI) (section 4.8 of the Summary of Product Characteristics for cefalexin most recently submitted and approved by Medicines and Healthcare products Regulatory Agency (MHRA).
Unexpected	An adverse event that is not consistent with known information about the trial related procedures and is not listed in the RSI.

If the event is unexpected, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event to assist in this.

10.5.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office.

10.6 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report details of all Serious Adverse Reactions (SARs) (including SUSARs) to the MHRA, REC, and the University of Birmingham (UoB) Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). Additionally, the Trial Office will report all events categorised as SUSARs to the MHRA, REC and RGT within the timelines required by the regulations[4].

[4] Ireland: SUSARs to be reported to EudraVigilance and annual listings for Ireland to the European Clinical Trials Information System.

10.7 Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken[5].

11. DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Source data is kept as part of the participants' medical notes generated and maintained at site. This will include notes made by local research team. For this study, the participant electronic completed questionnaires will also be regarded as source data.

Table 8: Source data in CURLY

Data	**Source**
Participant Reported Outcomes and health economics data	The original participant/parent-completed electronic form is the source data and will be entered directly into the Trial database via the CURLY app.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto the eCRF.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the parent/guardian, either in or out of clinic (e.g. phone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.

11.2 Case Report Form (CRF) completion

CURLY will use an eCRF system; site staff will enter data onto the trial database via the eCRF; parents/guardians will enter data onto the trial database via the study app.

[5] Ireland: Urgent safety measures and serious breaches to be reported to the European Clinical Trials Information System.

The CRFs will include (but will NOT be limited to) the following Forms (see

Table 9: Case report forms in).

Table 9: Case report forms in CURLY

Form Name	**Schedule for submission**
Eligibility CRF	At enrolment on the same day as randomisation
Consent/Assent CRF	At enrolment on the same day as randomisation
Contact details CRF	At enrolment on the same day as randomisation
Randomisation CRF	At enrolment on the same day as randomisation
Baseline CRF	At enrolment on the same day as randomisation
Urine microbiology report CRF	At microbiology report publication, typically 48 hours following scheduled urine collection timepoints, including enrolment and Day 16 and Day 30 follow up visit, along with any unscheduled urine samples.
Primary outcome assessment CRF including participant reported outcome measures	At the Day 16 assessment face-face visit
Serious Adverse Event CRF	If expedited: submitted within 24 hours of site research team becoming aware of event If non-expedited: submitted within 4 weeks of site research team becoming aware of event
Change of status CRF	As soon as possible after the point of changed participation
Parent and participant reported outcome measures	Throughout follow-up period as prompted by app

A CRF should be completed for each individual participant.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI or delegate. The Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to CURLY working instructions.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3

- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated in notes fields – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- **Protocol and GCP non-compliances should be reported to the Trial Office on discovery**.

11.2.1 Participant completed questionnaires

Participant completed questionnaires other than the CHU9D at baseline and Day 16 assessment follow-up will be completed using the study app. The study app will remind parents/carers by email or text (as per parent preferences) when assessments are due. A paper alternative will be made available if required.

11.3 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the sites via a bespoke BCTU REDCap trial database. As per section 5.1.3, a trial app will be used to collect data directly from the parents. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.3.1 Self-evident corrections

No self-evident corrections will be permitted.

11.4 Data security

UoB has policies in place designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

The database relating strictly to providing trial app functionality is also hosted at UoB in accordance with the same standards as the Trial Database System.

Morph will design and maintain the trial app. The data collected using the app will be processed and stored on a BCTU server with the same countermeasures listed above. After the last participant assessment is completed the app will be discontinued; parents will be instructed to delete the app once their follow-up is complete.

11.5 Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of paper CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The Trial Master File (TMF) will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12.QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a Delegation Log between the PI and the Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Delegation Log, which details which tasks have been delegated to them by the PI. The Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to starting recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a teleconference, which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow CURLY trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2 Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

12.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspections at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4 Notification of Serious Breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a "serious breach" is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial;
- the scientific value of the trial.

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action[6].

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13.END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs and sample analysis. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC, MHRA, and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA, and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial[7].

[6] Ireland: Reported to the European Clinical Trials Information System.

[7] Ireland: The appropriate end of trial reports will be submitted to the regulatory authority.

14. STATISTICAL CONSIDERATIONS

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. All participants will be analysed according to the duration they were randomly assigned to, regardless of adherence to the treatment protocol. A brief overview of the planned analyses is provided here.

14.1 Sample size

We aim to randomise 705 children in a 1:1:1:1:1 ratio to receive either 3, 5, 6, 8 or 10 days of cefalexin. We estimate that this will provide us with 500 patients (100 in each duration) for our microbiological population. The "DURATIONS design" estimates that a sample size of 500 patients divided into a moderate number of broadly equidistant arms (5–7 arms) is required to estimate the duration–response curve satisfactorily (29). Simulations based on plausible scenarios showed that such a sample size was enough to estimate the curve within 5% average absolute error in 95% of simulations. Power for the optimal duration analysis is dependent on the assumed shape of the response curve. We will task the DMC with assessing a more accurate simulation of the analysis at the end of the internal pilot period (using concurrent data) to ascertain if our sample size assumptions remain robust, or whether we require a larger sample size.

Analysis in both the microbiological-confirmed population (those with proven UTI who are not resistant to cefalexin) and the intention-to-treat (ITT) population will be carried out. Given that randomisation occurs before urine culture results are known, the number of patients not included in the microbiological-confirmed population should be equally distributed between treatment arms, thus limiting risk of bias.

Of the population it is estimated that:

- ~12% of participants will not have a proven UTI on urine culture, despite initial clinical symptoms and/or positive point-of-care test (information estimated from a local audit of 530 urine culture results at Birmingham Children's Hospital, 95% CI 9.3% - 14.9%).
- ~10% of proven UTIs (8.8% of entire population) involve a cefalexin-resistant pathogen (10).
- ~10% will be lost to follow up.

Therefore, it is estimated that a sample size of 705 is needed to ensure that at least 500 participants are in the microbiological-confirmed population. For the ITT population, assuming a loss to follow up of 10%, 705 participants will provide 634 participants for analysis. These assumptions will be closely monitored during the trial and, should the number of participants excluded from the microbiological-confirmed analysis be higher than our estimates, then adjustments to the recruited sample size will be made to ensure 500 for this analysis. Conversely, if the number of participants excluded from the microbiological-confirmed analysis is lower than our estimate, we will continue to recruit to a total of 705 participants, with the aim of increasing precision around our estimates. As our estimates are likely to be close to the actual numbers, any adjustment will be modest and unlikely to have major impacts on trial duration, given the expected rapid recruitment to this trial.

14.2 Primary analysis

In line with recommendations from the European Medicines Agency (32, 34), the primary analysis will be conducted on the microbiological-confirmed population.

The microbiological-confirmed population is defined as: All randomised patients who have a baseline bacterial pathogen on culture of urine that causes UTI against which cefalexin has antibacterial activity. As in clinical practice, a culture-positive UTI will be defined using the following thresholds (32):

Either:

(i) Pure growth of a single organism recognised as pathogenic for UTI with the following colony count:

- ≥100,000/ml (clean catch urine or midstream urine)
- ≥10,000/ml (catheter urine or suprapubic aspirate)

or

(ii) Growth of no more than 2 organisms. One predominant organism recognised as pathogenic for UTI with the following colony count:

- ≥100,000/ml (clean catch urine or midstream urine)
- ≥10,000/ml (catheter urine or suprapubic aspirate)

The trial sample size (Section 14.1) has been calculated to ensure sufficient participants for this microbiological-confirmed population.

14.3 Secondary Analysis

A secondary analysis will be performed on all randomised patients i.e. the ITT population, including those who do not have proven UTI, and those who have a cefalexin-resistant pathogen. This will be conducted using a series of assumptions regarding successful cure and failure to cure:

(i) **Cefalexin-resistant UTI**: The participants outcome will be classified as failure to cure, given that the causative organism is not susceptible to effective treatment by cefalexin. Sites will be responsible for ensuring that these participants receive an appropriate change of antibiotic and any necessary imaging and follow-up, in line with their standard local clinical practice.

(ii) **No growth in baseline urine culture**: The participants outcome will be classified as successful cure, given that, by definition, they do not have an untreated-UTI at the point of primary outcome assessment.

(iii) **Below threshold growth in baseline urine culture**: For the same reason as for (ii), the participant outcome will be classified as successful cure.

(iv) **Contamination (mixed growth) in baseline urine culture**: These participants will undergo the standard primary outcome assessment, as for the microbiological-confirmed population. Standard clinical practice will ensure that these participants receive additional investigation and/or change of antibiotic if this is clinically warranted.

(v) **Baseline urine culture result missing**: These participants will undergo the standard primary outcome assessment, as for the microbiological-confirmed population.

14.4 Primary outcome

The primary outcome is clinical UTI cure rate, defined as patients in whom there is (i) fever resolution and (ii) no additional systemic antibiotic prescription by 16 days post-randomisation. A duration-response curve will be fitted using a fixed-2 fractional-polynomial model. This curve will then be analysed to obtain the optimal number of days (D*), such that the UTI cure rate preserves at least 90% of the efficacy provided by the maximum length (10 day) course of antibiotics. A confidence interval will be constructed around D* using bootstrapping methods and the smallest

duration that is greater than the upper end of the confidence interval, will be the recommended duration required (30). Figure 3 provides an example of a hypothetical curve and how the optimal duration will be calculated. This analysis will be performed for both the primary and ITT analysis cohorts as described in Sections 14.2 and 14.3.

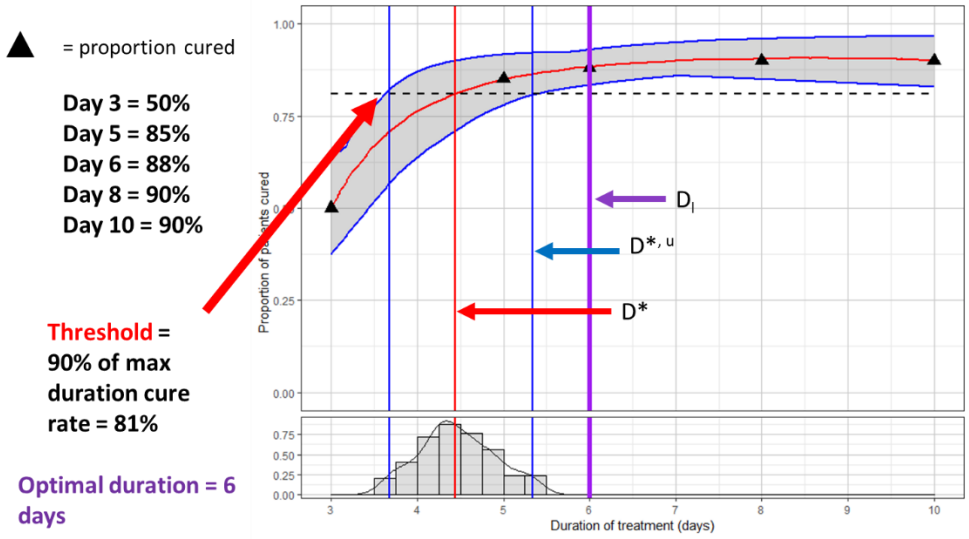

Figure 3: Hypothetical duration-response curve

14.5 Secondary outcomes

The component parts of the primary outcome – fever resolution, and no antibiotic prescription by 16 days post-randomisation – will be analysed using the DURATIONS method in the first instance. As a secondary analysis they will also be analysed as binary outcomes using logistic regression models and adjusting for duration group and minimisation variables: age and sex. The 10-day cefalexin treatment arm will be treated as the control group in these analyses. Microbiological cure (urine sterilisation) at day 16, and UTI recurrence (including relapse and reinfection) at 30 days will be analysed using the DURATIONS method. Quality of life (CHU9D) will be summarised using means and standard deviations at each timepoint. Longitudinal plots of the mean scores over time by treatment group will be produced for visual inspection. Difference in group means and associated confidence intervals at 16- and 30- days post randomisation will be estimated using a repeated measures method.

The number and percentage of participants experiencing any antibiotic-related adverse events will be presented by treatment group alongside the number of events reported. A p-value will be reported from a chi-squared test.

For antimicrobial resistance outcomes, we will describe the overall rates of antibiotic resistance of urinary pathogens within pre- and post-treatment urine samples. We will also describe regional rates of antibiotic resistance, and determine whether any differences that are found correlate with local antibiotic usage data (AMR local indicators) produced by the UK Health Security Agency (UKHSA) and published by the Office for Health Improvement & Disparities: Fingertips Public Health Data (43).

14.6 Subgroup analyses

Subgroup analyses of the minimisation variables: age (3 months - <3 years, 3 – 11 years) and sex, and also *E. coli* versus non-*E. coli* UTIs, will be assessed visually by producing curves for each of the strata

and assessing the optimal duration for each strata. Due to the use of fractional polynomials, at present it is not possible to include an interaction term, though we will continue to monitor any future work that may help us run these analyses. Construction of the duration-response curve by strata will be underpowered to produce accurate curves and so will be hypothesis generating only.

14.7 Sensitivity Analyses

Sensitivity analyses will include a per-protocol analysis. This will be performed on the microbiological population only and include only those who were adherent to their randomised treatment duration. Sensitivity analyses will also include an assessment around some of the assumptions made regarding missing data. An analysis of the primary outcome, where urine sterilisation is included as part of the primary outcome definition, will also be considered.

14.8 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the remote follow-up for recurrence at 30 days post-randomisation, the results of microscopy, culture and antibiotic sensitivity for this follow-urine sample have been reported, and the corresponding outcome data and results have been entered onto the trial database and validated as being ready for analysis.

15. HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

15.1 Within-trial economic evaluation

The base-case cost-effectiveness analysis will be conducted from an NHS/personal social services (PSS) perspective. A cost-consequences analysis will initially be reported, describing all the important results relating to costs and outcomes. Subsequently, an incremental cost-utility analysis will be undertaken to calculate a cost per quality-adjusted life year (QALY) gained over the follow-up period. To obtain QALYs, utility data will be estimated using the CHU9D questionnaire. Where appropriate, this will be self-completed (typically by children over 7 years of age). Proxy versions of the CHU9D will be used for younger children and for those lacking understanding. The proxy version can also be used for children over 7 years of age if they require parental assistance. The resulting descriptive profiles will be converted into utility values using the UK tariff (40).

Health service resource use will be collected using standard data collection forms and unit cost data will be derived from nationally represented sources such as the BNFC, the National Schedule for Reference Costs and the Unit Costs of Health and Social Care.

The incremental cost and benefit of the treatment durations will be estimated over the follow-up period. In accounting for the novel trial design, the various treatment durations will be compared incrementally with the optimal duration and the most cost-effective treatment duration will be determined using the principles of dominance and extended dominance. Results will be expressed as incremental cost-effectiveness ratios (ICERs) using ICER plots and cost-effectiveness acceptability curves to represent the probability of the treatment durations being cost-effective at different willingness to pay thresholds. Appropriate sensitivity analysis will be applied to explore how sensitive the results are to data parameters and assumptions within the analyses. A secondary analysis will adopt a wider societal perspective which would account for the effect of treatment

duration on nursery/school days missed and resulting parental leave from work, along with the cost of antimicrobial resistance. The approach to capturing the costs of antimicrobial resistance would be similar to those adopted in previous literature (44, 45). This would involve estimating costs of resistance associated with antibiotic use and adding this to the costs of each patient in the study based on their antibiotic use.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

The Sponsor for this trial is the University of Birmingham.

16.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit, based at the UoB.

16.3 Trial Management Group

The Trial Management Group (TMG) comprises individuals responsible for the day-to-day management of the trial: the CI, co-lead, Trial Manager, Trial Statistician and senior BCTU oversight staff. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

16.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

16.5 Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the CURLY trial and will meet as required depending on the needs of the trial. The TSC will be chaired by an independent member; membership, duties and responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

16.6 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence. The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed.

16.7 Finance

The research costs of the trial are funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme awarded to Dr Stuart Hartshorn at the Birmingham Women's and Children's NHS Foundation Trust.

17. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use (Clinical Trials) Regulations 2004, Human Tissue Act 2004 and the Data Protection Act 2018.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments)[8].

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

This is a randomised controlled trial therefore neither the parents/guardians nor the physicians will be able to choose the child's treatment.

There will be one additional hospital visit for children in the trial. Other additional contacts will be performed remotely, where possible, using the CURLY app or via email/SMS/telephone. All participants will receive reimbursement of follow-up visit travel expenses, along with a £20 voucher of appreciation for their time contributing to study data collection.

18. DATA PROTECTION AND CONFIDENTIALITY

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments)[9].

Participants will only be identified by their unique trial identification number and initials on correspondence with the Trial Office. For all participants full name, full date of birth, gender and NHS number will be collected on the Randomisation Form. The participant's full name will also be collected on the participant consent forms, in addition to their parents'/guardians' email address and/or mobile number. Participants and parents/guardians will give their explicit consent for the

[8] Ireland: In compliance with applicable EU and Irish regulations.
[9] Ireland: In compliance with the equivalent EU and Irish regulations.

storage of their consent form on the trial database held on secure servers controlled by the University of Birmingham. This will be used to perform in-house monitoring of the consent process.

The PI must maintain documents not for submission to the Trial Office (e.g. Participant Recruitment and Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party. Representatives of the Trial Office and Sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

20. INSURANCE AND INDEMNITY

The UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority[10].

21. POST-TRIAL CARE

Following completion of the trial, patients will be managed according to the standard clinical care that is deemed appropriate by their treating clinician(s).

22. ACCESS TO FINAL DATASET

The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in the absence of the CI) any of the following: The Trial Sponsor, the relevant TMG members, and independent TSC.

[10] Ireland: State Claims Agency clinical trial indemnity scheme.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION POLICY

The trial publications will be prepared by the co-investigator writing group at the completion of the trial, as defined in the trial publication plan. All manuscripts will be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review. No patient/parent/guardian identifiable information will be contained in any form of dissemination of study results.

In all publications, authors will acknowledge that the trial was performed with the support of the NIHR, UoB, BCTU and PERUKI. Intellectual property rights will be addressed in the Site Agreement between Sponsor and site.

Dissemination will be *via* traditional and novel methods as discussed below.

23.1 Information to patients and the public

- **Study participants**: Our PPI team will produce a plain English language summary of the study findings which will be posted to study participants using patient contact details provided at the initial trial consent. We will also develop an explainer animation (adapted from the trial recruitment animation) which will be added to the trial website. Our PPI parent group and Young Person's Advisory Group (YPAG) are keen to remain involved to help with the development of this material.
- **Consumer organisations**: We will produce lay information for relevant organisations such as Kidney Care UK and Kidney Voices for Research, for easier access to parents and carers.
- **Media**: A press release will be issued to the media upon publication of the results, after consultation with investigators and the journal. We will use social media, a webpage, and newsletters to highlight study progress and recruitment and disseminate findings.

23.2 Information to health care practitioners

- **Co-investigators and research staff:** Staff at study sites will be informed of results through newsletters and emails, as well as *via i*nvitations to a meeting at the end of the project, to help shape delivery of the findings and the direction of future work.
- **Peer reviewed publications and media**: We will aim to publish the findings in a high impact peer reviewed journal for wide dissemination.
- **Media**: Infographics will be produced for social media outlets and promoted to professional timeline streams. Stakeholder social media, FOAMed (e.g. Don't Forget the Bubbles) and podcast channels (e.g. "2 Paeds in a Pod") will be approached to provide reviews, commentaries and publicity at the time of journal publications.
- **Conferences and scientific meetings**: Findings will be presented at national and international conferences including annual meetings for the Royal College of Paediatrics and Child Health, British Association of Paediatric Nephrology, and the European Congress of Clinical Microbiology & Infectious Diseases (ECCMID). We will aim to access as wide an audience as possible, of professionals from the UK and around the world, as international interest is likely to be high.

- **National guidelines**: The information is expected to be incorporated into NICE guideline recommendations, and disseminated to primary, secondary and tertiary centres who care for children for implementation.
- **Publication in the NIHR Journals Library**: The NIHR Journals Library will help with dissemination of findings and will provide an important, permanent and comprehensive record of the study.

23.3 Information to policy makers

We will disseminate the published paper to the Department of Health, the Scientific Committee of the Royal College of Paediatrics and Child Health (RCPCH) and the Scientific Foundation Board of the Royal College of General Practitioners (RCGP).

24. APPENDIX

24.1 Future sample use

24.1.1 ESBL gene subtype

As described briefly in section 9.2.7, isolates of phenotypic ESBL producers will be stored on nutrient agar slopes and transferred to the UoB Microbiology laboratory for storage. Using separate funding, and reported separately, these samples will be used to determine ESBL gene subtype (CTX-M, TEM, SHV, Oxa).

24.1.2 Antimicrobial resistance (optional consent in a subset of children)

Using separate funding, and reported separately, we will seek consent (+/- assent) from participants at selected sites to undertake additional research into the impact of cefalexin duration on antimicrobial resistance:

- A stool sample (or a rectal swab) will be taken from patients at the primary outcome assessment visit. The samples will be transported to the UoB Microbiology laboratory for storage at -80, future DNA extraction, and genome sequencing and metagenomic analysis of the gut microbiome and resistome.
- For patients with a cefalexin-sensitive UTI, we will collect any bacterial isolates from the post-treatment urine samples to compare with the pre-treatment bacterial isolates in a future study to include whole genome sequencing of the isolates. The samples will be transported to the UoB Microbiology laboratory for storage at -80.

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