**ABSTRACT**

**Introduction** Febrile urinary tract infection is one of the most common bacterial infections in children. Currently, recommended antibiotic duration is 10 days. However, recent evidence suggests that 90%–95% of children with febrile urinary tract infections are afebrile and clinically improved 48–72 hours after treatment initiation. Accordingly, individualised duration of antibiotic therapy, according to the recovery time, might be more beneficial than current recommendations, but no evidence exists.

**Methods and analysis** An open-label randomised clinical trial equally randomising children aged 3 months to 12 years from eight Danish paediatric departments with uncomplicated febrile (≥38°C) urinary tract infection to either individualised or standard duration of antibiotic therapy. Children allocated to individualised duration of antibiotic therapy will terminate antibiotic therapy 3 days after clinical improvement with no fever, flank pain or dysuria. Children allocated to standard duration will receive 10 days of antibiotic therapy. Co-primary outcomes are non-inferiority for recurrent urinary tract infection or death within 28 days after the end of treatment (non-inferiority margin 7.5 percentage points) and superiority for the number of days with antibiotic therapy within 28 days after treatment initiation. Seven other outcomes will also be assessed. A total of 408 participants are needed to detect non-inferiority (one-sided alpha 2.5%; beta 80%).

**Ethics and dissemination** This trial has been approved by the Ethics Committee (H-21057310) and the Data Protection Agency (P-2022-68) in Denmark. Regardless of the trial’s findings (whether positive, negative or inconclusive), the results will be compiled into one or more manuscripts for publication in international peer-reviewed scientific journals and presented at conferences.

**Trial registration number** NCT05301023.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

⇒ Pragmatic trial with ‘hard patient-important outcomes’.
⇒ High external validity due to generalisable inclusion and exclusion criteria and multiple site inclusion.
⇒ Due to the experimental intervention’s nature, blinding personnel, parents and children will not be possible.
⇒ Our results will only be generalisable to sites that systematically conduct a follow-up when urine culture results are available and can conduct additional follow-ups if needed.

**INTRODUCTION**

Febrile urinary tract infection (UTI) is one of the most common bacterial infections in children overall and has a prevalence of approximately 7% in febrile children below 2 years of age.³ Febrile UTI is primarily caused by *Escherichia coli* (80%–90%)³ and is predominately treated with oral antibiotics for 10 days.⁶–¹⁰ However, observational evidence indicates that more than 90%–95% of children with febrile UTI are afebrile and clinically improved 48–72 hours after treatment initiation.¹¹–¹⁵ Hence, the recommended 10 days of antibiotic therapy is presumably antibiotic overuse. Antibiotic overuse may result in unnecessary adverse effects (e.g., diarrhoea, nausea, vomiting, loss of appetite, abdominal pain),¹⁴,¹⁵ disruption of gut microbiota (multiple studies show a possible association between disrupted gut microbiota and allergy, cardiovascular disease and obesity),¹⁶,¹⁷ and increased risk of antimicrobial resistance.¹⁸,¹⁹ Additional adverse effects of antibiotic overuse are an increased burden on the healthcare system and more frequent absence days from daycare/school and work for the child and parents, respectively.
A recent randomised clinical trial (RCT) in the USA included 693 children aged 2–10 years with both afebrile and febrile UTI who were clinically improved after 5 days of antibiotic therapy and randomised them to terminating antibiotic therapy vs continuing for 5 more days. Both randomised groups showed high success rates (96% vs 99%) when assessing the risk of treatment failure (symptomatic UTI) within 9 days after randomisation. Likewise, a retrospective study including 791 children aged 6 months to 18 years found that the effect of a short antibiotic course (median 8 days) compared with a long course (median 11 days) was similar when assessing the odds of treatment failure within 30 days after the end of treatment (OR 1.22; 95% CI 0.75 to 1.98).

Other RCTs in paediatric infectious diseases have shown that antibiotic therapy is unnecessary for most cases with respiratory infections and that antibiotic duration can be significantly reduced in most cases with pneumonia and bone and joint infection.

Currently, two ongoing RCTs in children with febrile UTI are investigating shorter antibiotic therapy duration. Daniel et al from Poland have planned to assess the incidence of recurrent UTI within 90 days after the end of treatment after 7 vs 10 days of oral cefuroxime in 221 children aged 3 months to 7 years. Penessi et al from Italy have planned to assess the incidence of recurrent UTI within 30 days after the end of treatment after 5 vs 10 days of oral amoxicillin–clavulanic acid in 520 children aged 3 months to 5 years. Both ongoing trials focus on a specific antibiotic duration, which might be problematic for some children due to a more severe infection, leading to a too-short antibiotic course.

Accordingly, it is of utmost importance to investigate whether individualised duration of antibiotic therapy, according to the recovery time, can reduce antibiotic use without causing harm.

**Objective**

The trial objective is to assess whether a treatment strategy with defined rules for individualised duration of antibiotic therapy is non-inferior compared with standard 10 days of antibiotic therapy on the risk of recurrent UTI or death within 28 days after the end of treatment and superior on the number of days with antibiotic therapy within 28 days after treatment initiation in children aged 3 months to 12 years with uncomplicated febrile UTI.

**METHODS AND ANALYSIS**

**Trial conduct**

The trial will follow good clinical research practice and the latest Declaration of Helsinki. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist was used when writing the protocol. The protocol was registered on ClinicalTrials.gov (NCT05301023) before trial inclusion was initiated. The trial registration data set can be found in online supplemental appendix 1. Data will be secured in the online database application Research Electronic Data Capture (REDCap) V.12.0.33. The principal investigator (NS) is responsible for managing and achieving data per current regulations.

**Trial design**

An investigator-initiated, parallel-group, open-label, multicentre RCT.

**Setting**

The children will be recruited from eight paediatric departments (Copenhagen University Hospital Hvidovre, Rigshospitalet, Herlev, Hillerød, Roskilde, Holbæk, Slagelse and Nykøbing Falster) in Denmark. Each department has a managing investigator responsible for the trial.

In Denmark, children are referred to the paediatric emergency department by their primary physician or a medical helpline (outside normal opening hours) if an upper UTI is suspected. According to Danish national guidelines, upper UTI should be suspected in children <2 years of age with suspected UTI regardless of fever; and all febrile children ≥2 years of age with suspected UTI.

**Randomisation**

Randomisation is computerised using a web-based randomisation module. The web-based randomisation will generate randomisation sequences with varying block sizes unknown to the investigators. No stratification will be conducted. Randomisation will be conducted by one of the investigators.

**Blinding**

Due to the experimental intervention’s nature, no blinding can be conducted. Hence, the personnel (ie, investigators, treatment providers and caregivers), parents and children will not be blinded. Likewise, the outcome assessor will also not be blinded.

**Selection of participants**

According to the inclusion and exclusion criteria below, children will be randomised once the urine culture is positive (figure 1).

**Inclusion criteria**

1. Clinical suspicion of febrile (≥38°C) UTI.
2. Positive urine culture of uropathogenic bacteria.
   a. Suprapubic bladder aspiration: monoculture with any growth of bacteria.
   b. Sterile intermittent catheterisation: monoculture with ≥10^5 colony-forming units per millilitre (CFU/mL).
   c. Midstream urine: monoculture with the same bacteria in two cultures with ≥10^6 CFU/mL.
   d. Midstream urine: monoculture with the same bacteria in two cultures with ≥10^5 CFU/mL in one culture and 10^3 CFU/mL in another.
   e. Midstream urine (≥10 years of age): monoculture in one culture with ≥10^6 CFU/mL.
3. Age 3 months to 12 years (corrected age in case of premature birth).
4. Parents fluent in Danish or English.
5. Informed consent from the holder(s) of parental authority.

Exclusion criteria
1. Non-Danish civil registration number.
2. Not resident in the Capital Region or Region Zealand in Denmark at the baseline visit.
3. Previous inclusion in the trial.
4. History of febrile (≥38°C) UTI in the last 28 days before the baseline visit.
5. Antibiotic treatment in the last 2 weeks before the baseline visit.
6. Three or more episodes with febrile (≥38°C) UTI within 1 year of the baseline visit (including the current episode).
7. Previous complicated episode of febrile (≥38°C) UTI (eg, renal abscess or urosepsis).
8. Non-compliance (≥3 doses of antibiotics during empirical therapy).
9. Elevated creatinine at the time of randomisation.
10. Prophylactic antibiotic treatment at the baseline visit.
11. Known urogenital abnormalities (ie, obstructing uropathies, vesicoureteral reflux, multicystic dysplasia, renal dysplasia, renal hypoplasia, renal agenesis, duplex kidney, polycystic kidney disease, neurogenic bladder dysfunction, hypospadias) at the time of randomisation.
12. Clinical suspicion of septicaemia at the time of randomisation.
13. Positive blood culture (if contamination is not suspected).
15. Systemic immunosuppressive therapy.

Children with a positive urine culture who have not received antibiotic therapy can be included if fever (≥38.0°C) is present at the time of randomisation. If the fever has subsided, the child cannot be included.

Participant withdrawal
The parents can withdraw the consent at any time for any reason. The parents will be asked whether they will still allow future outcome assessments.

Study procedure
All febrile (≥38.0°C) children with suspected UTI will be examined and treated by doctors and nurses per current guidelines. The visit to the paediatric emergency department will include a medical history, medical examination, urine test strip, urine culture, blood tests and blood culture. Most children will begin empiric therapy with oral antibiotics. Empirical therapy consists of amoxicillin–clavulanic acid 50 mg/kg/day divided into 3 doses or pivmecillinam 20–40 mg/kg/day divided into 3 doses, in line with current recommendations (figure 2).35

Parents of children suspected of uncomplicated UTI will receive oral and written information about the trial (see online supplemental appendix 2). A follow-up by phone will take place approximately 72 hours after treatment initiation. If includable according to the inclusion and exclusion criteria mentioned above, oral and written consent will be obtained before randomisation. Based on the sensitivity pattern of the positive urine culture, the antibiotics will be changed to narrow-spectrum, if possible.

Treatment allocation
The children will be randomised to either individualised or standard duration of antibiotic therapy (figure 1).

Individualised duration of antibiotic therapy
Our individualised approach is based on the duration of illness after treatment initiation. The antibiotic therapy will be terminated 3 days after the child has fulfilled the termination criteria; clinically improved with no fever (<38.0°C) without using antipyretics, flank pain or dysuria.

In case of antibiotic resistance towards the empiric antibiotic:
- If the termination criteria are fulfilled: further 3 days of antibiotic therapy with a sensitive antibiotic.

Figure 1 Selection of participants and randomisation.
If the termination criteria are not fulfilled: terminate antibiotic therapy with a sensitive antibiotic 3 days after the termination criteria have been fulfilled.

**Standard duration of antibiotic therapy**

The standard duration is based on current guidelines, that is, 10 days.35

**Co-intervention**

Participants will receive the same outpatient clinical follow-up. Radiological and nuclear medical examinations will follow current national guidelines.35

Participants with recurrent UTI after the baseline infection will be treated according to current guidelines.35

**Concomitant medication**

Participants will be examined for constipation and external genital abnormalities (ie, phimosis and labia synechiae). If present, the treating physician will treat these conditions according to current guidelines. The use of any additional medical intervention will be recorded.

**Outcomes**

**Co-primary outcomes**

1. Recurrent UTI regardless of the pathogen or death of any cause within 28 days after the end of treatment.
2. Number of days with antibiotic therapy within 28 days after treatment initiation.

**Secondary outcomes**

3. Absence from school or daycare due to illness within 28 days after randomisation.
4. Recurrent UTI regardless of the pathogen or death of any cause within 100 days after the end of treatment.

**Exploratory outcome**

5. Number of hospital days related to UTI symptoms within 28 days after the end of treatment.
6. Number of days with a physical or virtual (phone or online) consultation during antibiotic therapy for the baseline infection.

7. Recurrent infection with a bacterium resistant to the antibiotic given for the baseline infection within 100 days after the end of treatment.

**Safety outcomes**

8. Antibiotic-related non-serious adverse events within 28 days after randomisation. We will include non-serious adverse events of the following types:
   a. Diarrhoea.
   b. Nausea or loss of appetite.
   c. Vomiting.
   d. Abdominal pain.

9. Serious adverse events within 100 days after randomisation. We will define a serious adverse event as any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or jeopardises the patient.37

**Follow-up and outcome events**

Besides outcomes 3 and 8, all outcomes will be assessed using patient records at different time points. Outcomes 3 and 8 will be assessed weekly by having the parents answer an electronic questionnaire sent to their e-Boks (official Danish secure digital mailbox) through REDCap. In the case of missing data, parents will be contacted by phone.

**Data collection**

Besides ‘self-reported adherence’ and ‘parent satisfaction’, all data will be collected from patient records. ‘Self-reported adherence’ and ‘parent satisfaction’ will be assessed by having the parents answer an electronic questionnaire sent to their e-Boks through REDCap. In the case of missing data, parents will be contacted by phone. Each variable that will be assessed is listed in table 1 (excluding outcome data).

**Data and safety monitoring Committee during trial**

A data and safety monitoring committee (DSMC) independent of the investigators and the sponsor will be
created. The DSMC will consist of two paediatric nephrologists, and a biostatistician will be consulted if needed. The DSMC will have no conflicts of interest. The DSMC will immediately receive information on specific serious adverse events including death, septic shock, meningitis, urosepticaemia and renal abscess. Additionally, the DSMC will receive unblinded information on all serious adverse events in each randomised group every 6 months. The trial has no specific stopping rules. If the DSMC has clinical concerns about the safety of the participants, the trial will be paused until the DSMC and the steering committee (NS, ELMC, UN and LTS) have discussed whether the trial can continue or should be terminated.

**Statistical analysis plan**

**Sample size determination**

We have determined our needed sample size by assessing our first co-primary outcome (ie, recurrent UTI or death of any cause) based on a non-inferiority design. We anticipate the event proportion in the control group (ie, standard duration of antibiotic therapy) to be 7.5% based on a single-centre retrospective study (non-published data by Sethi et al). We assume no difference between the randomised groups. Our non-inferiority limit corresponds to a 7.5 percentage points higher proportion in the intervention group compared with the control group. The test will be conducted as a one-sided test with alpha of 2.5%. A total of 408 participants are needed to obtain a power of 80% to reject inferiority. We have accounted for a drop-out rate of 5%.

A sample size recalculation will be conducted if the overall observed event proportion is higher than 7.5% when follow-up is available for the first 204 participants to be able to achieve a power of at least 80%. The sample size recalculation will be blinded according to a United States Food & Drug Administration (FDA) rapport and Friede et al. The DSMC will oversee this analysis, and any changes will only be done after approval from both the DSMC and the ethics committee.

**Statistical analyses**

Subjects will be analysed in all analyses according to the randomised treatment allocation. Secondarily, per-protocol analyses will be conducted only including children who reported full adherence to the antibiotic therapy. To address the issue of multiplicity, both of our co-primary outcomes will be evaluated at an alpha of 2.5%. Nominal p values will be presented for secondary and exploratory analyses, but no statistical significance will be asserted. For safety analyses, a p value of less than 5% will be considered statistically significant. Clinically relevant, statistically non-significant differences will be addressed.

**Co-primary outcomes**

1. Recurrent UTI regardless of the pathogen or death of any cause within 28 days after the end of treatment.

The population-level summary measure will be the risk difference (RD), calculated as the proportion in the intervention group minus the proportion in the control group, with the upper one-sided 97.5% confidence limit (CL). Inferiority will be rejected if the upper one-sided 97.5% CL for the RD shows a difference of less than the non-inferiority limit of 7.5 percentage points. If more than 5% of data are missing, data will be imputed based on available knowledge of the patient and the observations of

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**Table 1 Data collection**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Infection characteristics</th>
<th>Treatment characteristics</th>
<th>Diagnostic imaging characteristic</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age at baseline visit</td>
<td>- Clinical symptoms</td>
<td>- Empirical antibiotic therapy</td>
<td>- Ultrasound findings</td>
<td>- Parent satisfaction</td>
</tr>
<tr>
<td>- Gender</td>
<td>- Temperature</td>
<td>- Antibiotic therapy after inclusion</td>
<td>- Nuclear medical findings</td>
<td></td>
</tr>
<tr>
<td>- Medical history and medication at baseline visit</td>
<td>- Blood pressure</td>
<td>- Dose of antibiotic therapy</td>
<td></td>
<td></td>
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<tr>
<td>- Constipation/phimosis/labia synechiae/hypertension at baseline visit</td>
<td>- C reactive protein</td>
<td>- Self-reported adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Current number of febrile UTI at baseline visit</td>
<td>- Leucocytes</td>
<td></td>
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<tr>
<td>- Age at first febrile UTI</td>
<td>- Creatinine</td>
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<tr>
<td>- Date of last febrile UTI</td>
<td>- Urea</td>
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<tr>
<td>- Total no of UTIs</td>
<td>- Urine sample technique</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Efficacy of treatment of constipation/phimosis/labia synechiae at the routine off-patient follow-up</td>
<td>- Results of the urine test strip</td>
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<tr>
<td></td>
<td>- No of urine cultures</td>
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<td></td>
<td>- Type(s) of pathogen in each urine culture</td>
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<td></td>
<td>- Level of bacterial growth for each pathogen in each urine culture</td>
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<tr>
<td></td>
<td>- Type(s) of bacterial resistance for each pathogen in each urine culture</td>
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</tr>
</tbody>
</table>

UTI, urinary tract infection.
the other patients in the same randomised group. Sensitivity analyses will include tipping point analyses for the imputation, and the potential importance of differences between hospitals will be evaluated in logistic regression models including the random effect of the hospital and the random treatment effect within the hospital. In case of deaths unrelated to infection and with no previous recurrent UTI, we will present analyses (1) excluding these children and (2) imputing that each child did not have recurrent UTI, respectively.

2. Number of days of antibiotic therapy within 28 days after treatment initiation

As the outcome, we will use the number of days the child was prescribed antibiotic therapy during the period. The two randomised groups will be compared using the Wilcoxon-Mann-Whitney test. The population-level summary measure will be the difference in the mean number of days with two-sided 97.5\% CIs based on the normal approximation for the estimated mean difference. In case of death, we will add the remaining days up to 28 days after treatment initiation to the number of days with antibiotic therapy. In a secondary analysis, we will exclude the children who died.

Non-primary outcomes

The statistical analysis plan for the non-primary (ie, secondary, exploratory and safety outcomes) outcomes can be found in online supplemental appendix 3.

Subgroup presentations

These subgroup presentations will be regarded as hypothesis-generating and will only be used to facilitate the planning of future research. Hence, we will not base any conclusions on these subgroup presentations.

We will present summary statistics for both our co-primary outcomes for the following subgroups:

- Age:
  - 3–23 months old.
  - 2–5 years old.
  - 6–12 years old.
- Sex.
- First episode (yes/no) with febrile UTI.
- Empirical antibiotics given for the baseline infection:
  - Amoxicillin–clavulanic acid.
  - Pivmecillinam.
  - Gentamicin and ampicillin.
- Empirical antibiotics given intravenously or orally.
- Participants with different bacterial aetiology at baseline:
  - *E. coli*.
  - *Non-E. coli*.
- Urogenital abnormality diagnosed after randomisation (yes/no).
- The four groups given by the combination of a positive result (yes/no) of the urine test strip (leucocyturia and/or positive nitrite test) at baseline and whether the participants at baseline fulfilled at least one of the more restrictive criteria for uropathogenic bacterial growth:
  - Suprapubic bladder aspiration: monoculture with any growth of bacteria.
  - Sterile intermittent catheterisation: monoculture with ≥10^4 CFU/mL.
  - Midstream urine (regardless of age): monoculture with the same bacteria in two cultures with ≥10^5 CFU/mL.

Patient and public involvement

Parents of patients were involved in designing the participant information. No patient, parent or the public was involved in designing, writing or editing the protocol.

Current status and protocol amendments after trial initiation

The trial was initiated on 1 April 2022 according to protocol V.1.0 preregistered on ClinicalTrials.gov (NCT05301023) 29 March 2022. All sites are active, and we anticipate completing inclusion within 24 months (1 April 2024).

Recently, the protocol was amended with the inclusion of outcome 6. Outcome 6 was added after initial trial registration and initiation and has been listed as an exploratory outcome.

Ethics and dissemination

The trial has been approved by the Ethics Committee (H-21057310) and the Data Protection Agency (P-2022-68) in Denmark. All personal data will be protected according to the Danish Data Protection Act and General Data Protection Regulation. Any protocol amendments will need to be approved by all relevant authorities. All participants’ parents will receive oral and written information, and oral and written consent will be obtained before trial inclusion and randomisation.

Regardless of the trial’s findings (whether positive, negative or inconclusive), the results will be compiled into one or more manuscripts for publication in international peer-reviewed scientific journals and presented at national and international conferences. Co-authors must fulfil the criteria for co-authorship according to the International Committee of Medical Journal Editors.

DISCUSSION

This investigator-initiated, multicentre RCT aims to assess the benefits and harms of individualised duration of antibiotic therapy, according to the recovery time, versus standard 10 days of antibiotic therapy in children aged 3 months to 12 years with uncomplicated febrile UTI. We hypothesise that our individualised approach is non-inferior on the risk of recurrent UTI or death within 28 days after the end of treatment and superior on the number of days with antibiotic therapy within 28 days after treatment initiation. Moreover, we presume that our individualised approach will lead to fewer absence days
from daycare or school, fewer side effects and reduced risk of recurrent resistant infections.

Our trial has several strengths. It is a pragmatic trial that will consider ‘hard patient-important outcomes’. The external validity will be high due to our inclusion and exclusion criteria being established from national and international guidelines, consequently being generalisable nationally and internationally. Children will be included at multiple sites increasing the external validity. Our current sample size calculation is based on updated evidence from the largest site, and if necessary, we will conduct an updated sample size calculation halfway through inclusion to achieve enough power. We have evaluated the risk of multiplicity and planned a statistical approach that secures the 5% level for the type 1 error. Hence, the majority of analyses will be considered hypothesis-generating only. We have also taken measures to reduce the risk of bias by using computer-generated randomisation, registering our trial methodology on a clinical registry before initiating patient inclusion and having no funding or affiliation with the industry. Moreover, the risk of missing outcome data will be minimal because all Danish citizens have a unique number (Central Person Register) from which a complete follow-up of hospitalisation, urine culture assessment, antibiotic prescriptions and death are available.

Our trial also has limitations. Primarily, blinding the personnel, parents and children will not be possible due to the nature of the experimental intervention, which may introduce bias. The open-label design might result in parents of children randomised to standard duration of antibiotic therapy stopping therapy prematurely due to information about fewer days of antibiotics possibly being sufficient. We will assess this by questioning the parents about adherence and conducting per-protocol analyses only including the children with full adherence. Secondarily, selection bias towards more seriously ill children is possible due to the lack of referral of clinically well febrile children suspected of UTI who are treated by their primary physician instead. However, if our individualised approach is proven safe, the findings of this study are also generalisable to a more clinically well population. Third, the non-inferiority margin of 7.5 percentage points might be assessed as too liberal, and it might be discussed whether a more restrictive margin is needed before our individualised approach can be used in clinical practice. Another limitation is that our results will only be generalisable to sites that systematically conduct a follow-up when urine culture results are available and can conduct additional follow-ups if needed. Yet another limitation is the lack of power to assess different subgroups, making it difficult to interpret whether specific subgroups might benefit more or less from our individualised approach.

We expect that the trial’s results will have an important impact on future recommendations on the duration of antibiotic therapy for children aged 3 months to 12 years with uncomplicated febrile UTIs.


37 International Conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) adopts consolidated guideline on good clinical practice in the conduct of clinical trials on medicinal products for human use. *Int Dig Health Legis* 1997;48:231–4.
