ISRCTN18390724 https://doi.org/10.1186/ISRCTN18390724

# Impact of duration of antibiotic treatment on the effectiveness, safety and selection of antibiotic resistance in adult women with urinary tract infections (UTI): a randomised controlled trial.

**Submission date**
06/04/2023

**Recruitment status**
No longer recruiting

**Registration date**
31/08/2023

**Overall study status**
Completed

**Last Edited**
14/03/2024

**Condition category**
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

## Plain English summary of protocol

Background and study aims
This research aims to find the shortest antibiotic treatment duration needed to treat urinary tract infections (UTIs) effectively. We will look at the impact of each antibiotic and treatment duration on antibiotic resistance.
UTIs, both bladder and kidney infections, are among the most common infections treated with antibiotics. Over four million prescriptions for UTIs are issued to women in the UK every year. However, there is little evidence to help clinicians decide how many days of antibiotic treatment are necessary. We need to use the shortest treatment duration which ensures that the infection is properly treated. This could avoid bacteria becoming antibiotic resistant, ensuring antibiotics remain effective.

Who can participate?
We will recruit 2,248 adult women with UTI symptoms for whom the doctor judges that antibiotics are needed for a suspected bladder or kidney infection. We will include women with symptoms of bladder and kidney infections.

What does the study involve?
The clinician will randomise women with bladder infection to receive one of two commonly used antibiotics for this condition. Women with kidney infection will be offered one of a family of antibiotics which will work in similar ways depending on the local prescribing policy. Because we don't know for how many days women should take a particular antibiotic to get the best results from treatment, we will randomise women to take their antibiotic treatment for one of five or six different treatment durations in days. Our main focus will be to compare how many women have got fully better 6 weeks after starting antibiotics. We will also measure how long each woman experiences UTI symptoms, whether the bacteria in their urine are killed by the antibiotic, whether they develop further UTIs, and the value for money of each treatment

duration.
We will invite women who join the main study to take part in an optional rectal swab sub-study about the effect of antibiotic duration on antibiotic resistance in bacteria in their gut.

What are the possible benefits and risks of participating?
Benefits:
Although we do not anticipate an immediate benefit to participants, in the longer term understanding how many days of antibiotics should be prescribed for their UTI will benefit patients by avoiding unnecessary antibiotic side effects and reducing the risk of antibiotic resistance.
Risks:
Time will be needed for collection of research data from the trial participants collected by the questionnaires the participants complete; We are keeping all questions to a necessary minimum to reduce the burden as much as possible. The participants may incur an expense during purchase of the prescribed antibiotics. A £20 voucher will be provided to all participants to reimburse them for their input into the study. Those taking part in the qualitative sub-study will also receive an additional £10 voucher to reimburse them for their time. We currently don't know what the implications are of taking shorter or longer courses of antibiotics: shorter courses could result in an infection that s not fully treated, but longer courses could result in increased resistance to antibiotics.
The participant will be asked to supply urine samples to the trial team that are extra to those for clinical care, and also potential rectal swabs if they are part of the sub-study. These can be difficult to collect and they will have to post them. We will provide all materials they need for taking and posting the samples and will aim to make the process as straightforward as possible for them.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
April 2023 to July 2025

Who is funding the study?
National Institute of Health and Care Research (UK)

Who is the main contact?
DURATION UTI Trial team, duration@phc.ox.ac.uk

# Contact information

### Type(s)
Principal investigator

### Contact name
Dr . DURATION UTI Team

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# Additional identifiers

### Integrated Research Application System (IRAS)
1006965

### Central Portfolio Management System (CPMS)
56161

### Protocol serial number
16719

# Study information

### Scientific Title
Impact of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in adult women with urinary tract infections (UTI): a randomised controlled trial.

### Acronym
DURATION UTI

### Study objectives
Primary objectives:
To determine the minimum duration of antibiotic treatment which maintains good clinical outcomes for UTIs.

Secondary objectives:
1. To explore the impact of antibiotic agent and treatment duration for each agent on time to resolution of symptoms
2. To explore the impact of antibiotic agent and treatment duration for each agent up to day 42
3. To explore the impact of antibiotic agent and treatment duration for each agent on antibiotic-associated harms
4. To explore the impact of antibiotic agent and treatment duration for each agent on total antibiotic use over 42days
5. To explore the impact of antibiotic agent and treatment duration for each agent on risk of microbiological failure and antimicrobial resistance
6. To explore adherence to different antibiotic drugs and treatment durations
7. Explore the impact of different antibiotic drugand treatment durations on health-related quality of life, costs, and cost-effectiveness
8. Explore patient acceptability of and satisfaction with different antibiotic agents and treatment durations and understand the interaction between patient behaviour and antibiotic duration

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approval pending, ref: 23/NE/0087

## Study design
Open-label parallel-group multi-arm randomized trial with two sub-trials enrolling patients with cystitis and pyelonephritis

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Urinary tract infections (UTI), cystitis, pyelonephritis

## Interventions
Cystitis interventions: participants will be randomised to nitrofurantoin or pivmecillinam (1:1), and subsequently randomised to one of five antibiotic durations: one, two, three, four or five days (1:1:1:1:1). Participants who are allergic to one of nitrofurantoin or pivmecillinam will be allocated to the antibiotic they are not allergic to and then will be randomised to one of five durations.
Pyelonephritis interventions: participants will be randomised to one of six antibiotic durations (four, six, eight, ten, twelve or fourteen days (1:1:1:1:1:1) of beta-lactam treatment).
N.B. One day is a 24-hour period and may cover two calendar days.
We will thus be evaluating the optimal treatment duration for adult women for the following treatments and conditions:
-Nitrofurantoin for uncomplicated cystitis
-Pivmecillinam for uncomplicated cystitis
-Beta-lactams for uncomplicated pyelonephritis.

## Intervention Type
Drug

## Phase
Phase IV

## Drug/device/biological/vaccine name(s)
Nitrofurantoin [Nitrofurantoin macrocrystals], Pivmecillinam hydrochloride [Each film-coated tablet contains 200 mg of pivmecillinam hydrochloride (pro-drug of mecillinam)], Cefalexin [Cefalexin (as monohydrate)], Amoxicillin [Amoxicillin Trihydrate BP/EP], Co-amoxiclav [Amoxicillin trihydrate. 574 mg corresponding to 500 mg amoxicillin Potassium Clavulanate. 149 mg corresponding to 125 mg clavulanic acid], Cefadroxil [cefadroxil (as monohydrate)], Distaclor [cefaclor monohydrate Ph.Eur.], Nitrofurantion [Nitrofurantoin macrocrystals]

## Primary outcome(s)
Proportion of participants in each arm experiencing sustained clinical cure without medically attended symptomatic recurrence through to day 42. Defined as no contact with a healthcare provider for UTI symptoms between randomisation and day 42. For patients recruited during a hospital admission for UTI, healthcare contacts will only be included in this definition if they are for new or worsening symptoms of UTI. Measured using records review and patient report.

## Key secondary outcome(s))

1. Daily through to day 42 measured using patient reported seven-point symptom severity scale, ranging from 0 (no problem) to 6 (as bad as it could be), participants will record the severity of several common presenting symptoms of urinary tract infection.
1.1. At day 42 measured using patient reported seven-point symptom severity scaleDuration of moderately bad (symptom severity score 3) and/or worse symptoms (symptom severity score 4-6) - measured using a patient-reported seven-point symptom severity score ranging from: 0 (no problem), 3 (moderately bad), 6 (as bad as it could be).
1.2. Total duration of symptoms – using the symptom severity scale described above, we will define the first day on which all symptoms are scored 0 as the day of complete symptom resolution.
1.3. Worsening or progression of symptoms
2.1. Number of symptomatic recurrences – defined as per our primary outcome definition;
2.2. Number of hospitalisations/prolonged hospitalisation/readmission for the treatment of urinary tract infection, urosepsis or a drug-related adverse event measured using records review and patient report at day 42
3. Frequency of adverse antibiotic effects (diarrhoea, nausea/loss of appetite, skin rash) measured using symptom diary, and records review at day 42
4. Total quantity of antibiotic use for the treatment of UTI including any non-NHS prescription usage measured using records review and patient report at day 42
4.1. Courses
4.2. days of treatment
4.3. total defined daily doses
5. Number of microbiological treatment failures 2 days after end of treatment measured through culture of a urine sample provided by all study participants
6. Resistance profile of urine culture isolates obtained from participants who experience treatment failure through to day 42 compared with baseline samples measured though culture of urine samples provided by participants alongside any urine samples they submit for clinical purposes during follow up period.
7. Measured and reported in accordance to the ABC taxonomy, EMERGE guidelines:
7.1. Treatment initiation –whether a participant starts their antibiotic treatment;
7.2. Treatment implementation –the proportion of doses taken as prescribed (accounting for dosing frequency and timeframe over which the course was prescribed);
7.3. Treatment persistence –the number of days treatment was taken before stopping (regardless of dosing frequency or timeframe over which treatment was taken)
8. Within-trial incremental net (monetary) benefit evaluation; health-related quality of life (EuroQol-5D (EQ-5D)) questionnaire, resource utilisation (antibiotic prescriptions, healthcare contacts); days off work due to illness.
9. Qualitative interviews among a subset of participants from each sub-trial

### Completion date
31/07/2025

# Eligibility

### Key inclusion criteria
1. Female, aged 18 years or above
2. Participant is willing and able to give informed consent for participation in the trial.
3. Urine sample for culture has been/can be obtained prior to starting antibiotics
4. For pyelonephritis sub trial (primary and secondary care):
4.1. Presenting with acute pyelonephritis symptoms for which the responsible clinician considers antibiotic treatment is either indicated or for whom an antibiotic has already been started within

the previous 48 hours.
4.2. Temperature of >38.0oC measured at presentation AND loin/flank pain or costovertebral angle tenderness AND ≥1 symptom of acute UTI (frequency, dysuria, urgency, nocturia, change in urine smell or appearance (e.g. cloudy or bloody urine), suprapubic pain).
4.3. If recruited in secondary care, willing to allow their General Practitioner, to be notified of participation in the trial
5. For the cystitis sub trial (primary care only):
5.1. Presenting with acute cystitis symptoms for which the responsible clinician consider antibiotic treatment is indicated
5.2. ≥two of the following symptoms of acute UTI (frequency, dysuria, urgency, nocturia, change in urine smell or appearance (e.g. cloudy or bloody urine), suprapubic pain).
6. English speaking

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Adult

## Lower age limit
18 years

## Sex
Female

## Key exclusion criteria
1. Antibiotics for the prevention or treatment of UTI within the previous month (n.b. Pyelonephritis patients that have started antibiotics within 48 hours are included).
2. Previous participation in the DURATION UTI Trial
3. Indwelling catheter
4. Inclusion in the trial is inappropriate in the judgement of the responsible clinician
5. Known anatomical abnormality of the urinary tract
6. Neurogenic bladder
7. Known pregnancy (pregnancy test not required for participation)
8. Unable to comply with study procedures
9. All antibiotic agents available to the participant in the trial are precluded in the view of the responsible clinician for example by:
9.1. patient factors (such as allergy, degree of renal impairment)
9.2. antibiotic susceptibility results (e.g. known carrier of antibiotic resistant organisms or resistance profile of the current infection if known at randomisation).

## Date of first enrolment
30/07/2023

## Date of final enrolment
31/01/2025

# Locations

**Countries of recruitment**
United Kingdom

**Study participating centre**
**Participants will be enrolled at participating GP practices in the United Kingdom when they present with symptoms of a suspected UTI.**
United Kingdom
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# Sponsor information

**Organisation**
University of Oxford

**ROR**
https://ror.org/052gg0110

# Funder(s)

**Funder type**
Government

**Funder Name**
National Institute for Health and Care Research

**Alternative Name(s)**
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

### Individual participant data (IPD) sharing plan

The datasets used and analysed during the current study contain potentially sensitive and identifiable patient information under the definitions of UK data protection legislation. Requests for de-identified participant level data collected during this study should be made to the Nuffield Department of Primary Care hosted Datasets Independent Scientific Committee (PrimDISC): primdisc@phc.ox.ac.uk which will include the chief investigator Professor Gail Hayward and representation from the CTU directors. Data will be released following review and approval by PrimDISC of a protocol, statistical analysis plan and the signing of a suitable data sharing agreement.

### IPD sharing plan summary

Available on request