Trial 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.

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Please declare any/no potential conflicts of interest

Confidentiality Statement

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

Aims

This research aims to find the shortest antibiotic treatment duration needed to treat urinary tract infections (UTIs) in women effectively. We will also look at the impact of each antibiotic and treatment duration on antibiotic resistance in bacteria found in the patient's urine.

Background

UTIs are among the most common presumed bacterial infections treated with antibiotics and are far more common in women than men. 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 reduce the risk of bacteria becoming antibiotic resistant, and help ensure the antibiotics remain effective for treating UTIs in the future.

Design and methods

We will recruit 2248 adult women with UTI symptoms who visit a clinician in either a hospital, Urgent Care Centre, pharmacy or GP surgery, and for whom the clinician judges that antibiotics are needed for a suspected bladder or kidney infection. For clarity throughout the protocol, the term 'clinician' is used to describe a suitably qualified person who would assess and prescribe treatment for UTIs as part of their normal role, including a GP, a nurse prescriber or a pharmacist. The clinician will randomise women with bladder infection to receive one of 2 commonly used antibiotics for this condition. Women with kidney infection will be offered one of a family of antibiotics which 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 (for example comparing one, two, three, four and five days of treatment with the same antibiotic for a bladder infection). Our focus will be to compare how many women recover fully six weeks after starting antibiotic treatments. 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 sub-study about the effect of antibiotic duration on antibiotic resistance in bacteria in their gut. Those joining this part of the study will be asked to provide self-taken rectal swabs. Subject to further funding, we will use these samples to find out how treatment duration affects antibiotic resistance in bacteria in the gut, and if so, whether this affects their health going forward.

3. SYNOPSIS

Trial 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.		
Internal ref. no. (or short title)	DURATION UTI		
Trial registration	ISRCTN 18390724		
Sponsor	University of Oxford		
Funder	National Institute of Health Research		
Clinical Phase	IV		
Trial Design	Open-label, parallel group, multi-arm "durations" randomised trial with two sub-trials 1) cystitis and 2) pyelonephritis.		
Trial Participants	Adult women		
Sample Size	2248		
Planned Trial Period	Total length of the project: 36 months A pilot phase will precede progression to the full trial recruitment. Progression will be according to recruitment; site set up and follow up criteria agreed with the funder.		
Planned Recruitment period	November 2023 - July 2025 (18 months)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine the minimum duration of antibiotic treatment which maintains sustained clinical cure for UTIs.	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	**Day 42** measured using records review and patient report.

		worsening symptoms of UTI	
Secondary	See table below (section 6)		
Intervention(s)	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.		

4. ABBREVIATIONS

ABC (taxonomy)	Ascertaining Barriers to Compliance
AE	Adverse Event
AMR	Antimicrobial Resistance
AR	Adverse Reaction
BSCTU	Brighton and Sussex Clinical Trials Unit
CFU	Colony-Forming Unit
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DAGs	Directed Acrylic Graphs
DMC	Data Monitoring Committee/Data Monitoring and Safety Committee
DMP	Data Management Plan
DPA	Data Protection Act
DSUR	Development Safety Update Report
eMERGe	meta-ethnography reporting guidelines
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
IB	Investigator's Brochure
IP	Intellectual Property
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
LFTs	Liver Function Tests
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
NMB	Net Monetary Benefit
OTU	Operational Taxonomic Unit
RES	Research Ethics Service
PC-CTU	Primary Care-Clinical Trials Unit

PI	Principal Investigator
PIC	Participant Identification Centres
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Year
QDS	Four times daily
R&D	NHS Trust R&D Department
RBC	Red Blood Cells
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SEC	Squamous Epithelial Cells
SMI	Standards for Microbiological Investigation
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U+Es	Urine and Electrolytes
UKHSA	United Kingdom Health Security Agency
UTI	Urinary Tract Infection
WBC	White Blood Cells

5. BACKGROUND AND RATIONALE

Minimising antibiotic use, while ensuring good clinical outcomes, protects patients from antibiotic resistance and conserves antibiotics for future use. Historically, durations in arbitrary multiples of five or seven days were used, aiming to avoid undertreatment. Shorter durations may be equally effective, but evidence for this in the treatment of Urinary Tract Infections (UTIs) is lacking, including for the first-line antibiotics currently recommended in the UK.

UTIs are common, affecting one in ten women annually, and takes two main forms: uncomplicated lower-tract infection (**cystitis**) and uncomplicated upper tract infection (**pyelonephritis**) [1]. For clarity we use the terms cystitis and pyelonephritis throughout this protocol. There is a lack of evidence that currently recommended treatment durations for UTIs minimise the emergence of resistance and maintain patient outcomes. Treatment of UTIs with antibiotics that are active against the causative organisms typically

improves symptoms quickly, but ~30% of patients suffer recurrences, increasing cumulative antibiotic use [2]. Longer treatment *may* increase sustained cure but risks more drug side-effects and increased antibiotic resistance selection. Alternatively, prescriber concerns that short treatment could result in antibiotic-resistant recurrences may undermine adherence with short-duration recommendations.

International guidelines vary widely (one-10 days for cystitis, five-14 days for pyelonephritis). In the UK, recommended durations are shorter than elsewhere, but practice varies and **there is substantial over-prescription**, with >50% of prescriptions for cystitis longer than recommended [3]. For pyelonephritis, trials have shown short durations of treatment with quinolone antibiotics (three-seven days for different agents) to be as effective as longer durations, but there is an almost complete lack of robust evidence for the beta-lactam antibiotics, which are the mainstay class of antibiotics used for this indication, below 14 days. The duration of treatments within this trial have therefore been chosen to give a full range of the potential options of prescription that might be given to those presenting with a UTI. The duration ranges we will evaluate are largely consistent with those recommended across different international guidelines, recently reviewed by the WHO and vary from 2-10 days for cystitis and from 5-14 days for pyelonephritis[4]. Some current UK UTI guidelines (SIGN)[5] recommend no antibiotics be offered for women presenting with cystitis without the presence of nitrates on urine dip, which in practice is the majority of women. The durations trial design is a highly efficient trial design which allows evaluation of multiple antibiotic durations in a single trial[6,7]. This approach requires evaluation of a range of at least 5 durations which fall either side of current most common practice. This allows a duration-of-treatment: response curve to be constructed by treating "Duration of treatment" as a continuous variable and parameterising it as a fixed-2 fractional polynomial) overcoming several major limitations of conventional non-inferiority trial designs in antibiotic research (with the major one being having to make a trade-off between studying a limited number of arbitrarily chosen treatment durations or conduct unfeasibly large trials). As with any non-inferiority trial, the possibility has to exist for the intervention being assessed to be inferior, in this case the possibility of shorter durations being associated with lower rates of sustained cure, although there is growing evidence that the converse may be the case, i.e. that antibiotic use in UTI may be associated with relapsing or recurrent infection[8]. This is the question the trial will answer. In the trial we therefore include durations between 1-5 days for cystitis and 4 –14 days for pyelonephritis.

A step change in our approach to antibiotic stewardship is needed now to avoid a potentially catastrophic reduction in clinically useful antibiotics for future generations. Optimisation of antimicrobial use to combat AMR was a priority of the health agenda at the June 2021 G7 meeting [9]. Optimal duration is one key element of this and yet the evidence base needed to guide practice is lacking, especially for the first-line drugs now in use for UTIs. Aside from the large burden of prescribing for UTIs, the importance of optimal treatment in this challenge is illustrated by its relationship to Gram-negative bloodstream infections. Cases of antibiotic resistant Gram-negative blood stream infections have increased 32% since 2015 and >50% of cases are linked to a UTI [10].

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine the minimum duration of antibiotic treatment which maintains good clinical outcomes for UTIs.	Proportion of participants in each arm experiencing sustained clinical cure without symptomatic recurrence resulting in contact with a healthcare professional 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	**Day 42** measured using medical notes review and patient report.
Secondary Objectives		
1. To explore the impact of antibiotic agent and treatment duration for each agent on time to resolution of symptoms.	a) **Duration 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). b) **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. c) Worsening or progression of symptoms.	Daily symptom diary for the first 14 days followed by weekly symptom diary completion through to and including 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 UTIs. At day 42 measured using patient reported seven-point symptom severity scale.

		At day 42 measured using patient reported seven-point symptom severity scale.
2. To explore the impact of antibiotic agent and treatment duration for each agent on sustained cure up to day 42.	a) **Number of symptomatic recurrences** – defined as per our primary outcome definition. b) **Number of hospitalisations**/prolonged hospitalisation/readmission for the treatment of UTIs or urosepsis.	**Day 42** measured using symptom diary, and records review.
3. To explore the impact of antibiotic agent and treatment duration for each agent on antibiotic-associated harms.	**Frequency of adverse antibiotic effects** (diarrhoea, nausea/loss of appetite, skin rash).	**Day 42** measured using symptom diary, medical notes review and patient report.
4. To explore the impact of antibiotic agent and treatment duration for each agent on total antibiotic use over 42 days.	**Total quantity of antibiotic use** for the treatment of UTIs including any non-NHS prescription usage: a) Courses b) Days of treatment c) Total defined daily doses.	**Day 42** measured using medical notes review and patient report
5. To explore the impact of antibiotic agent and treatment duration for each agent on risk of microbiological failure and antimicrobial resistance.	**Number of microbiological treatment failures** two days after end of treatment. Defined as further microbiologically confirmed UTI using the criteria detailed in section 9.8.1. **Resistance profile of urine culture isolates** obtained from participants who experience treatment failure through to day 42 compared with baseline samples.	**End of randomised treatment duration + 2 days** measured through culture of a urine sample provided by all study participants **Up to day 42** measured though culture of urine samples provided by participants alongside any urine samples they submit for clinical purposes during follow up period.
6. To explore adherence to different antibiotic drugs and treatment durations.	Measured and reported in accordance to the ABC taxonomy, eMERGe guidelines:	Day 21 through patient diaries.

	a) **Treatment initiation** – whether a participant starts their antibiotic treatment b) **Treatment implementation** – the proportion of doses taken as prescribed (accounting for dosing frequency and timeframe over which the course was prescribed) c) **Treatment persistence** –the number of days treatment was taken before stopping (regardless of dosing frequency or timeframe over which treatment was taken).	
7. Explore the impact of different antibiotic agents and treatment durations on health-related quality of life, costs, and cost effectiveness.	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.	Baseline, day 7 for cystitis sub trial, day 16 for pyelonephritis sub trial, day 42 and at 6 months.
8. Explore patient acceptability of, and satisfaction with, different antibiotic drug and treatment durations and understand the interaction between patient behaviour and antibiotic duration.	**Qualitative interviews** among a subset of participants from each sub-trial.	Once patients have completed study procedures.
Tertiary objectives		
1) To understand the impact of antibiotic agent and treatment duration for each agent on gut microbiome bacterial species composition and change in antibiotic	Impact of antibiotic drug and treatment duration on gastrointestinal bacterial species and AMR gene diversity and abundance in rectal swab samples. Impact of antibiotic drug and treatment duration on	For bacterial taxonomic and AMR gene endpoints, we will evaluate at treatment end, at day 42, and at six months, all relative to baseline (pre-treatment) samples. For the evaluation of microbiome changes on

resistance genes in faecal bacteria.	colonisation with *Clostridioides difficile.* Impact of microbiome perturbation and AMR gene selection on subsequent healthcare attendances and infection rates.	subsequent healthcare attendances and infection rates we will use a 6 month questionnaire, records review and also data linkage via UKHSA
2) Explore impact of incorporation of AMR selection/emergence metrics into the health-economic **evaluations.**	Cost-effectiveness analysis incorporating healthcare attendances and infection rates up to one year post-treatment, i.e. going beyond the within trial 42-day endpoint Threshold analysis to assess at what cost (willingness to pay) per change in i) prevalence of important AMR genes from baseline, and ii) in alpha diversity (Shannon index) decisions about optimal duration in terms of cost-effectiveness would be changed.	6 months post randomisation
3) Understand the impact of antibiotic treatment on the clinical course of pyelonephritis.	Change in physiological measurements, biochemical and haematological blood tests, which are captured as part of routine clinical care.	Data captured using baseline and daily inpatient Case Report Forms (CRFs) in hospitalised patients, and at baseline in primary care, with ongoing data capture for hospitalised patients until day 5 or discharge, whichever is sooner

7. TRIAL DESIGN

This will be an open-label, parallel group, multi-arm randomised trial with two sub-trials enrolling patients with: 1) cystitis, and 2) pyelonephritis. Participants with cystitis will be recruited only from primary care. Participants with pyelonephritis will be recruited from primary and secondary care. It uses a novel trial design called 'durations', in which participants are randomised to one of a range of antibiotic treatment durations rather than just a comparison of two pre-specified durations. This allows a duration-of-treatment: response curve to be constructed overcoming several major limitations of conventional non-inferiority trial designs in antibiotic research.

We will 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.

Within each of these three treatment-condition combinations the primary aim will be to investigate the minimum duration of antibiotic therapy that provides an acceptable level of clinically sustained cure at day 42.

For full antibiotic information, please see IMP section (10.1).

Data will be collected at baseline and up to and including 42-days post-randomisation via urine samples, self-completed questionnaires, and medical notes review. There will be additional data collection at 6 months post randomisation for health economics outcomes.

Appendix A is a flow chart of participation and procedures.

Pilot phase: A pilot phase will precede progression to the full trial. Progression will be according to recruitment; site set up and follow up criteria agreed with the funder.

The recruitment and follow up of primary care participants will be managed by the Primary Care Clinical Trials Unit (PC-CTU) and the University of Oxford and the recruitment and follow up of secondary care participants will be managed by the Brighton and Sussex Clinical Trials Unit (BSCTU) at the Brighton and Sussex Medical School.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Adult women (age ≥18) being prescribed antibiotics for cystitis or pyelonephritis.

8.2. Inclusion Criteria

- Female, aged 18 years or above
  *Participants will be included only if they are assigned female at birth. Transgender men can be included provided that they have an anatomically normal female urological tract.
- Participant is willing and able to give informed consent for participation in the trial.
- For pyelonephritis sub trial (primary and secondary care):
  - Presenting with acute pyelonephritis symptoms for which the responsible clinician considers antibiotic treatment is either indicated or has been started within the previous 72 hours.
  - All three of:
    1. Fever, evidenced by either a measured temperature of ≥38.0°C at any time since onset of symptoms (including by the patient prior to presentation) OR, if the patient has taken antipyretics or antibiotics in the last 24 hours, reported fever, chills or rigors since the onset of symptoms
    2. Loin/flank pain or costovertebral angle tenderness
    3. ≥ 1 symptom of acute UTI (frequency, dysuria, urgency, nocturia, change in urine smell or appearance (e.g. cloudy or bloody urine), suprapubic pain).
  - If recruited in secondary care, willing to allow their General Practitioner (GP) to be notified of participation in the trial.

- For the cystitis sub trial (primary care only):
    - Presenting with acute cystitis symptoms for which the responsible clinician considers antibiotic treatment is indicated.
    - ≥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.
    - Urine sample for culture has been / can be obtained prior to starting antibiotics.
- For the Qualitative Sub-study only: English speaking

8.3. Exclusion Criteria

- Previous participation in the DURATION UTI Trial.
- Indwelling catheter.
- Inclusion in the trial is inappropriate in the judgement of the responsible clinician.
- Known anatomical abnormality of the urinary tract.
- Neurogenic bladder.
- Known pregnancy (pregnancy test not required for participation-see section 8.4 for further details).
- Unable to comply with study procedures.
- All antibiotic agents available to the participant in the trial are precluded in the view of the responsible clinician, for example by:
    - Patient factors (such as allergy, degree of renal impairment).
    - Antibiotic susceptibility results (e.g. known carrier of antibiotic resistant organisms or resistance profile of the current infection, if known at randomisation).

Cystitis sub-trial:

- Antibiotics for the prevention or treatment of UTI within the previous 28 days.

Pyelonephritis sub-trial

- Antibiotics for the prevention of UTI within the previous 28 days
- Antibiotic treatment for this episode of pyelonephritis for >72 hours
    - Where patients are already on antibiotic treatment for this episode of pyelonephritis at the time of randomisation the duration of pre-randomisation treatment is included in the total randomised duration
    - Of note, antibiotic treatment for indications ***other than pyelonephritis*** (including for cystitis) prior the start of antibiotic treatment for pyelonephritis does ***NOT*** exclude patients from participation irrespective of duration and this treatment is ***NOT*** included in the total randomised duration.

8.4. Clarification of Approach of Pregnancy

In routine primary care clinicians assess the risk of pregnancy before prescribing for UTI because prescribing guidance advises longer durations of antibiotics. This risk assessment will include menopause status, use of long acting contraceptives, correct use of oral contraceptives and whether the patient is sexually active. In cases where it is possible that a patient is pregnant but unaware of it, a pregnancy test will be performed as usual care. However, since this risk assessment is conducted in usual care and in the majority of cases the risk will be low, we have not made a negative pregnancy test a requirement for study

entry. In secondary care all patients will have a pregnancy test as standard of care where pregnancy could be physiologically possible. This is Standard of Care and would be undertaken as part of a clinician's normal role, but this will be reinforced to sites during training.

9. TRIAL PROCEDURES

Please see Appendix B for a schedule of procedures for primary and secondary care.

9.1. Site Recruitment

GP surgeries, pharmacies, out-of-hours, urgent or acute Primary Care Centres and hubs, PIC sites and acute hospital trusts will be invited to participate via the National Institute for Health Research (NIHR) Clinical Research Network. Sites will be selected based on their likelihood of recruiting successfully (e.g. for secondary care sites considering emergency and acute medicine pathways) and to ensure we recruit a diverse population of patients from across the country. We will also advertise the trial by displaying posters at the trial sites and, where possible, at pharmacies adjacent to the sites to direct participants who visit pharmacies for UTI treatment. Additionally, we have worked with pharmacies to allow recruitment at selected sites where the Pharmacy First initiative has been adopted to treat women with UTIs. The new Pharmacy First service, launched 31 January 2024, enables community pharmacies to complete episodes of care for 7 common conditions following defined clinical pathways.

9.2. Screening and Eligibility Assessment

In primary care, patients will be screened by the site research team on presentation with UTI symptoms. Screening will be based on the inclusion and exclusion criteria detailed above.

In the secondary care setting, patients starting antibiotic treatment for pyelonephritis will be made aware of the trial by their attending clinical team. If they agree to discuss participation, they will be assessed for eligibility by the site research team within 72 hours of starting antibiotic treatment for pyelonephritis. Eligible consenting patients will be randomised and prescribed the antibiotic treatment to complete their randomised duration. Pre-enrolment antibiotic treatment for pyelonephritis (IV or oral) will be considered as part of the randomised course duration. Pre-enrolment treatment for other indications including for cystitis will not be considered part of the randomised course duration.

In a pharmacy setting, patients that present to the pharmacy with suspected UTI symptoms at selected pharmacies are currently entered into the Pharmacy First pathway. At pharmacies taking part in DURATION UTI, patients with UTI symptoms that are confirmed by pharmacy to require treatment via their clinical pathway will be asked if they would like to take part in the study. If the patient agrees, following a discussion, they will complete informed consent procedures and be screened for eligibility by an Independent Pharmacist based on the inclusion and exclusion criteria detailed above. Following randomisation, treatment will be dispensed to the participant as per randomised allocation. Pharmacies may only recruit participants into the cystitis sub-study and all study procedures and CRFs will be completed as they would be in a Primary Care setting.

Participants (primary or secondary care) will be offered the opportunity to take part in an optional rectal swab sub-study prior to randomisation (thus limiting selection effects as this is an open-label trial) until n=50 have been recruited for each drug-duration of interest (i.e. total n=550 participants). These participants will provide a self-taken rectal or faecal swab at baseline, two days after the end of treatment,

at day 42 and at six months for evaluation of species diversity and AMR gene carriage (i.e. four time-points, total n=2,200 samples). Participants will be invited into this sub-study from the pyelonephritis sub trial and the cystitis sub trial.

9.3. Informed Consent

Eligible participants will be asked to provide informed consent after a discussion between an appropriately trained member of the site research team and the potential participant, where the risks and benefits of taking part and follow-up procedures will be explained. Where required we will translate the study documents into required languages (up to five different languages based on the most commonly used languages in our recruiting sites) or we will allow a family member to act as an interpreter to directly translate the required information and aid the consent and data collection process. This will also apply to secondary sites, if a local trust has an interpreter they could use they will be allowed to do so according to their local policy.

In keeping with increasing remote clinical consultation for UTIs, consent may be either face-to-face or given remotely, using online paperless consent forms and via telephone/video discussion. If remote consent is being taken, participants will be sent a link to the consent form which they will go through with the person taking consent. They will initial the boxes on this form and type in their name and date as requested to indicate their consent. Participants will be sent a link through which they should download their consent form after completion, or a copy sent to them through the post if the participant does not have an email address. Electronic consent forms will be held securely on the trial database and a copy will be attached to the participant's medical records.

Prior to consent, written versions of the Participant Information Sheet (PIS), and Informed Consent Form (ICF) will be available to participants detailing the exact nature of the trial and the known side-effects, and risks involved in taking part. It will be clear that the participant is free to withdraw from the trial at any time. Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. This time will often be less than 24 hours so that there is minimal delay to the starting of antibiotic treatment for the participant's infection. After consent, participants will enter baseline information, including their address and contact details into the electronic case report form (or alternative back-up paper form should they be unable to access an electronic case report form).

9.4. Randomisation

Participants entering the cystitis sub-trial (primary care only) will be allocated to one of two antibiotic treatments (nitrofurantoin or pivmecillinam) and to one of five antibiotic durations (one, two, three, four, or five days) using block randomisation with randomly permuted blocks. 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.

Participants entering the pyelonephritis sub-trial (primary and secondary care) will be allocated to one of six antibiotic durations (four, six, eight, ten, twelve, or fourteen days) also using block randomisation with randomly permuted blocks. However, in this sub-trial we will stratify randomisation by the setting from which the participant was recruited, treating 'primary care' as one site and 'secondary care' sites individually. This will help ensure durations are distributed evenly across sites using different beta-lactam

antibiotics, although beta-lactam choice may depend on, for example, antibiotic sensitivity of bacterial causing UTIs in individual patients.

We will use our in-house online randomisation software Sortition® to allocate participants to trial arms. Upon confirmation of eligibility and consent, the recruiting clinician or appropriately delegated member of the site research team will log into Sortition®, indicate the sub-trial to which the participant is entering (cystitis or pyelonephritis), and confirm eligibility and consent. For the pyelonephritis sub-trial, the setting and site from which the participant is presenting (primary or secondary care) will be confirmed.

The use of randomly permuted blocks, the sizes of which will not be revealed to the recruiting team member, will preclude the predictability of allocations.

The attending clinician will then prescribe the randomised agent and duration through the normal prescription process at their site. An automated alert generated by the Sortition® system will notify the site-PI and central trial manager that a new participant has been randomised.

9.5. Blinding and Code Breaking

DURATION UTI is an open-label trial. The participant and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required.

The trial team and recruiting clinicians will be blinded to emerging results of interim analyses. During the trial, only the unblinding statisticians and the independent members of the Data and Safety Monitoring Committee (DSMC) will have access to the unblinded interim results.

9.6. Baseline Assessments

Following consent, participants will complete a baseline CRF including details of their symptoms, their ethnicity, relevant medical history, and quality of life using an EQ5D-5L, dietary habits, previous travel, their home and work environment, and their smoking history. Additional relevant medication history will be given via a clinician completed CRF at baseline. For those who are in hospital when they are recruited this also will include basic clinical and physiological assessments and blood results captured as part of routine care and available at baseline. If a participant is being recruited after they have started their antibiotics they will complete the baseline form retrospectively to reflect their symptoms on the day they started antibiotics. The participant will be randomised, or told their randomised allocation, once their baseline form has been completed.

Participants recruited in to the cystitis arm will be asked to give a urine sample before they start their antibiotics which will need to be brought to their recruiting site.

In the pyelonephritis arm, if antibiotics have not yet been started, sites will be asked to attempt to obtain a urine sample for study purposes. Results from any urine and blood cultures performed as part of routine care during this episode of infection will be collected. Also in secondary care, where possible, cultured isolates will be sent from the local NHS laboratory to the Trial laboratory for research purposes, see section 9.8 for further details.

Participants who have consented to the optional rectal swab sub-study will provide a self-taken rectal or faecal swab, they will post this directly to a central research laboratory using a postage paid envelope.

9.7. Subsequent Visits

1) Participants will complete a symptom diary daily for the first 14 days and thereafter complete a weekly symptom diary up to and including Day 42 from randomisation, to include severity of key UTI symptoms, any healthcare contacts and any antibiotics, analgesics or other products used for treating the UTI (e.g. cystitis sachets, D-mannose, methenamine hippurate, probiotics). This will be online, but completion by telephone with a member of the study team will be offered to participants unable to complete it online. Text messages or emails will act as a reminder to complete the diary. This will include the EQ5D-5L at day 7 or day 16 for cystitis and pyelonephritis participants respectively. If a participant is being recruited more than one day after they have started their antibiotics they will be asked to complete the first day of their diary retrospectively to reflect their symptoms for the first day after starting antibiotics. Participants may also be called to aid in their completion of the daily diary where there is significant non response.
2) Participants will complete a day 42 follow-up questionnaire including the EQ5D-5L, overall symptom duration, and details of any antibiotics taken, and any medical contacts up to day 42; and a medical notes review will be performed
3) Participants will submit a urine sample two days after completion of treatment and further urine sample(s) if they contact a healthcare provider with symptoms of UTI (which could be multiple times) up to and including day 42.
4) For participants who are recruited when admitted to hospital, a daily CRF will capture bloods and physiological observations taken as part of routine care, until the point of discharge or day 5 after randomisation, whichever is sooner.
5) Participants will complete a final questionnaire and the EQ5D-5L at 6 months and a medical notes review will be performed
6) Participants in the optional rectal swab sub-study will provide a self-taken rectal or faecal swab at baseline, two days after the end of treatment, at day 42 and at six months for evaluation of species diversity and AMR gene carriage, and complete an additional questionnaire at day 42 and six months. Data linkage with UKHSA will be used to access the results of urine culture tests for the year before up until the year after study entry (subject to further funding)

9.8. Sample Handling

9.8.1 Urine sample handling for trial purposes

Urine samples for the research will be transported to, and processed at, Specialist Antimicrobial Chemotherapy Unit (SACU), Microbiology Cardiff, Public Health Wales, University Hospital of Wales, Cardiff, CF14 4XW according to current UK Standards for Microbiological Investigation (SMI) of Urine (Standards in Microbiological Investigations (B41) [11].

All urine sample details will be logged, along with time/date of arrival and processing plus associated isolate storage in electronic files kept on Public Health Wales password protected computers.

At baseline in the cystitis arm: If the clinician requests a urine culture result to support clinical care the sample will be split into two, with one fraction sent to a central trial laboratory for research analysis, and the second other fraction sent by the clinician to their usual NHS laboratory. No results from any trial laboratory procedures will be fed back to the participants.

At baseline in the pyelonephritis arm: If the patient has not yet started antibiotics, sites will be asked to attempt to obtain a baseline sample for study purposes and send to a central trial laboratory for research analysis **.** If samples have already been sent for urine or blood culture for this episode of infection as part of standard of care, the results will be noted, and in secondary care, where possible, isolates will be sent by the local NHS laboratory to the study reference laboratory for antimicrobial susceptibility testing. Details of colony counts and white blood cell counts (WBC) performed by the local NHS laboratory will be retrieved from the microbiological records.

At follow-up: participants recruited in both primary and secondary care will post their urine samples directly to the trial laboratory using appropriate packing and pre-paid postage at two days after completing their randomised antibiotic course and if they experience another infection for which they present to a healthcare setting up to and including day 42.

Sample processing: Sample processing will be described in detail in a separate microbiology sample processing document.

Samples will be stored until 12 months after the end of study declaration – after that everything will be rendered acellular or disposed of. Within that 12 months samples which have consent for future use will only be released after confirmation by the trial team that consent is in place and trial analyses are complete.

9.8.2 Rectal and faecal swab sample handling

Rectal Swabs will be posted directly to the Modernising Medical Microbiology research laboratory at the John Radcliffe Hospital, Oxford where they will be stored. An electronic log of all rectal swab samples received, together with storage locations and details of sequencing procedures undertaken, will be maintained during the study, using password protected secure systems hosted within the University of Oxford. An overarching log of all expected samples will also be kept at the PC-CTU. Other laboratories might be contracted to do these analyses, in which case the samples will be shipped, to that laboratory for the purposes of the described and approved analysis.

Participants who agree to take part in the optional rectal swab sub-study will be provided with swabs and associated materials for posting. They will provide a self-taken rectal swab at baseline, two days after they have completed their course of antibiotics, at day 42 and at six months.

Swabs will be e.g. Copan FecalSwab®, or an equivalent. Approved Sampling packs (including packs approved for sample return in regular mail) and instructions will be sent to participants in the sub-study; the study team will be available to provide advice on any issues related to sampling.

In addition to self-taken rectal swabs, participants will be asked to fill in an online questionnaire in relation to each of the sampling timepoints – questions will include details on medications, diet, smoking status and recent travel.

If future funding allows, where consent has been given, we will biobank these samples.

9.9. Early Discontinuation / Withdrawal of Participants

Participants may choose to withdraw early from the trial at any time and for any reason. Participants who wish to withdraw will be asked to allow the trial team to continue to access their medical records to ascertain the trial's primary outcome measure of further contact with healthcare for symptoms of UTIs within 42 days.

Participants who do not agree to this will be withdrawn completely from the study, however, it will be made clear to the participants that any data and samples already collected will still be used in the final study analysis.

The reason for withdrawal will be recorded in the CRF. However, subjects will not be obliged to provide a reason for withdrawal.

Any information that has already been pseudo-anonymised, e.g. samples and interview transcriptions, will not be able to be removed from analysis. Where qualitative interviews have not yet been transcribed, and consent is withdrawn, these interview recordings will be destroyed.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening).
- Significant protocol deviation.
- Significant non-compliance with treatment regimen or trial requirements.
- A significant event which results in inability to continue to comply with trial procedures.

If the participant is withdrawn due to a serious medical occurrence, the Investigator will arrange for follow-up visits or telephone calls until the event has resolved or stabilised.

9.10. Definition of End of Trial

The end of trial is the point at which all the data has been entered and queries resolved, and the database has been locked.

10. TRIAL INTERVENTIONS

10.1. Investigational Medicinal Product(s) (IMP) Description

The trial aims to gain further information about the use of antibiotics already licensed for the treatment of UTIs. Specifically, it will evaluate different antibiotic treatment durations which act as comparators for each other. The medications will each be used at standard therapeutic doses, according to local practice, but treatment will vary in the number of days the antibiotics are prescribed for. There will be no medication provided by the study team and the clinicians and participants will not be blinded.

As the medication is being provided at standard therapeutic doses for their licensed indication from general site stock, trial-specific labels are not provided for the IMP.

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).

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.

For Pyelonephritis participants that have already received antibiotic treatment (up to 72 hours) prior to randomisation, this treatment time will be included as part of the randomised treatment duration. E.g. if participant has had 72 hours of antibiotics prior and was randomised to four days of treatment then the site research clinician will prescribe one day of beta-lactam antibiotics for the trial.

10.1.1. Dosing schedule

Cystitis sub-trial:

- Participants receiving nitrofurantoin 100mg Modified Release twice daily or 50mg four times daily (QDS)
- Participants receiving pivmecillinam 400mg single dose then 200mg three times daily

Pyelonephritis sub-trial:

Beta-lactam antibiotics (i.e. a penicillin or cephalosporin) dosed for systemic use as per local policy and clinical judgement will be used for the trial e.g. cephalexin 1g three times a day, co-amoxiclav 625mg three times a day, amoxicillin 1g three times a day.

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.

10.1.2. Blinding of IMPs

There is no blinding of IMPs

10.1.3. Storage of IMP

The IMPs in this trial are commercially available, UK-licensed drugs taken from routine hospital or pharmacy stock. They are not supplied by the Sponsor as trial drugs and should be ordered, stored and destroyed in the usual way according to local hospital and pharmacy policy. Any generic brand may be used**.**

10.1.4. Compliance with trial treatment

Compliance will be monitored in symptom diaries. We will measure and report the following in accordance with the ABC taxonomy, eMERGe guidelines [12,13,]

- Treatment initiation – whether a participant starts their antibiotic treatment.
- Treatment implementation – the proportion of doses taken as prescribed (accounting for dosing frequency and timeframe over which the course was prescribed).
- Treatment persistence – the number of days' treatment was taken before stopping (regardless of dosing frequency or timeframe over which treatment was taken).

There will be no action taken if non-compliance is detected, but this data will be incorporated in a sensitivity analysis of the primary outcome.

10.1.5. Accountability of the trial treatment

As the medication will be provided from general pharmacy stock, there are no procedures needed to track drug accountability. Only compliance to medication will be monitored, as outlined in section 10.1.4.

10.1.6. Concomitant medication

It is the responsibility of the prescribing clinician to check the interactions between the trial IMP and other medication.

10.1.6. Post-trial treatment

There will not be provision of the IMP beyond the trial period.

10.2. Other Treatments (non-IMPS)

There are no non-IMPs in the trial design.

10.3. Other Interventions

There are no additional interventions in the trial design.

11. SAFETY REPORTING

11.1 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*.

	Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. NOTE: If participant experiences a miscarriage during the follow-up period, this will be assessed as per our safety reporting procedures, and the participants will be withdrawn from the trial and treated as in standard care.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

11.2 Reporting Procedures

This trial is evaluating licensed medications for their licensed indication, and all the medications that might be prescribed already have extensive safety data already available. Therefore, the risk associated with this trial is similar to that of standard care, and we consider this trial to be a Type A trial, according to the MHRA categorisations. As such, hospitalisations, symptoms and antibiotic reactions will be recorded through patient symptom diaries and notes review by GP, site research team in secondary care and Research Nurses from the CTU or the local RDN for participants recruited through pharmacies, but there is no requirement for expedited safety reporting as the IMP is licensed for the indication in this trial. Given the extensive safety profiles these licensed medications already have we do not expect any suspected unexpected serious adverse reactions (SUSARs), but should any occur these will be reported according to the standard timelines for SUSAR reporting (see section 11.1). We will use the IMP Dossier submitted as a

representative sample of SmPCs for approval by the MHRA and these will be used for our reference safety information in this trial.

All hospitalisations that occur up to and including day 42 will be reported to the trial team through participant-completed questionnaires or through medical notes reviews. The reporting clinician or a clinician from the trial team will assess these hospitalisations for relatedness to UTIs, or to treatment reactions (e.g. anaphylaxis). This will all be done as part of the main trial reporting process. We will also be fully documenting the symptoms associated with UTIs and antibiotic use in participant symptom diaries. Additionally, participants will be able to highlight any additional symptoms they are experiencing through their symptom diary. All hospitalisations and symptom recovery information will be reviewed by the Data Monitoring Committee (DMC) which will meet regularly throughout the trial.

For participants recruited through the Pharmacy First pathway, Boots and other pharmacies have their own internal processes for reporting safety events and incidents, which they have aligned to link in with those of the study. The safety reporting procedures for the trial remain unchanged.

11.3 SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Potential SUSARs will be identified through the reporting of symptoms, reactions and hospitalisations in the participant symptom diaries and through the medical notes reviews. Regular data monitoring will look to identify any unexpected reactions and the DMC will review this data when they meet.

Expectedness of any potential SUSARs will be assessed by the CI or appropriately qualified clinician within the trial team.

11.4 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

12. STATISTICS

12.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a SAP that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place, following approval by the Trial Management Group (TMG), DMC, and Trial Steering Committee (TSC).

12.2. Description of Statistical Methods

Descriptive statistics will be summarised using frequencies and percentages, means and standard deviations, or medians and interquartile ranges, as appropriate. The analysis of internal pilot outcomes will focus on estimation and hence no hypothesis testing will be performed. Estimates will be accompanied by 95% confidence intervals, with these used to inform decision making around trial continuation/modification.

For our primary analysis, we will estimate the duration-response curve using logistic regression with sustained cure regressed onto duration, which will be modelled as a fixed 2 fractional polynomial[20]. Each antibiotic class (i.e. nitrofurantoin, pivmecillinam, and beta-lactams) will be modelled separately. We will adjust for IV antibiotic use and setting (primary/secondary care) in the duration-response curve for the pyelonephritis sub-trial. Bootstrapping will be used to estimate 95% confidence intervals around the difference in response between each duration and the longest duration. Bootstrapped confidence intervals will be used to identify the shortest duration non-inferior to the longest duration, with respect to the acceptability frontier. The primary analysis will include all randomised participants in their original allocated arm, regardless of protocol (including treatment) deviations (i.e. following the intention-to-treat principle). We expect primary outcome data availability to be high. However, we will explore the extent and mechanisms underlying any missing primary outcome data over the course of the trial and consider appropriate statistical methods for handling these (e.g. multiple imputation) [14].

Secondary outcomes will be analysed similarly, with linear, Poisson (or negative binomial), and flexible parametric survival models fitting as appropriate.

Sub-group analysis will explore the extent to which the duration-response curve differs for our primary outcome depending on the following sub-groups:

- Participants with a microbiologically-confirmed UTI;
- Participants with a microbiologically-confirmed UTI for which the infecting organism is sensitive to the antibiotic being used;
- The setting from which the participant is recruited – primary or secondary care (pyelonephritis sub-trial only);
- Whether the participant received IV antibiotics prior to study entry (pyelonephritis sub-trial only).

To explore these subgroup effects, we will extend our primary analysis by including a subgroup by duration interaction term [15,16].

As two sensitivity analyses, we will re-fit the primary analysis:

- Excluding individuals who do not initiate treatment;
- Excluding individuals who do not persist with treatment for their allocated duration.

These will form the basis of two per-protocol analyses, and while prone to selection bias due to post-randomisation exclusion, may be more conservative in assessing non-inferiority than relying purely on an intention-to-treat analysis set.

As further sensitivity analyses, we will construct directed acyclic graphs (DAGs), illustrating our hypothesised data generating mechanisms underpinning our two “per-protocol” analysis sets described above and thus identifying important confounders (e.g. symptom severity) and mediators (additional

treatment) between actual antibiotic consumption (exposure) and sustained clinical cure at day 42 (outcome) [17]. We will explore the use of allocated duration as an instrument in order to minimise selection bias between exposure and outcome [18,19].

12.3. Sample Size Determination

Each sub-trial is powered on the primary outcome of sustained clinical cure at day 42.

In the cystitis sub-trial, we will randomise 151 participants to each of five durations (755 total) for each antibiotic (i.e. 1,510 participants in total). Two recent similar trials have reported sustained cure rates at 4-6 weeks of 70-80% [20,21] and routine practice data from the Infections in Oxfordshire Database[22] are that 15% of women have a repeat urine culture sent within 42 days of a positive index culture. We have therefore used a sustained cure rate at day 42 of 80% and an acceptability frontier of 12.5% in our simulations which demonstrate >90% acceptable power across duration-response curve scenarios and Type-I error <0.025. Sample sizes for the cystitis sub-trial are inflated to account for 70% of included participants having a microbiologically proven UTI and 95% antibiotic sensitivity to the infecting organism based on recent routine laboratory surveillance data[23].

In the pyelonephritis sub-trial, we will randomise 123 participants to each of six durations (i.e. 738 participants in total). This is based on the same sustained clinical cure of 80%, acceptability frontier of 10%, and simulations with similarly good operating characteristics as for the cystitis antibiotic durations.

For the pyelonephritis sub-trial, the sample size has also been inflated using assumptions that 80% of participants will have a microbiologically-proven UTI and 80% of infections will be sensitive to the antibiotic prescribed. The acceptability frontiers we have used (12.5% and for cystitis and 10% for pyelonephritis (both absolute)) reflect FDA guidance on non-inferiority margins in this field[24,25], were approved by patient and clinician stakeholders, and differ between cystitis and pyelonephritis to reflect the different severity of the two conditions.

The simulations used to estimate our Power and Type-I error were modified from the simulations used in Quartagno et al (2020) [26]. Quartagno's paper generated 500 simulated datasets per scenario. Taking this as a guide (given our own design parameters are close to those used in that paper) and owing to the computationally intensive nature of these simulations, we generated 20 simulated datasets across eight plausible duration-response curve scenarios. To test the robustness of our estimates to this smaller number of simulations, for two differing duration-response curves we generated a further 100 simulations.

We will regularly monitor the assumptions underpinning these calculations (including the percentage of participants with a microbiologically proven UTI with a susceptible infecting organism) through our DMC determination.

12.4. Analysis Populations

We will consider four analysis populations:

1. Intention to treat analysis population: this will include all randomised participants in the arm to which they were originally allocated, regardless of protocol deviations or non-adherence to treatment or treatment duration. Randomised participants, for whom outcome data are not available, will have missing observations imputed and will thus be included in this analysis population.

2. Complete case population: this will include all randomised participants in the arm to which they were originally allocated, regardless of protocol deviations or non-adherence to treatment or treatment duration, for whom outcome data are available.
3. Per-protocol population 1: this will include all randomised participants, in the arm to which they were originally allocated, who initiate antibiotic treatment, for whom outcome data are available.
4. Per-protocol population 2: this will include all randomised participants, in the arm to which they were originally allocated, whose persistence with antibiotic treatment corresponds to their allocated duration, for whom outcome data are available.

When developing the SAP, we will expand on these and incorporate them into an estimand framework.

12.5. Decision Points

The study total duration 36 months split into Setup (months 1-9), Internal Pilot trial phase (months 10-15), Full trial phase (months 16-30) and Outputs phase (months 31-36).

Progression criteria from Internal Pilot to Full trial phases have been agreed with the funder and are set out in the table below.

Additionally, in the pilot phase we will:

- Assess the acceptability (to patients and clinicians) of randomisation into each sub-trial
    - Qualitatively (via patient interviews).
    - Quantitatively (via a survey of recruiting sites, scrutiny of screening logs and exploring reasons for post-randomisation dropouts).
    - Test the assumptions underpinning our sample size calculations (e.g. retention, % of participants allocated to the longest duration with sustained cure at day 42; % of participants with a microbiologically proven UTI; % of participants with a microbiologically proven UTI to which the infecting organism was sensitive to the prescribed antibiotic) and stopping rules.

Progression criteria for the Pilot trial are set as follows. Green indicates progression onto the Full trial and amber the need for minor modification.

Outcome	Outcome definition	Time assessed	Progression criteria		
			Green (100%)	Amber (66%)	Red (33%)
Site open to recruitment	Primary care	End month 15	≥30	11-29	≤10
	Acute trusts	End month 15	≥6	4-5	≤3
Participants recruited	Primary care	End month 15	≥140	92-139	<92
	Acute trusts	End month 15	≥90	60-89	<60
Recruitment rates per site	Primary Care	End month 15	≥1/site/ month	1/site/6 weeks	1/site/2months
	Acute trusts	End month 15	≥3/site/month	2/site/month	1/site/month

12.6. The Level of Statistical Significance

For assessments based on non-inferiority/acceptability frontiers, we will use one-sided significance levels of 0.025. For assessments based on superiority, we will use two-sided significant levels of 0.05.

12.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

We expect primary outcome data availability to be high. However, we will explore the extent and mechanisms underlying any missing primary outcome data over the course of the trial and consider appropriate statistical methods for handling these (e.g. multiple imputation). An imputation model that aims to adequately capture the missing mechanisms will be developed, with the aim to fit models that are valid under a Missing At Random (MAR, given observed data) assumption.

12.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the finalised SAP will be agreed by TMG members and reported as post-hoc analyses, with justifications given.

12.9. Health Economics Analysis

Health-related quality of life will be recorded using the EuroQol-5D (EQ-5D) questionnaire at baseline, two days after completion of the longest course of antibiotics in each subgroup (day 7 in cystitis arm and day 16 in pyelonephritis arm), and day 42 after treatment allocation.

Costs will be estimated by multiplying resource utilisation (antibiotic prescriptions, healthcare contacts) by corresponding unit costs. While the primary health economic evaluation will be performed using a UK NHS perspective, days off work due to illness will also be recorded for a secondary cost-effectiveness evaluation from the societal perspective.

As detailed above, the primary outcome is analysed using a logistic regression model with a fixed 2 fractional polynomial, based on the clinically reasonable assumption that there is a monotonic relationship between duration of antibiotic treatment and cure. For the two drivers of the net monetary benefit (NMB), costs and Quality-Adjusted Life Year (QALYs), this monotonicity assumption does not necessarily hold because total costs and QALYs gained are driven by multiple outcomes, including clinical effectiveness and side effects, which may result in non-monotonic relationships when combined, even when the relationship for individual components have a monotonic relationship with the duration of antibiotic treatment. Therefore, we will choose the appropriate regression model for QALYs and costs – using separate regression models for these two composite outcomes (generalised linear models with gamma distribution and identity link for costs and linear regression for QALYs) – by assessing the model fit of regression models with different functional forms for the duration effect (fractional polynomials vs splines) interacting with the time since intervention allocation. QALYs gained will be obtained from the regressions by estimating the area under the curve using Simpson's rule.

We will estimate and compare the NMB of each duration, using a UK NHS perspective. The NMB is calculated using a willingness to pay of £30,000/QALY gained. Confidence interval for duration specific NMB estimates will be estimated non-parametrically using bootstrapping. Incremental NMB will be estimated by measuring the difference in NMB between interventions.

12.10. Process Evaluation

We will embed a qualitative process evaluation study to understand patient experiences, behaviours and perceptions when receiving different antibiotic durations, and the acceptability of these to women. This is essential to guide approaches to the implementation of successful interventions and explain unsuccessful ones. Antimicrobial stewardship interventions depend on patient behaviour and co-operation for success [27]. Women's views on antibiotic prescription for UTIs are complex [28, 29]

An embedded qualitative individual interview study will enable us to explore this issue in-depth. Within our trial it will inform the transition from pilot to full phase by revealing barriers to recruitment and participation which we can address.

We will recruit 15-20 patients from both cystitis and pyelonephritis sub trials. We will continue recruitment until data saturation has been reached and there is sufficient information power for the emerging themes. We will use a Topic Guide developed from the literature and from previous experiences in conducting trials around UTIs in women. Topics to be raised in the interviews would include patients' experiences and perceptions of:

- Recruitment to, and participation in a trial requiring antibiotic treatment.
- Symptoms of the UTIs which resulted in their participation in the trial.
- Previous antibiotic-taking for cystitis and/or pyelonephritis, including adherence, side-effects, and outcomes.
- The antibiotic course to which they were randomised, expectations and outcomes.
- Antibiotic resistance and ways in which to promote antibiotic stewardship.

The semi-structured nature of the interviews has the flexibility to ensure detailed coverage of the topics of interest to the researchers but also to allow women to spontaneously raise issues of their own, which can then be taken forward into subsequent interviews.

For participants' convenience, interviews will be conducted either by telephone or online e.g. via Microsoft Teams, according to their preference. We will ask for participants' consent to audiotape the interviews and sound files will be transcribed verbatim.

Thematic analysis of the interviews will consider issues identified from the literature and clinical research context, as well as inductively allowing new themes and ideas to emerge from the data. Analysis will be guided by the constant comparative method, which will include reading and familiarisation with the transcripts, noting and recording initial themes, and then conducting systematic and detailed open coding using NVivo. Analysis will proceed in an iterative manner – thus, the coding of a first set of interviews will generate an initial coding framework, which will be further developed and refined as further interviews are conducted and analysis proceeds. A reflexive journal will be kept by the researcher throughout the study, which will assist in interpreting data and forming conclusions.

To ensure trustworthiness, the researcher conducting the qualitative work will draw on the clinical expertise of the rest of the research team, in developing the coding framework and critically discussing ideas for categories emerging from the data. The Patient and Public Involvement (PPI) group will also play an important role in monitoring the data collection and analysis processes, to ensure that findings are authentic, credible, and dependable.

12.11. Gut Microbiome Analysis

To enable the efficient generation of cost-effective and high-resolution data on large numbers of samples (n=2,200) we propose a joint strategy using metagenomic sequencing to evaluate species diversity and

AMR gene profiling, and a highly multiplexed, targeted PCR/sequencing-based approach (AmpliSeq for Illumina Antimicrobial Resistance Research Panel [AmpliSeq™]) to optimise the sensitivity to detect AMR genes that may be present in low abundance and not be picked up with shotgun metagenomics. Detailed analysis is described in the microbiology sample processing document.

As part of this sub-study additional questionnaire information to identify potential confounders impacting the gut microbiome will be evaluated at each sampling timepoint (baseline, end of treatment, day 42 and six months) including: date of menopause (if relevant), smoking status (current, ex-smoker, never), all other medications/supplements being taken (including probiotics, antibiotics, HRT), diet (including meat, pescatarian, vegetarian, vegan), travel (destination and dates [within the last year at baseline]).

12.11.1 Microbiome/resistome sequencing methods – workflow and comparative analysis

This will be detailed in a microbiology sample processing document.

12.11.2 Modelling associations between antibiotic exposure, changes in the abundance of gut bacteria and AMR gene variants

For each antibiotic class, we will fit generalised linear mixed models with the baseline outcome measurement included as a fixed effect and penalised splines or fractional polynomial terms (based on model fit, where the latter is expected to perform best in case of a monotonic relationship) for the assigned antibiotic duration interacting with time. This will allow us to evaluate how changes in AMR gene detection and semi-quantitative levels on a per class basis at consecutive time points varies by treatment duration and agent.

Given variation in swabbing and sequencing, the observed apparent gene abundance and diversity may not reflect the true abundance and diversity with 100% accuracy. *A priori* we would expect this measurement error to be random, i.e., not different by allocation, leading to unbiased estimates, but an increase in type-II error (failing to reject a null hypothesis that is actually false)[30,31].

To simultaneously account for measurement error in the outcome and model the association between different antibiotic exposures (i.e., antibiotic type and treatment duration) and longitudinal changes in species, and AMR gene abundance and diversity, we will also adopt a Bayesian state-space model that decomposes the data into an observation component (capturing measurement error) and a process component (capturing within-host dynamics). These models will be used to evaluate direct selective effects (i.e. the acquisition or selection of AMR genes conferring resistance to the prescribed antibiotic) and co-selective effects (i.e. the acquisition or selection of AMR genes conferring resistance to other classes of antibiotic to those prescribed), as well as AMR gene acquisition (negative at baseline [below a detection threshold] and positive on post-treatment samples) and carriage duration (out to a maximum of six months post-enrolment).

We will use the species diversity data to identify whether colonisation with significant pathogens such as *Clostridioides difficile* is an issue, and the relationship of these events with antibiotic type/treatment duration.

12.11.3 Sample size calculations

A sample size of 50 participants receiving each drug-duration (250 participants for pvmecillinam, and 300 for the pyelonephritis antibiotic class; 550 participants in total) will provide sufficient power (≥80%, all simulated scenarios) to define a duration-response curve for changes in AMR gene carriage between baseline and day 42 for each of the three antibiotic classes, assuming 10% resistance gene detection at

baseline, rising to 20% with the longest duration at day 42. By including additional post-randomisation measures we will thus be adequately powered to be able to detect meaningful changes in AMR gene carriage over time by antibiotic duration and class.

13. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan (DMP).

13.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections. The transcription company will also have access to the recorded interviews for transcribing. When the transcribed interview has been returned they will delete all files they have.

13.3. Data Recording and Record Keeping

Data Management will be performed in accordance with Primary Care-Clinical Trials Unit (PC-CTU) Data Management Standard Operating Procedures (SOPs). Trial specific procedures will be outlined in a DMP to ensure that high quality data are produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician prior to the first participant being enrolled.

All participants will be consented using electronic consent forms. Sortition® will be used for randomisation and to record eligibility. Sortition® is a secure, web-based, system developed in conjunction with the PC-CTU. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. Data protection requirements will be embedded into the design of the web-based system and enforced by best practice study management procedures. The data manager will oversee the process of electronic data validation and manual listings, sending out data queries when required and following these up until the queries are resolved.

Once the last participants are enrolled, prior to database lock, a dataset review will be undertaken by a member of the IT and/or Data Management team and the trial statistician. All critical data items are 100% checked against original source data documents to ensure accuracy, an error rate is established across all fields to ensure a consistently accurate dataset.

Participants' contact information will be collected using a secure online platform. The contact details will be stored by the trial team separately from all other trial data. The trial staff at the PC-CTU will have access to the personal identifiable information of all recruited participants. The trial staff at the BSCTU will only have access to the personal identifiable information of those recruited in secondary care. Other third parties, such as the laboratories, will only have access to pseudo-anonymised information.

We will seek consent from participants to allow us to keep their contact details on record so that we can invite them to take part in future research related to UTIs at the University of Oxford. Participants can decline to give consent for this and still be eligible for the main trial. All personal identifiable data will be destroyed as soon as it is practicable to do so after the end of the trial, but at least within 6 months (other than that included in essential documents retained for five years for archiving purposes – see section 21), unless we have been given permission to store this information to contact the participants about possible future research.

Qualitative sub study: Consent will be sought for the qualitative recordings to be stored securely for five years. We wish to retain recordings following transcription as issues of interpreting text can arise and the audio-recording can clarify these. Transcription will be carried out by an approved transcribing company with whom we have a confidentiality agreement. Once the transcript has been received from the transcription company, it will be anonymised. Transcripts will also be retained for a period of five years and stored securely in line with the University of Oxford best practice. The transcription company will delete the record once the transcripts have been transferred to the university.

The trial team will preserve the confidentiality of all data obtained which are to be kept by the DURATION UTI trial team in compliance with the Data Protection Act (DPA) 2018, the UK General Data Protection Regulation (GDPR), and PC-CTU Data Management SOP, this includes data of trial participants.

For the data linkage, and with individual participant consent, name, date of birth and NHS number will be shared with the UK Health Security Agency (UKHSA) by the trial team as an encrypted transfer. Within UKHSA these identifiers will be used to generate an extract of relevant second generation surveillance system (SGSS) data (i.e. microbiology records from 1 year before the study to up to 1 year after the participant's enrolment in the study) for consenting participants. Data linkage will be performed by designated UKHSA data managers given the authority to undertake this task. Linked data will be exported – again by encrypted transfer – to designated members of the study trial team for analysis. Any personal identifiable data will be destroyed as soon as practicable at the end of the study, and at the very latest within 6 months of this timepoint. Efforts will be made to anonymise the dataset where possible and these data will only be used for the purpose of the study. Study-related extracts will similarly be stored within UKHSA until 6 months of the study end, at which point they will be destroyed. We anticipate a requirement to extract the data from UKHSA at several timepoints (at minimum an early extraction timepoint within 6 months of the study start to ensure that data capture is relevant and appropriate and to develop analytical workflows, and a late extraction timepoint at the end of the study to capture data out to a year of follow-up on all participants).

14. QUALITY ASSURANCE PROCEDURES

14.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and SOPs. A risk assessment and monitoring plan will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Monitoring

Regular monitoring will be performed according to the trial specific Risk Assessment and Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Risk Assessment and Monitoring Plan. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.3. Trial committees

A DMC, TSC and TMG will be appointed in line with standard PC-CTU procedures. The responsibilities of each group are as follows:

- DMC – to review the data at regular intervals, to review and monitor the accruing data to ensure the rights, safety, and wellbeing of the trial participants.
- TSC – will provide oversight of the trial, initially meeting before the trial opens to recruitment and within six months of recruitment commencing. Thereafter they will decide the frequency at which they meet.
- TMG – is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to.

15. PROTOCOL DEVIATIONS

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the Trial Master File (TMF).

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the Medicines and Healthcare products Regulatory Agency (MHRA) within seven days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial”.

If a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the Chief Investigator (CI) the serious breach will be reviewed by the Sponsor and, if appropriate, the

Sponsor will report it to the Research Ethics Committee (REC), regulatory authority, and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

The CI will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2. Guidelines for GCP

The CI will ensure that this trial is conducted in accordance with relevant regulations and with GCP.

17.3. Approvals

Following Sponsor approval, the protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate REC, Health Research Authority (HRA) (where required), regulatory authority/ies (MHRA in the UK), and host institution(s) for written approval.

The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.5. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to a publicly accessible database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of trial date, as specified on the trial declaration.

17.6. Participant Confidentiality

The study will comply with the UK GDPR and DPA 2018, which require data to be pseudo-anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant trial number only on all trial documents and any electronic database(s).

All documents will be stored securely and only accessible by trial team and authorised personnel. The trial team will safeguard the privacy of participants' personal data.

17.7. Expenses and Benefits

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.

18. FINANCE AND INSURANCE

18.1. Funding

The NIHR will fund this trial

18.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

18.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

19. PUBLICATION POLICY

The Investigators (those listed on the protocol and others to be decided at publication) will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial. Authors will acknowledge the trial funders and the PPI contributors. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

20. DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of Intellectual Property (IP) generated by employees of the University vests in the University of Oxford. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

21. ARCHIVING

Archiving will be completed according to PC-CTU SOP and trial specific working instructions. Essential documents will be held for 5 years after the end of the study. Research documents with personal information, such as consent forms, will be held securely and separately at the University of Oxford's archiving facility according to the PC-CTU Archiving SOP.

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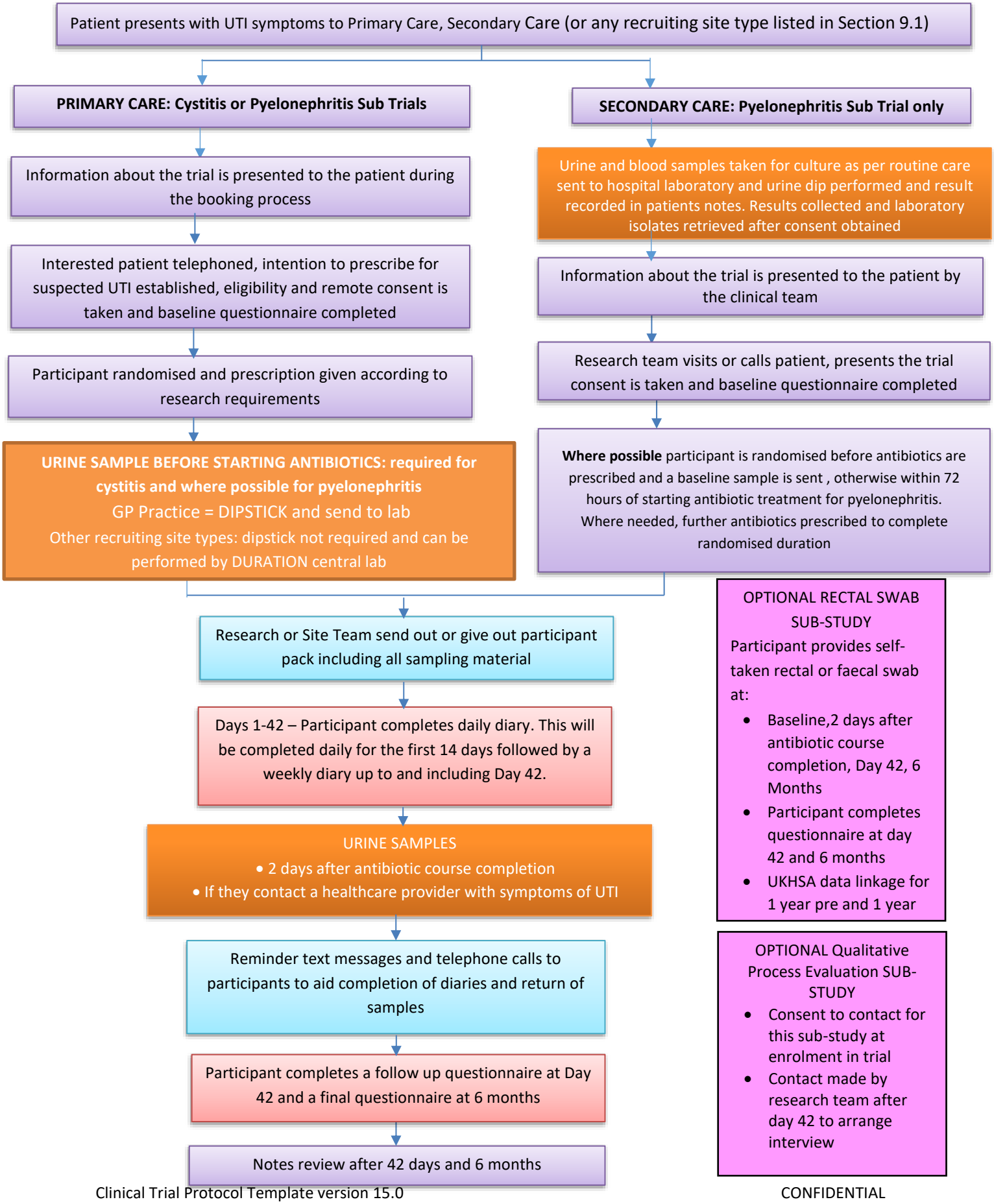
23. APPENDIX A: TRIAL FLOW CHART



24. APPENDIX B: SCHEDULE OF PROCEDURES

	Recruitment	Follow up			
	Day 0	Day 1-42	Day 42	6 months	1 year
Informed consent	x				
Demographic data and medical history	x				
Eligibility Criteria	x				
Randomisation	x				
Baseline e-CRF completion – participant and clinician	x				
Vital signs (BP, pulse, temp)*	x				
U&Es*	x				
Urinalysis – at central lab	x	x**			
Urine dipstick	x				
Antibiotic prescription	x				
Antibiotic treatment	x***	x***			
Patient symptom diary		x*****			
Completion of Questionnaire			x	x	
Medical Notes review			x	x	
Adherence checks	x	x			
Self-taken rectal or stool specimen****	x	x	x	x	
Rectal sub-study questionnaire****	x		x	x	
*hospitalised participants only – daily CRF until day 5 or discharge, whichever is first	x	x			
UKHSA Data Linkage****					x

* pyelonephritis participants recruited in Secondary Care only

** two days after antibiotic course is completed

*** taken for the prescribed number of days

**** for those in rectal swab sub-study only

***** symptom diary completed once a day for the first 14 days, weekly thereafter up to and including Day 42

25. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1.	2.0	23Aug2023	Naomi Kamau	• Timepoint of measurement of microbiological failure clarified to End of randomised treatment duration + 2 days • Changed exclusion criteria for clarity by replacing 'previous month' with 'previous 28 days' use of antibiotics for prevention or treatment of UTI. • Section 9.7 Complete daily diary every day up to day 42 from randomisation. If they are not symptomatic only 2 questions will require a response. • Section 10.1.5 logistics for participants return blisters packs updated and will be sent to PC-CTU for storage and disposal/destructions in the line with PC-CTU IMP disposal.
2.	3.0	08Mar2024	Naomi Kamau	• Page 26 in section 11.1 Adverse Event Definitions has been amended to remove the pregnancy safety follow-up in the Serious Adverse Event (SAE) section. • Page 13 in section 6.0 Objectives and Outcome Measures, we amended the outcome measures for the second secondary objective. We removed the statement 'or an adverse event related to the prescribed antibiotic ' from the outcome measures. • Page 16 in section 8.2 Inclusion criteria, the first inclusion criteria for the Pyelonephritis sub-trial has been amended to also include participants who may not present with a temperature of

				≥38.0°C but had recorded symptoms of fever, chills, or rigors since the onset of symptoms and taken antipyretics or antibiotics before the visit. • Page 17 in section 9.1. Site Recruitment, we have added Out-of-hours, urgent care or acute Primary Care centres and hubs and PIC sites to the list of recruitment sites for our trial • Page 26 in section 11.2 Reporting Procedures has been amended to state that the IMP Dossier submitted as a representative sample of the SmPCs for approval by the MHRA will be used for our reference safety information in this trial. • Page 26 in section 11.1 Adverse Events Definitions, we included a note to describe how pregnancy and miscourage cases would be handled in the trial. Other administrative changes made to the protocol include: • Page 1 of the Protocol, we added the ISRCTN Number. • Page 1 of the protocol, we updated the investigators list • Page 5 section 1. Key Trial contacts, we added the duration email addresses • Page 7 section 3. Synopsis, we changed the planned recruitment period to include the actual recruitment period in months. • Corrected a few minor typos and errors in the protocol • Page 42 section 24 Appendix B: Schedule of procedures updated to reflect the data collection in the study. We also clarified that one asterisk (*) in the table represents pyelonephritis participants recruited in Secondary Care only.
3.	4.0	06Jun2024	Ye To	• Page 16 in section 8.2 - Removal of the inclusion criterion requiring

				a baseline urine sample in the pyelonephritis sub study only. • Page 16 in section 8.2 Inclusion Criteria amended the inclusion criteria for the pyelonephritis sub trial to increase the time allowed for antibiotic treatment prior to randomisation from 48 to 72 hours • Page 17 in section 8.2 exclusion criterion specific for the pyelonephritis sub trial which clarifies for patients who have been taking antibiotics for indications other than pyelonephritis to be included in the pyelonephritis sub trial irrespective of the duration • Page 18, section 9.1 is amended to reflect that the study will be advertised in trial sites and where possible, at pharmacies adjacent to sites to help promote the study and direct participants who visit pharmacies for UTI treatment • Page 18 section 9.2 Screening and Eligibility Assessment is amended in accordance with the changes above. Clarification in primary care screening and eligibility will be performed by the site research team • Page 20 section 9.6 Baseline assessments and Page 21 section 9.8 are amended to reflect removal of the inclusion criterion requiring a baseline urine sample in the pyelonephritis sub study. Sites will be asked to attempt to obtain a urine sample where antibiotics have not yet been started. Also, where possible, in pyelonephritis sub study – secondary care sites to retrieve any bacterial isolates cultured from blood or urine cultures performed as part of routine clinical care and send these to the

				research laboratory for study purposes • Page 40 appendix A: Trial Flow Chart is amended in accordance with the changes above, specifically that bacterial culture isolates from blood and urine samples processed in the local NHS laboratory. Other administrative changes made to the protocol include: • Page 19, section 9.4 – clarification that it could be recruiting clinician or appropriately delegated member of the site research team that will randomise participant at either primary or secondary care. • Page 23-24, section 10.1 – updated to reflect the change for antibiotic treatment prior to randomisation from 48 to 72 hours (see above) • Corrected a few minor typos and errors in the protocol
4.	5.0	16Jul2024	Naomi Kamau	• Page 16, Section 8.2 amended to clarify the female inclusion criteria. • Page 18, Section 9.2_and page 22 9.8.2 Removed mention of the Pivmecillinam antibiotic to include all participants into the rectal swab sub-study. • Page 24, section 10.1.4 Compliance with trial treatment and section 10.1.5 Accountability of the trial treatment amended to remove the requirement for participants to return blister packs. • Page 27, Section 11.2 reporting procedures section amended to include the safety follow up and

				reporting procedures for patients recruited through pharmacies. • Changes to symptom diaries, from once daily for 42 days, to daily for 14 days then weekly thereafter, up to and including Day 42. • Addition of pharmacies as a recruiting site, including recruitment processes and clarification of 'clinician' to ensure pharmacists are included. • Updated Appendix A to reflect the new types of recruiting sites. • Updated Appendix B to reflect the new frequency of completing symptom diaries. • Clarification for the rectal swab sub-study: collecting a faecal swab is also acceptable if participant finds a rectal swab difficult. This is in line with the new version of the sub-study sample instructions.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.