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Improving primary care antibiotic prescribing to reduce antibiotic resistant urine infections: the IPAP-UTI series of cluster randomised controlled trials

Submission date
30/07/2024

Recruitment status
No longer recruiting

Registration date
15/08/2024

Overall study status
Ongoing

Last Edited
31/12/2025

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Our overall aim is to provide reliable evidence to support UK policy regarding the choice of antibiotics for urinary tract infections (UTIs) in primary care, in response to local antibiotic (antimicrobial) resistance (AMR) challenges. We also seek to deliver a step-change in antibiotic stewardship research by focussing primarily on modifying AMR, as well as antibiotic use.

AMR is a serious threat to public health. Unchecked, bacteria become resistant to more antibiotics until infections become untreatable. By 2050, some predict more people will die from AMR than cancer. UTIs are the most common bacterial infection treated in the NHS, mostly using antibiotics prescribed by GPs, nurses and other 'primary care clinicians'. Recent research suggests up to 50% of bacteria which cause UTIs are resistant, resulting in longer, more severe infections, requiring multiple antibiotic courses and in some cases hospital admission. GPs and nurses have recently been encouraged to prescribe nitrofurantoin instead of trimethoprim (both first-line antibiotics for UTI). Some studies suggest this reduced trimethoprim AMR rates, but not everywhere, and concerningly may have led to higher AMR against other antibiotics. These results lead policy makers to ask two key questions. First: 'are these results reliable?' and second: 'what should be done?'. First, the data are not reliable (because methods used mean there could be other reasons for the changes), and second, nobody knows what to do next. There are lots of ideas, but we do not know if the benefits outweigh the harms.

Who can participate?
Individual participants are not recruited.

What does the study involve?
Individual participants are not recruited.

What are the possible benefits and risks of participating?
The RCTs are low-risk studies. The intervention will seek to modify antibiotic prescribing

behaviour in intervention practices within the Study ICB. The intervention will be designed to encourage prescribers to chose an Alternative Antibiotic/s (this will be the antibiotic/s which will be recommended for use instead of the Target Antibiotic/s in the selected ICB). The intervention will not deviate from NICE recommended usual practice – i.e. both intervention and control practices will be acting on the guidance from their ICB Medicines Optimisation Team, which will be in line with NICE recommendations. Therefore, risks to patients are no higher than that of standard medical care. No identifiable data (e.g. name and address, or any data from which a participant might be identified) will be collected in this study. Participants in the qualitative process evaluation, will be required to give up some of their time (i.e semi-structured interviews 20-30 minutes). There are no anticipated risks involved in taking part in the qualitative interviews. Participants are reminded that they are free to withdraw at any time. Interviews will be conducted by telephone or virtually at a time convenient to the participant. Risks for study ICB and GP practice, the RCT will require additional staff time to deliver intervention and data collection.

Where is the study run from?
Bristol Trials Centre, University of Bristol (UK)

When is the study starting and how long is it expected to run for?
July 2023 to July 2028

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)
341598

Protocol serial number
CPMS 61476, NIHR204400, IRAS 341598

Study information

Scientific Title
Improving primary care antibiotic prescribing to reduce antibiotic resistant urine infections: the IPAP-UTI series of cluster randomised controlled trials

Acronym
IPAP-UTI

Study objectives
Our overall aim is to provide reliable evidence to support UK policy regarding the choice of antibiotics for urinary tract infections (UTIs) in primary care, in response to local antibiotic (antimicrobial) resistance (AMR) challenges. We also seek to deliver a step-change in antibiotic stewardship research by focussing primarily on modifying AMR, as well as on antibiotic use.

The IPAP-UTI cluster RCTs will estimate the effectiveness and costs of interventions to encourage the primary care use of 'Alternative Antibiotic/s' instead of 'Target Antibiotic/s' in reducing resistance to 'Target Antibiotic/s' in routinely submitted urine and/or blood culture samples.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 12/08/2024, London - Westminster Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8283; westminster.rec@hra.nhs.uk), ref: 24/LO/0486

Study design
Interventional cluster randomized trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Urinary tract infections

Interventions

The IPAP-UTI RCTs will be conducted in areas of England with the worst AMR problems, and will include the patient groups most affected, reporting differences across age, socioeconomic and ethnic groups. The RCTs are efficient, pragmatic, two-group (intervention vs. usual care) cluster-randomised trials. Within each RCT, some GP practices (randomly chosen within our target areas of high AMR) will receive an intervention encouraging them to use one or more alternative antibiotics, while remaining GP practices continue with usual care. At the end, we will compare AMR rates and antibiotic use. Where we see differences, we expect they will be due to the intervention.

The IPAP-UTI RCT master protocol describes the principles of conduct for three RCTs of antibiotic prescribing interventions seeking to reduce antimicrobial resistance (AMR) in UTIs in primary care and/or secondary care. Each RCT will be delivered in an Integrated Care Board (ICB, possibly more than one for smaller ICBs). Each will test an intervention agreed with, and tailored to the needs of, that ICB.

The details of each RCT intervention, sample size calculation and data analysis will be fully described in Appendices to be developed and submitted for regulatory approval as amendments, once ICBs have been identified and interventions agreed.

We will recruit ICBs from across England, in areas where the AMR 'problem' is greatest (i.e. ICBs with persistently high or increasing AMR against one of the NICE recommended antibiotics in E. coli UTIs) using routinely collected, national UTI AMR surveillance data from the UK Health Security Agency (UKHSA).

We will approach eligible ICBs using a mixture of formal and informal routes including via: (i) our Host ICB Bristol, North Somerset and South Gloucestershire (BNSSG) research and medicine optimisation teams; (ii) the national and regional AMR leads for pharmacy and prescribing; and (iii) known existing links.

The RCT "site" is the ICB (Study ICB), specifically the Medicines Optimisation Team (or the ICB equivalent responsible for optimising and stewarding GP practice antibiotic use) within an ICB because they will take responsibility for promoting and supporting intervention roll-out to GP practices via ICB/ practice pharmacists.

The intervention will seek to modify antibiotic prescribing behaviour in intervention GP practices within the Study ICB. The intervention will be tailored for its use in the Study ICB to encourage prescribers to choose an Alternative Antibiotic/s (this will be the antibiotic (or antibiotics) which will be recommended for use instead of the Target Antibiotic/s in the Study ICB). Alternatives will be selected from the list of antibiotics approved for UTI treatment by NICE (expected to be mostly trimethoprim, nitrofurantoin, pivmecillinam and fosfomycin) instead of the Target Antibiotic.

GP practices will be advised (via ICB communications and a short video) about the study but they will also be advised that they are not being asked to deviate from NICE recommended usual practice – i.e. both intervention and control practices will be acting on the guidance from their ICB Medicines Optimisation Team, which will be in line with NICE recommendations.

Data collected in the RCTs includes; data collected from study ICBs related to the ICB and their GP practice characteristics, quantitative process evaluation and serious adverse event data; routinely collected data provided by UKHSA; GP practice primary care health record data, if available (ICB Systemwide Dataset (or equivalent)) and qualitative process evaluation data collected from semi-structured interviews with prescribing clinicians and ICB staff.

A random sample of sequential urinary isolates meeting UTI laboratory diagnostic criteria (>105 colony forming units (CFU)/mL) will also be requested from the NHS laboratories within the study ICB to allow a comparison of urinary isolate AMR patterns in these with those seen in data routinely reported by the UKHSA. Following this independent confirmation of AMR patterns, whole genome sequences will be determined using the urinary isolates. All resistance mechanisms will be identified, and their genetic linkage confirmed, along with linkage to virulence factor genes associated with serious infection, including urosepsis. The presence of mutational pre-resistance will also be identified. Results from both of these will be fed back to the Intervention Refinement Group (IRG) to consider if any changes are needed to the intervention . Southmead Hospital Antimicrobial Reference Laboratory will only receive bacterial isolates cultured from routinely collected urine samples, rather than the urine samples themselves, therefore these samples are not classed as Relevant Material under the Human Tissue Act.

The intervention and follow-up period for each RCT will be typically 24 months (≥12 and ≤36 months), with outcomes assessed throughout.

Intervention Type
Other

Primary outcome(s)
RCT 1:
Target (trimethoprim) AMR measured in E. coli urinary isolates between episodes of UTI in women aged 16+ years

RCT 2 & RCT 3:
The details of each RCT including outcomes will be developed once the ICBs have been identified and interventions agreed, and they will be fully described in Appendices and submitted for approval when ready.

Key secondary outcome(s))
RCT 1:
1. Treatment failure within episodes of UTI in women aged 16+ years; this is defined as the samples ≤14-days from the 1st sample of each episode
2. Alternative Antibiotic (pivmecillinam and fosfomycin for penicillin allergic patients) AMR in E. coli urinary isolates between episodes of UTI* in women aged 16+ years.
3. Non-Target and Non-Alternative Antibiotic AMR rates in E. coli urinary isolates between episodes of UTI* in women aged 16+ years
4. AMR risk in all E. coli urinary isolates from women aged 16+ years
5. Rates of positive UTI urine samples per 1,000 registered patients in women aged 16+ years
6. Dispensing rates of specific and total antibiotics per 1,000 registered patients in all adults aged 16+ years
7. Rates per 1,000 registered patients for: (i) Emergency Department (ED) attendances for UTI; (ii) Emergency Department (ED) attendances for sepsis (iii) hospital admissions for UTI; (iv) hospital admissions for BSI; and (v) all cause death in those attending the ED for UTI or sepsis, or admitted for UTI or BSI. S7 i-v will be linked to AMR status where available in women aged 16+ years
8. This will repeat the primary and all of the secondary outcomes (P1, S2-S4) that were specific to E. coli urinary isolates using all urinary isolates from all adults aged 16+ years
9. The primary and selected secondary outcomes (P1, S2-S5, S8) tabulated alongside the costs of the intervention and healthcare utilisation at the GP practice level, including hospital admissions

for UTI-related conditions, ED attendances due to the symptoms of UTI and antibiotic prescriptions for UTI, and where accessible primary care consultations for UTI
10. Rates per 1,000 registered patients for: (i) repeat UTI primary care consultations; and (ii) repeat antibiotic dispensing ≤2 weeks, and ≤4 weeks of UTI, in women aged 16+ years

RCT 2 & RCT 3:
The details of each RCT including outcomes will be developed once the ICBs have been identified and interventions agreed, and they will be fully described in Appendices and submitted for approval when ready.

Completion date
01/07/2028

Eligibility

Key inclusion criteria
This is a cluster RCT and individual patients are not recruited. Data for the study will only include male and female patients, aged 16 years and over.

Inclusion criteria for ICBs:
ICBs in England are eligible for the study if they are actively contributing to the UKHSA voluntary national surveillance of UTI AMR. See master protocol, supplementary material A for further details of ICB selection criteria, which was developed to assess ICB eligibility based on UKHSA routinely collected national UTI AMR data, and UKHSA national antibiotic dispensing data (both datasets at ICB and GP practice level).

Inclusion criteria for GP practices:
GP practices will be eligible if providing within office hours standard NHS care. We will consider additional eligibility criteria where necessary, including restricting to NHS GP practices where:
1. >=40% of registered patients are female
2. There are at least 100 registered patients
GP practices supporting individually randomised patient RCTs of different antibiotics for UTIs may take part in the IPAP-UTI RCTs.

Qualitative interviews:
A purposive sample, of up to 20 prescribing clinicians and ICB staff involved in implementation of the intervention will be recruited to take part in interviews for the qualitative process evaluation. We will aim for a maximum diversity sample in terms of practice population diversity, to ensure data is captured from a range of settings.

Participant type(s)
Other

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Upper age limit
100 years

Sex
All

Total final enrolment
3

Key exclusion criteria
1. ICBs taking, or planning to take, part in other cluster RCTs involving an intervention to change antibiotic prescribing for UTIs will be excluded.
2. GP practices taking part in other cluster RCTs involving an intervention to change antibiotic prescribing for UTIs will be excluded.
3. The routinely collected data used in the RCTs will be restricted to male and female patients aged 16 years and over.

Date of first enrolment
21/10/2024

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
West Yorkshire Integrated Care Board
White Rose House
West Parade
Wakefield
England
WF1 1LT

Study participating centre
Kent and Medway Integrated Care Board
2nd floor
Gail House
Lower Stone Street
Maidstone
England
ME15 6NB

Study participating centre
Greater Manchester Integrated Care Board
4th Floor
3 Piccadilly Place
Manchester
England
M1 3BN

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository
University of Bristol Research Data Storage Facility https://www.bristol.ac.uk/staff/researchers/data/publishing-research-data
Relevant anonymised 'meta-data' about the trial and the full data set

IPD sharing plan summary
Stored in non-publicly available repository