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Final Protocol

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Plain English Summary

What is the problem?

Urine infections can be difficult to diagnose. This means patients may not get the best treatment straight away, or may be given antibiotics that they do not need.

At the moment, a urine infection is diagnosed by the GP based on your symptoms and by sending a urine sample to the lab to check whether you have a urine infection, and if so whether you have been given the right antibiotics for your infection. Labs can take up to a week to get the result of your urine test back to the GP. Antibiotic treatment is usually started straight away after seeing your GP. As they don't yet have the results of your lab tests, this means that some people will be given antibiotics when they do not have a urine infection and some will be given the wrong type of antibiotics for the bug that is causing their infection.

In some people, dipstick tests can be used to help make a quicker diagnosis. Dipstick tests are plastic strips that are dipped into urine and then change colour if you are likely to have a urine infection. But these tests are not very good at telling us whether you have a urine infection, and they cannot tell us anything about what treatment will work for you.

Some new rapid tests have recently been developed that can be done in the GP surgery or pharmacy and will tell you quickly (some in just a few minutes) whether you have a urine infection. Some of these tests are also able to tell your doctor which bug is causing your infection, and which antibiotic will work best.

What are we trying to find out?

We want to know whether introducing new rapid tests to diagnose UTIs will mean that more people are correctly told whether or not they have a urine infection, whether patients can get a correct diagnosis more quickly, and whether they can be treated with the right antibiotic more quickly. We also want to know whether introducing this type of testing is a good use of NHS money.

What are we going to do?

We are going review existing research and develop economic (cost) models to answer the following questions:

1. Do people who have symptoms that suggest they might have a urine infection have better outcomes (right diagnosis, quicker diagnosis, quicker access to the right antibiotic, and better improvement in their symptoms) if they are diagnosed with a new rapid tests compared to current practice?
2. Can rapid tests reduce the amount of antibiotics that are prescribed?
3. Which test should people have to diagnose their urine infection and is it still necessary to send a urine sample to the lab to be tested?
4. Are new "point of care" tests a cost-effective use of NHS money?

1 Background

1.1 Epidemiology and burden of UTI

Urinary tract infections are one of the most common causes of infection worldwide, and are the most commonly seen bacterial infections in general practice.(1) UTI is also the most common hospital acquired infection in the UK, accounting for almost 1 in 4 of all infections, most of which are associated with catheter use.(2) UTIs can affect the lower urinary tract when the infection is in the urethra (urethritis) or bladder (cystitis), or the upper urinary tract when the infection is in the kidney (pyelonephritis). Incidence of UTI generally increases with age and is higher in women than in men – a 2019 study reported that around 83% of UTIs in primary care between 2011 and 2015 in England were in women. Lifetime incidence of UTI in women is estimated at approximately 50-60%.(3) Risk factors for recurrent uncomplicated UTIs include frequent intercourse, vulvovaginal atrophy, change of the local bacterial flora, history of UTIs, diabetes mellitus and a non-secretor blood type.(1, 4)

There are several classifications of UTI, depending on the location and frequency of infection and whether the patient is symptomatic. Classifications for uncomplicated UTI are summarised in Table 1. A proportion of patients will suffer from chronic UTI with an estimated 1.7 million women in the UK suffering from chronic lower urinary tract symptoms.(5) There is no accepted definition of this and the prevalence is unclear, but it is generally accepted that these patients will suffer ongoing symptoms with no or little relief between attacks(5) – this is in contrast to recurrent UTI where symptoms do resolve completely between attacks.

Table 1 Overview of classification of uncomplicated UTI, reproduced from Medina et al. (2019)(6)

Classification	Definition
Uncomplicated UTI	UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications
Acute uncomplicated cystitis	Lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute pyelonephritis	Upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	Positive urine culture (>105 colony-forming units/ml) in the absence of urinary symptoms
Recurrent uncomplicated UTIs	Recurrent UTI refers to the occurrence of ⩾2 symptomatic episodes within 6 months or ⩾3 symptomatic episodes within 12months

Complications including pyelonephritis, kidney failure, and sepsis may arise as a consequence of UTI. Additionally, infections during pregnancy can cause pre-term delivery and low birth weight. Risk factors for complicated UTI include structural or neurological

abnormalities, pregnancy, catheterization, certain infecting organisms and co-morbidities such as immunosuppression.(2)

The most common cause of UTI is *Escherichia coli* (*E. coli*) in both uncomplicated and complicated UTIs.(3) A recent UK based surveillance study found that E. coli was isolated from 67% (113/169) of positive urine samples. Other bacteria identified in positive samples included Kllebsiella pneumoniae (9%), Citrobacter koseri (5%), Enterococcus spp. (5%) and Staphylococcus saprophyticus (3.5%).(7)

1.2 Presentation of UTI

Clinical presentation of UTI varies according to patient group, and can be non-specific making it difficult to identify those who may have a UTI. Up to 65% of women who present with symptoms suggestive of UTI have been shown not to actually have a UTI.(8) Table 2 provides an overview of the different presenting symptoms for uncomplicated UTI in different risk groups:

Table 2 Presentation of UTI in different populations

Population	Presenting symptoms
Children aged <5 years (9)	• Pain when passing urine • Smelly urine • Abdominal pain
Men or women aged <65 years (10) (2)	• Dysuria — discomfort/pain/burning with urination. • Frequency — passing urine more often than usual. • Urgency — a strong desire to empty the bladder • Changes in urine appearance or consistency • Haematuria e.g. red/brown discolouration of urine. • Nocturia — passing urine more often than usual at night. • Suprapubic discomfort/tenderness.
Women age >65 years (2)	May present with similar symptoms to younger women but in addition may present with generalized non-specific features including: • Delirium • Lethargy • reduced ability to carry out activities of daily living and anorexia
Men aged >65 years(2)	Dysuria alone or two or more of the following: • Temperature 1.5ºC above normal twice in 12 hours. • New frequency or urgency. • New incontinence. • New or worsening delirium/debility. • New suprapubic pain. • Visible haematuria.

Symptoms of chronic UTI are similar to those of acute UTI, but patients fail to get better after a short course of antibiotics.(5) Chronic UTIs can be debilitating causing ongoing symptoms such as urinary frequency, urinary urgency, pain, difficulty sleeping and can have a substantial negative impact on day to day life.(5)

1.3 Diagnosis

Accurate and timely diagnosis of urinary tract infection (UTI) is important to ensure appropriate treatment to help resolve symptoms and improve quality of life, but also to reduce the risk of long-term complications such as pyelonephritis, kidney disease and sepsis.(11)

UTIs are currently diagnosed using a combination of dipstick tests and laboratory-based urine culture which usually includes antimicrobial sensitivity testing (AST). Dipstick tests involve dipping a specially treated paper or plastic strip into a urine sample to identify the presence of leukocyte esterase (LE), nitrites and blood. These can be used as an initial screening test for UTI as they can be performed in a GP surgery and give a result very quickly (within a few minutes), but their accuracy is limited, particularly in certain populations such as those aged over 65 years or in those who are catheterised. They are also unable to provide information on the pathogenic cause of the infection or on AST. Thus, even when these tests are used to help diagnose a UTI, follow-up laboratory testing using culture is often needed to confirm the infection and to determine AST. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides guidance on AST which includes definitions of susceptibility testing categories with the aim of harmonising breakpoints in Europe.(12)

Culture can take 24 to 72 hours depending on geographical location and local laboratory facilities, and in some cases where there are delays in getting urines to the laboratory or a delay in processing the test once samples arrive at the laboratory, results can take up to a week to be returned to the GP. Culture is recommended in the following groups:(13)

- Suspected UTI in men
- Age > 65 years
- Babies <3 months
- Children <16 years who do not respond to treatment within 24-48 hours
- Pregnant women
- Suspected complicated UTI (pyelonephritis or sepsis)
- Failed antibiotic treatment or persistent symptoms
- Recurrent UTI
- Catheterised patients
- Dipstick negative for nitrites but positive LE
- Age <3 years, positive dipstick for nitrite and LE
- Risk factor for resistance:
    - Abnormalities of genitourinary tract

- Renal impairment
- Care home resident
- Hospitalisation for >7 days in last 6 months
- Recent travel to country with increased resistance
- Previous resistant UTI

1.4 Treatment of UTI

Acute uncomplicated UTI generally resolves within a few days without treatment, but most UTIs will be prescribed antibiotics. Treatment also involves giving advice on self-care such as analgesia and hydration. NICE guidance on antimicrobial prescribing for UTI recommends that antibiotics are prescribed immediately in pregnant women, men and children under 16 years.(14) In non-pregnant women, a back-up antibiotic (to be taken only if symptoms persist for 48 hours or worsen) or immediate antibiotic may be prescribed. Whilst dipstick tests and culture are often used to inform the diagnosis and decision on whether to prescribe antibiotics, in some patients antibiotics will be prescribed based on symptoms and examination alone. If urine is sent for culture and AST then the antibiotic choice should be reviewed when results of AST are available. The NICE guidance contains detailed guidance on which antibiotic to prescribe as first or second choice (if first choice is not effective or suitable) in different populations. First choice antibiotics are based on empirical treatment usually with nitrofurantoin or trimethoprim. Second choice antibiotics include pivmecillinam (a penicillin) or fosfomycin in adults and amoxicillin or cefalexin in children.(14) Empiric antibiotics have side effects, can be less effective than targeted antibiotics and increase the risk of antibiotic resistance developing (see section 1.5). A recent study of treatment of lower UTI in primary care in England found that the majority of patients (80%) were given empirical antibiotic treatment on the day of diagnosis and that the majority (83%) had no evidence of urine sample collection for laboratory investigation in their electronic health records.(6)

A recurrent UTI is managed in the same way as acute UTI. NICE guidance on antimicrobial prescribing for recurrent UTI recommends giving advice on behavioural and personal hygiene measures and self-care treatment to reduce the risk of future UTI. Postmenopausal women with recurrent UTI may be recommended vaginal oestrogen if other measures are not effective. Antibiotic prophylaxis can be considered if none of the other measures are effective. This should not be started until the acute UTI has been treated and resolved. Initial prophylaxis should include single-dose antibiotics, if this is not effective then daily antibiotic prophylaxis can be trialled. This has associated risks of resistance and possible adverse effects.(14)

There is currently no NICE guidance on treatment of chronic UTI. Patient organisations suggest that treatment may involve high-dose, extended course (3-6 months) oral antibiotics or instillation of antibiotics directly into the bladder. (15) Many patients will also seek relief from alternative therapies with little evidence of effectiveness.(16)

1.5 Antibiotic prescribing and resistance

Almost 75% of antibiotic prescribing occurs in primary care,(17) with UTIs contributing to a large proportion of this use. Antimicrobial resistance, and in particular antibiotic resistance, is one of the greatest public health challenges faced today. The WHO highlight this as one of the biggest threats to global health, food security and development today.(18)

The 'English Surveillance Programme for Antimicrobial Utilisation and Resistance' (ESPAUR) report from 2017 says more than 1 million UTI samples were analysed in NHS laboratories across England in 2016, and that resistance was a "common" observation. A recent surveillance study found that around 30% of E.coli, the most common cause of UTI, was resistant to trimethoprim and around 1% was resistant to nitrofurantoin. (7) This is consistent with data from a study that evaluated the Flexicult test, which reported that around 20% of those with a microbiologically confirmed UTI had an infection that was resistant to any first-line antibiotic (nitrofurantoin, trimethoprim, or fosfomycin).(7)

2 Decision Problem

2.1 Population

The population for this scope is people with suspected UTI. Subgroups of interest include:

- People with suspected acute UTI
- People with suspected recurrent UTI
- People with suspected chronic UTI
- Women under 65
- Women over 65
- Men under 65
- Men under 65
- Adults with indwelling urinary catheters
- Babies, children and young people under 16
- Children under 3 months
- Pregnant women
- People who are frail or have dementia
- People who are pre-, peri- or post-menopausal
- People on prophylactic antibiotics for treatment of UTI
- People of different ethnicities
- People with a higher risk of complicated UTIs (for example people with neurogenic bladder, diabetes, polycystic kidney disease or people who are immunocompromised)
- People with suspected pyelonephritis

2.2 Technologies of interest

Guidance from Public Health England on 'Health matters: antimicrobial resistance' (17) published in 2015, highlights the need for rapid diagnostic tools to help GPs quickly (within minutes) identify the strain of bacterial infection present and the antibiotics to which it is

resistant or susceptible. This is also highlighted in the 2021/2022 English surveillance programme for utilisation resistance (ESPAUR). Tests that are able to give a more accurate, rapid diagnosis of UTI than current dipstick testing, with or without identifying bacteria or providing information on AST, would have the potential to substantially improve diagnosis of UTI in primary care and to reduce inappropriate antibiotic prescribing (see section 1.5).(19) Such tests would be particularly useful in those groups in whom dipstick testing is not recommended. Given the high proportion of those presenting with symptoms of UTI who are subsequently found not to have a UTI, novel tests would also have the potential to rule out UTI reducing the need for samples to be sent for laboratory testing.

The technologies of interest for this appraisal are novel point of care tests (POCT) that may detect the presence of a UTI, provide information on the strain of bacterial infection present and/or the antibiotic(s) to which the bacteria is susceptible. POCT are defined as technologies that can be done by a healthcare professional outside a conventional laboratory setting (20). Table 3 Overview of POCT tests for diagnosing UTI within the scope of this assessment appraisal. The aim of these tests is to provide a more accurate, rapid diagnosis of UTI and improve antibiotic prescribing. The extent to which these POCT can improve antibiotic prescribing will depend on how quickly they are able to provide results, whether they provide additional information on the specific pathogen present in the urine, and whether they provide information on AST.

Table 3 Overview of POCT tests for diagnosing UTI within the scope of this assessment

Test name	Test basis	Sample	Antibiotics/bacteria targeted	Time to detect bacteria	Time to identify bacteria	Time to result AST	Test interpretation	CE-IVD marked
Astrego PA-100 analyser and PA-AST panel U-0501 (Sysmex Astrego)	Microfluidics	Urine	5 commonly used antibiotics (amoxicillin-Clavulanic acid, ciprofloxacin, fosfomycin, nitrofurantoin, trimethoprim)	Less than 30 minutes	NA	30 to 45 minutes for full results	Digital display shows which antibiotics sample is susceptible to	Yes
Flexicult Human (SSI Diagnostica)	Culture	Urine	5 commonly used antibiotics (mecillinam, nitrofurantoin, ampicillin, sulfamethizol and trimethoprim).	16-24 hours	NA	16 to 24 hours	Visual assessment of number & type of growths on agar plate.	Yes
Lodestar DX (Llusern Scientific)	Molecular diagnostic test	Urine	Escherichia coli (E-coli), Klebsiella spp, Proteus mirabilis, Staphylococcus saprophyticus, Enterococcus spp, Pseudomonas aeruginosa	40 minutes	40 minutes	NA	Digital display – light indicates which bacteria is detected	Expected <12 months
TriVerity (Inflammatix)	Detects 29 target mRNAs	Blood	Identifies presence type and severity of infection.	30 minutes	NA	NA	Unclear	Expected <12 months
Uriscreen (Savyon Diagnostics Ltd)	Catalase based test	Urine	Detects catalase activity as indicator of bacteria in somatic cells	2 minutes	NA	NA	Visual detection – white foam indicates positive result	Yes
Diaslide, Dipstreak, Chromostreak (Novamed)	Semi-quantitative culture	Urine	Total bacterial count; presence of gram-negative bacteria; growth of common UTI causing bacteria (E. coli, Proteus, and enterococci) – chromastreak only	18-24 hours	18-24 hours	NA	number of bacterial colonies is compared with the Colony Density Chart	Yes
Uricult, Uricult trio and Uricult plus (Aidian; formerly Orion Diagnostica)	Culture	Urine	Uricult identifies presence of gram-negative bacteria; Uricult plus also detects enterococci; Uricult trio also detects gram-negative, β-glucuronidase-producing organisms e.g. E. coli	16-24 hours	16-24 hours	NA	Visual assessment of growth on agar plate.	Yes

NA: Not applicable

2.3 Potential alternative technologies

There are a number of technologies currently in development that are able to provide a rapid indication of the presence of bacteria, identify the bacteria present and/or provide information on antimicrobial susceptibility, but these do not have a CE or UKCA mark, and are not expected to obtain this in the next 12 months, and so cannot yet be considered for recommendation by NICE.

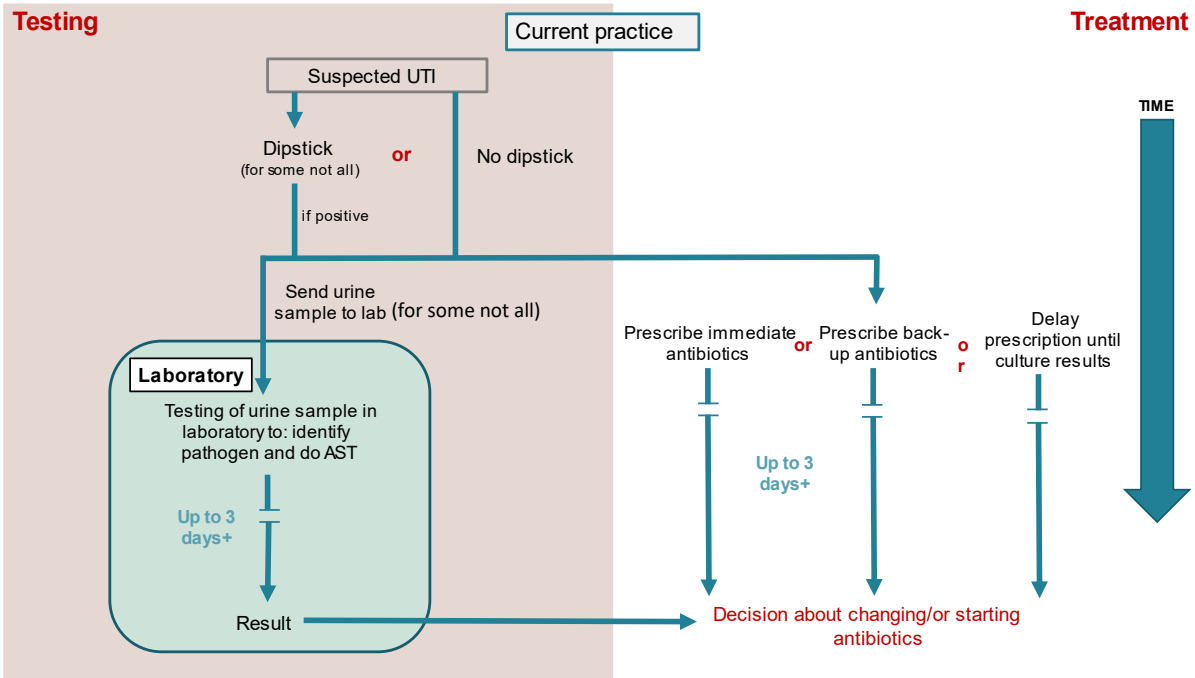
2.4 Comparator

The comparator for this assessment is the current standard of care: (1) urine dipstick followed by confirmatory culture and AST or (2) urine culture and AST done in the laboratory. This varies according to population. Further details on the treatment pathway are provided in section 2.5.

2.5 Current treatment pathway

The exact treatment pathway varies according to the population. Figure 1 gives a general overview of the treatment pathway. People present to their GP with symptoms suggestive of UTI. Depending on the patient population, they may receive dipstick testing. If this is positive for nitrite and LE they will be diagnosed with UTI, in some populations (e.g. women aged <65 years) a diagnosis can also be made based on a positive nitrite alone or LE, if also positive for blood. A sample will usually be sent to the laboratory for susceptibility testing. Decisions about whether to prescribe antibiotics, and which antibiotic to prescribe, are often made before culture results are available, particularly if the patient is presenting with severe symptoms. This means that antibiotics may need to be changed if culture and AST suggest that the patient is taking an antibiotic that is not likely to be effective against their infection, or stopped if no infection is detected on culture.

Figure 1 Outline treatment pathway



Public Health England has separate pathways for infants/children under 16 years, women under 65 years, men under 65 years, adults who are catheterised, and adults over 65 years.(13)

The treatment pathways differ in terms of whether an initial dipstick test is done, whether a urine sample should be sent to a laboratory for culture testing and when or if to prescribe antibiotics. Table 4 provides an overview of recommendations from the treatment pathways for these different groups:

Table 4 Summary of recommendations for dipstick, culture and antibiotics in different patient groups(13)

Population	Dipstick	Culture	Immediate antibiotics
Children (age <16 years)	Yes	If do not respond to treatment in 24-48 hours or age <3 years & positive dipstick for nitrite and LE	Yes
Men age <65	Yes – but not to rule out infection	Yes	Yes
Women age<65	Yes – those without risk factors for complicated UTI. Not needed if have 2 or 3 key diagnostic signs/symptoms	Dipstick negative for nitrites but positive LE	Delayed prescription may be offered in some patients
Pregnant	Yes	Yes	Yes
Catheterised	No	Yes	Yes
Men age >65	No	Yes	Yes
Women age>65	No	Yes	Yes

2.6 Place of the technology in the treatment pathway

POCT for suspected UTIs will be used as an initial test to diagnose UTI. If performance is sufficient, then the place of the test in the treatment pathway, as an initial test to diagnose UTI, will be the same in all populations and pre-specified subgroups (section 2.1).

The role of these new innovative tests for UTI will depend on whether they provide additional information on the specific pathogen present in the urine and whether they provide information on AST. This will also affect the potential impact of the tests. Table 5 provides an overview of the potential role and impact of the new POCT based on the features of the test.

Table 5 Overview of the potential role and impact of the new POCT based on the features of the test

Test features	Role	Potential impact
Detection of UTI	• Triage – rule out UTI or identify those in whom further testing for AST is required. This includes groups in whom dipstick testing is not currently recommended. • Replacement of dipstick in populations where dipstick testing is recommended	• Inform need for antibiotics • Reduce unnecessary antibiotic prescription • Quicker access to antibiotics when needed • Reduce need for culture
Detection of UTI plus pathogen identification	• Triage – rule out UTI or identify those in whom further testing for AST is required. This includes groups in whom dipstick testing is not currently recommended. • Replacement of dipstick in populations where dipstick testing is recommended	• Inform need for antibiotics • Reduce unnecessary antibiotic prescription • Quicker access to antibiotics when needed • Reduce need for culture • Provide some indication for initial antibiotic prescription based on type of bacteria but not to AST
Detection of UTI plus AST	• Replacement of dipstick & laboratory testing	• Inform need for antibiotics • Reduce unnecessary antibiotic prescription • Quicker access to antibiotics when needed • Target initial antibiotic prescription to AST • Reduce need for culture & AST

3 Aim and Objectives

The overall aim of this project is to determine whether POCT for people with suspected UTI have the potential to be clinically and -cost effective to the NHS. We will summarise the available evidence to support the value proposition outlined in the scope and outline where there are evidence gaps.

1. What is the impact on clinical outcomes of using POCT to diagnose UTI, with or without additional pathogen identification and AST?
2. What is the accuracy of the POCT for UTI diagnosis, pathogen identification and AST?
3. What is the technical performance (other than accuracy) of POCT for UTI?
4. What are the costs, from a UK NHS and Personal Social Services perspective, of using POCT for UTI diagnosis, pathogen identification and AST?
5. How might a conceptual model be specified in terms of structure and evidence required for parameterisation in order to estimate the cost effectiveness of POCT for UTI diagnosis, pathogen identification and AST?

4 Methods for assessing clinical effectiveness

A systematic review will be conducted to summarise the evidence on the accuracy, technical performance and clinical effects of using POCT for people with suspected UTI. The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and the NICE Health Technology Evaluations Manual.(21-23)

4.1 Inclusion and exclusion criteria

Studies that meet the criteria summarised in Table 6 eligible for inclusion:

Table 6 Inclusion Criteria for Objectives 1, 2 and 3

	Obj 1: Clinical Impact	**Obj 2: Accuracy**	**Obj 3: Technical performance**
Participants	Patients with suspected UTI. Studies in patients with suspected acute, recurrent or chronic UTI will be eligible.		
Technology	Astrego PA-100 system, Flexicult Human, Lodestar DX, TriVerity, Uriscreen, Diaslide, Dipstreak, Chromostreak, Uricult, Uricult trio or Uricult plus		
Comparator/ Reference standard	Standard care – dipstick plus culture or culture alone	Culture or other reported reference standard	NA
Outcome	• Morbidity, including: ○ Recurrence ○ Pyelonephritis ○ Sepsis ○ Adverse effects of antibiotics • Any outcome related to antibiotic use or prescription • Mortality • UTI associated healthcare resources • Health-related quality of life	Test performance to detect pathogens or assess susceptibility to antimicrobials	• Test failure rate • Ease of use/ acceptability • Time to test results • Any outcome related to antibiotic use or prescription • UTI associated healthcare resources • Health-related quality of life • Test costs • Any reported data on clinical outcomes e.g. morbidity/mortality
Setting	Primary care or community setting	Any	Any
Study design	RCT or non-randomised study of interventions (NRSI)	Diagnostic test accuracy (DTA) study	Any

Given the tight timelines to conduct an Early Value Assessment (EVA), it is necessary to restrict the review so that it can be undertaken within the available time. The following pragmatic approach will be adopted. For each test, if studies are identified that fulfil inclusion criteria for objectives 1 or 2, then these tests will not be evaluated for objective 3

i.e. only tests where there are no studies included for objectives 1 and 2 will be evaluated for technical performance. Any studies excluded at this point will be summarised in tables. The review will also be restricted to studies published after 2000. We consider it likely that clinical practice, the spectrum of bacteria causing UTI, and the technical performance of tests evaluated before will have changed such that studies published before this date are unlikely to provide useful information to inform this appraisal. Animal studies will be excluded.

4.2 Study identification

Studies will be identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual and recent guidance on searching.(24, 25)

4.2.1 Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid SP)
- EMBASE (Ovid SP)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCOhost)

We will use a sensitive search strategy based on terms for each of the technologies eligible for inclusion and for the manufacturers of these technologies. A draft search strategy is reported in Appendix 10.1.

4.2.2 Non-bibliographic search methods

Completed and ongoing trials will be identified through searches of the following trial registries:

- ClinicalTrials.gov via https://www.clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) via https://www.who.int/clinical-trials-registry-platform

Additional relevant studies will be identified by:

- Screening reference lists of any reviews (systematic or non-systematic) identified by our searches
- Reviewing the reference lists of any study report included at full-text
- Hand searching the websites of the manufacturer/or licence holders for each test
- Information submitted by test manufacturers

4.2.3 Managing the searches

Search results will be exported to EndNote 20 for deduplication using the default deduplication settings and manual review of records. Search results will be exported to Microsoft Access for screening.

4.3 Review strategy

Two reviewers will independently screen titles and abstracts identified by the searches. Full copies of all reports considered potentially relevant will be obtained and two reviewers will independently assess these for inclusion. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted using standardised data extraction forms developed in Microsoft Access or Microsoft Word depending on the quantity of data available. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Data will be extracted on the following: study design (RCT, NRSI, DTA or other), objective that study addresses, funding sources (public, industry, mixed), study location, presentation (symptomatic/asymptomatic), sex, age, inclusion criteria, rapid test details (manufacturer, antibiotics targeted), comparator or reference standard test(s), and outcomes specified in inclusion criteria (section 4.1). If data are reported on any of the following subgroups of interest, these will be extracted separately:

- People with suspected acute UTI
- People with suspected recurrent UTI
- People with suspected chronic UTI
- Women under 65
- Women over 65
- Men under 65
- Men under 65
- Adults with indwelling urinary catheters
- Babies, children and young people under 16
- Children under 3 months
- Pregnant women
- People who are frail or have dementia
- People who are pre-, peri- or post-menopausal
- People on prophylactic antibiotics for treatment of UTI
- People of different ethnicities
- People with a higher risk of complicated UTIs (for example people with neurogenic bladder, diabetes, polycystic kidney disease or people who are immunocompromised)
- People with suspected pyelonephritis

Dichotomous data will be extracted as number of patients with events and/or number of events and total number of patients in each treatment arm. For categorical data, we will extract details on the categories assessed, the total number of patients in each treatment arm and the number of patients in each outcome category. For continuous data we will extract means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) for the outcome at baseline, follow-up and for change from baseline in each treatment group. For all types of data, summary effect estimates together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted.

Accuracy data will be extracted as 2x2 tables comparing the rapid test with culture as the reference standard where available. If measure of accuracy (e.g. sensitivity, specific, ROC plot) are reported without providing the information needed to calculated 2x2 tables, then these data will be extracted. We will consider accuracy separately for the following target conditions:

- Presence of UTI
- Pathogenic cause of UTI
- Antimicrobial sensitivity

Where multiple sets of 2x2 data are reported in a single study, for example for different tests, target conditions, thresholds, or subgroups of interest, all data will be extracted.

4.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the updated Cochrane Risk of Bias Tool (ROB 2.0).(26) NRSI will be assessed using the ROBINS-I tool.(27) DTA studies will be assessed for methodological quality using QUADAS-2.(28) Quality assessment will be undertaken by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Synthesis methods

For each of the three systematic review objectives (obj 1 to 3), a narrative summary of all of the included studies will be presented. This will include a summary of the study characteristics (e.g. study designs, sample size, geographical location, year, baseline population characteristics, rapid test evaluated), outcomes reported and study quality. The synthesis will be stratified by technology evaluated. Where data are available, the analysis will also be stratified on the following subgroups:

- People with suspected acute UTI
- People with suspected recurrent UTI
- People with suspected chronic UTI
- Women under 65
- Women over 65

- Men under 65
- Men under 65
- Adults with indwelling urinary catheters
- Babies, children and young people under 16
- Children under 3 months
- Pregnant women
- People who are frail or have dementia
- People who are pre-, peri- or post-menopausal
- People on prophylactic antibiotics for treatment of UTI
- People of different ethnicities
- People with a higher risk of complicated UTIs (for example people with neurogenic bladder, diabetes, polycystic kidney disease or people who are immunocompromised)
- People with suspected pyelonephritis

If sufficient data are available for any reported outcome, meta-analysis will be carried out to generate summary effect estimates. For studies of effectiveness, random effects meta-analysis will be performed to enable a between-studies heterogeneity parameter (tau) to be estimated. A restricted maximum likelihood (REML) approach will be used to estimate tau. Heterogeneity and inconsistency across studies will be quantified using the tau and I^2 statistics.(29) Fixed effect meta-analyses will be performed as sensitivity analyses, or as the sole analyses if insufficient data are available to estimate tau. Where observational (cohort) studies are synthesised, estimates that have been adjusted for potential confounders will be used where available.

For accuracy data, bivariate random effects meta-analysis of sensitivity and specificity will be performed, with binomial likelihoods.(30, 31) Analyses will be stratified according to type of test. Summary estimates of sensitivity and specificity together with 95% confidence intervals (CIs) will be calculated. Coupled forest plots of sensitivity and specificity will be used to display results from individual studies, to allow visual assessment of heterogeneity. Study-level and pooled results will also be plotted in Receiver Operating Characteristic (ROC) space, with 95% confidence ellipses around pooled estimates representing the joint uncertainty in sensitivity and specificity. We do not anticipate having sufficient studies for formal investigation of heterogeneity.

A detailed description of any gaps in the evidence will be provided together with any methodological limitations of the existing studies. This will help inform recommendations for future research and requirements for a full diagnostic assessment.

5 Methods for synthesising of cost effectiveness

5.1 Identifying and systematically reviewing published cost-effectiveness studies

The search for the clinical effectiveness review will also inform the cost-effectiveness analysis. This is possible because the search strategy is not limited by study design or publication type search filters. The search strategy is reported in Appendix 10.1. We will include any relevant papers/reports on cost-effectiveness identified in the clinical effectiveness reviews, search citations in relevant publications that we identify, search the manufactures' websites, and ask experts in the field.

5.2 Conceptual modelling of costs, quality of life and cost-effectiveness

A decision-analytic model will be conceptualised to estimate the incremental costs and quality-adjusted life years (QALYs) for POCT for UTI in comparison to culture with or without dipstick tests. The model described below is for all possible comparators and populations/subgroups in the scope. Separate models would be required for each population/subgroup but development will focus on where the clinical evidence identified as described in Section 4, is greatest. A simple coded model for tests and subgroups where the clinical evidence and impact are strongest may be implemented in the R programming language. This would only be if evidence is deemed sufficient and test/subgroup is not too narrow to lack impact.

5.2.1 Testing strategies

The tests to be compared are those included in the scope outlined in Table 3. These include POCT that also perform AST (e.g. Astrego PA-100 and Flexicult Human) and POCT that diagnose UTI but do not perform AST (e.g. TriVerity, Uriscreen, Lodestar DX).

The comparator is diagnosis based on clinical features plus dipstick tests with culture confirmation (in population 1) or diagnosis based on clinical features plus culture without dipstick test (in population 2).

In cases where the test results (e.g. dipstick with culture confirmation) take more than a day, it is assumed that some patients would be prescribed and begin antibiotics.

5.2.2 Conceptual model

Our planned conceptual model is illustrated in Figure 2. This will be refined during model development in response to evidence from Section 4 and feedback from clinical advisers and patient representatives. Arrows indicate the influence of components on the rest of the model.

Our conceptualisation is divided into short-term and long-term components. In the short-term, the important elements to consider are the symptoms of complicated and uncomplicated UTI, characteristics and consequences of antibiotics, expected efficacy of

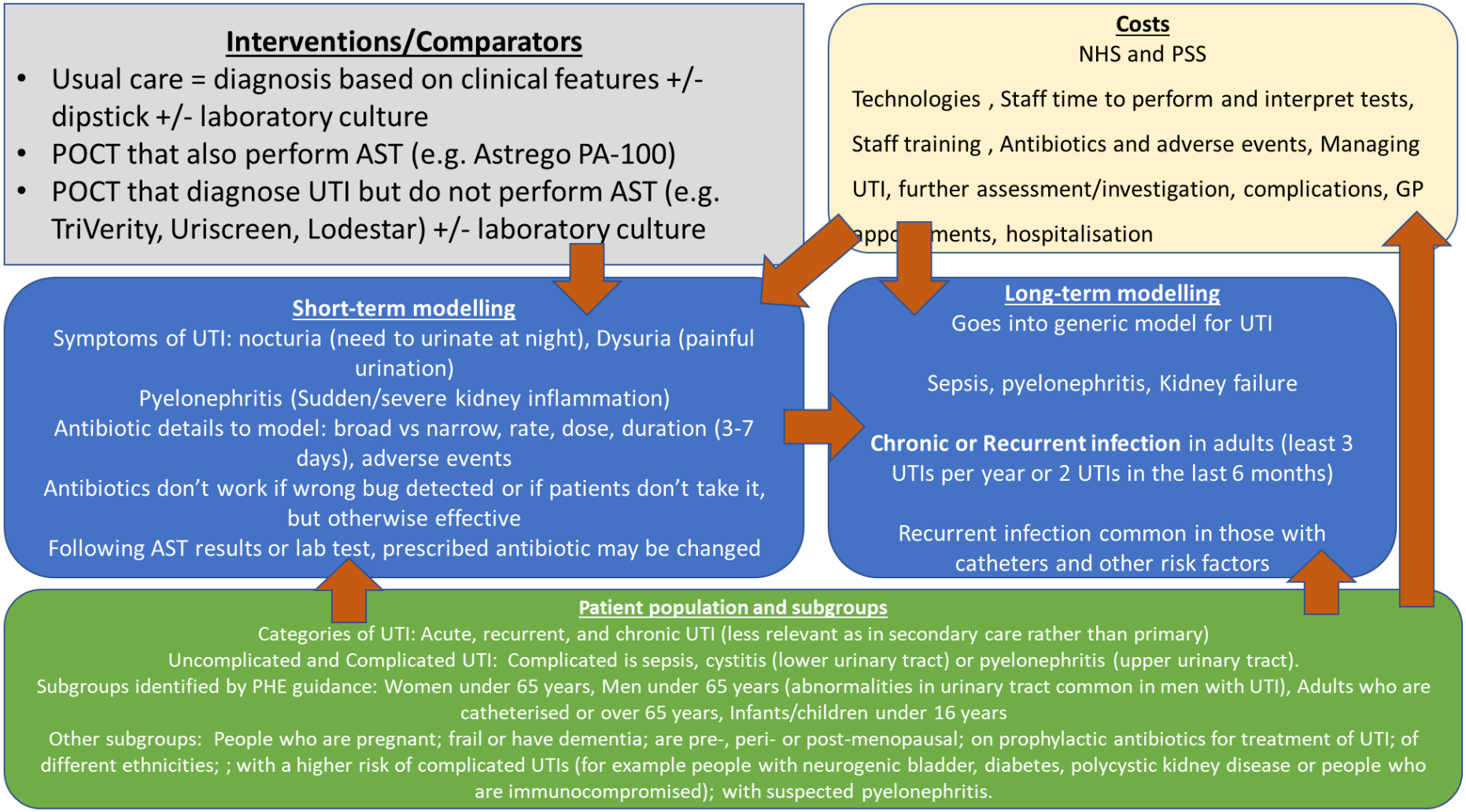
antibiotics, and any response to ineffectiveness of antibiotics. In the long-term, the model would link to a generic model for UTI and cover the key complications of sepsis, pyelonephritis, and kidney failure. Furthermore, the development or continuation of chronic or recurrent UTI must be considered, and it is recognised that this would be particularly common in patients with risk factors such as catheters.

Costs would be taken from an NHS and PSS (Personal Social Services) perspective and include all elements from the short-term or long-term components. The tests to compare are those described in Section 5.2.1.

Our conceptual model reflects the influence on the costs, health outcomes and model structures of the choice of populations and subgroups. UTIs themselves are categorised in acute, recurrent, and chronic. Furthermore, UTIs divide into those that are uncomplicated and complicated at GP presentation, while our model reflects that patients with either uncomplicated or complicated UTI can still suffer complicated UTI at the end of testing and treatment.

UTI themselves are divided into suspected acute, recurrent, and chronic. Rates of complicated UTI, and the costs and health outcomes of the model, also depend on the subgroup under investigation. We conceptualised these to be broad and include the subgroups identified as categories in the PHE UTI guidance: Women under 65 years, Men under 65 years (abnormalities in urinary tract common in men with UTI), Adults who are catheterised or over 65 years, Infants/children under 16 years. Other subgroups, recognised to be important but likely to have weaker evidence, include frail, immunocompromised, and ethnic minority patients. Modelling will focus on the population and subgroup on which most evidence is found

Figure 2 Conceptual model for point of care tests in UTI*



*Boxes illustrate important elements to consider. Arrows illustrate influence. AS=antibiotic susceptibility; AST=antibiotic susceptibility test; GP=General Practice; NHS=National Health Service; PHE=Public Health England; POCT=Point of Care Test; PSS=Personal Social Services

5.3 Evaluating costs, quality of life and cost-effectiveness

We will develop a structure and identify the necessary evidence to evaluate costs, quality of life and cost-effectiveness of point of care tests for UTI using the model conceptualised in Figure 2. Our model would also assess the reduction in use of empiric/broad spectrum antibiotics, and therefore antibiotics use overall, as POCT with AST can yield targeted treatment and POCT without AST can indicate when no UTI is present. An NHS and PSS perspective would be taken with a life-time horizon where costs and QALYs are discounted at an annual rate of 3.5%.

Our conceptual model could be extended to a full model, with systematic literature reviews and other evidence gathering exercises; analyses below are therefore what should be done if a full timescale for this work were ever to be made available, rather than the truncated timing of an EVA. However, a simple coded model for tests and subgroups where the clinical evidence and impact are sufficiently strong may be implemented in the R programming language. Any evaluations would be preliminary and not represent a comprehensive assessment of value of POCT.

5.3.1 Model structure

The recommended model structure would comprise a decision tree for short-term outcomes and either a cohort Markov or individual level discrete event simulation (DES) for long-term outcomes.

A possible short-term decision tree is illustrated in Figure 3. This structure is for tests that also perform AST (e.g. Astrego PA-100 and Flexicult Human), tests that diagnose UTI but do not perform AST (e.g. TriVerity, Uriscreen, Lodestar DX), and culture testing (with or without dipstick). The model could be extended to include no testing, as is often the strategy for women with uncomplicated UTI and typical symptoms.(32) Our conceptualisation is that these tests would either identify patients as having UTI and a specific antibiotic to which the patient is susceptible, identify patients as having UTI but not identify a specific antibiotic to which they are susceptible, or identify them as not having UTI. It is assumed that tests that do AST may not always detect the antibiotic to which the UTI is susceptible as they do not detect all possible bacteria; probabilities would differ between tests as per analyses in Section 4.5.

The model would then assume that antibiotics would be assigned accordingly (e.g. targeted if specific susceptibility is known, empiric or broad if unknown, and not treated if known not to be a UTI). Treatment is then successful without complications resulting from UTI, or unsuccessful with complications resulting from UTI. This is only one potential model that will be considered during the EVA; it is also possible that a patient would be cured of UTI but still experience complications from the UTI. Dipstick with lab testing, or lab testing alone, is assumed to initially lead to empiric antibiotic treatment as specific susceptibility is unknown. Further options (e.g. Lab testing with no initial treatment) will also be considered for the final decision tree model.

Terminal nodes would be modelled further in the long-term model illustrated in Figure 4. This illustration is for a state-based model but event-based will also be considered. Microsimulation and cohort modelling will both be considered. The “Recurrent UTI” state would be modelled by readmission to the decision tree as patients would be assumed to be eligible for further testing and treatment.

Figure 3 Possible decision tree structure for short-term modelling

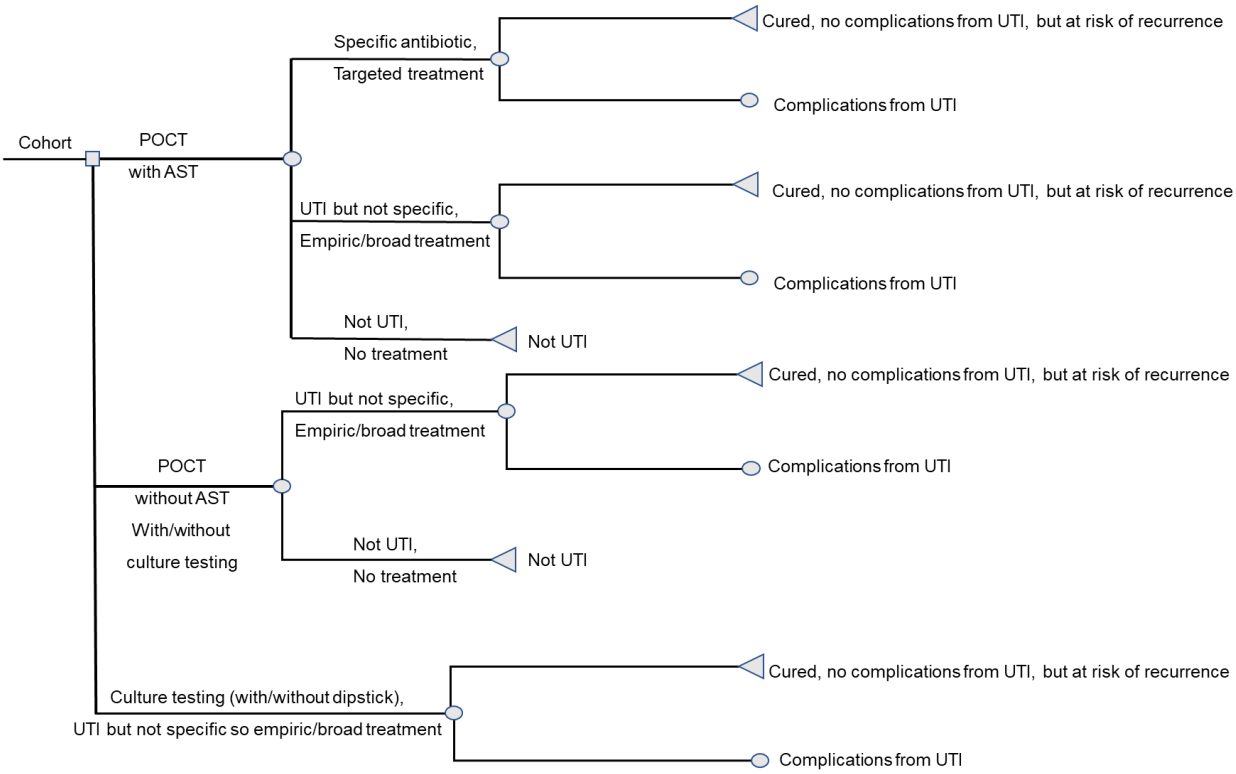
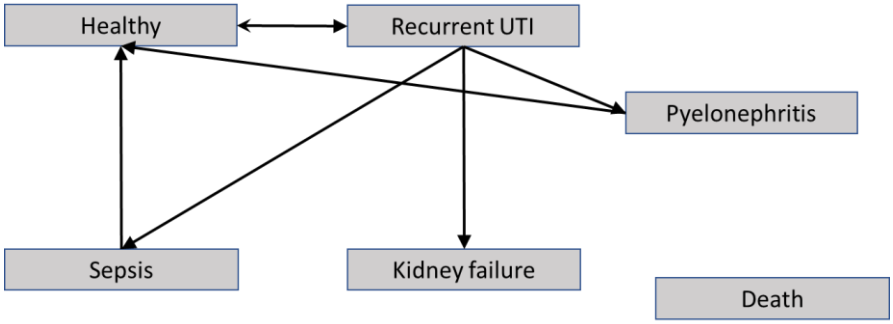


Figure 4 Possible long-term Markov model from decision tree ‘Cured’ and 'Complications' branches*



*Hospitalisation is a factor for each of the complication states. Death is possible from any state.

5.3.2 Model inputs

Where possible, model inputs will be derived from the clinical review, and from our additional searches in Section 5.1. These will be supplemented by pragmatic searches of, for example, PubMed. Where there is insufficient evidence available, we will base parameters on expert opinion and recommend scenario analyses to explore the impact of these assumptions on the results.

5.3.3 Health outcomes

In the short-term model, we would need quantify the quality of life with a complicated or uncomplicated UTI, impact on quality of life of testing and of the 3-7 day course of antibiotics, including their adverse events. We will do this using utilities, disutilities, or quality adjusted life years (QALYs) over a defined time period. For example, a disutility for antibiotic AE along with a proportion of the cohort expected to suffer these AEs; the QALYs accrued by patients with complicated or uncomplicated UTI over the 2 weeks, say, of the short-term model.

In the long-term model, we would need instantaneous utilities or QALY estimates for each of the states/events being modelled. These include pyelonephritis, sepsis, kidney failure, and cystitis. Utility/QALY for 'healthy' patients recovered from UTI are also needed.
The utility and QALY estimates will be used to generate total QALYS over the time horizon of the overall model for each strategy.

The model will additionally estimate the extent of use of empiric antibiotic treatment (i.e. broad spectrum antibiotics) under each treatment pathway. This would aim to assess the impact on antibiotic resistance.

5.3.4 Costs

Costs of testing technologies, staff time to perform the tests, GP appointments, antibiotics courses, managing complicated/uncomplicated UTI, managing each complication, will be gathered from routine NHS sources (NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), our reviews of previous cost-effectiveness models and pragmatic literature searches, and through discussions with clinical advisors.
Cost of training staff to utilise innovative tests will be considered but are a budget impact rather than a cost to include in cost-effectiveness analysis as they relate to cost of setup rather than routine use.

5.3.5 Analyses

Probabilistic analysis where parameter uncertainty is captured with probability distributions and simulation would be recommended to estimate incremental cost-effectiveness ratios and expected net benefits at commonly used NICE willingness to pay thresholds.
Uncertainty would be presented using cost-effectiveness planes and cost-effectiveness acceptability frontiers. One way sensitivity analyses would be performed for all key parameters, including all parameters based on expert opinion.

Some of all of these may be conducted for tests/subgroups identified as feasible for preliminary R modelling.

5.3.6 Scenario and subgroup analyses

Scenario and subgroup analyses would be conducted to explore the sensitivity of results to key model assumptions.

6 Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 19/01/2023. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted. If confidential information is included in economic models then a version using dummy data or publicly available data in place of confidential data will be provided.

7 Competing interests of authors

None of the authors have any competing interests.

8 Timetable/milestones

Milestone	Date to be completed
Draft protocol	30/11/2022
Final protocol	5/12/2022
Draft assessment report	26/1/2023
Final assessment report	16/2/2023

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10 Appendices

10.1 Literature searches

Search purpose: to identify studies reporting data on the clinical or cost effectiveness, accuracy, or the technical performance, of the technologies specified in the scope.

Database: MEDLINE (MEDALL)
Host: Ovid
Data parameters: 1946 to present
Date of search: 5 Dec 2022

Search strategy	**Search narrative**
1 (Astrego* or ("PA-100" and (urin* or infect*))).ti,ab,kw,kf. (4) 2 "Sysmex Astrego".ab,in. (0) 3 flexicult*.ti,ab,kw,kf. (12) 4 ("SSI Diagnostica" or "Statens Serum Institut" or "Statens Serum Institute").ab. (162) 5 Lodestar*.ti,ab,kw,kf. (22) 6 "Llusern Scientific".ab,in. (0) 7 TriVerity*.ti,ab,kw,kf. (0) 8 Inflammatix.ab,in. (40) 9 "Uriscreen*".ti,ab,kw,kf. (16) 10 "Savyon Diagnostics".ab,in. (25) 11 (Diaslide* or Dipstreak* or Chromostreak*).ti,ab,kw,kf. (6) 12 Novamed.ab,in. (51) 13 Uricult*.ti,ab,kw,kf. (66) 14 (Aidian or Orion Diagnostic*).ab,in. (145) 15 (NCT02323087 or ISRCTN65200697 or NCT02585115 or NCT03835104 or NCT02368847).af. (6)	Lines 1 to 15 search for test name or manufacturer for each of the technologies specified in the scope. The manufacturer is searched using straight-sided quotation marks, meaning that manufacturer names are searched as phrases in the order of words as presented. Truncation (indicated by *) is used after the test name to identity study reports which use the test name (e.g. Flexicult) and where this is reported using the Trade Mark symbol (e.g., FlexicultTM). Searching is undertaken in the following fields: ti = title ab = abstract kw = keyword kf = author keyfield in = institution (for searching manufacturers) af = all fields
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (544)	Line 16 combines the search terms for the tests and manufacturers using the Boolean connector OR meaning that all search terms are searched for.
17 exp animals/ not humans.sh. (5070893) 18 16 not 17 (526)	Line 17 restricts the search to studies in humans.