

Point of care urine culture to inform appropriate antibiotic prescribing for uncomplicated urinary tract infection in primary care (POETIC): a randomised controlled trial of clinical and cost effectiveness

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Abstract

Background: Urinary tract infection (UTI) is common and widespread use of antibiotics contributes to antimicrobial resistance. The effectiveness of point of care test (POCT) for urine culture is unknown.

Aim /Design: Individually randomised trial of the clinical and cost effectiveness of Flexicult™ SSI-Urinary Kit (that identifies and quantifies bacterial growth and antibiotic susceptibility) to guide antibiotic treatment of uncomplicated UTI in adult women in primary care vs. standard care.

Methods: Multi-level regression compared outcomes between the two groups controlling for clustering.

Results: 329 were randomised to POCT and 325 to standard care. Mean age was 47.6, and 90% had two or more of dysuria, frequency and urgency. Fewer women randomised to POCT were prescribed antibiotics at the initial consultation (82.4% (267/324) vs. 88.4% (282/319), OR = 0.56, 95% CI 0.35 to 0.88). Clinicians indicated that they had contacted **176/303 (58.1%) women in response to the test result and that it had** influenced management for 190/301 (63.1%): 14 (7.4%) were advised not to start taking an antibiotic, 10 (5.3%) were advised to stop taking an antibiotic they had already started, 29 (15.3%) to start taking an antibiotic, 63 (33.2%) to keep taking an antibiotic that was prescribed at the baseline visit, and 74 (38.9%) were prescribed a new antibiotic. Despite this, there was no significant difference in antibiotic use that was concordant with laboratory culture results (primary outcome) at day 3 (39.3% POCT culture vs. 44.1% standard care, OR 0.84, 95% CI 0.58 to 1.20), and there was no evidence of any differences between study arms in recovery, patient enablement, UTI recurrences, re-consultation and hospitalisations at follow up. POCT culture was not cost-effective.

Conclusions: Point of care urine culture slightly reduced initial antibiotic prescribing and influenced management for two thirds of women, but antibiotic use was not more concordant with laboratory culture results, and patient reported outcomes did not improve, and therefore it was neither clinically nor cost effective when used mainly to adjust immediate antibiotic prescriptions. Further research should explore approaches to encourage use of the test to guide *initiation* of 'delayed antibiotics'.

Trial Registration: ISRCTN65200697. <http://www.isrctn.com/ISRCTN65200697>

How this fits in

Point of care urine culture used mainly for adjusting empirical antibiotic prescribing decisions for uncomplicated urinary tract infection in primary care did not lead to an increase in concordant antibiotic prescribing or improve patient outcomes, and was not cost effective.

Background

Point of care tests (POCTs) for infections are being promoted to reduce antimicrobial resistance and improve patient outcomes.¹ POCTs are frequently subject to evaluations of analytic performance, but are often introduced into practice without rigorous trials evaluating clinical and cost effectiveness.²⁻⁵

About 10% of adult women experience a urinary tract infection (UTI) in any given year, and around half experience a UTI at some point in their lives.⁶ UTI accounts for about 15%-20% of antibiotics prescribed in primary care.⁷⁻⁹ However, up to 60% of women with uncomplicated UTI who are treated with antibiotics do not have a positive urine culture, and while antibiotics shorten duration of symptoms on average, not all individual affected benefit from antibiotic treatment.^{10,11} Furthermore, some women with a positive urine laboratory culture are not prescribed antibiotics.¹² Better targeted antibiotic prescribing may reduce unnecessary risk of side effects and subsequent infections that are antibiotic resistant and thus may reduce symptom duration and burden on health services in the future.¹³⁻¹⁵

Current strategies to predict microbiologically confirmed UTI in adult women need to be improved so that: more women who will benefit from antibiotic treatment are prescribed them, antibiotic treatment is better targeted to the sensitivity of the infecting organisms, and antibiotics are prescribed less often for women who will not benefit. Better targeted antibiotic use is important for antibiotic stewardship, as antibiotic use drives resistance. There is thus an urgent need to support clinicians in the community in deciding both *whether* to prescribe antibiotics and in selecting the most appropriate antibiotic when indicated.

Point of care urine culture has been proposed as a solution in primary care as results can be available within 24 hours.^{16,17} The approach is already widely used in Denmark, but has never been evaluated in a rigorous randomised controlled trial to determine whether it benefits patients.

We therefore aimed to determine the clinical effects and costs of POCT urine culture for symptoms of uncomplicated UTI on the overall appropriateness of antibiotic prescribing compared to current best practice alone.

Methods

The point of care testing for urinary tract infection in primary care (POETIC) trial was a pragmatic, parallel two-arm, individually randomised, open, test-treatment⁴ controlled trial to compare the effects and costs of an optimised POCT guided diagnostic and treatment strategy for symptoms of uncomplicated UTI in adult women on the overall appropriateness of antibiotic use when compared to a 'practice based on best available local guidelines' strategy (standard care).

This multinational trial was implemented in four primary care research networks (Wales, England, Spain and the Netherlands), selected based on past research experience and variation in resistance rates and usual management of UTI. The trial was approved in the UK by the Research Ethics Committee for Wales (Reference: 12/WA/0394) and Jordi Gol i Gurina Ethics Committee in Barcelona (Ref: AC13/01), and the Utrecht Medical Ethics Testing Committee (Ref: 13/304) in the Netherlands.

The full POETIC protocol has been published elsewhere.¹⁸ A brief summary of trial procedures is presented below.

Participants

Network Coordinators invited clinicians in four primary care networks to take part. Participating clinicians (GPs or nurse prescribers) identified eligible patients during routine general practice consultations. Women (18 years or older) were eligible if they were presenting in primary care with at least one of dysuria, urgency and frequency, and with a clinical diagnosis of uncomplicated UTI. Women with suspected pyelonephritis, on long-term antibiotic treatment, antibiotics for UTI in the preceding four weeks, or with significant genitourinary tract abnormalities or terminal illness, were excluded. Patients were randomised before any dipstick testing and management decisions were made.

Randomisation

Remote, online randomisation was stratified by practice, and used minimisation (with a random element) to balance for number of key symptoms (dysuria, frequency and/or urgency) at presentation. Practice stratification was kept confidential to help with allocation concealment.

Clinical examination

Clinicians recorded the presence and severity (on a seven-point scale from 0 – not affected to 6 – 'as bad as it could be') of baseline clinical features, including fever, pain in the side (costovertebral angle tenderness), blood in urine, smelly urine, burning or pain when passing urine, urgency, daytime

frequency, night time frequency, abdominal pain, restricted activities, and feeling generally unwell. The scale was similar to previously used instruments¹⁹ and to the scale used in the patient diary. Clinicians also recorded use of diagnostic tests (i.e. urine dipstick testing), antibiotics prescribed and planned follow-up.

Sample Collection

Participants were asked to provide urine and stool (optional) samples on the day of recruitment. Urine samples were collected using the Peezy mid-stream urine (MSU) Collection Kit. For participants randomised to intervention, urine samples were split with a portion for the intervention test and the rest sent for culture in containers with boric acid to local network laboratories using routine clinical sample transport arrangements (Spain and the Netherlands) or to a central laboratory by post (England and Wales). Participants were asked to return stool samples by post to their designated local laboratory within 24 hours of collection. Participants were also asked to provide further urine and stool samples at day 14. Stool samples were obtained to estimate effect on resistance in faecal flora.

Trial Intervention

Clinicians were asked to use the Flexicult™ POCT urine culture to guide the management of participants randomised to intervention, but it was left up to them to decide or negotiate with the patient how best to use the test. For example, they could avoid empirical prescribing and use the test to determine whether and what antibiotic class to prescribe the following day, prescribe empirically and use the test to aid in a next day review of the initial prescribing decision, or provide a delayed antibiotics prescription and use the test to guide use of the delayed prescription. Flexicult™ POCT urine culture involves fresh urine being poured onto a chromogenic agar plate which is then incubated at 35-37°C overnight in a small desktop incubator within the practice, and the results are reviewed 18-24 hours later. The chromogenic agar plate is sub-divided into six segments: the largest allows for the identification of species (by colour of colonies) and bacterial growth, and the other five segments contain agar impregnated with antibiotics and are used for the assessment of antibiotic susceptibility (*Figure 1*). Clinicians were provided with face-to-face training, a country specific Flexicult™ brochure, and a poster to aid interpretation of results. Further training resources were available online (www.POETIC-study.co.uk).

When reading the Flexicult™ urine culture test, clinicians recorded bacterial growth based on number of colonies, bacterial identification based on the colour of colonies and the antibiotic resistance of the pure or predominant organisms based on presence of bacterial growth in the antibiotic sections. Antibiotic susceptibility was only recorded if growth was $\geq 10^3$ CFU/mL in the large plate section.

Clinicians were asked to delay prescribing until the results of the test were known or, if appropriate, to prescribe empirically and then adjust their prescription according to the result of the test by contacting the patient the following day. Management decisions were recorded after reading the test in the intervention arm.

Patients randomised to the standard care arm received care informed by national guidelines, and clinicians received a summary of relevant national treatment guidelines.

Participant Follow Up

All participants were asked to complete a two-week daily symptom diary, which covered medical history and included the Patient Enablement Instrument.²⁰ On each of the 14 days, participants were asked to rate the presence and severity of symptoms (using the same scale used at baseline) and record any antibiotic use. On day 14, participants were asked to record all resource use associated with UTI and time off work. Non-responders were reminded by telephone and given the opportunity to complete minimum data set questions. At three months, the primary care medical records were examined for re-consultations with primary and secondary care, recurrences of UTI and further antibiotic use.

Microbiological procedures

Local laboratories were provided with a POETIC microbiology manual and standard operating procedures.¹⁸

Definition of a UTI

The definition of a UTI used by the laboratory serving the participating clinicians was used to compare results of the point of care Flexicult™ test, as the test was designed to give them their usual information quicker. In Wales, England and Spain, the definition of a UTI on laboratory culture was $\geq 10^5$ colony forming units per millilitre (CFU/mL) of a pure/predominant recognised uropathogen (where predominant was defined as a $\geq 10^3$ CFU/mL difference between the first and second highest bacterial growths). For the Netherlands, the definition was 10^4 CFU/mL growth of a pure/predominant recognised uropathogen.

Statistical Considerations

Sample Size Calculation

A sample of 460 (230 for each arm) patients for final analysis was required (significance level $\alpha = 0.05$, statistical power $(1-\beta) = 0.90$) to allow for an increase in concordant antibiotic usage from 55% in the standard care arm to 70% in the intervention arm. This was inflated to 614 to allow for a 25% loss to follow up. The analysis took clustering by practice into account.

Primary outcome

The primary outcome was concordant antibiotic use defined as consumption of an antibiotic on Day 3 (or Days 1 or 2 for fosfomycin, and Day 1 the initial consultation and randomisation) for which a pathogen considered to be causing a UTI isolated in a laboratory was sensitive *in vitro*, or, no antibiotic use by women who did not have a UTI on laboratory culture *Figure 2*). Sensitivity analyses were undertaken using the primary outcome calculated using the Flexicult™ plate results and initial antibiotic prescribing.

Secondary outcomes

Secondary outcomes, also defined at the outset in the protocol, comprised initial antibiotic prescription (i.e. on Day 1) and at any point during the two week follow-up period, dose and duration of antibiotic, antibiotic consumption, adherence to national prescribing guidelines, recovery (duration of symptoms and symptom burden)^{19,21}, antibiotic resistance in urine and stool samples (at two weeks), patient Enablement²⁰, re-consultation, recurrence of UTI, hospitalisation, direct/indirect costs (within a three-month period), and cost-effectiveness.

Statistical Analysis

Analysis of primary and secondary outcomes were based on a modified intention-to-treat population. A sensitivity analysis was conducted using multiple imputations to account for missing outcome data (see online supplementary material). Multilevel regression models were used to account for clustering of patients within practices. Country (England, The Netherlands, Spain, and Wales), key symptoms (1, 2 or 3) and stratifying and balancing variables were included as covariates in all models.

Logistic, linear or futility (survival) analyses were undertaken as appropriate. Urinary symptom burden was calculated using the Area Under the Curve (AUC) of the total symptom score for urgency, day time frequency and night time frequency on each day. Due to its distribution, the AUC symptom burden was natural logged, and patient enablement was dichotomised for analysis.

Health economic evaluation

We aimed to assess mean total cost (including the cost of the POCT) per unit increase in concordant antibiotic prescribing.¹⁸

Intention to treat analysis was used to determine the difference in resource use and difference in effectiveness between intervention and control group. Where cost data were skewed, 10,000 replications and bias corrected non-parametric bootstrap methods were used to determine 95% confidence intervals, analysis accounted for cluster effect.²² A cost effectiveness acceptability curve is used to show the probability of the intervention having an incremental cost effectiveness ratio below a range of acceptability thresholds.²³

Results

Participants were recruited between July 2013 and August 2014, with 329 randomised to the intervention (Flexicult™) arm and 325 to standard care. Baseline data were available for 324 in the intervention arm and 319 in the standard care arm. We ascertained initial antibiotic prescribing for 100% of participants, obtained primary outcome data for 252 (76.6%) and 245 (75.4%) respectively, and had three-month follow up data for over 98.6% (Figure 3). There were no important measured differences between those with and without primary outcome data (see supplementary material). The two arms were well balanced in terms of baseline variables. The most frequent symptoms were frequency, urgency and dysuria, and the least frequent symptoms were fever and blood in the urine (Table 1). Approximately a third had a microbiologically confirmed UTI (35.9%, 220/612).

More participants in the standard care arm reported concordant antibiotic use at day 3 than in the intervention arm (44.1% (108/245) vs. 39.3% (99/252)) although this was not statistically significant (OR 0.84, 95% CI 0.58 to 1.20). The main driver of discordant usage was use of antibiotics with no laboratory microbiological confirmation of UTI (44.9% (110/245) patients in the standard care arm and 54.0% (136/252) patients in the intervention arm). Only 4.1% (10/245) and 2.0% (5/252) in standard care and intervention arms respectively received an antibiotic to which the infecting organism was resistant. Sensitivity analyses, including full ITT analyses using multiple imputations, did not alter the conclusions (see Table 2 and online supplementary material).

Secondary outcomes (Table 2) include lower prescribing at initial consultation in the intervention arm (82.4% (267/324) vs. 88.4% (282/319), OR = 0.56, 95% CI 0.35 to 0.88), but no differences in antibiotic prescribing at any point, antibiotic resistance and consumption, adherence to national prescribing guidelines, patient enablement, recovery, recurrence, re-consultation, hospitalisation or resistance in urine and stool samples at 2 weeks.

Clinicians reported using the Flexicult™ POCT for 96.6% (313/324) of participants randomised to the intervention. Clinicians indicated that they had contacted **176/303 (58.1%) women in response to the test result and that it had** influenced management for 190/301 (63.1%) : 14 (7.4% of those with a change of management) were advised not to start taking an antibiotic, 10 (5.3%) were advised to stop taking an antibiotic they had already started, 29 (15.3%) to start taking an antibiotic, 63 (33.2%) to keep taking an antibiotic that was prescribed at the baseline visit, and 74 (38.9%) were prescribed a new antibiotic (Table 3). There were two reports of Flexicult™ use in the standard care arm.

It took an average of nine minutes to prepare the Flexicult™ test, six minutes to obtain and record the results, and seven minutes to discuss the results with the patient. The total cost of the intervention, including the cost of the POCT, was £48 (UK), €56 (The Netherlands) and €32 (Spain); the delivery costs contributed to nearly 90% of the total cost. At day three the average cost of antibiotic prescribing was similar between the two groups. There were no differences in any other health care costs by day 3, patient borne costs at 14 days, or health care resource use at three months.

A cost effectiveness ratio showed that the intervention is never cost savings and it is cost effective only in limited cases and against a high willingness to pay for the intervention. However, the cost of antibiotic resistance is not included in estimates.²⁴

Discussion

Summary

In this clinical and cost effectiveness randomised controlled trial of a point of care urine culture test for uncomplicated UTI in women in primary care, we found marginally fewer antibiotics were prescribed at the initial consultation for patients in the POCT arm. Clinicians indicated that they had contacted nearly 60% patients in response to the test, that it had influenced their management in two thirds of cases, and had prescribed a new antibiotic in almost half of those for whom they had a test result. However, they generally prescribed antibiotics empirically at the initial consultation without waiting for the test result, and seldom withdrew antibiotic treatment that had already been started when the test indicated no UTI. Despite the influence the test had on clinicians' advice and decisions

about antibiotics for UTI, we found no evidence of any difference in the primary outcome of patient reported antibiotic use that was concordant with laboratory (as opposed to the POCT) culture results.. Patient reported recovery was not influenced by test use, and costs were higher for clinical management using the Flexicult™ urine culture.

Clinicians could decide or negotiate with the patient how best to use the test, for example, to aid in a next day review of an initial antibiotic prescribing decision, to guide starting a delayed antibiotic prescription, or to determine whether and what antibiotic class to prescribe the following day. Flexicult™ is a point of care test in that it is performed outside the clinical laboratory setting where the patient is receiving care. It is however, not a rapid test, even though the results are available within 24 hours, which is generally far more rapid compared to the availability of laboratory culture results. The test can therefore be used in a number of ways, and about 30% of the test results led to treatment changes in this study.

Strengths and weaknesses

This large, pragmatic trial involved multiple sites in four countries, recruited to target, and achieved high ascertainment rates, so external validity should be high. Clinicians were not able to reliably keep logs of eligible patients that were not recruited. There were no meaningful differences in baseline characteristics between those for whom we did and did not ascertain the primary outcome. We used patient reported antibiotic consumption in order to take into account adherence, prescribing from other sources such as use of left over antibiotics, and prescribing by out of hours and other emergency care clinicians. However, we retrieved information on antibiotic prescriptions in primary care and ascertained care data over there months for almost all patients. We found little evidence of contamination (use of the POCT in the standard care arm), and clinicians reported using the POCT in 96.6% of those randomised to management guided by Flexicult™.

This was an open trial of the influence of a point of care test on clinicians prescribing behaviour and ultimately on patients' adherence to those prescribing decisions. Open studies capture the influence of clinicians' and patients' expectations of interventions on help seeking, which is important for accurate estimate of health care costs. Delivering the entire intervention took a median of 17 minutes, which constitutes a substantial opportunity cost of alterative use of health professional time.²⁵ This may reduce once greater familiarity is established. Point of care urine culture was therefore not cost effective in primary care when use mainly for guiding changes to empirical antibiotic prescribing decisions, largely because antibiotic prescribing decisions were not delayed until results were known,

and antibiotics were not stopped when there was no evidence of a UTI on POCT. The main driver of discordant antibiotic use for women was antibiotic consumption without a microbiologically confirmed UTI, rather than use of antibiotics to which the UTI pathogen was not susceptible.

Comparison with existing literature

Although all participants were presenting with symptoms of uncomplicated UTI, only 35.9% had a UTI confirmed on culture. This is similar to the 25-50% culture positivity rates found in observational studies.^{12,26-28} Possible explanations include UTIs caused by pathogens that are not identifiable on routine urine culture, problems with sample transportation, or contamination masking true UTIs. Any of these possibilities may have affected results according to our primary outcome. Although routine laboratory urine culture provides the diagnostic information that clinicians would usually get if they chose to submit a sample, it is not a perfect reference standard as routine culture may produce inconsistent results and vary between laboratories.²⁹

In a separate analysis, we examined clinicians' interpretations of the Flexicult™ urine culture results in this study, and found clinicians overestimated the proportion that was positive for UTI when compared to the results of laboratory culture of urine from the same patient.³⁰ Observing some growth on a culture plate from fresh urine from a symptomatic patient may have made clinicians reluctant to stop antibiotics despite the level of growth on the POCT culture not technically meeting the threshold for a UTI. It is also not clear whether routine laboratory culture with associated delays in transport and processing, or more rapid point of care culture, gives a more valid answer.

We have previously examined the analytic performance of the Flexicult™ test using routinely submitted urine samples,³¹ and the analytic performance of other POCT culture approaches have been assessed.^{16,32-34} However, we could not identify previous evaluations of the implementation of interventions to improve the management of UTI in terms of inappropriate antibiotic use, costs, resistance, and health outcomes. Holm and colleagues have also found that point of care culture was better at ruling in, rather than ruling out, a UTI diagnosis based on laboratory culture.³⁴

Implications and recommendations for further research

In test-treatment trials,⁴ patient outcomes are only likely to be affected if patients received a valid test, an appropriate diagnosis and management decisions are made, and treatment is implemented and taken. In interpreting the plates, clinicians may have assumed that low threshold bacterial growth in women with symptoms suggestive of UTI justified antibiotic treatment, and therefore not adjusted their treatment. Had clinicians prescribed or adjusted their initial prescriptions according to POCT urine culture results, and patients had changed their antibiotic consumption behaviour accordingly,

then the intervention may have been effective. This underlines the importance of attention to targeted behaviour change strategies in conjunction with the introduction of new tests.

Flexicult™ POCT was not clinically or cost effective when used mainly for adjusting antibiotic prescribing decisions for UTI following the result becoming available. Given the low levels of resistance we identified in these systematically sampled patients with uncomplicated UTI and the challenges associated of stopping short courses of antibiotics when the patient is in the community, the focus of future research should be on assessing the effect of culture based POCTs, such as Flexicult™ in the context of advising patients to delay starting antibiotics until the results of the test are known. Symptomatic treatments offered at the point of consultation may improve the acceptability and uptake of this approach.

Few POCTs have been subjected to rigorous pragmatic clinical trials of cost effectiveness using a range of outcomes including patient orientated measures.² This study underlines the importance of conducting a rigorous pragmatic trial of cost effectiveness (and not simply of analytic performance), and evidence-based identification of their place in clinical pathways, before new diagnostic technologies are adapted into usual care.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CCB was the chief investigator and act as guarantor of the trial in its entirety. CCB led the development of the research question, study design and implementation of the study protocol, along with KH, NF, MG, CL, PL, MM, and TV. JB was the Trial Manager and ETJ the Senior Trial Manager who coordinated the operational delivery of the study protocol across the 4 regions. NK provided data management support for all 4 regions and TP was the statistician supervised by DG and KH. DG performed the quality assurance for the statistical analysis, and the multiple imputation. PL, MM, CL and TV were principal investigators, responsible for study oversight, at Southampton, Spain and the Netherlands respectively with KR, MM and CB coordinating recruitment. MW and RH provided expert microbiology input and MW supervised the microbiological work in SACU. All authors listed provided critical review and final approval of the manuscript.

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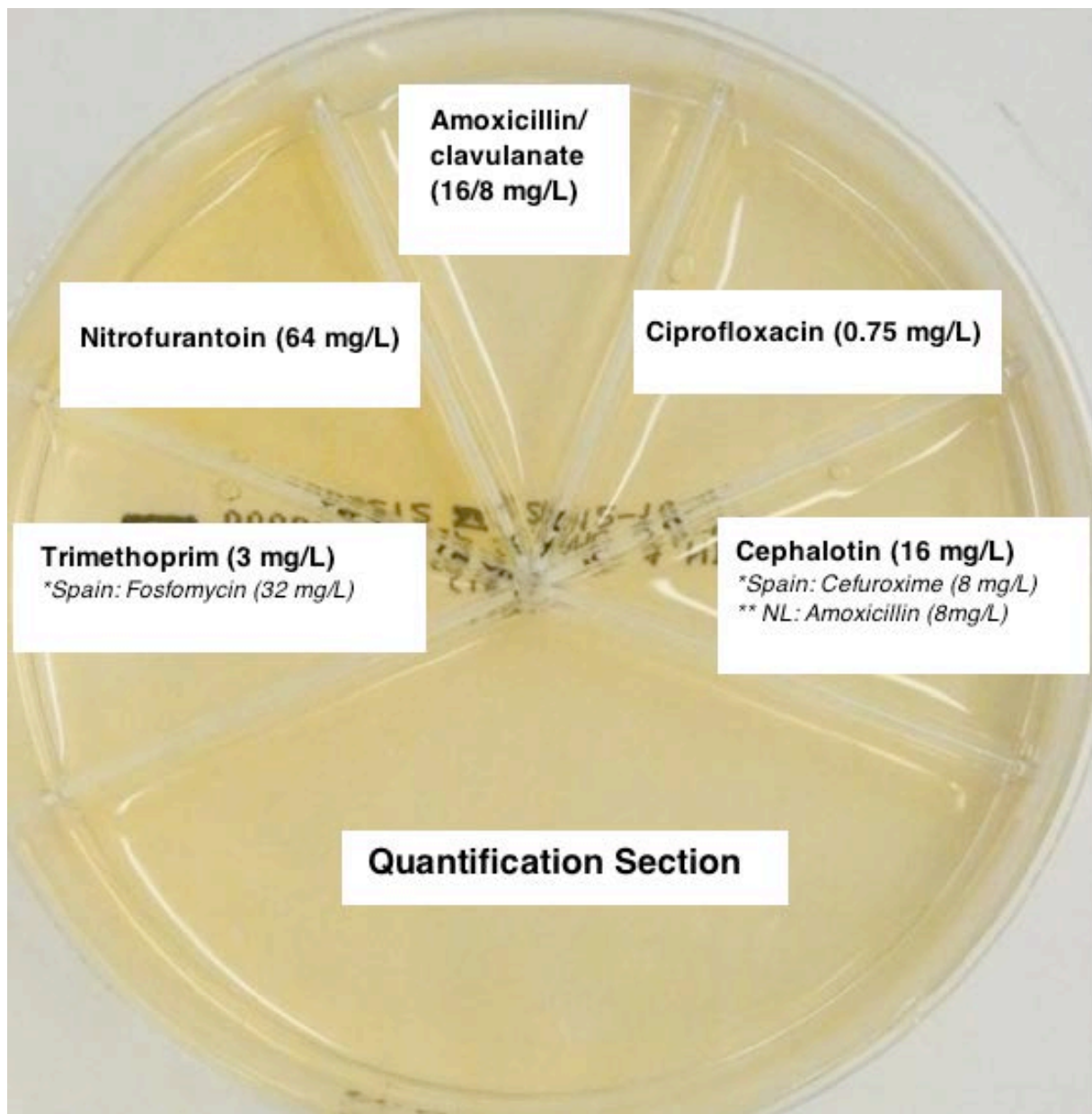


Figure 1. The UK Flexicult SSI-Urinary Kit

** Spain: Fosfomycin instead of Trimethoprim, Cefuroxime instead of Cephalothin*

*** Netherlands: Amoxicillin instead of Cephalothin*

Figure 2 – Concordant / discordant antibiotic prescribing decision tree

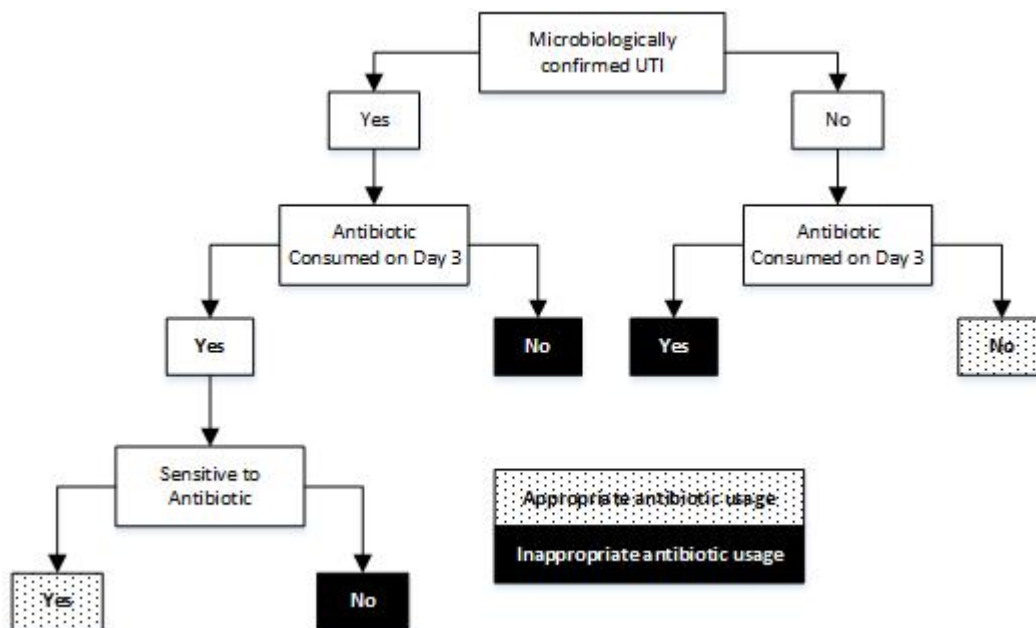
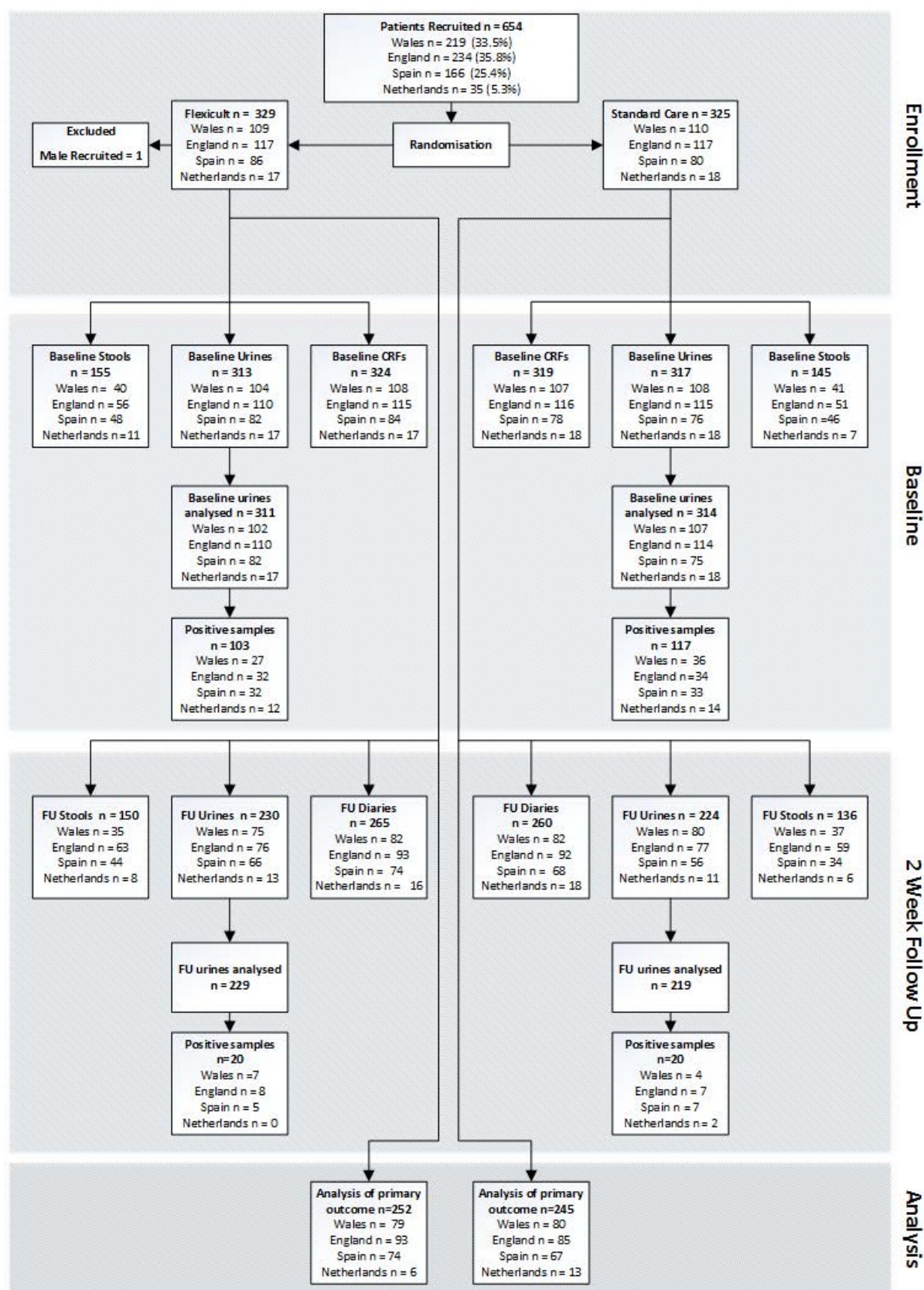


Figure 3. Consort Diagram



Data for derivation of primary outcome analysis required each participant to have two week diary and have urinalysis data available. CRF = case report form

Table.1: Participant baseline data on presentation by management allocation (intervention vs. standard care)

		Flexicult™	Standard Care	Overall
	N	Mean (SD¹)	Mean (SD¹)	Mean (SD¹)
Age	643	47.6 (22.5)	47.6 (22.4)	47.6 (27.6)
Temperature in degrees Celsius	613	36.6 (0.95)	36.6 (0.85)	36.6 (1.18)
		n (%)	n (%)	n (%)
Symptoms reported by patient as a 'problem' ²	643	294 (90.7)	295 (92.5)	589 (91.6)
Daytime frequency	643	288 (88.9)	286 (89.7)	574 (89.3)
Urgency	642	268 (83.0)	252 (79.0)	520 (81.0)
Burning	643	261 (80.6)	260 (81.5)	521 (81.0)
Night time frequency	637	231 (72.0)	220 (69.6)	451 (70.8)
Generally unwell	641	209 (64.7)	203 (63.8)	412 (64.3)
Tummy pain	642	177 (54.6)	190 (59.7)	367 (57.2)
Smelly urine	643	171 (52.8)	163 (51.1)	334 (51.9)
Restricted activities	642	155 (48.0)	142 (44.5)	297 (46.3)
Pain in side	638	92 (28.8)	93 (29.2)	185 (29.0)
Fever	641	88 (27.2)	72 (22.6)	160 (25.0)
Blood in urine				
Number of symptoms (dysuria, frequency, urgency) ³	643			
One		34 (10.5)	29 (9.1)	63 (9.8)
Two		96 (29.6)	97 (30.4)	193 (30.0)
Three		194 (59.9)	193 (60.5)	387 (60.2)
Microbiologically confirmed UTI	612	103 (33.4)	117 (38.5)	220 (35.9)
UTIs with causative organism resistant to any first line antibiotic (nitrofurantoin, trimethoprim or fosfomycin)	220	16 (15.5)	24 (20.5)	40 (18.5)
Previous UTI in the last 12 months:	431			
None		67 (31.3)	70 (32.3)	137 (31.8)
1-2		88 (41.1)	85 (39.2)	173 (40.1)
3 or more		52 (24.3)	58 (26.7)	110 (25.5)
Don't know		7 (3.3)	4 (1.8)	11 (2.6)

¹inflated for clustering by practice

²symptoms reported as a problem include all categories from 'Very little problem' to 'As bad as it could be'

³balancing variable in randomisation

Note: The Overall SDs for Age and Temperature are substantially higher than those of either arm due to the nature of the inflation calculation: given that this is an individually randomised trial, the cluster size is essentially doubled for the overall calculation.

Table 2: Comparison of Intervention vs. Standard Care for Primary and Secondary Outcomes

		Category	Flexicult™		Standard Care		Odds Ratio	95% Confidence Interval	ICC
			n	%	n	%			
Primary Outcome									
Concordant Antibiotic Usage	Yes	UTI+Antibiotic + Sensitive	58	23.0	67	27.3	0.84	0.58 to 1.20	0.02
		No UTI + No Antibiotic	41	16.3	41	16.7			
		Total	99	39.3	108	44.1			
	No	UTI+ Antibiotic + Resistant	5	2.0	10	4.1			
		UTI+ No Antibiotic	12	4.8	17	6.9			
		No UTI+ Antibiotic	136	54.0	110	44.9			
		Total	153	60.7	137	55.9			
Secondary Analyses of Primary Outcome									
Concordant Antibiotic Usage Sensitivity: Flexicult™*			99	39.4	108	44.1	0.84	0.58 to 1.20	N/A
Concordant Antibiotic Prescribing Sensitivity: Initial**			98	33.1	114	38.5	0.79	0.57 to 1.11	0.01
Secondary Outcomes									
Antibiotic Prescribing at Initial Consultation			267	82.4	282	88.4	0.56	0.35 to 0.88	0.46
Prescribe to guidelines at Initial Consultation ¹			156	58.9	166	59.5	0.99	0.67 to 1.45	0.67
Drug type and duration ²	UTI-specific and 1-3 days		182	69.2	185	67.8	(ref)		N/A
	UTI-specific and greater than 3 days		50	19.0	57	20.9	1.15	0.71 to 1.87	
	Broad-spectrum and 1-3 days		0	0.0	0	0.0	(empty)		
	Broad-spectrum and greater than 3 days		31	11.8	31	11.4	1.00	0.58 to 1.75	
Patient Enablement (dichotomised)			171	70.1	177	69.7	0.99	0.66 to 1.48	N/A
Antibiotic consumed (day 3)			217	79.2	200	76.6	1.24	0.81 to 1.89	0.24
Antibiotic consumed (during 2 weeks)			234	85.1	217	81.6	1.38	0.87 to 2.19	0.33
Second Antibiotic prescribed (within 2 weeks)			33	10.3	30	9.7	1.11	0.65 to 1.89	N/A
Re-consultation (within 2 weeks)			41	12.9	41	13.2	0.99	0.62 to 1.60	N/A
Hospital Stay (within 2 weeks)			3	0.9	4	1.3	Numbers too small for analysis		
Microbiologically confirmed UTI (at 2 weeks)			20	8.7	20	9.2	0.94	0.49 to 1.81	N/A

Stool Sample Resistance (at 2 weeks)	Ciprofloxacin	33	22.4	34	24.5	0.96	0.54 to 1.71	0.396
	extended-spectrum beta-lactamases (ESBL)	12	8.2	8	5.8	1.35	0.53 to 3.46	N/A
	Gentamicin	16	10.9	9	6.5	1.75	0.74 to 4.42	N/A
	Carbapenem	0	0.0	1	0.7	Numbers too small for analysis		
Recurrence (within 3 months)		54	17.0	69	22.3	0.72	0.48 to 1.07	N/A
		median	IQR	median	IQR	Hazard Ratio	95% CI	ICC
Duration of all symptoms		8.0	5.0 to 14.0	8.0	5.0 to 14.0	1.02	0.83 to 1.25	N/A
Duration of moderately bad symptoms		4.0	2.0 to 6.0	4.0	2.0 to 6.0	0.98	0.82 to 1.17	N/A
		Mean	SD	Mean	SD	Mean Difference	95% CI	ICC
Overall urinary symptom burden (AUC over 2 weeks) ³		39.5	36.56	38.2	34.56	0.99	0.84 to 1.19	N/A

1: Prescribe to guidelines based on prescription made at the initial consultation. This excludes those who did not receive a prescription and those for which the prescribed drug is unknown:

- England and Wales: trimethoprim, 3 days; nitrofurantoin, 3 days;
- Spain: fosfomycin, 1 day; nitrofurantoin, 7 days;
- The Netherlands: nitrofurantoin, 5 days; fosfomycin, 1 day; trimethoprim, 3 days

2: As a multinomial model, relative risk ratios, rather than odds ratios, are given.

3: Effect/95% CI are back-transformed from a natural log transformation

*UTI and antibiotic resistance in the Flexicult™ arm defined by the clinician's reading of the Flexicult™ plate. **antibiotic prescribed at initial consultation, or, if available, the antibiotic prescribed after reading the Flexicult™ plate

Table 3: Clinician advice about antibiotic treatment in response to Flexicult™ result

		Did the Flexicult™ result indicate that a UTI was present?					
		No		Yes		Missing	
		n	%	n	%	n	%
“Was patient’s management changed in response to the test result?”	No	78	38.8	31	33.0	2	33.3
	Yes	123	61.2	63	67.0	4	66.7
	<i>Total</i>	<i>201</i>	<i>100.0</i>	<i>94</i>	<i>100.0</i>	<i>6</i>	<i>100.0</i>
Change of management	No antibiotic needed/don’t start antibiotic	14	11.4	0	0.0	0	0.0
	Stop taking antibiotic	10	8.1	0	0.0	0	0.0
	Start taking antibiotic	16	13.0	11	17.5	2	50.0
	Continue with antibiotic	35	28.5	27	42.9	1	25.0
	New antibiotic prescribed	48	39.0	25	39.7	1	25.0
	<i>Total</i>	<i>123</i>	<i>100.0</i>	<i>63</i>	<i>100.0</i>	<i>4</i>	<i>100.0</i>

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