SIGN Bacterial UTI Consultation

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Please note that section numbers refer to the consultation version of the draft guideline unless otherwise noted.

Invited reviewers			**Type of response and declared interests**
AP	Mrs Audrey Pringle	Advanced Health Protection Nurse, NHS Lothian, Edinburgh	*Individual response* *Remuneration from employment* As a nurse, working within the NHS, any SIGN publication will be accessed by me and used in my daily work, to help inform the care I deliver to my patient's.
AW	Ms Ashley Williamson	Prescribing Support Pharmacist, NHSGGC, Glasgow	*Individual response* Nothing declared.
CC	Miss Clare Colligan	Lead Pharmacist - Primary Care, Forth Valley, Falkirk	*Individual response* Nothing declared.
EMcG	Mrs Elizabeth McGovern	Specialist Pharmaceutical Public Health, NHSGGC, Glasgow	*Individual response* Nothing declared.
EO	Dr Ewan Olson	Consultant Medical Microbiologist, Edinburgh Royal Infirmary, Edinburgh	*Individual response* *Non-financial interests* BMA - member of BMA Scottish Council and Scottish Consultants Committee. Thirlestane Lane Association – (Vice Chairman). I am not sure if the management committee of a private road is relevant but I was asked to declare all office positions in associations.
JD	Dr Jennifer Dow	General Practitioner, Ballieston, Glasgow	*Individual response* Nothing declared.
SMc	Ms Sheila McGhee	Volunteer worker, Forth Valley	*Individual response* Nothing declared.
SR	Mrs Stacey Reid	Charge Nurse, Dalmellington Care Centre, Dalmellington	*Individual response* *Remuneration from employment* I am currently employed by Dooncare limited at Dalmellington Care Centre as a charge nurse. This is a privately run nursing home for over 65s.

			Urinary tract infections are particularly prevalent in my area of work
VH	Dr Victoria Henderson	Consultant Geriatrician, Gay's Hospital, Elgin	*Individual response* Nothing declared.
Open consultation			**Type of response and declared interests**
AMT		Jo McEwen, Advanced Nurse Practitioner Antimicrobial Stewardship - Antimicrobial Management Team	*Group response* *Nature and purpose of group* - Strategic and operational delivery of antimicrobial stewardship within Health Board *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* Our team feel that our position around the management of UTI in adult women would be weakened as a result of this guideline. The main reasons for this are detailed below however, they will be expanded on within the main review. Concerns that moving towards increased use of urinalysis as a diagnostic tool will increase antimicrobial use and pose a significant burden on staff time, operational logistics (for example pharmacy first), laboratory capacity and flow and cost. Drive to use urinalysis as a diagnostic tool contradicts key messages and evidence from the last 10 years and recently updated national and international guidance (namely NICE – to which the management of UTI in other population groups will default to) Changes to guideline recommendations confuses management of UTI across all age groups which could lead to adverse events associated with the management of UTI.
AMT-CP		Carol Philip, AMT Lead Pharmacist – commenting on behalf of Antimicrobial Management Team,	*NO DOI SUBMITTED – (Comment removed)*

		NHS Lothian	
BHUK		Jacqueline Emkes Trustee and Susannah Fraser, Trustee /Communication & Media Manager – commenting on behalf of Bladder UK,	*Group response* *Nature and purpose of group* - Bladder Health UK Is A Registered UK Charity: 1149973 What Does Bladder Health UK Do? Bladder Health UK gives support to people with all forms of cystitis, overactive bladder and continence issues together with their families and friends. We are the largest bladder patient support charity in the UK. We have a busy chat room/Forum, a widely used website and active Twitter and Facebook accounts for those bladder illness sufferers seeking information, help and support. OUR VISION To work in partnership with key stakeholders to aim for a future free from the pain, stigma and isolation of bladder illness We will do this by... Ensuring people with bladder health issues can expect a consistent level of healthcare support and treatment Encouraging research into new treatments and personal management strategies Working pro-actively with other like-minded organisations and charities to raise the profile of bladder illness issues *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* The draft SIGN recommendation is helpful to our organisation as we constantly seek to find evidence which is well reasoned, rigorous and appropriate to patient needs.
HPS		Ms Jennifer Macdonald, Senior Nurse Infection Control – commenting on behalf of Health Protection Scotland	*Group response* *Nature and purpose of group* - Providing advice, support and information to the following groups: health professionals,

			national and local government, the general public, a number of other bodies that play a part in protecting health. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* "the draft SIGN recommendations supports recommendations within National Point Prevalence Survey of Healthcare Associated Infection and Antimicrobial Prescribing in Long Term Care Facilities, 2017
JL	Dr James Larcombe	GP Locum, County Durham, Stockton-on-Tees	*Individual response* *Remuneration from employment* Co-moderator for NICE GP panel *Remuneration from consultancy* Member of ANTiC study group (referenced in the guideline) *Non-financial interests* Steering group Public Health England UTI Reference Guide
JR	Dr Jane Ramsay	Consultant Obstetrician, University Hospital Crosshouse, Kilmarnock	*Individual response* Nothing declared.
ME	Dr Morgan Evans	Consultant Physician, NHS Lothian, Edinburgh	*Individual response* Nothing declared.
NDAA		Ms Holly Bekarma, Consultant Urologist – commenting on behalf of Neurology Department, Ayrshire and Arran	*Group response* *Nature and purpose of group* - Department of urology *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* Draft recommendations in this guideline need some review.
NHSB		Dr Edward James, Consultant Microbiologist, NHS Borders	*Group response* *Nature and purpose of group* -

			NHS Board. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* The draft SIGN guidelines would influence the protocols and advice in the board.
PI	Ms Pamela Innes	Prescribing Support Pharmacist, Glasgow City HSCP, Glasgow	*Individual response* *Remuneration from employment* Prescribing Support Pharmacist, NHS GGC. *Remuneration from self employment/director* J&P Innes Ltd (pharmacy shops) *Shares* Shares held as part of investment policy – AZ Plc & Worldwide Healthcare Trust
PCIU		Professor Cliodna McNulty, Head of PHE's Primary Care Interventions Unit – commenting on behalf of Public Health England's Primary Care Interventions Unit	*Group response* *Nature and purpose of group* - The PCIU conduct research in primary care to develop interventions around antimicrobial stewardship. Such interventions include diagnostic and antibiotic management tools. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/ status/productivity?* Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
SS	Dr Sarah Smith	Field Medical Director, EU, Asia Pacific, Glasgow	*Individual response* *Remuneration from employment* I'm a Pharmaceutical Physician but practice in Oncology. Employed by The Medical Affairs Company, no professional interests in UTI.

Section	Comments received		Development group response	Editorial response
General				
General	JD	Well presented, clear information suitable for clinical General Practice. Small corrections to be made noted • Page 21, 4th line 1,045 (1045) • Page 11, 5th paragraph nest approach (best) • Page 9 recommendation do not diagnosis (diagnose)	Thank you. Noted – typos have been corrected.	
	AMT	• Guideline too lengthy - some of the evidence could be concisely summarised. • Inclusion of executive summary may be of benefit. • Where recommendations cannot be made an expert consensus on best practice may be of benefit to optimise and guide the management of UTI in Scotland. • Concerns that move to increasing the use of urinalysis as a diagnostic tool will increase antimicrobial use. • Drive to use urinalysis as a diagnostic tool contradicts key messages and evidence from the last 10 years. • Changes to guideline recommendations confuses management of UTI across all age	Noted. The GDG has reviewed all sections and made language as clear as possible. The guideline will be accompanied by a quick reference guide. The guideline cross refers to other Scottish publications which include consensus recommendations. One aim of the guideline is to make better use of antimicrobials. There is no evidence that use of dipsticks will increase antibiotic prescribing, however it is likely to increase the diagnostic accuracy meaning that those who do receive antibiotics are doing so with a greater assurance of infection. In contrast, the guideline has systematically reviewed evidence from the last 10 years and based recommendations therein. Disagree. The GDG has chosen to present information on	

		groups. • Inclusion of algorithms would be useful from a clinical perspective. • Guidelines begin to discuss the burden of treating asymptomatic bacteriuria particularly in older adults, however the only recommendation on this is not to treat ASB in women <65.	diagnosis and management within chapters based on age of the patient, with further chapters on catheter-associated UTI and recurrent UTI. This matches the approach in primary care where the patient age is the most fundamental characteristic of the patient before consideration of acute v recurrent infection or prevention v treatment. Agreed. An algorithm has been added (see Figure 1). ASB was not included in the key questions for this guideline, however we are aware of the importance of the issue. We have provided further comments in the diagnosis sections, where appropriate, and cross referred to other guidelines which include recommendations in this area. We have also added Annex 3 which provides details of the range of prevalence of ASB in different populations.	
	ME	It is a shame that this document only focuses on women or rather it includes catheter associated urinary tract infection where I am unclear whether the evidence and practice significantly differs between men and women. I think a separate section for recurrent UTI should be made rather than including it within management of an acute UTI (i.e. don't include recommendations for recurrent UTI in sections 3.2 and 4.2 as this is confusing). Separate sections for those < and > 65 if the evidence used	As the remit of the guideline is UTI in women, it would not be appropriate to describe recommendations for men, however a comment has been added to the introduction of the CA-UTI section to note that the shared aetiology between all	

		relates differently to these groups. Are guidelines for men and pregnant women planned?	people with CA-UTI may allow greater overlap in diagnostic and management strategies between the sexes. Although the evidence for recurrent and acute infections was not separated into different questions, meaning that there may not be binary split of information for all age groups, the guideline has been restructured to move all relevant information for recurrent UTI into a single chapter. SIGN is not planning to develop guidelines on management of UTI in men or pregnant women. See section 1.2.1	
	AP	Very timely document. Maybe, as a nurse, I am looking for something a bit more prescriptive, something that will influence the delivery of care and therefore this may be reflected in my comments, which may not be relevant for this document. Thank you for the opportunity to comment.	Noted. Thank you.	
	EMcG	I think a very useful document and will be welcomed by professionals. I think given the availability of Pharmacy first there needs to be more support for professionals who will not be using dipstick diagnostic tests. In the key recommendations I would commend something around prevention/self-management as this in my experience is a key interest of professionals and patients Other small comments regarding the intro: Section 1.1, Para 4 *The percentage of residents with urinary catheters was higher in those with UTI compared with those without (23.1% v 8.2%, p=0.003).* Comment: Is there a definition of catheterised or is it only “current”?	Noted. Thank you. Dipstick testing is one part of the diagnostic pathway and can only be used where feasible. Self-care recommendations are included – see sections 3.2.1, 4.2.1 and 5.1.1. Prevention is not within the remit as the initial presentation is an individual with symptoms suggestive of UTI. This has been clarified to “…residents with	

		In para 5 , line 5 there is a definition of "*catheterised at some point in the last seven days"* Para 6: typo E.coli not E.Coli Section 1.2.3 Why are community pharmacists specifically mentioned as they are healthcare professionals otherwise list relevant interest groups of HCWs?	*indwelling* urinary catheters *at the time of data collection*…" Agreed. This has been corrected Agreed – community pharmacists have been removed.	
	EO	As mentioned before the use of R for both strong and conditional recommendations is not helpful separate symbols would help. A one page quick reference guide would be appreciated by clinicians. There is a flaw in the introduction Definitions 1.1.2 There is no citation given for the definition of relapsed UTI versus reinfection. The definition used seems over simplistic and arbitrary stating that most recurrences within two weeks are relapses. Other definition I could find are this one from the Canadian Urology Society which seems close to what actually happens. *"Recurrent UTIs occur due to bacterial reinfection or bacterial persistence. Persistence involves the same bacteria not being eradicated in the urine 2 weeks after sensitivity-adjusted treatment. A reinfection is a recurrence with a different organism, the same organism in more than 2 weeks, or a sterile intervening culture (Level 4 evidence, Grade C recommendation)."* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202002/ I would suggest you have three options 1. Do a literature review to provide evidence and a citation behind the	The symbol is the same as both types of recommendation should be implemented irrespective of their category. The strength of recommendation is associated with factors relating to the evidence, rather than the importance. A quick reference guide will be published with the guideline. Disagree. The definitions in the table in this section are from the European Association of Urology guideline. A further reference has been added to the definitions of relapse / reinfection.	

		statement 2. Use the alternative definition from Canada which reflects the complexity of the subject 3. The simpler option - as the definitions are not used anywhere else in the guideline and the terms do not come up in the current Canadian/ American guidance; European Urology guidance or in NICE guidance simply delete them as not relevant to the rest of the document. When launching the guidelines it would be helpful to have a statement about whether SIGN 88 is still valid for managing patients not covered in this guideline.	SIGN 88 will be withdrawn on the publication of this guideline. A sentence has been added to section 1.2.1 to clarify this. Sources of advice for healthcare professionals on managing patients who are not covered in this guideline are included in section 1.2.1	
	JL	Guideline is very clear and well set out Easy to identify relevant sections	Noted. Thank you.	
	SR	The draft guideline is presented very well. It is clear, concise, easy to read and find information regarding certain aspects. It is very interesting and informative and as a professional I will find it useful in my practice.	Noted. Thank you.	
	VH	I think some of the data is prevented in an overcomplicated manner and some recommendations, ie acupuncture and use of BNO 1045 are based on poor quality studies.	Noted. The draft has been revised to ensure maximum clarity and an algorithm developed to simplify the diagnostic pathways and treatment options (see Figure 1). The evidence for these treatments was assessed using a robust methodology. These treatments are not currently provided by the NHS in Scotland and recommendations have been removed.	
	BHUK	Very useful. Perhaps a plain English version and a flowchart decision tool	Thank you. A quick reference guide and	

		would assist patients and clinicians.	patient version will be published. An algorithm which summarises the key diagnostic and management decisions has been included (see Figure 1).	
	AMT	We are generally disappointed in this revised guideline having anticipated its publication for some time. This revised version is not user friendly and takes clinical practice back 10 years.	The guideline has been carefully edited for maximum clarity. We note your opinion on clinical practice and direct your attention to our systematic review of the evidence from 2003 to 2018.	
	PCIU	We agree that we really like the way you've visually represented the study qualities down the side of the text - this makes it very easy to see and identify the study grades.	Noted. Thank you.	
	NHSB	Within the text of the guideline the difficulties in extrapolating from the available evidence to specific age groups is acknowledged and the specific recommendations for the >65 years age group are qualified by including 'in residential care'. However the overall impression is that 65 years provides a clear cutoff in the natural history and management of the UTI. This could lead to inappropriate assumptions by organisations and clinicians. As the elderly population cohort becomes fitter the use of an historical socioeconomic dichotomy with diminishing biological relevance carries risks of discrimination on basis of age.	Noted. We agree and have qualified this distinction in section 4.1, however have added a comment *("The diagnosis of UTI is particularly difficult in older patients, who are more likely to have asymptomatic bacteriuria, and may experience increased frailty and comorbidities, therefore urine culture ceases to be a diagnostic test unless there are other signs of infection.")* to the introduction of the guideline. We have also added a Good Practice Point to section 4.2 which suggests that UTI in fitter ambulatory women over the age of 65 years without comorbidities may be managed as in younger women.	
	HPS	Section 7.1 Implementation strategy - *Implementation of national clinical*	Thank you. This is a standard section in all	

		guidelines is the responsibility of each NHS Board. Should there be reference to Integrated Joint Boards here?	SIGN guidelines. As the organisations formed as part of the integration of services provided by Health Boards and Councils in Scotland are Health and Social Care Partnerships this paragraph has been revised to refer to these structures.	
Section 1				
1.2.1	PI	Repetition of what the guideline does not cover. Last two sentences in the first paragraph are repeated in the third paragraph down.	Agreed. Repetition has been removed. A note has been added to clarify the guideline's status with respect to pregnant women *"Although the guideline excludes pregnancy, the possibility a woman of childbearing age may be unknowingly pregnant must always be considered."*	
Section 3				
3.1	SS	I wondered if it would be possible to include a sentence about taking a sexual history from women to detail if they are at risk of trichomonas, STI that may present with urinary symptoms alone.	Agreed. Sentence has been added to emphasise the importance of differential diagnosis and GPP updated in section 3.1.3	
	AMT	A urine dipstick test does not confirm the presence of a UTI – it confirms the presence of bacteria which may be suggestive of a UTI when accompanied with signs and symptoms.	Agreed. This has been reworded.	
	SMc	Feeling unwell. Sick, back pains in kidney area.	We do not fully understand the meaning of this comment. We acknowledge that these are among the common symptoms of upper UTI.	
	ME	I disagree with the initial premise statement: *"The current standard for diagnosing patients with suspected UTI is microscopy, culture and antibiotic sensitivity analysis of a midstream, clean-catch urine specimen, although this is not recommended for first-time*	Noted. This advice was summarised from the NIHR horizon scanning report on point of care testing but has been revised to indicate that it is an	

		uncomplicated UTI." The current standard for the majority of suspected UTIs is by clinical diagnosis, the history alone.	approach, rather than a standard, and to refer to symptoms. A new paragraph has been added to reference the European Association of Urology guidelines which emphasise that culture is not recommended for first-time uncomplicated UTI suggesting that clinical diagnosis is more likely in this context.	
		I disagree with this statement: *"In routine practice, clinicians can perform a urine dipstick test which confirms the presence of a urinary tract infection with 30–40% sensitivity and 95–98% specificity based on positive urine nitrites."* Patients with asymptomatic bacteriuria have both positive urine dip so a positive urine dip confirms the likelihood that bacteria are present not an infection.	Noted. This advice was summarised from the NIHR horizon scanning report on point of care testing but has been revised to refer to bacteriuria and the requirement for co-occurring symptoms. The term "in routine practice" has been removed.	
		This statement contradicts the previous statement: *"Standard practice when patients present with UTI symptoms, is the prescription of empirical antibiotics (for broad-spectrum coverage of the most common uropathogens) or based on a positive urine dipstick test."* I disagree that empirical antibiotic recommendations are broad spectrum.	Noted. In fact, many antibiotics used empirically are broad spectrum – see Table 4, however we have clarified this sentence by changing the words *"for broad spectrum coverage"* to *"for coverage of"* and highlighted that antibiotics targeting the most common pathogens are commonly used.	
	EO	A key problem with the guidance is that the microbiological standards used to define UTI in the research studies are not those used in the UK for the routine diagnosis of UTI. UK SMI B41 uses ≥ 10,000 cfu/ml the studies use ≥1,000 cfu/ml. https://www.gov.uk/government/publications/smi-b-41-investigation-of-urine This means that patients who will be predicted to have UTI by the criteria	The GDG notes that no single threshold is suitable for the detection of UTI in every clinical circumstance, however UK SMI B41 indicates that ≥10^5 CFU/ml is the standard for bacterial infection in most contexts in UK labs. Isolates at 10^4–10^5	

		may not have this confirmed by urine culture. There are three ways to resolve this study - 1. Replicate the study methods in microbiology labs- expensive and thresholds valid for plates inoculated in a clinic may not be valid for samples that have been transported for several hours to a central laboratory. 2. Reanalyse or repeat the validation studies using the UK SMI criteria. 3. Make an arbitrary assessment that the differences do not matter. Interestingly the reference cited for table 2 does calculate the likelihood of having UTI at different culture thresholds. It might be worth exploring this further in the discussion of diagnosis as there is approximately a 10% drop in the positive rate between, 100 and 1000 cfu/ml and a further 10% between 1000 and 100,000 cfu/ml. This implies current UK lab methods underdiagnose UTI by 20% compared to the research methods. However there is a problem that the research study thresholds may not be appropriate where there is a significant delay in plating the samples as there is time for bacterial growth to give false positive results.	CFU/ml are usually subjected to repeat culture, and not considered evidence of infection unless white blood cells are confirmed on microscopy or other clinical contexts. We acknowledge that these scenarios are not within our remit. We do not believe that the differences do not matter, but we can provide a range of estimates within which pre- and post-test probabilities are likely to fall when using 10^5 CFU/ml thresholds as reference values. The study from which these thresholds are taken contains data on diagnostic probabilities at $\geq 10^2$ CFU/ml, $\geq 10^3$ CFU/ml, and $\geq 10^5$ CFU/ml, but not $\geq 10^4$ CFU/ml. Noted, although this may be a technical definition of 'underdiagnosis' given that the accepted UK threshold is 10^5 CFU/ml. Actual performance against this standard does not imply underdiagnosis.	
	BHUK	I am concerned that use of cultures in the elderly is not encouraged. I would hope diagnosis of UTI in the elderly is taken very seriously and acted upon quickly. Please see references below. *Abrams, P., Andersson, K. E., Apostolidis, A., Birder, L., Bliss, D., Brubaker, L., & Cotterill, N. (2018). 6th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation And Treatment Of Urinary*	We agree that diagnosis of UTI in the elderly is important and provide recommendations on this topic in section 4. We note this reference to a book on incontinence. As the scope of the	

		Incontinence, Pelvic Organ Prolapse And Faecal Incontinence. Neurourology and urodynamics, 37(7), 2271.	guideline focuses on uncomplicated UTI we would not consider specific recommendations for people with incontinence and/or prolapse, however have added a comment to section 4.1.1 to consider other causes of incontinence as a specific symptom.	
	PCIU	I like how you explain the pre- and post-test probabilities in relation to the likelihood ratios • Should there be recommendations for excluding sepsis and pyelonephritis? • It isn't immediately clear how diagnostics for women with recurrent UTI should be managed in light of the guidance here – are they excluded from the diagnostic section? The studies used in this section often exclude them. • It would be more intuitive if the layout started with prevention, then diagnosis, then management, then selfcare/safety netting. This is how patients and users wanted the patient facing leaflet – so maybe you can do this if you develop one?	Noted. Thank you. These topics are not within the scope of this document, therefore we will not provide recommendations As recurrent UTI is defined as repeated UTI within a given frequency, there is no difference in the diagnostic criteria. We have added a statement to clarify this in sections 3.1 and 4.1 and collected information on management of recurrent UTI in section 5.1 Noted, however the starting point of the guideline is the patient presenting with symptoms suggestive of UTI, so primary prevention is not included. In this context, diagnosis is the first step, followed by acute management and secondary prevention. No change required.	
	AW	The title for section 3 should be specific that this is for non-pregnant, non-catheterised women.	Disagree. The remit of the guideline is stated in section 1.2 which explicitly notes the exclusion of pregnant	

			women. Adding “non-pregnant” to the title may imply that there is guidance on pregnant women elsewhere within the guideline.	
		The standard diagnosis for first time uncomplicated UTI should be clearer in the opening statement.	Agreed – a statement on the importance of symptoms as part of the diagnostic assessment has been added to section 1.1.	
		Additionally the setting in which management for UTIs for this patient group has shifted nationally towards community pharmacy in recent years. This may be worth mentioning if appropriate with data.	The guideline presents the available evidence rather than the full range of settings, irrespective of evidence. Additionally, the context regarding community pharmacy is dynamic and subject to continual change. A general comment has been added to the guideline introduction to place this into context for 2020.	
	NDAA	The wording of this is very difficult to understand - it really is not clear as to when UTI should be considered, who should be tested and in what way. I wonder if it would benefit from some sort of diagram to ease understanding.	Thank you. The advice is structured around the evidence for the diagnostic utility of symptoms and testing. We have added an algorithm to summarise the diagnostic pathways (see Figure 1).	
3.1.1	SMc	Urine tested by hospital lab.	We do not understand the meaning of this comment.	
	EMcG	Table 1 - Really useful table but perhaps reformatting the table highlighting LR+ve and LR-ve might be helpful?	Disagree. These terms are not exclusively relevant to the table. Any LR >1 produces a post-test probability which is higher than the pre-test probability. Any LR <1 produces a post-test probability which is lower than the pre-test probability.	

		Para underneath table last line inclusion of “either” may be helpful? ….probability is *either* high or low.	A positive LR is the probability that an individual with the target disorder has a positive test result divided by the probability than an individual without the target disorder has a positive test. Either positive or negative LRs can be large or small, indicating that the presence or absence of a test result can increase or decrease the likelihood of having a condition. Agreed. This has been added.	
	SR	I agree with the clinical assessment guidelines. To avoid sensitivity it is important to treat the patient and their symptoms with antibiotics that the pathogen is sensitive to.	Thank you. Noted.	
	VH	The whole section on pre-test and post-test probability is very complicated and not easy to follow to a natural conclusion.	Noted, however, other reviewers disagree. The description of the test definitions is there to enable readers to more easily interpret the literature results which are important to show the justification for recommendations.	
	BHUK	Symptoms including OAB, Stress and urge continence issues must be mentioned as a part of the work up on this. Comorbidities are important cross overs.	This guideline considers acute presentation of UTI symptoms as the starting point for the working diagnosis. Bladder pain syndrome was specifically excluded from the literature searches. As the guideline is dealing with uncomplicated UTI we would not consider recommendations for people with incontinence and/or prolapse within the scope, however see	

			section 4.2.1. Although UTI may make pre-existing incontinence worse, no evidence was identified for incontinence as a predictive factor for UTI in adults.	
	AMT	Recommendation – replace “diagnosis” with “diagnose”. Recommendation – contradicts document in Annex 2. Unclear whether Annex 2 should be used a decision aid or not – no guidance provided on the purpose of its inclusion.	Agreed – typo has been corrected. Annex 2 was a late addition to the draft guideline. Further comments have been added to support the reader.	
	NDAA	The wording of this is very difficult to understand - it really is not clear as to when UTI should be considered, who should be tested and in what way. I wonder if it would benefit from some sort of diagram to ease understanding.	See above	
3.1.2	SMc	Urine cloudy with pungent smell.	We do not fully understand the meaning of this comment. Cloudy urine was not identified as a predictive diagnostic criterion in any of the meta-analyses used in this section (see comment to JL below)	
	EMcG	Para 1 and 2 do not mention total number of patients included in meta-analysis while para 3 does (n=948) Really useful section.	Agreed – the numbers which are available have been added.	
	EO	The paragraph beginning *"While likelihood ratios of individual symptoms "* is confusing. It says that it might be a good idea to sequentially apply likelihood ratios it then states if the symptoms are not independent this may over estimate post-test probability. Is the correct conclusion *“that as the symptoms of UTI are not likely to be independent of each other, as they probably relate to the severity of the inflammation, it is not possible to apply likelihood ratios sequentially.”*	Agreed - the underlying concepts are themselves confusing. We accurately describe the situation in which LRs may be applied and the risk of overestimation in the context that individual symptoms are connected. The determination of whether it is valid to calculate LRs for combinations of symptoms may be	

		The use of the same R symbol for both strong and conditional recommendations is unhelpful. It would be helpful to distinguish between the two.	subjective, however as this approach has been used in published studies in the evidence base we identified, we felt it helpful to observe the possible effect. See response to EO comment in 'General' section.	
	JL	I'm very glad to see a return, in this version of the UTI guideline, to simple urinary symptoms. The place of abdominal pain/ tenderness was previously misconstrued, and increased urination is often indicative of increased fluid intake. One omission: cloudy urine is included in Little et al's primary symptoms.	Noted. Cloudy urine was not identified as a predictive diagnostic criterion for UTI in the <65 years group in any of the meta-analyses used in this section. While it is identified in Little, et al, British Journal of General Practice 2010; 60: 495–500, as a single cohort study, this level of evidence has not been used in this question. However, data from this same cohort is used in Giesen et al which provides the data for our Table 2, but which does not report cloudy urine as a factor which is predictive of UTI, presumably as it is not reported in the remaining body of studies used in the meta-analyses.	
	SR	The symptoms identified are typical of a UTI There are other symptoms such as foul smelling urine, pain when passing urine, pyrexia, increased confused which are not mentioned but are highly typical of the elderly residents I nurse. I agree with the recommendation in this section	Noted. See above. Please note that this section relates to diagnosis of UTI in non-elderly women only.	
	VH	*"Suprapubic pain is a negative predictor of UTI and yet is frequently used by clinicians to strengthen the argument for probable UTI*..." Could this be highlighted more? Is suprapubic pain	We note that this is not a quotation from the draft guideline. The symptom of suprapubic pain was	

		more in keeping with urinary retention rather than infection?	significantly inversely related to diagnosis of UTI in only one of the three meta-analyses used in this section. It showed no significant relation to UTI in the other two meta-analyses. On balance the interpretation is that presence of suprapubic pain either slightly reduced the likelihood of UTI as the cause or had no effect.	
	BHUK	Reference - *Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do?. International urogynecology journal, 29(7), 1035-1043*.	We note that this is a single observational study describing management of a complicated UTI. In line with SIGN methodology, the GDG has used meta-analyses and systematic reviews of observational data in forming recommendations for this section, therefore evidence at the level of this study has not been systematically identified and it is not appropriate to use this individual study.	
	PCIU	3 Meta-analyses included cover a wide range of populations and cover groups over the age of 65 with studies of varying size, quality and age. Other diagnosis can also present with symptoms similar to UTI – these include urethritis, STIs, menopause – should these be considered as well as vaginal discharge?	The populations included in the meta-analyses are described in the guideline, and although the upper age limit is over 65 years, the mean age is below this threshold and the majority of participants are <65 years in each case. The symptom of vaginal discharge was specifically identified in the evidence referenced in this section, unlike the other conditions on this list. We have revised the GPP to emphasise the	

		Cloudy urine as a sign of UTI in women under 65 isn't discussed or ruled out as a sign in any. In practice, it is used as a sign of UTI and should be considered. *Little, P., et al. (2010). "Validating the prediction of lower urinary tract infection in primary care: sensitivity and specificity of urinary dipsticks and clinical scores in women." Br J Gen Pract 60(576): 495-500.*	importance of differential diagnosis to rule out other unrelated conditions which may present in similar ways to uncomplicated UTI. See response to JL above. There is insufficient evidence to identify this as a predictive factor and single observational studies, such as this, have not been used to develop recommendations.	
	NHSB	It should be mentioned that the thresholds of $\geq 10^3$ CFU/ml mentioned as being used in the studies referenced are not those used by most clinical labs.	Agreed. This is a known issue. See response to EO in section 3.1	
	CC	I was surprised to see nothing on role of methenamine hippurate I think the guideline overall is very helpful.	A Cochrane review of methenamine hippurate was identified and originally rejected due to mixed populations (men and women, all ages, renal tract abnormalities and post-surgical procedures), poor study quality, variation in dose used, variation in length of treatment and other factors. It has now been added to clarify the significant methodological problems discussed above which suggest that this should be treated cautiously (see section 5.2.2).	
	AW	Recommendation would be better read as the following: If a woman presents with a combination of new onset vaginal discharge or irritation and urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) do not diagnose as a UTI.	Agreed – recommendation has been revised to be more consistent with all recommendations in this section.	
	NDAA	The wording of this is very difficult to understand - it really is not clear as to	See above	

		when UTI should be considered, who should be tested and in what way. I wonder if it would benefit from some sort of diagram to ease understanding.		
3.1.3	ME	Recommendation for routine use of urinary dipstick in all women under 65 years old is a terribly negative and retrograde step. It adds nothing to those with symptoms and possibly only has a role in those with minimal symptoms where actually a urine culture may be better. This recommendation to use in those under 65 is not in line with NICE guidelines or SAPG guidance and will cause significant confusion. Furthermore it would place Pharmacy First at risk of providing sub-standard care with regard to the ability to provide urine dip in the way most health boards have rolled this out.	Noted. The advice is not for routine use of dipsticks in all women, and the wording has been clarified to explain this. While these recommendations change current practice, they reflect evidence published since 2012. NICE guidelines relate to antimicrobial prescribing and therefore have no position on diagnosis. This guideline is consistent with SAPG guidance which is for older people where no dipstick testing is recommended in both documents. A minority of health boards currently use dipstick testing as part of their Pharmacy First service. This would have both practical service provision and education/training implications if adopted across all health boards. For example, raising awareness in the public about the importance of bringing urine samples in appropriate containers to pharmacy consultations.	
		Is this table mislabelled*: "Table 2: Post-test probabilities of significant symptoms alone and in the context of positive and negative dipstick tests."* Should it read post-test probability of infection based on symptoms alone and with positive or negative dipstick? Given that 40% of women under 65 with dysuria who have a negative	Agreed. The table has been retitled.	

		dipstick could have an infection (bacteriuria) then a negative dipstick cannot rule out infection (a useless test).		
	EMcG	This section along with 3.1.2 I think are key and really helpful. Although a decision tree is included are there any patient aid decision tools available to help guide therapy which can be a useful resource for professionals deciding on antibiotic or not? The recommendations for HCWs using dipstick very helpful but there should be equivalent recommendations in absence of dipstick testing (for community pharmacists).	Noted. Thank you. It is not SIGN's role to develop decision aids, however we have added an algorithm (see Figure 1) and both this and the decision tree can be used to guide professionals in appropriate diagnosis and management choices.. Dipsticks can only be used where feasible, and as they only form part of the diagnostic pathway, can be omitted, although at the cost of reducing predictive accuracy of diagnosis made using clinical assessment alone.	
	EO	This is an interesting approach of using dipsticks to alter management decisions in UTI which has not been recommended by either the European Urology Society or NICE or PHE guidelines. However I would describe the proposal as an interesting question to try out in a study to see if it works and not a proposal that is supported by enough evidence to recommend introduction. It would be good to have a protocol that recommends: "Two or more symptoms plus positive dipstick - no culture consider treating with antibiotics. Two or more symptoms negative dipstick culture – encourage self care pending culture result as only 53% have a positive urine culture One symptom only advise to return if symptoms fail to improve or worsen." This would have a significant impact on antibiotic prescribing for UTI. Such a protocol seems to be what you are trying to achieve however there are some problems:	Noted. In the absence of such evidence, the GDG has interpreted the existing evidence base to develop the current recommendations.	

		First of all internal consistency 1. I am puzzled by the recommendation not to diagnose a UTI based on a single symptom and a positive nitrite test. If the nitrite test does not alter the advice to return if symptoms fail to improve or worse why do it at all? 2. The Decision tree in Annex 2 is not based on 2 or more symptoms it is based on one or more symptoms.	Agreed. While correct, this is a confusing recommendation that could inadvertently suggest that dipstick testing in those with a single urinary symptom is a helpful option. This has been revised to remove the comment about nitrite testing in the context of a single urinary symptom.	
		Secondly evidence base: NICE, PHE and the European Urology Society guidelines do not endorse this approach. The European Urology Society describes the evidence for using dipsticks to diagnose UTI as weak. PHE endorse managing patients with one symptom and a positive dipstick as likely to have UTI.	NICE does not include diagnosis in the remit of its antimicrobial guidelines. The most up-to-date reference on dipsticks in the EUS guideline is from 2002. The PHE document is a "quick reference tool [which] is not all-encompassing, as it is meant to be 'quick reference'." No methodology for its development is included and it does not appear to have been developed using systematic review methodology. We consider it to be good practice guidance based on informal consensus. Therefore, the recommendations in the SIGN guideline reflect the most robust review of current evidence on this area.	
		The flow diagram in Annex 2 of this document quotes post-test probabilities of 78% of having a UTI with a positive nitrite test without vaginal discharge and 68% if you have a vaginal discharge. SIGN 88 quotes an 80% chance of bacteruria with one symptom and a positive dipstick for nitrites or leukocytes.	The evidence on which this diagram is based has been published subsequently to SIGN 88 and updates its recommendations. Note that the decision tree probabilities have been revised to reflect a diagnostic threshold for bacteriuria of 10^5	

			CFU/ml which lowers the overall probabilities of UTI across all categories.	
		All these guidelines suggest stating that one symptom and a positive nitrite test is highly likely to have a UTI and so the recommendations as currently worded is not supported by the literature.	The evidence provides probabilities of infection based on symptom and test results. All the evidence cited confirms that a single urinary symptom is not sufficient to rule in UTI.	
		Thirdly, Resource implications. The practical implications from changing from treat on symptoms to test all patients with two symptoms and culture those with negative dipsticks need to be explored. The SIGN 88 approach allows UTI symptoms to be managed by telephone triage with patients collecting prescriptions from reception. Now all patients will need to bring a urine sample in for testing. The practical implications on the overstretched primary care system need to be evaluated before this is launched. This may be the straw that breaks the camel's back.	Noted. It was not possible to complete a budget impact appraisal on this recommendation (see section 8.2). Savings in avoiding empirical treatment of all patient with symptoms may or may not be offset by costs of dipstick testing, however as the recommendation is only to test urine in patients with at least two symptoms, the impact may not be as negative.	
		Practical tips that could be added to the recommendation if it goes ahead - A strong recommendation not to use leukocyte esterase in evaluating UTI would have a significant practical impact. At the moment urine dipstick testing is done in a plain universal container and the sample transferred to a boric acid container for transport to the lab. This is because boric acid interferes with leukocyte esterase testing. If we are not interested in leukocyte esterase results the urine could be collected in a boric acid container for both dipstick testing and culture. This could go in as a good practice point recommendation. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3936984/	Combination of nitrite and leukocyte esterase dipstick testing is more useful for ruling out UTI, however nitrite alone is more useful to rule in UTI. With the additional logistical difficulties described here, and the context of the test being to confirm the diagnosis in patients presenting with positive symptoms, the GDG believes nitrite testing to rule in UTI offers the most useful and practical compromise for a single dipstick reagent.	
		It would be helpful for SIGN to endorse	Noted, though this	

		as a good practice points "use urine dipsticks that contain the fewest possible reagents" , as apart from the waste, positive unnecessary reagents such as urobilinogen have resulted in samples being sent for urine culture and unnecessary antibiotics being given. The authors should reflect on whether there is sufficient evidence base to justify a separate Scottish guideline or whether they should endorse the NICE and PHE guidelines pending a study to demonstrate the practicalities of the novel approach being proposed in this guideline. I do not think the current draft is superior to the NICE and PHE guidance. A major review of the PHE guidelines closed for consultation in May 2018 and must be due soon. Multiple guidelines will just confuse Scottish clinicians as they are likely to see educational messages about the new PHE guidance when it comes out.	has nothing to do with testing for UTI, just using the correct tool for the correct job. Evidence has only been considered relating to nitrite and or LE for the diagnosis of UTI. The NICE guideline does not include diagnosis in its remit. The PHE document is a “quick reference tool [which] is not all-encompassing, as it is meant to be ‘quick reference’.” No methodology for its development is included and it does not appear to have been developed using systematic review methodology. We consider it to be good practice guidance based on informal consensus. Therefore, the recommendations in the SIGN guideline reflect the most robust review of current evidence on this area. There is enough evidence to support a SIGN guideline on this topic, however individual questions are associated with different volumes and levels of evidence, as in any guideline. All recommendations are formulated with explicit reference to the supporting evidence base. SAPG will publish a commentary on the PHE guidance for Scotland to clarify which elements are consistent with Scottish practice.	

	JL	Table 2 is very informative and relevant to practice. However, you seem subsequently to ignore its findings that a single symptom and positive dipstick is associated with a very high likelihood of UTI (almost the same as dysuria + frequency). The subsequent recommendation single urinary symptom and positive dipstick) is do not confirm UTI. I suggest you rethink the recommendation - delayed antibiotics? send MSU? - or was this recommendation a misprint? The subsequent table in Giesen et al is very useful for undiagnosing UTI and I recommend that you include the results from this: the absence of leucocytes and nitrites substantially reduces the likelihood of UTI for all symptoms.	Noted. Thank you. The guideline has been updated with likelihood ratios and probabilities associated with 10^5 CFU/ml threshold. This reduces the overall probability of infection (due to the higher threshold of diagnosis). The post-test probabilities of one urinary symptom plus a positive nitrite dipstick result is therefore lower The GDG considered the impact of using combined nitrite + LE dipstick diagnostic accuracy results to inform this recommendation, however these are more likely to rule out UTI and, in the context of women presenting with suspected UTI, the test which more effectively rules in disease is held to be more relevant.	
	SR	The recommendations for dipstick testing are clear and I fully agree with them. Previously in my area there has been debates around urinalysis, will certain GPs insisting on them and other stating these are not necessary with no clear rational, these recommendations will assist us as nurses to ensure we are demonstrating best practice.	Noted. Thank you.	
	VH	Many people with urinary frequency will not retain urine in the bladder for at least 4hrs so is a common reason why they may test nitrite negative.	We acknowledge the risk of false negative results in this specific context but the evidence we have reviewed suggests dipstick testing for nitrites is a valuable diagnostic test. We have added a GPP to support retaining urine in the	

			bladder for at least 4 hours before dipstick testing.	
	BHUK	The indication that patient symptoms over-ride dipstick test is valuable. *Sathiananthamoorthy, S., Malone-Lee, J., Gill, K., Tymon, A., Nguyen, T. K., Gurung, S. & Spratt, D. A. (2019). Reassessment of routine midstream culture in diagnosis of urinary tract infection. Journal of clinical microbiology, 57(3), e01452-18.*	Noted. Thank you. The GDG has not reviewed individual observational studies in relation to this question due to the availability of systematic review evidence.	
	AMT	Recommendations – In a woman presenting with 2 or more signs or symptoms of UTI, the result of a dipstick test is unlikely to have any bearing on the decision to treat. Pointless step in the diagnosis process. Dipstick only occasionally required in mild/mod symptoms. Increasing the use of urinalysis will have significant impact on HCW time, limits the possibility of UTI in this age group being managed in community pharmacy as no facilities for disposal or function to request sample, contradicts other recent Scottish work (SAPG, NES/HIS). The recommendation contradicts other UK UTI guidance. Suggest adding in a statement of what would indicate symptoms of upper UTI.	Disagree – see Annex 2. The evidence indicates that adding a positive nitrite dipstick test result to urinary symptoms increases the post-test probability of UTI by 25-30%. NICE does not include diagnosis in the remit of its antimicrobial guidelines. The most up-to-date reference on dipsticks in the EUS guideline is from 2002. The PHE document is a “quick reference tool [which] is not all-encompassing, as it is meant to be ‘quick reference’.” No methodology for its development is included and it does not appear to have been developed using systematic review methodology. We consider it to be good practice guidance based on informal consensus. Therefore, the recommendations in the SIGN guideline reflect the most robust review of current evidence on this area. This is not within the scope of this document, therefore	

			we will not provide diagnostic recommendations.	
		Recommendation – Further clarity required around other permutations that may be indicative of UTI where symptoms are mild in nature (<2 symptoms).	The presence of only one urinary symptom without a dipstick result increases post-test probability of UTI by only around 2–5%. The guideline advises women to return to GP if the single symptom fails to resolve or worsens. Clinical judgement may be used, however there is no evidence-based recommendation in this context for empirical treatment.	
	PCIU	It would make more sense if the symptoms and dipsticks were considered together and then recommendations for diagnosis provided. Recommendations indicate that all presenting women will have a urinary dipstick done. They base this on recommendations that it is cost effective. However, it will mean that every woman has a urine sample dipsticked in the surgery. The summary did not mention if time was considered as a factor in the cost analysis. Would it be more effective to have an option to treat based on strong symptoms alone? It is unclear what evidence is the basis for the last recommendation that a woman with only a single symptom and a positive dipstick not have a UTI confirmed. Should there be room for consideration here? Patients with a single symptom and a negative dipstick still have a 45–52% chance of UTI (unless vaginal discharge when you wouldn't do it anyway) – so will a patient with cardinal symptoms be happy not to have antibiotics or at least a delayed antibiotic. Unclear why leucocytes have been excluded from the dipstick rules – how should these be considered or why should they not be considered?	Agreed. All recommendations have been moved to after the sections on urinary symptoms and dipstick testing. It was not possible to carry out a budget impact analysis of this recommendation (see section 8.2). The implication is not to carry out dipstick testing on every woman presenting to a GP with possible UTI, and the recommendation on single urinary symptoms has been revised to emphasise this. Combination of nitrite and leukocyte esterase dipstick testing is more useful for ruling out UTI, however nitrite alone is more useful to rule	

			in UTI. As boric acid containers (which are most often used to transport urine samples to labs) interfere with leukocyte esterase testing, and as LE is not reported as a binary result and may also reflect the presence of STIs or non-infectious renal diseases such as glomerulonephritis, the nitrite test is preferred. The context of the test is to confirm the diagnosis in patients presenting with positive symptoms, the GDG believes nitrite testing to rule in UTI offers the most useful and practical compromise for a single dipstick reagent.	
		Think is it important to stress that incorrect results can occur if dipsticks are read at the wrong time. There is not a recommendation for women who have one of the main symptoms and/or other less descript ones without a positive dipstick test. We assume you consider another diagnosis and self care.	We agree that it is important to carry out all testing accurately at the correct times.	
	CC	I didn't find the paragraph on page 10 which starts "In the second meta-analysis, pooled likelihood ratios were used to increase the post-test prediction for a UTI...." particularly clear - can this be explained better? The recommendation to use dipstick testing to diagnose every UTI will have major implications for established practices where Pharmacies in Scotland are working to a PGD which does not include dipstick testing. While there was some discussion of the evidence of diagnosing UTIs on symptoms only, there was no recommendation made on whether symptoms alone could be used.	Noted. A minor revision has been made to clarify this paragraph. The question of how and where dipstick testing should be carried out has not been addressed, however service reconfiguration may take place over time to alter the facilities available to support more accurate diagnosis. The guideline notes that a single symptom is	

			insufficient to support a diagnosis. Two urinary symptoms alone alter the post-test probability of UTI by around 10%.	
	AW	Dipstick testing - I acknowledge the data with regard to nitrate and test probability stats. However I disagree with the recommendation for routine dipstick testing as a standard for diagnosis in uncomplicated UTI. Significant work has been undertaken at national level to train community pharmacies to be able to treat uncomplicated UTI empirically and manage patients based on symptoms. As I interpret the recommendation a negative nitrite does not rule out UTI therefore if a patient who has two or more symptoms and a negative nitrate, a prescriber is still being encouraged to culture and will likely consider treatment if patient is symptomatic therefore practically I do not see how adding the dipstick will actually influence practice. Additionally logistics would need to be considered around retraining and the costs associated if community pharmacists are being recommended to routinely dip urine.	Neither one nor two urinary symptoms alone increase the pretest probability of infection to a level where antibiotic prescription can be made routinely without risking inappropriate increase in antibiotic resistance. The addition of a positive nitrite dipstick test increases probability by ≥30%. Depending on the combination of presenting features, in some cases this can prompt treatment. Many UTIs are self limiting and not all treatment may involve antibiotics. As was the case when community pharmacies moved from a situation of not providing antimicrobial management for UTI to being organised to do so, some reconfiguration and change in practice will be required.	
	PI	The first recommendation in this section details diagnose a UTI in the presence of two or more urinary symptoms and a positive dipstick test for nitrites. This is a change in the current guidance and differs from public health England's guidance. Appreciate the data on pretest probability based on symptoms, however this just lists individual symptoms. If someone has two or more urinary symptoms surely this would put the pretest probability higher as they have a combination of symptoms. Therefore do these individuals really need dipsticked. In terms of the economic evaluation was the patients time, cost of sundries (dip	Noted. The presence of two symptoms may alter the probability of UTI by around 10% - see decision tree in annex 2 for further information. The baseline (pretest) probabilities available from the literature indicated that ≥1 symptom was the blanket grouping for population prevalence statistics. It was not possible to	

		stick and sample bottle) and staff time (to dip sample and record findings) all taken into consideration? One of the recommendations suggests if a woman presents with a single urinary symptom and a positive dipstick for nitrites, do not confirm diagnosis of UTI. I just wonder the need for dipsticking this patient group, especially if they have one symptom. Dip sticking is not going to change the course of treatment here, as if +ve or -ve for nitrites and one single symptom a UTI cannot be confirmed. Therefore dip sticking this group of patients will just increase costs in terms of sundries sample bottle, dip sticks and staff time to dip and record findings.	carry out a budget impact analysis of this recommendation (see section 8.2). Agreed – this recommendation has been revised to remove the reference to dipstick testing which is redundant.	
3.2	SMc	Prescribed double course of antibiotics.	We do not understand the meaning of this comment.	
	EO	No comments apart from the issue about the R symbol for both strong and conditional recommendations.	See previous response to this comment.	
	SR	I agree with all aspects of the management recommendations. Encouragement with fluid intake is one of the first things I would do to manage symptoms of a UTI, we promote continence in elderly residents by encouraging regular bathroom breaks throughout the day, promote good hygiene habits such as wiping front to back.	Noted. Thank you.	
	VH	Should it be made clearer that the recommendation of at least 2.5L fluid intake/day excludes those on fluid restriction such as congestive cardiac failure and renal dialysis patients?	Agreed. We have added a GPP highlighting exceptions to this recommendation.	
	BHUK	High dose Vitamin C, Hipprex, uromune and urovax are not considered or evaluated?	We found no robust evidence for most of these treatments. A Cochrane review of methenamine hippurate was identified and originally rejected due to mixed populations (men and women, all ages, renal tract abnormalities and post-surgical procedures), poor study quality, variation	

			in dose used, variation in length of treatment and other factors. It has now been added to clarify the significant methodological problems discussed above which suggest that this should be treated cautiously (see section 5.2.2).	
	AMT	Typo in second last sentence of 2nd paragraph. Change "nest" to "best".	Thank you. We have corrected this typo.	
	PCIU	There needs to be more information on safety-netting if women are not going to be diagnosed if they are symptomatic and have a positive dipstick.	Section 3.1.3 contains the good practice point "*Advise the patient that a UTI cannot be confirmed based on a single urinary symptom and to return if the symptom fails to improve or worsens."* and section 3.2.2 contains the good practice point "Patients receiving NSAIDs should be informed to contact their prescriber if UTI symptoms do not resolve within three days or worsen." Patients with two urinary symptoms and a positive dipstick result ARE likely to receive a diagnosis, while those with a single symptom should not receive a dipstick test. No change required.	
	AW	I do not feel we need to add specifics of "children or other dependents" but maybe adding consideration of work, activities and any responsibilities to care for others? Typo appears as "nest" instead of best approach in this section.	Agreed. We have revised as suggested. Typo has been corrected.	
	NDAA	The wording of this is very difficult to understand - it really is not clear as to when UTI should be considered, who should be tested and in what way. I wonder if it would benefit from some sort of diagram to ease understanding.	Noted. There have been revisions to the wording of the guideline in several sections, and an algorithm has been	

			added (see Figure 1).	
	PI	Second-last sentence states 'determine the nest approach for them.' Typo think should read 'determine the best approach for them.'	Thank you. Typo has been corrected.	
3.2.1	SMc	Taking care every morning to clean suprapubic site with saline solution. Cover area with a dressing. If changes are noted by myself in cloudiness and smell I would take an Oregano Oil capsule.	Thank you.	
	ME	Placing guidance regarding recurrent infection within the acute UTI sections is incoherent.	The evidence for recurrent and acute infections were not separated into different questions, meaning that there may not be binary split of information for all age groups however the guideline has been restructured and the advice relevant to recurrent infection collected into a single chapter.	
	EMcG	Again a very important section and perhaps the info on cranberry, NSAIDs etc better here with an acknowledgement about lack of evidence with other prevention strategies. It would be useful to mention the alkalinising agents here as frequently used and cross refer to NF section.	Thank you The GDG considered that, as a non-pharmacological treatment, cranberry products should be included in that section to separate it from pharmacological prophylaxis of recurrent UTI. As licensed drugs, NSAIDs are included in the section on pharmacological management of acute UTI. We found no evidence for use of alkalinising agents. However we note that these are available and used by some patients so have added a paragraph about their use (section 3.2.3).	
	EO	The problem with the use of two small randomised controlled trials for acupuncture is that there is a possibility that the results are derived by chance.	Thank you. The quality of evidence is related to	

		In such cases it is best to go back to the scientific principles behind the test. Please can someone explain the science behind acupuncture preventing development of UTI? I can see an effect on symptoms but not on bacteriuria. If there is not a logical explanation the effect may be due to chance and you might wish to downgrade the evidence quality to good practice point.	technical aspects of its construction and it is not appropriate to downgrade it in this circumstance. However, although there is some supporting evidence, acupuncture is not likely to be a strategy considered in Scotland and the recommendation has been removed.	
	JL	I agree with your conclusion on the evidence against spermicides - all the available, albeit low quality evidence, points this way. Several studies have looked at postcoital voiding with contradictory results. Evidence is limited on the benefits of other physio-mechanical interventions. You have, however, quoted just one case-control study (perhaps as the most recent) which contradicts previous studies. Given the level of evidence and previous negative results, the conclusion should perhaps be 'uncertain benefit'.	Thank you. The only recent evidence identified on fluid intake are cited in the guideline. A non-systematic review from 2003 noted contradictory results in earlier literature.	
	SR	As above		
	BHUK	Bladder diaries, Clean Intermittent Self Catheterisation	No evidence was identified on the use of bladder diaries as self care for management of uncomplicated UTI in women <65 years or in those with catheters.	
	AMT	Recommendation - Suggest removing volume of fluid required for adequate hydration as this will vary from person to person. Perhaps use SUTIN hydration campaign material to promote adequate hydration. Recommendation - Population size and supporting evidence would be useful to see for the acupuncture recommendation. A one-sentence statement extrapolated from another paper is not sufficient to produce a	Thank you. [Material now moved to section 5.1.1] The GDG believe it helpful to state a volume of fluid. The SUTIN hydration campaign is referenced in the good practice point within this section. SIGN has not reviewed the primary studies cited in the guideline which provides this recommendation.	

		recommendation.	Although there is supporting evidence this is not likely to be a strategy routinely considered in Scotland and the recommendation has been removed. The guideline clarifies that this is an option which patients may choose to pursue independently rather than receive via prescription.	
	PCIU	Fluid intake. Be aware this recommendation is different to NICE, as they considered that the single study was very weak and was sponsored by a bottled water company. Acupuncture - Please check NICE as the Committee did not recommend.	[Material now moved to section 5.1.1] Thank you. We acknowledge recommendation is based on one study. Our review identified some weaknesses but these did not render the study conclusions invalid. The findings are in line with national hydration campaigns. See above. Although there is supporting evidence this is not likely to be a strategy routinely considered in Scotland and the recommendation has been removed.	
	NHSB	The reference to acupuncture seems to be contained within a review that is not freely available, and given the controversy around the area the specific reference to the study demonstrating the effect should be given.	[Material now moved to section 5.1.1] Thank you. The Canadian review – "Epp A, Larochelle A. No. 250-Recurrent Urinary Tract Infection. Journal of Obstetrics & Gynaecology Canada: JOGC 2017;39(10): e422-e31 is available on request from SIGN, as are all evidence cited in this guideline. SIGN has not reviewed the two studies which are cited in the Canadian	

			guideline relating to acupuncture, and will therefore not reference these directly. Although there is supporting evidence this is not likely to be a strategy routinely considered in Scotland and the recommendation has been removed.	
	CC	Is the recommendation on acupuncture robust considering it is based on 2 small RCTs - think that needs to be expanded giving it is a recommendation but there is no info on size of trial and quality of trials.	[Material now moved to section 5.1.1 and the recommendation has been removed] See above	
	AW	The voiding behaviours and hygiene could be elaborated further and highlighted to make this guidance clearer as these interventions are valid and effective. A recommendation and bullet points as in fluid intake would emphasise the recommendations as they appear lost in the text. A general recommendation in this section should be that all women who are symptomatic of UTI receive appropriate self-care advice at every consultation regardless of diagnosis and treatment.	[Material now moved to section 5.1.1] There is limited and conflicting evidence for voiding and hygiene behaviours therefore we cannot make a recommendation. Agreed. We have added a sentence about self-care advice at every opportunity to section 3.2.	
3.2.2 [Material now located in section 3.2.4]	ME	Section 6.1 states: *"Explain the difference between a 3-day and a 7-day course of antibiotics and the reasons for using one or the other"* I cannot find a reference to this is the text of the document. I think there is a lack of guidance for management of catheter associated UTI. Change catheter, yes or no, before or after antibiotics, how long to treat after antibiotics etc.	Section 6.1 provides suggested discussion points for healthcare professionals to raise with patients/carers. A 3-day course is recommended for non-catheterised women (see section 3.2.4). A 7-day course is often used for catheterised women. There is limited and conflicting evidence for changing the catheter. While changing the catheter appears to be a useful intervention there is a lack of evidence on when to do this and in practice it may not be possible before	

			starting antibiotics.	
		Why is cephalexin recommended for 7 days?	As above. The duration of therapy has been removed from Table 4.	
	EMcG	Para 3 is the primary dilemma of whether to use antibiotics or recommend self-care. Useful to know if ref 56 was adequately powered I queried some of the ordering/inclusion in this section.	The trial was reported as a pilot equivalence study and was not sufficiently powered to give definitive answers. This has been reflected in the guideline. [Material now moved to section 5.2.1]	
		Antimicrobials for recurrent UTI Para 2: Should that not be better in non-pharmacological treatment?	The paragraph describes the use of antimicriobials for recurrent UTI compared with cranberry products and shows an advantage for antimicrobials, so the GDG prefers to keep it in this section to provide advice on the benefits of antimicrobials.	
		Treatment of asymptomatic bacteriuria in non-pregnant women. Is this referring to just recurrent UTI or should it be moved to earlier in this section?	This review includes all women (excluding pregnant women) and men and therefore relevant to this section.	
	JL	Evidence for trimethoprim's superior performance for LUTI - but not UUTI - in vivo compared to in vitro. *Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med 2001;135(1):41-50.* This is suggested to be due to a high bladder concentration of the antibiotic far exceeding the reference MICs.	Thank you for sharing this reference. This is a non-systematic review published outside the inclusion period for the SIGN literature review and will therefore not be further considered. Trimethoprim is already noted as a first-line treatment option in Table 4.	
	JR	"*Nitrofurantoin should be avoided*	Agreed.	

		during pregnancy and when breastfeeding" There is no reference to evidence this statement. This is first line antibiotic in most maternity patients for 1st and 2nd trimester UTI. Usually say avoid in 3rd trimester. BNF advises only "avoid at term". Also your guideline suggests will not be providing guidance on infection in pregnant women but this comment is included and also on page 15 in table 3 in reference to Cefalexin "*Main use is in pregnancy where trimethoprim and nitrofurantoin are less suitable*".	We have removed this comment as the guideline does not cover UTI in pregnant women and this statement is not supported by evidence. When making prescribing decisions, pregnancy should be considered in all women of childbearing potential.	
	SR	I agree with all the recommendations in this section. With increasing resistance to antibiotics it is important to ensure that the pathogen is sensitive to the antibiotic prescribed and appropriate monitoring of symptoms is carried out.	Noted. Thank you.	
	VH	BNF advises half dose of trimethoprim based on renal impairment, similar to nitrofurantoin. By not including this suggests it is safe in renal impairment which is not necessarily the case. NHS Grampian antimicrobial pharmacists are now recommending 2–3 doses of fosfomycin 3 days apart (only if confirmed as sensitive)...is this evidence based and standard practice across other parts of Scotland?	Thank you. We have removed dosage information from Table 4, as local formulary rules may make context-specific decisions for regions with different prevalence of antimicrobial resistance.	
	AMT	Last paragraph - Not required. Guidance has already stated that it does not apply to pregnant women. Table 3 – Cefalexin section – suggest changing "penicillin sensitive patients" to "penicillin allergic patients" for absolute clarity.	Thank you. We have removed the specific restriction on use in pregnancy, however when making prescribing decisions, pregnancy should be considered in all women of childbearing potential. We have added a note to this effect to section 3.1 Although this is describing true allergy, some patients may also experience delayed onset rash which is not immediate hypersensitivity, and for whom cephalosporins may be safely used.	

		Pivmecillinam section – suggest adding that pivmecillinam is one of few oral options available in the treatment of gram-negative resistant organism infections. Our current practice would be to use 400 mg dose three times a day, evidence of failure with lower dose. Fosfomycin section – remove "against organisms sensitive to fosfomycin" this is implied through the use of targeted treatment.	We note this opinion which does not match the dose indicated in the BNF. We have removed the dosages from this Table (see above) Disagree. For clarity we have added this phrase to the description of targeted treatments for both pivmecillinam and fosfomycin.	
		Page 15, Adverse events heading – requires context as next paragraph discusses asymptomatic bacteriuria.	The heading has been revised to "*Adverse events associated with antimicrobial treatment of LUTI in women aged <65 years"*	
		Asymptomatic bacteriuria paragraphs – suggest moving to page 17 under Treatment of asymptomatic bacteriuria in non-pregnant women	Agreed. The first paragraph of the "adverse events" subsection has been moved to the "Treatment of asymptomatic bacteriuria in non-pregnant women" subsection.	
		Recommendation or consensus opinion required for recurrent UTI - Recommendation or expert consensus required on duration of prophylaxis for UTI.	A good practice point has been added to section 5.2.1 – "To minimise the development of resistance antimicrobial prophylaxis should be used as a fixed course of three to six months in women with recurrent UTI."	
		Recommendation – asymptomatic bacteriuria should not be treated in non-pregnant women of any age.	Agreed – this recommendation has been revised to remove the age restriction and added to section 3.2.4 and	

			4.2.2.	
	PCIU	In line with PHE and NICE – but check pregnancy. Consider a recommendation about review of antibiotic prophylaxis and self-care in recurrent UTI. Canephron is not recommended by NICE – Pyelonephritis occurred in 2% of those treated with Canephron – Option should be .1 plus careful safety netting	The remit of this guideline does not include management of UTI in pregnant women, however we have revised a caution for nitrofurantoin use in pregnancy which was inaccurate. Recommendations on self care in women with recurrent UTI have been added to section 5.1.1 The scope of NICE's guidelines only included antimicrobial prescribing therefore this product would be excluded from consideration.	
	CC	I think there needs to be more emphasis on the MHRA warning on quinolones in the recommendations section I wondered where the evidence for drug dosages came from in Table 3? This is not referenced. Under adverse events, there is no mention of quinolone side effects yet this has resulted in MHRA warning which while mentioned in initial text under choice of agent, should be mentioned here also. Should there be a recommendation either for or against delayed prescriptions given that is something that is being promoted by stewardship programmes?	Thank you. We have added additional warnings about use of quinolones. Drug doses have been removed from Table 4 (formerly Table 3). A note has been added to clarify that there was insufficient evidence to support a recommendation for or against delayed prescriptions.	
	AW	First statement which provides dates and notes self-limiting disease may be better placed and highlighted earlier in the guidance as opposed to within the antimicrobial section. Table 3 may benefit from separating agent, dose and duration into separate columns instead of having agent with prescribing information in brackets. This may make this clearer for prescribers and assist with adherence to the 3-day rule, applicable for most agents. It may also be beneficial in table 3 to highlight	Thank you. We have moved this text to section 3.2. We have revised the table and removed dose and duration information.	

		further first line from second line agents.		
3.2.3 [Material now located in section 3.2.2]	EMcG	Para 1: Should this not be moved to earlier in section 3.2.2? *Predicting patients more likely to benefit from immediate antibiotic therapy rather than NSAIDs.* Is this a misleading title? Should it be 'Predicting patients more likely to benefit from NSAIDs?' The subsequent recommendations mention moderate and severe but what about when no dipstick results are available?	Thank you. We have moved this text to section 3.2. Agreed. We have made this change The assignation of symptom severity is based on subjective patient self report, rather than dipstick result.	
	EO	As an aside there is a debate about whether NSAIDs have significant antibacterial properties. There is some work that suggests they do https://aac.asm.org/content/61/4/e02268-16/article-info It is probably not worthy including in the guidance as it is of no practical significance.	Thank you. We acknowledge this potential action of NSAIDs but this was not found within the evidence so we will not highlight within the guideline.	
	SR	The use of NSAIDs for treatment of UTI is an interesting alternative for younger women. Although antibiotics according to the studies have a more rapid success rate of reducing the pathogen the use of NSAID could improve symptoms in the first few days and reduce the likelihood of antibiotic therapy being required. Therefore reducing the risk of antibiotic resistance later in life.	Noted. Thank you.	
	BHUK	We wondered why self instillation of gentamicin is not mentioned.	The guideline scope is diagnosis and management of lower UTI in non-pregnant women and is therefore focused on uncomplicated infections in patients without urological problems. The use of gentamicin would not be an approach used in this patient group.	
	AMT	Did the evidence suggest the use of methenamine as a beneficial antibiotic-sparing agent in recurrent UTI?	We acknowledge that methenamine is used in practice but did not find robust evidence	

			for its use. However, we have added a new section describing the limitations associated with a Cochrane review which includes mixed populations, including patients outwith the scope of this guideline. See section 5.2.2	
	PCIU	NSAIDs. There is some evidence that there is increased risk of upper UTI if NSAIDs are not given without a delayed/back-up antibiotic. Therefore, in mild symptoms paracetamol may be a better recommendation as CRP will not be taken routinely. Your section on risk analysis for benefits of immediate antibiotics on p18 include Leucocytes and erythrocytes which are NOT included in your original algorithm. NSAIDs with moderately severe symptoms is not wise unless given with delayed antibiotics script. I think you need to give in summary the actual risks and Pyelonephritis rate.	Thank you. We did not find evidence supporting the use of paracetamol. A new algorithm has been developed (see Figure 1). The recommendations for NSAIDs are in line with principles of national antimicrobial stewardship and subject to shared decision making between patient and clinician.	
	CC	Speed and resolution and risk of pyelonephritis - It states that between 2–5% of patients receiving NSAIDs were diagnosed with pyelonephritis, there is no mention if this was higher than those receiving antibiotics.	Thank you. These results are presented in Table 3.	
3.2.4	ME	If there is no funding for acupuncture of herbal remedies it should not be recommended. Canephron® use should not be recommended as the trial basically showed that many women will settle with or without antibiotics and I don't think it shows that this specific product can be recommended.	Thank you. Acupuncture is discussed (in section 3.2.1) for women to consider as a self-management option. Although there is supporting evidence this is not likely to be a strategy routinely considered in Scotland and the recommendation has been removed. The recommendation for healthcare professionals to provide advice to women about the use of Canephron (in section 3.2.5) as a	

			self-management option has been removed.	
	EMcG	Much of this section refers to prevention and should be a separate section rather than treatment? Under 6.1 prevention and lifestyle advice is mentioned.	Thank you. We have restructured the guideline to include a chapter on recurrent UTI which contains relevant information on prophylaxis.	
	EO	I have looked at the study cited for Canephron (BNO 1045) and there are some flaws in the study. For example the proportion of patients without culture positive UTI at 1000 CFU differ between the two arms. The higher proportion in the antibiotic control arm than the trial drug may reduce the effectiveness of the antibiotic and therefore make it easier for the trial drug to make non inferiority. The most worrying thing about the study is 54% of the study patients would not have been diagnosed with UTI at a threshold of 10,000 CFU/ml so it is difficult to translate this study into UK clinical practice. I would suggest that the paper is subject to a detailed critical analysis to see if the statistics are still valid if reanalysed excluding patients who do not have UTI by the study criteria or by the UK criteria. I would suggest that it might be worthwhile weakening the recommendation to "noting BNO 1045 has potential however it needs further research to determine its usefulness in the UK setting. As the product does not have a product licence in the UK or EU we are reluctant to endorse it use until it meets the appropriate regulatory standards for a medicinal product "	Thank you. The study has been critically appraised by Information Scientists in Healthcare Improvement Scotland. Independent patient data are not publically available for this study, therefore we are not able to re-analyse the results. The recommendation for healthcare professionals to provide advice to women about the use of Canephron (in section 3.2.5) as a self-management option has been removed.	
	SR	The recommendations for non-pharmacological treatment are appreciated, cranberry juice is a well-known option that many people will advise however as the evidence shows there is little to prove it as an effective	Noted. Thank you.	

		treatment. The data on Canephron is interesting and I agree it may be an alternative for younger women with suspected uncomplicated UTIs.		
	VH	Based on available evidence I do not feel there is sufficient evidence to recommend Canephron can be considered as a treatment option. The only available study was small and sponsored by the manufacturer.	Thank you. See above The recommendation for healthcare professionals to provide advice to women about the use of Canephron as a self-management option has been removed.	
	BHUK	Uromune and Urovax have been used successfully in Spain and trial in UK. *Steve Foley Yang, B., & Foley, S. (2018). First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®. BJU international, 121(2), 289-292.*	Thank you. We did not identify evidence for these treatments and believe they are not used in current practice in Scotland.	
	AMT	Independent evidence required on BNO 1045 before making a recommendation on this product. HCW & patients should not be encouraged to obtain medicinal products online.	Thank you. See above. We note that Canephron is not a licensed medicine. The recommendation for healthcare professionals to provide advice to women about the use of Canephron as a self-management option has been removed.	
	PCIU	The recommendation around acupuncture is based on a non-systematic review that cites two small RCTs. Concern that evidence of benefit isn't large enough to justify a recommendation that will incur considerable cost to patients. Should recommendations include the use of d-mannose for women who are	Thank you. Acupuncture is discussed (in section 3.2.1) for women to consider as a self-management option. Although there is supporting evidence this is not likely to be a strategy routinely considered in Scotland and the recommendation has been removed. We did not identify evidence for D-mannose although we	

		at risk of recurrent UTI? *Kranjcec, B., et al. (2014). "D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial." World J Urol 32(1): 79-84.* Note most recent NICE systematic review suggesting cranberry products may be useful in some women for prevention not treatment if under 65 yr.	acknowledge that it is recommended by NICE. The cited trial by Kranjcec et al is included in the Cochrane review which we describe in section 5.2.3 We describe evidence for the use of cranberry in preventing recurrent UTI in section 5.2.4 As this evidence is conflicting, we are unable to form a recommendation.	
	CC	Recommendation for BNO 1045 - needs stated as part of recommendation that it is an OTC product There are also typos in this section.	Thank you. We have added the sentence “BNO 1045 is not used routinely in Scotland and cannot be supplied on prescription. Patients can buy BNO 1045 via online retailers.” The recommendation for healthcare professionals to provide advice to women about the use of Canephron (BNO 1045) as a self-management option has been removed.	
	AW	I do not agree with the recommendation to advise women to use Canephron due to the data presented at this stage.	Noted. Thank you. The recommendation for healthcare professionals to provide advice to women about the use of Canephron (BNO 1045) as a self-management option has been removed.	
	NDAA	BNO 1045 - this is not common practice in our urology department, we don’t have women asking for this. Our local microbiologist says this is used widely in Europe but not commonly in the urological community in the UK. Hipprex – only mention of this is as a comparison to cranberry in trials but I believe is recommended by public	Thank you. The recommendation for healthcare professionals to provide advice to women about the use of Canephron (BNO 1045) as a self-management option	

		health England.	has been removed. We acknowledge that methenamine is used in practice but did not find robust evidence for its use. However, we have described the limitations associated with a Cochrane review which includes mixed populations, including patients outwith the scope of this guideline. See section 5.2.2	
Section 4				
General	AP	I think throughout this section we should be considering the terms we use to describe 'places' where care is given. We mention residential care, care homes, long tern residential care. To bring things in line with the HALT recommendations, I think we could be using the term 'Care Home' and/or 'Long Term Care Facilities'.	Thank you. We have made revisions to ensure consistency in use of these terms.	
	VH	Many people remain at home now with extensive packages of care to support them with all Activities of Daily Living (ADLs). Until recent years these people would more than likely have been resident in long-term care facilities. I think it needs to be made clear that frail elderly living in their own home with significant social support (and largely housebound) are at the same risk as those in long-term residential care of developing asymptomatic bacteriuria.	Agreed This point has been added to section 4.1.	
	PCIU	There is no section on prevention. I would suggest providing recommendations for prevention strategies, i.e. personal hygiene, diet and hydration. *Charach, G., greenstein, A., Rabinovich , P., Groskopf, I. & Weintraub, M. 2001. Alleviating constipation in the elderly improves lower urinary tract symptoms. Gerontology, 47, 72-6.* *Amiri, F. N., Rooshan, M. H., Ahmady, M. H. & Soliamani, M. J. 2009. Hygiene practices and sexual activity associated with urinary tract infection in pregnant women. Eastern Mediterranean Health Journal, 15.*	Thank you. Where evidence was available, this information is included within the self-care section (4.2.1).	

		Moore, E. E., Hawes, S. E., Scholes, D. , Boyko, E. J., Hughes, J. P. & Fihn, S. D. 2008. Sexual intercourse and risk of symptomatic urinary tract infection in post-menopausal women. J Gen Intern Med, 23, 595-9. *Scholes, D., Hooton, T. M., Roberts, P. L., Stapleton, A. E., Gupta, K. & Stamm , W. E. 2000. Risk Factors for Recurrent Urinary Tract Infection in Young Women. The Journal of Infectious Diseases 182, 1177–82* *Hooton, T. M., Vecchio, M., Iroz, A., Ta ck, I., Dornic, Q., Seksek, I. & Lotan, Y. 2018. Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial. JAMA Intern Med.*		
	AW	Addition of non-catheter and not recurrent in title?	Thank you. The GDG discussed this suggestion but felt that addition of these terms would make the title overlong so agreed not to change the original title.	
4.1	ME	I find this statement confusing: "*Do not send urine for culture to rule in urinary tract infection in women aged 65 years and above in residential care*." It requires some context as outlined in the text above it. This is not a helpful statement: "*Be aware that women aged 65 years and above, especially those in residential facilities, may not display the traditional symptoms and signs of UTI that are seen in a younger cohort. Be aware that functional deterioration and/or changes to performance of activities of daily living may be indicators of infection in frail older people."* So how is a GP to differentiate things - how about suggesting use of the Canadian flow chart or parts from it to help make a diagnosis. *J Antimicrob Chemother 2018; 73 Suppl 3: iii2–iii78.*	Thank you. This recommendation has been removed. The evidence supports the text included. The GDG considered the development of an algorithm, however felt that in this age group in particular, single criteria were not appropriate for diagnosis, and care must be individualised for each person, so it was not possible to develop an algorithm.	

		Send urine for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above PRIOR TO STARTING started on antibiotics for a UTI.	Agreed. We have included this suggested additional text (to section 4.1.3).	
	JL	The introduction is very helpful especially the section suggesting that health status is more important than age, per se. Perhaps it would be more helpful to increase the age range to 75 as this would allow more homogenous guidance.	Thank you. The GDG discussed the age cut off of 65 years but agreed to retain it as much of the evidence base uses this age segregation.	
4.1.1	AP	Change 'acts of daily living' to 'Activities of Daily Living'.	Thank you. We have made this change.	
	VH	Temperature >37.9° is quoted as being one of the reasons for considering starting antibiotics in frail elderly with urinary symptoms. The small studies quoted report that fever is not predictive of UTI. Were these studies sufficiently powered and what was defined as "fever"?	These studies (n=101 and 550) appear within a meta-analysis and have not been independently critically appraised by SIGN. The meta-analysis reports one study at low risk of bias in six out of seven domains of the QUADAS-2 tool, and high risk of bias in the remaining domain. The other study was rated at low risk of bias in four of seven domains, at high risk of bias in one domain and unclear risk of bias in two domains. Power was not discussed in the meta-analysis and fever defined in one study as temperature >37.9° C (100° F) or 1.5° C (2.4° F) above baseline temperature. One study suggested that presence of fever reduced the probability of UTI by 38%.	
	PCIU	As PHE flowchart identifies delirium as a possible predictor of UTI. The evidence as you say is weak. You cite a systematic review meta-analysis of low quality studies. The two studies in the	Thank you. We have clarified this point as suggested.	

		systematic review which identify delirium as a predictor relied on clinician diagnosis which may be biased. I think it should be made clearer that delirium can be an indication of a variety of other conditions. *Ahmed, S., Leurent, B. & Sampson, E. L. 2014. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. Age Ageing, 43, 326- 33.* *Inouye, S. K. 1999. Predisposing and Precipitating Factors for Delirium in Hospitalized Older Patients. Dement Geriatr Cogn Disord, 10, 393–400.* *Inouye, S. K. 2006. Delirium in Older Persons. The New England journal of medicine, 354, 1157¬ 1165.* *Pryor, C. & Clarke, A. 2017. Nursing care for people with delirium superimposed on dementia. Nurs Older People, 29, 18-21.* *Siddiqi, N., Harrison, J. K., Clegg, A., Teale, E. A., Young, J., Taylor, J. & Simpkins, S. A. 2016. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev, 3, CD005563* *Young, J. & Inouye, S. K. 2007. Delirium in older people. BMJ, 334, 842-6.*		
	AW	Sepsis to be discussed in this section? Additionally temperature? Signs of pylenophritis? Exclude other common conditions and or infections? Care homes should have protocols in place to provide clinical information, i.e. obs to prescriber to allow clinical review before any treatment is initiated in this setting.	Sepsis and pyelonephritis are usually indications for upper UTI and excluded from the remit of this guideline. Fever is referred to in this section. A GPP in section 4.1.2 advises a holistic assessment to rule out other causes of symptoms.	
4.1.2	AP	I think we should consider that there will be some overlap in symptoms with the under 65 age group and the over 65. Especially, with the heightened awareness around urinary sepsis there will be some clinical features that should be discussed e.g. fever.	Thank you. We do note this in the introduction and have added a good practice point to section 4.2 highlighting that management in fitter, ambulatory women aged <65 and >65 may be the same.	

	JL	It is very helpful to state that we should be aware of non-traditional symptoms. However, more specific recommendations should be included to reduce over-diagnosis of UTI and when treatment is given (to a more select group) ensure that it is more effective. Is there any evidence that functional deterioration can be attributed to lower urinary symptoms? The supposition is that such symptoms are more likely to be associated with upper urinary infection. Many elderly people with functional deterioration do not have UTI but are treated as LUTI e.g. with nitrofurantoin, but others have UUTI where a systemically available antibiotic is necessary.	The evidence supports using functional deterioration as a marker for UTI but we acknowledge that there are many other causes. The evidence does not support more specific recommendations. The systematic review used in this section did not stratify UTI into lower and upper, which may partly explain the presence of traditional urinary symptoms (eg dysuria) and non-traditional activities of daily living as predictive of UTI in their analysis.	
	VH	Recommendation – *"Be aware that functional deterioration and/or changes to performance of ADLs may be indicator of infection in frail older people.*" Functional deterioration could just as likely (if not more so) be due to dehydration, constipation, electrolyte abnormality, polypharmacy, pain, urinary retention, etc, etc. Primary care need to be encouraged to assess properly and not blame every functional decline on a UTI!	The evidence supports using functional deterioration as a marker for UTI but we acknowledge that there are many other causes. We have added a sentence to the GPP in this section to emphasise the range of other conditions which may cause functional decline.	
	PCIU	It would be helpful in this section to say which symptoms there is evidence for. There is no mention here of evidence around cloudy urine, temperature, suprapubic pain and visible haematuria. The authors may want to consider looking at the following papers: *Arinzon, Z., Shabat, S., Peisakh, A. & Berner, Y. 2012. Clinical presentation of urinary tract infection (UTI) differs with aging in women. Arch Gerontol Geriatr, 55, 145-7.* *Loeb, M., Brazil, K., Lohfeld, L., Mcgeer, A., Simor, A., Stevenson, K., Zoutman, D., Smith, S., Liu, X. & Walter, S. D. 2005. Effect of a multifaceted intervention on number of antimicrobial prescriptions for*	Thank you. Temperature, constipation and tachycardia are already referenced in this section. We have added further details of the evidence for and against specific symptoms derived from the Gbingie et al systematic review. We note that this systematic review included studies which were: • of cohort and cross-	

		suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. BMJ, 331, 669. *Chu, C. 2018. Diagnosis and Treatment of Urinary Tract Infections Across Age Groups. American Journal of Obstetrics and Gynecology.* *Berman, P., Hogan, D. B. & Fox, R. A. 1987. The atypical presentation of infection in old age. Age Ageing, 16, 201-7.* *Loeb, M., Bentley, D. W., Bradley, S., Crossley, K., Garibaldi, R., Gantz, N., Mcgeer, A., Muder, R. R., Mylotte, J., Nicolle, L. E., Nurse, B., Paton, S., Simor, A. E., Smith, P. & Strausbaugh, L. 2001. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. Infect Control Hosp Epidemiol, 22, 120-4.* This section concludes that there is no association between dysuria or urgency and UTI. This is different to PHE guidelines as dysuria can be used as a lone symptom to diagnose UTI. You use a systematic review meta-analysis of weak studies. We suggest the following references: *Arinzon, Z., Shabat, S., Peisakh, A. & Berner, Y. 2012. Clinical presentation of urinary tract infection (UTI) differs with aging in women. Arch Gerontol Geriatr, 55, 145-7.* *Loeb, M., Brazil, K., Lohfeld, L., Mcgeer, A., Simor, A., Stevenson, K., et al. 2005. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. BMJ, 331, 669.* *Chu, C. 2018. Diagnosis and Treatment of Urinary Tract Infections Across Age Groups. American Journal of Obstetrics and Gynecology.* *Loeb, M., Bentley, D. W., Bradley, S., Crossley, K., Garibaldi, R., Gantz, N., et al 2001. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference.*	sectional design; • assessing the diagnostic accuracy of symptoms and/or signs in predicting UTI; • providing a reference standard for confirming diagnosis of infection; • conducted in the outpatient setting of developed countries (e.g. General Practice, nursing homes, and outpatient clinics); and • in patients over 65 years The guideline notes that "*Only one of four studies which contained data from women alone recorded a significant association between urinary incontinence and UTI*" We note that these suggested references are outwith the inclusion period of our literature searches and do not match similar inclusion criteria.	

		Infect Control Hosp Epidemiol, 22, 120-4.		
	CC	Recommendations - Functional deterioration and/or changes to performance of ADLs - need to be careful as this can also be related to other causes - good to highlight but don't think it should be a recommendation as this often drives inappropriate prescribing particularly in care homes where other causes such as dehydration may be the cause I would advise caution here.	The evidence supports using functional deterioration as a marker for UTI but we acknowledge that there are many other causes.	
	AW	The recommendations and the good practice could all be recommendations rather than good guidance?	The good practice points cover areas of standard practice which do not have evidence directly supporting and therefore have a different status to recommendations.	
4.1.3	EMcG	Para 1, line 9 - blood cultures or urine culture?	Thank you We have clarified that this refers to urine cultures.	
	EO	Please could there be an explicit statement that dipstick testing as outlined in Section 3 is appropriate for non-frail elderly women. The guideline implies this but does not state it.	There is insufficient evidence available to support this statement. We have added a comment to clarify this ("*Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years*").	
	VH	Recommendation - urine dipstick in residential care is not recommended. Should this not include those in supported accommodation (ie sheltered housing and housebound frail elderly with significant packages of care)?	Agreed. We have clarified the recommendation.	
	AMT	Recommendation - *Do not use dipstick to diagnose UTI in women in residential care homes.* Are dipsticks then advocated in non-residential women >65? If so, this will increase diagnosis of UTI and antimicrobial consumption in this population as up to 20% of non-residential women will have asymptomatic bacteriuria.	Incidence of asymptomatic bacteriuria varies according to the study, frailty, residential care, comorbitities. Any bacteriuria at any age should be interpreted	

		Recommendation contradicts work conducted in Scotland and the rest of the UK over the last 2 years as well as recent studies published in JAMA which states that 83% of antibiotic use in ASB was inappropriate and primarily driven by dipstick testing. Recommendation – suggest changing the recommendation to read "Send urine culture to confirm antibiotic susceptibility (NOT diagnosis) in women aged 65 years and above started on antibiotics for UTI". This population is most susceptible to UTI and likely to have had prior antibiotic exposure and appropriate targeted therapy is a key stewardship intervention. Current recommendation is likely to discourage appropriate microbiological sampling in this cohort.	in the light of background ASB. We have added a GPP and revised the recommendation to clarify this. See also response to reviewer EO above. Thank you – we have revised this GPP to "Send urine for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI."	
	AW	Only send urine for culture for women >65 years who have been commenced on at start of good practice point on sending culture to confirm.	We do not fully understand this comment, but have revised wording of the GPP to emphasise sending culture before starting antibiotics.	
4.2.1	AP	In this section, I think it is important to mention the importance of regular cleansing, bathing or showering, especially for those who require assistance with their personal care. Regular changes in continence products and underwear should also be highlighted and not just mentioned. If this document is to be used to improve/influence practice, we need to be clearer with ur recommendations.	Thank you. There is limited and conflicting evidence for voiding and hygiene behaviours therefore we are unable to form a recommendation.	
	AW	Other healthcare professionals - continence teams? Care Home liaisons, locally may help with self care in community.	Noted	
4.2.2	CC	Duration of treatment - it would be helpful to see some evidence stated here as GPs struggle with explaining this to patients/relatives.	Thank you. The single RCT which was identified in the literature searches is included here.	
[material moved to section 5.2.1]	AW	Recommendation that prophylactics are reviewed at minimum of 6 monthly intervals. Good practice that patients in care homes have MARS updated and processes in place to discontinue any antimicrobials once course is complete.	Noted. A GPP has been added to the section on treatment of recurrent UTI which indicates duration of prophylactic therapy should be three to six	

			months (see section 5.2.1)	
4.2.3	PCIU	We agree with this section states that there is no evidence for NSAIDs in the treatment of UTI in women over 65. The authors may want to consider this study which showed that NSAIDs may be associated with an increased risk of pyelonephritis. *Kronenberg, A., Butikofer, L., Odutayo, A., Muhlemann, K., Da Costa, B. R., Battaglia, M., et al 2017. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ, 359, j4784.*	Thank you. This study was considered in making recommendations for those under 65 years and is described in Table 3 and section 3.2.2	
	AW	Recommendation re: NSAIDs and other non-antimicrobials to be mindful of renal function, ADR's and polypharmacy in this group.	Thank you We agree, however there is no recommendation for using non-antimicrobials in this group.	
4.2.4	AMT	Cranberry – evidence described in detail – a recommendation or expert consensus statement would be beneficial and if recommended advice about whether it is available on prescription or a self-care product (as per NICE recommendation).	Thank you. The evidence was described in detail due to the conflicting results published in different studies, and, in this case, within the same study based on different definitions of UTI. Section 5.2.4 also has evidence on cranberry in which it is stated that it is not possible to form a recommendation due to the inconsistency of the evidence.	
	AW	Recommendation that cranberry capsules not be routinely advised for this group of patients - lacking evidence.	Noted – see above.	
Section 5 (now located in Section 6)				
5.1.1 **[now 6.1.1]**	AP	No mention of Catheter Passports.	Thank you. We have include a paragraph with information and a GPP about catheter passports.	
	SR	The guidelines for clinical assessment are clear and are appropriate.	Noted, thank you.	
5.1.2 **[now**	SR	Fully agree that urinalysis is not necessary to diagnose CA-UTI.	Noted, thank you.	

6.1.2]				
	VH	Should there not be a "R" recommending that urine dipstick is not performed for patients with indwelling catheters?	The guideline clearly states that no evidence was identified for or against the use of dipstick testing in patients with indwelling catheters and symptoms suggestive of CA-UTI. However, due to the relationship between presence of catheter and presence of bacteriuria, dipstick test results are likely to be positive, irrespective of the presence of infection, so we have added a good practice point to avoid using dipsticks for diagnostic purposes in this group.	
	AW	A clear recommendation not to routinely dipstick in this patient group.	See above.	
5.2.1 **[now 6.2.1]**	SR	I agree that indwelling catheters should be replaced if suspected CA-UTI is evident, all catheter have bacteria and it is rare that a person who is catheterised will have no bacteria present. The replacement may not prevent the use of antibiotic therapy however it may ease some symptoms such as pyrexia, some pain.	Noted. Thank you	
	VH	Last paragraph - evidence is insufficient to recommend catheter replacement to prevent recurrence of CA-UTI...is that what was meant? Replacing catheter when initiating treatment is standard practice...are the guidelines suggesting this should not be done? I am unclear?	Thank you. We have clarified this point. While evidence is lacking we acknowledge that this is current practice and there are theoretical reasons for doing so.	
	AMT	Recommendation, expert consensus statement or good practice point required on catheter removal in CA-UTI diagnosis. Document already links to SAPG algorithm which suggests catheter replacement/removal as does the national catheter passport which advocates replacement/removal within 72 hours of diagnosis. By applying the principles of infection prevention and control, catheter removal should be	Thank you. We have further clarified this point. There is limited and conflicting evidence for changing the catheter. While changing the catheter appears to be a useful intervention there is a lack of evidence on	

		advocated.	when to do this and in practice it may not be possible before starting antibiotics.	
5.2.2 **[now 6.2.2]**	EMcG	3rd last para. This is the first time QALYs have been mentioned. Should they be mentioned in other contexts discussed?	Limited cost effectiveness evidence was identified for this guideline, of which, this was the first study to use QALYs. A further study to report quality-adjusted life days is reported in section 5.2.1	
	JL	(CoI noted in overview- member of ANTiC study team) Rather than 'do not prescribe.. for intermittent self-catheterisation', the evidence would support 'do not *routinely* prescribe' - consider only after full discussion of pros and cons/ temporary benefit.' There will be a few patients who derive benefit from having a rest from severe UTIs.	Thank you. We have revised the wording of this recommendation as suggested.	
	SR	I agree with antimicrobial treatment guidelines.	Noted, thank you.	
5.2.3 **[now 6.2.3]**	SR	Not indicated for CA-UTI.	No evidence was identified to provide data on pharmacological non-antimicrobial management of CA-UTI.	
	BHUK	We are surprised that the indication of prophylaxis for self-catheterisation is not encouraged. Whilst Prof James Malone Lee is a proponent of large doses of antibiotic prophylaxis and not everyone agrees with his methods. It is known practice for at least some prophylaxis on a rotational basis, this view is supported by microbiologists. *Swamy, S., Barcella, W., De Iorio, M., Gill, K., Khasriya, R., Kupelian, A. S.,. & Malone-Lee, J. (2018).*	We note that this is a case series of patients with recalcitrant bladder pain, which reflects complicated UTI and outwith the scope of this guideline.	
Section 6 (now Section 7)				
6.1 **[now**	EMcG	What is the evidence for healthy lifestyle advice (diet, exercise, sleep) for prevention of UTI - has not been	Primary prevention of UTI in patients without symptoms is outwith	

7.1]		mentioned before.	the remit of this guideline.	
	SR	Very informative section for professionals to use when UTI with patients/careers. Set out in bullet points means it will be easy to follow and allows professionals the opportunity to expand on each section.	Noted, thank you.	
	AW	Explain rationale for not prescribing as applicable/ delayed prescribing.	Thank you. We have added this point to ensure the reasons for a delayed prescribing approach are discussed with the patient.	
	PI	Appreciate the checklist is not exhaustive however could we add voiding behaviours and hygiene in her as described in section 3.2.1?	Thank you. We have added these terms.	
6.3	SR	Very informative sources of further information provided.	Noted, thank you.	