National Institute for Health and Clinical Excellence

Lower Urinary Tract Symptoms

Guideline Consultation Comments Table

28 August 2009 – 23 October 2009

Status	Organisation	Order no.	Version	Page no	Line no	Comment	Response
SH	American Medical Systems, UK-Ltd.	1	Full	62	30	Statement - "If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a centre specialising in the technique." Comment – We propose that the current evidence base on KTP, or 532 nm, laser vapourisation, as presented in the attached document of our independent analysis of the literature on 532 nm laser vapourisation versus TURP trials and review of the analysis by Lourenco et al. (LOURENCO2008), is such that 532 nm laser vapourisation can be offered as an option for surgery in managing LUTS due to BPE in a manner similar to HoLEP (See attached review).	Thank you for this comment and for the submission of your analysis. After careful consideration we do not agree that 532nm laser vaporisation merits separate consideration to other laser vaporisation techniques and do not agree that it should be given equivalent recommendation to TURP and HoLEP without a stronger evidence base derived from RCTs. Your clinical review included six studies which do not meet our inclusion criteria (preliminary results only or non-randomised studies and therefore subject to bias) and one foreign language paper. The other paper (Horasanli) was included in our review. The studies in your economic review were excluded because they were not as well conducted as Lourenco 2008 and Keoghane 2000 (the only two studies included in our review) or they are not published studies. To assess the real cost-effectiveness of interventions for the UK NHS we prefer UK studies. In detail these are the reasons for exclusion of

							the studies included in your review: - Bouchier-Hayes: study from Australia, costs only, not clear what components were considered in the calculation. - Stovsky: study from USA, assumption was that KTP was performed as a daycase procedure and TURP as an inhospital procedure. The authors had financial interest or relationship with Laserscope. - Goh: only published as an abstract, costs only. - Tugcu: study from Turkey, costs only, not clear what components were considered in the calculation. - Liatsikos: only published as an abstract, costs only. After careful consideration we have decided not to consider your cost model because it was not based on RCT studies and it did not evaluate the effectiveness of interventions. In addition, some important cost components (i.e. cost of equipment) were missing. Despite the fact that the cost of KTP might have been underestimated, your cost analysis shows virtually no difference between the two interventions in terms of costs. In conclusion, we do not think KTP should be recommended as an alternative to TURP.
SH	American Medical Systems, UK-Ltd.	2	Full	68	16	Statement - “If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer laser vapourisation, bipolar TUVP or monopolar or bipolar transurethral vapourisation resection of the prostate (TURVP) as part of a clinical trial” Comment - The use of the term “laser vapourisation” here and throughout the document refer to multiple	Thank you for this comment. After careful consideration we have concluded that there remains insufficient evidence to single out one vaporisation modality from another and that the recommendation relating to these technologies should remain the same but apply generically to the whole group.

						types of lasers including: • Neodymium-doped-yttrium-aluminium-garnet (Nd:YAG) • Potassium-titanyl-phosphate (KTP) • Holmium as stated on page 222 line 1. All of these lasers affect and penetrate tissue differently. • Nd:YAG (1064 nm) 4 mm penetration depth, not affected by water or hemoglobin • KTP (532 nm) 1 mm penetration depth, absorbed by hemoglobin • Holmium (2100 nm) 0.8 mm penetration depth, absorbed by water Thus, attempting to pool clinical results from each of these technologies can result in analyses that misrepresent vapourisation technology on the market today. We feel that KTP and/or holmium laser vapourisation should be considered separately from Nd-YAG. (See also #17) KTP laser vapourisation on its own has established clinical efficacy and safety similar to or better than TURP such that clinical trials to show these outcomes are unnecessary. (See comments #4, #13 and #14) References – 1. Smith JA Jr, Stein BS, Censon RC Jr. Lasers in urologic surgery (3rd ed.): Urethra. St. Louis, Mosby, 1994, chap. 1.	
SH	American Medical Systems, UK-Ltd.	3	Full	68	c	Statement - “Current evidence on the safety and short-term efficacy of potassium-titanyl-phosphate (KTP) laser vaporisation of the prostate for benign prostatic obstruction appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance. (NICE interventional procedure guidance 120). However research is necessary to understand its role compared with other treatments.”	Thank you for your comment and submitted documents. After careful consideration of your own clinical and economic reviews and your cost model we have decided that they do not meet our inclusion criteria. Your clinical review included six studies which do not meet our inclusion criteria (preliminary results only or non-randomised studies and

						Comment - Both short- and long-term efficacy and safety of KTP/532 nm laser vapourisation have been demonstrated in the literature out to 5 years (See below). Current randomized and nonrandomized comparative trials published on KTP laser vapourisation versus TURP are not considered or fully utilized by the guideline (see below). These have shown that the efficacy and safety of KTP laser vapourisation are similar to or surpass that of TURP in patients with similar demographics (See attached review). The use of this procedure under the restriction of clinical trials is unnecessary and will greatly limit physician and patient access to this beneficial procedure without due cause. Sufficient research data already exists such that the use of 532 nm laser vapourisation has been adopted worldwide with over 375,000 patients treated. Published KTP laser vapourisation literature with 5 year data – 1. Hai MA. Photoselective vaporization of prostate: five-year outcomes of entire clinical patient population. Prostatic Dis. 2008;73(4);807-10. 2. Te AE, Malloy TR, Stein BS, Ulchaker JC, Nseyo UO, Hai MA. Impact of prostate-specific antigen level and prostate volume as predictors of efficacy in photoselective vaporization prostatectomy: analysis and results of an ongoing prospective multicentre study at 3 years. BJU Int 2006 Jun;97(6):1229-1233. 3. Malek RS, Kuntzman RS, Barrett DM. Photoselective potassium-titanyl-phosphate laser vaporization of the benign obstructive prostate: observtions on long-term outcomes. J Urol 2005;174(4 Pt 1):1344-1348. 4. Ruszat R, Seitz M, Wyler SF, Abe C, Rieken	therefore subject to bias) and one foreign language paper. The other paper (Horasanli) was included in our review. The studies in your economic review were excluded because they were not as well conducted as Lourenco 2008 and Keoghane 2000 (the only two studies included in our review) or they are not published studies. To assess the real cost-effectiveness of interventions for the UK NHS we prefer UK studies. In detail these are the reasons for exclusion of the studies included in your review: - Bouchier-Hayes: study from Australia, costs only, not clear what components were considered in the calculation. - Stovsky: study from USA, assumption was that KTP was performed as a daycase procedure and TURP as an inhospital procedure. The authors had financial interest or relationship with Laserscope. - Goh: only published as an abstract, costs only. - Tugcu: study from Turkey, costs only, not clear what components were considered in the calculation. - Liatsikos: only published as an abstract, costs only. After careful consideration we have decided not to consider your cost model because it was not based on RCT studies and it did not evaluate the effectiveness of interventions. In addition, some important cost components (i.e. cost of equipment) were missing. Despite the fact that the cost of KTP might have been underestimated, your cost analysis shows virtually no difference between the two

						M, Reich O, Gasser TC, Bachmann A. GreenLight laser vaporization of the prostate: single-center experience and long-term results after 500 procedures. Eur Urol 2008;54(4):893-901. Published KTP laser vapourisation literature - 5. Bouchier-Hayes DM, Anderson P, Van Appledorn S, Bugeja P, Costello AJ. KTP laser versus transurethral resection: early results of a randomized trial. J Endourol 2006 Aug;20(8):580-585. 6. Bachmann A, Schürch L, Ruszat R, Wyler SF, Seifert HH, Müller A, Lehmann K. Photoselective vaporization (PVP) versus transurethral resection of the prostate (TURP): a prospective bi-center study of perioperative morbidity and early functional outcome. Eur Urol 2005;48(6):965-972. 7. Tasci AI, Tugcu V, Sahin S, Zorluoglu F. Photoselective vaporization of the prostate versus transurethral resection of the prostate for the large prostate: a prospective nonrandomized bicenter trial with 2-year follow-up. J Endourol 2008;22(2):347-353. 8. Tugcu V, Tasci AI, Sahin S, Zorluoglu F. Comparison of photoselective vaporization of the prostate and transurethral resection of the prostate: a prospective nonrandomized bicenter trial with 2-year follow-up. J Endourol 2008;22(7):1-7. 9. Bouchier-Hayes. Photoselective vaporization of the prostate - towards a new standard. Prostate Cancer Prostatic Dis. 2007;10:S10-14. (Study update to #5) 10. Nomura H, Seki N, Yamaguchi A, Naito S. Comparison of photoselective vaporization and standard transurethral resection of the prostate on urodynamics in patients with benign	interventions in terms of costs. This would justify not recommending KTP laser vaporisation as it is less effective than TURP at improving symptom score and Qmax (see our clinical review). In conclusion, we do not think KTP should be recommended as an alternative to TURP.

						prostatic hyperplasia. Int J Urol. 2009 Aug;16(8):657-62.14. 11. Ruszat R, Wyler SF, Seitz M, Lehmann K, Abe C, Bonkat G, Reich O, Gasser TC, Bachmann A. Comparison of potassium-titanyl-phosphate laser vaporization of the prostate and transurethral resection of the prostate: update of a prospective non-randomized two-centre study. BJU Int. 2008 Nov;102(10):1432-9. (Study update to #6) 12. Yang Y, Hong BF, Fu WJ, Xu Y, Chen YF, Zhang CE. A comparative study on the photoselective vaporization of the prostate and transurethral electrovaporization resection of prostate for the treatment of benign prostatic hyperplasia. Zhonghua Wai Ke Za Zhi. 2007;45(14):951-3.	
SH	American Medical Systems, UK-Ltd.	4	Full	77	21	Statement – "Research recommendation on green light laser prostatectomy: What is the clinical and cost effectiveness of green light laser prostatectomy compared to TURP in men with moderate to severe bothersome LUTS considering surgery for bladder outlet obstruction?" Comment – Over 400 articles and abstracts have been published to date on GreenLight laser. (See attached product bibliography) Clinical efficacy and safety compared to TURP have been clearly demonstrated as discussed in comment #3. Further study on cost-effectiveness of GreenLight laser prostatectomy would add beneficially to existing literature but should not constrain the use of KTP laser vapourisation to clinical trials only (See comment #15).	Thank you for this comment. After careful consideration we came to the conclusion that we disagree. The GDG considers the current evidence poor and recommends that laser vaporisation techniques including KTP laser vaporisation should be assessed in the context of a RCT.
SH	American Medical Systems, UK-Ltd.	5	Full	77	25	Statement – "The evidence base is inadequate to give clear guidance. This research would help plan future guidance on the use of green light laser prostatectomy for men with LUTS who are having surgery. The potential advantages of reduced blood loss, shorter hospital stay and earlier return to normal activities	Thank you for this comment. After careful consideration we came to the conclusion that we do not agree. The GDG considers the current evidence poor and recommends that laser vaporisation techniques including KTP laser vaporisation should be assessed in the

						make Green Light Laser prostatectomy attractive to patients and healthcare providers although there is uncertainty around degree of symptom improvement and improvement in quality of life in the short and longer term. The study design should be a randomised controlled trial." Comment – See comment #3. Randomized and nonrandomized comparative trials on KTP laser vapourisation compared to TURP have already shown comparable symptom and quality of life improvements as demonstrated by the AUA or IPSS questionnaire. Data from an independent analysis of these trials has shown that pre-operative as well as post-operative IPSS and QOL scores are similar between KTP laser vapourisation and TURP in the short-term as well as out to 24 months (See comments #13 and #14 and attached review). In addition, both short- and long-term efficacy and safety of KTP laser vapourisation have been demonstrated in the literature out to 5 years (see comment #3). Several randomized trials are currently ongoing with results expected sometime next year. Randomized trials exclude high risk patients which are growing in numbers due to the aging population. For patients not treatable by TURP due to health risk factors (i.e. anticoagulation therapy, large gland, cardiovascular disease, etc.), GreenLight offers the potential for treatment. This impact cannot be studied within a randomized trial and should be considered separately.	context of a RCT.
SH	American Medical Systems, UK-Ltd.	6	Full	200	18	Statement – "Laser vapourisation:" Comment – The only laser referenced in this section is the GreenLight 532 nm laser. However, in the clinical evidence sections, clinical data for holmium, Nd-YAG and hybrid (KTP/Nd-YAG) lasers are also included. A clear definition of all lasers that fall under the heading of "laser vapourisation" would be helpful.	Thank you for your comment. We agree. We have added a clear definition of laser terminology in the text.

SH	American Medical Systems, UK-Ltd.	7	Full	200	21	Statement – "Now KTP (Green light) laser, generated by passing the Nd-YAG generated beam through a potassium-titanyl-phosphate (KTP) crystal, is used." Comment - Our suggestion is to replace this sentence with the following: "Now photoselective vapourisation of the prostate (PVP) is used which emits 532 nm laser energy created by doubling the frequency of Nd-YAG laser energy."	Thank you for your comment, We agree. We have altered the wording to say "Now 532 nm KTP laser is used, generated by passing the Nd-YAG generated beam through a potassium-titanyl-phosphate (KTP) crystal, The light is absorbed by haemoglobin and results in minimal tissue penetration (1mm)".
SH	American Medical Systems, UK-Ltd.	8	Full	200	24	Statement – "Requires similar anaesthesia and operating conditions to TURP with operating time increased by a factor of approximately 1.5." Comment – KTP laser vapourisation does not require the same anaesthesia requirements as TURP as cases can be done under general, regional, spinal, or even light sedation as demonstrated in the literature which is different to TURP. Thus the removal of "anaesthesia and" is recommended. Reference – 1. Pedersen JM, Romundstad PR, Mjønes JG, Arum CJ. 2-year followup pressure flow studies of prostate photoselective vaporization using local anesthesia with sedation. J Urol 2009;181(4):1794-1799. In addition, based on the analysis of comparative literature, TURP appears faster but not 1.5 times fast when accounting for differences in per-operative gland size. The findings in the seven articles in our analysis show a total standardized inverse variance weighted mean difference for procedure time of 1.02 minutes, 95% confidence interval (CI) (0.86,1.18), and prostate volume (PV) was 0.15 ml (95% CI -0.01,0.31) with KTP laser vapourisation procedures taking longer than TURP and treating larger prostates (See attached	Thank you for your comments. We disagree on your first point and we think KTP laser vaporisation and TURP require similar anaesthesia. We agree we cannot be too specific on the length of procedures and we have altered the wording to say "require similar anaesthesia and operating conditions to TURP but with longer operating times"

						review).	
SH	American Medical Systems, UK-Ltd.	9	Full	203	12	Statement – "We searched for RCT evidence comparing the effectiveness of different surgical interventions for lower urinary tract symptoms." Comment - We would like to comment on the decision to search for only randomized controlled trials (RCT) as part of the collection of clinical evidence for comparing effectiveness of the different surgical options. While level I evidence, RCTs, are the top standard for clinical trials, they are not always feasible or advantageous. In the case of BPE/BPH, using only RCTs excluded evidence from trials on patient populations not treated with TURP or typically not the focus or inclusion into RCTs such as large gland, high risk patients and those in urinary retention.	Thank you for your comments. For intervention clinical questions, we searched for randomised controlled trials because the results from these designs have the lowest risk of bias, and therefore we are more confident in using this evidence to support our recommendations. We understood the limitations in conducting trials on surgical interventions have included non-blinded studies. Therefore, we believe that randomised controlled trials in of these interventions have not been unfairly excluded. We disagree that populations not treated with TURP were excluded. In fact, we search for studies which compared the safety and efficacy of different types of surgical interventions (as shown in matrices in Section 8.2) of the full guideline, surgical interventions versus conservative treatments (Chapter 11) or surgical interventions versus medical therapy (Chapter 12). Therefore, it is untrue that trials from populations not typically treated with TURP were not included. It is highly unlikely that if any randomised controlled trial evidence in these populations were available that we would not have found them. The search terms used are detailed in Appendix C.
SH	American Medical Systems, UK-Ltd.	10	Full	221	2	Statement – Table 8-99 Laser vapourisation vs. TURP – Clinical study characteristics Comment – Despite the inclusion of only two KTP laser vapourisation studies (references 28 and 103): • Reference 28 - Bouchier-Hayes DM, et al. KTP laser versus transurethral resection: early	Thank you for your comment. We have reviewed the studies mentioned to ensure that no data was missed. Bouchier-Hayes 2006 (reference 28) reports 6 week endpoints. The 2007 study reports preliminary data as not all of the patients had

						results of a randomized trial. J Endourol 2006 Aug;20(8):580-585. • Reference 103 - Horasanli K, et. al. Photoselective potassium titanyl phosphate (KTP) laser vaporization versus transurethral resection of the prostate for prostates larger than 70 ml: a short-term prospective randomized trial. Urology 2008;71(2):247-251. and two hybrid device studies (KTP/Nd-YAG) (references 38 and 235): • Reference 38 - Carter A, et. al. A prospective randomized controlled triral of hybrid laser treatment or transurethral resection of the prostate, with a 1-year follow-up. BJU Int. 1999 Feb;83(3):254-259. • Reference 235 - Shingleton WB, et. al. A randomized prospective study of laser ablation of the prostate versus transurethral resection of the prostate in men with benign prostatic hyperplasia. Urology 1999;54(6):1017-1021. in this table, some symptom score, QOL and Qmax data were available but not included in the clinical evidence. Data omissions consist of the following: Reference 28 • IPSS, QOL and Qmax data now published in: Bouchier-Hayes. Photoselective vaporization of the prostate - towards a new standard. Prostate Cancer Prostatic Dis. 2007;10:S10-14. Reference 38 • IPSS and Qmax at 1 year, Qmax at longest available follow up Reference 235 • IPSS and Qmax at 3 months and 6 months	reached the 12 month end point. The symptom score results are a mixture of different end point times and can not be included in our meta-analysis. Shingleton 2002 (reference 235) does report the mean symptom score at 3 months but without standard deviations we are unable to combine this with the other data to include this in the meta-analysis. Carter 1999 (reference 38) – Thank you for drawing our attention to the missing data from this study. The paper reports the symptom score and Qmax results in graphical form and we have estimated the results. We have updated the evidence tables and results in the full guideline to include this study.

SH	American Medical Systems, UK-Ltd.	11	Full	221	2	Statement - Table 8-99 Laser vapourisation vs. TURP – Clinical study characteristics Comment – Reporting of adverse event results were done inconsistently with KTP laser vapourisation data. This includes the following omissions: Reference 28 • Urinary infection, reoperation Reference 38 • Urinary infection	Thank you for your comment. We have checked the reporting of the adverse event results for KTP laser vaporisation. Urinary infection does include data from references 28 and 38. The studies listed were incorrect and we have amended this so that they are cited. Thank you for bringing our attention to the missing study data for reoperation. We have added reference 38 data into the GRADE analysis, evidence tables and forest plots.
SH	American Medical Systems, UK-Ltd.	12	full	223	9	Statement – Literature used for CEA. Comment – The analysis by Lourenco et al. (LOURENCO2008) was forced to pool laser vapourisation outcomes and most articles included in the analysis were of Nd-YAG studies. Furthermore, NdYAG/532nm hybrid laser treatments and a single 532nm paper were included but were seldom used in the analyses. Therefore the analysis is pertinent to 1064 laser vapourisation and not to 532 nm laser vapourisation. Therefore, this is not an accurate cost-effectiveness analysis for 532 nm.	Thank you for your comment. The GDG believe the effectiveness of laser treatments depend on their mode of action (e.g. vaporisation, coagulation, etc) and it would be inappropriate to compare every single type of laser to each other, Therefore the GDG has decided to consider laser vaporisation as a whole intervention and single types of lasers were not reviewed. Therefore no separate analysis is reported for 532 nm laser.
SH	American Medical Systems, UK-Ltd.	13	Full	223	23	Statement – “There is no statistically significant difference between laser vapourisation and TURP in improving… • symptom score at 3 months, 1 year, 2 years and at 5 years or longer follow up • IPSS QoL score at 3 months, 1 year and at 5 years or longer follow-up” “laser vapourisation is less effective than TURP in improving… • symptom score at 6 months and 3 years follow up	Thank you for your comment. After careful consideration of your own clinical review we have decided that we do not agree that this statement should be changed. The conclusions of your clinical review are based on studies that do not meet our inclusion criteria and would not be considered in our review.

						• IPSS QoL score at 3 years follow up • Qmax at 3 months follow up but there is no statistically significant difference at longest available follow up" Comment – We conducted an independent analysis of all randomized (2) and nonrandomized comparative trials (5) evaluating KTP laser vapourisation and TURP clinical outcomes to date (see attached review). Key findings on KTP laser vapourisation clinical outcomes were the following: • Baseline and post-operative values for Qmax, IPSS and IPSS QoL were comparable to TURP, i.e. not statistically significant • Improvement for Qmax was slightly favourable for KTP laser vapourisation and IPSS was slightly favourable for TURP, but neither were statistically significant • Improvement in IPSS QoL was the same for both Thus, without clinical and statistical significance, both treatments would appear to be equally effective. We recommend removing the statements of "Laser vapourisation is less effective than TURP in improving…"	
SH	American Medical Systems, UK-Ltd.	14	Full	223	23	Statement – "Fewer patients treated with laser vapourisation compared to TURP experienced transfusions or strictures. More patients treated with laser vapourisation compared to TURP experienced urinary retention. There is no statistically significant difference between laser vapourisation and TURP in the number of patients with all cause mortality, UTI, reoporation, incontinence, TUR syndrome or retrograde ejaculation."	Thank you for your comment. After careful consideration of your own clinical review we have decided that we do not agree that this statement should be changed. The conclusions of your clinical review are based on studies that do not meet our inclusion criteria and will not be considered in our review.

						Comment - We conducted an independent analysis of all randomized (2) and nonrandomized comparative studies (5) evaluating KTP laser vapourisation and TURP adverse event outcomes to date (See attached review). Key findings on KTP laser vapourisation adverse event outcomes compared to TURP were the following: • Two events occurred at higher rates with KTP laser vapourisation (risk ratio = RR): ➢ acute urinary retention (RR = 1.27) ➢ dysuria (RR = 1.71) • Other adverse events were not reported with KTP laser vapourisation, RR = 0, for: ➢ capsular perforation ➢ erectile dysfunction ➢ hematuria ➢ TUR syndrome • Several other events occurred at much lower rates with KTP laser vapourisation, RR < 1: ➢ clot retention (R = 0.05) ➢ urethral stricture or bladder neck contracture (R = 0.46) ➢ excessive bleeding (R = 0.19) ➢ urinary incontinence (R = 0.28) ➢ blood transfusion (R = 0.07) ➢ retrograde ejaculation (R = 0.50) We suggest these data be taken into consideration when making these statements.	
SH	American Medical Systems, UK-Ltd.	15	Full	223	23	Statement – "Economic TURP is less costly and more effective than laser vapourisation." Comment – Based on the analysis presented in comments 13 and 14 and the lack of statistically significant findings in the clinical evidence statements, there is not enough evidence to support the conclusion that TURP is more effective than laser vapourisation. Additionally, we conducted a review of all cost analysis	Thank you for your comment and submitted documents. After careful consideration of your own clinical and economic reviews and your cost model we have decided that they do not meet our inclusion criteria. Your clinical review included six studies which do not meet our inclusion criteria (preliminary results only or non-randomised studies and

						data available on KTP laser vapourisation and a critique of the Lourenco analysis (reference 140 or LOURENCO2008)(see attached review). The Keoghane study (reference 118) did not include any KTP532 nm laser vapourisation studies and thus is not directly applicable based on the arguments presented in comment #1. The main cost analysis findings from this review were the following: • Bouchier-Hayes (randomized) – KTP 22% less than TURP (3368.12 vs. 4291.68 AU$, p<0.005) • Stovsky (Medicare data) – KTP less costly out to 24 months • Per case: $2852 KTP vs. $3748 TURP • Per patient: $3589 KTP vs. $4927 TURP (24 months) • Goh – Outpatient hospital costs similar, $4313.99 vs. $4578.67 – Increased greatly for TURP inpatients more than 532 nm laser inpatients, $10,265 vs. $7065, p<0.05 – Similar outcomes • Tugcu – KTP cost of treatment higher than TURP, $3500 vs. $1000 • Liatsikos – 532 nm laser more cost effective than TURP with a true cost of €1572 vs. €1782 respectively according to the NHS, including sickness disability this increased to €2471 and €1790 – Reimbursement was €554 for TURP and €1311 for 532 nm laser – Loss of productivity cost to patient was €1917 for TURP and €671 for 532 nm laser	therefore subject to bias) and one foreign language paper. The other paper (Horasanli) was included in our review. The studies in your economic review were excluded because they were not as well conducted as Lourenco 2008 and Keoghane 2000 (the only two studies included in our review) or they are not published studies. To assess the real cost-effectiveness of interventions for the UK NHS we prefer UK studies. In detail these are the reasons for exclusion of the studies included in your review: - Bouchier-Hayes: study from Australia, costs only, not clear what components were considered in the calculation. - Stovsky: study from USA, assumption was that KTP was performed as a daycase procedure and TURP as an inhospital procedure. The authors had financial interest or relationship with Laserscope. - Goh: only published as an abstract, costs only. - Tugcu: study from Turkey, costs only, not clear what components were considered in the calculation. - Liatsikos: only published as an abstract, costs only. After careful consideration we have decided not to consider your cost model because it was not based on RCT studies and it did not evaluate the effectiveness of interventions. In addition, some important cost components (i.e. cost of equipment) were missing. Despite the fact that the cost of KTP might have been underestimated, your cost analysis shows virtually no difference between the two

						The main critiques of the Lourenco analysis include the following: • Only included randomized studies • Additional data (6 studies) published since cut-off date of September 2006 • Outcomes based on pooled laser vapourisation data from 11 studies (See comment #2): ➢ Nd:YAG (7) ➢ KTP/Nd-YAG (2) ➢ KTP (1) ➢ Holmium (1) • KTP outcomes not consistently used in analyses • Results not supported by other KTP vs. TURP studies (See comment #3) Lastly – as it is recognized that cost-effectiveness may differ depending on the local cost structure we have developed a cost model that can be adjusted according to site specific requirements. Using UK data in this model it shows that when treating 100 BPE patients with KTP/532 nm laser vapourisation there is a monetary benefit of 2.591,52 £ over TURP (See attached cost model).	interventions in terms of costs. This would justify not recommending KTP laser vaporisation as it is less effective than TURP at improving symptom score and Qmax (see our clinical review). In conclusion, we do not think KTP should be recommended as an alternative to TURP.
SH	American Medical Systems, UK-Ltd.	16	Full	278	1	Statement - "If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation, or holmium laser enucleation of the prostate (HoLEP)." Comment – Based on the supporting clinical, safety and cost-effectiveness data presented herein for KTP laser vapourisation compared to TURP (see comment #3), we recommend adding KTP laser vapourisation to the list of surgical options for men suffering from LUTS due to BPE (See comment #5).	Thank you for your comment and submitted documents. After careful consideration of your own clinical and economic reviews and your cost model we have decided that they do not meet our inclusion criteria. Your clinical review included six studies which do not meet our inclusion criteria (preliminary results only or non-randomised studies and therefore subject to bias) and one foreign language paper. The other paper (Horasanli) was included in our review.

							The studies in your economic review were excluded because they were not as well conducted as Lourenco 2008 and Keoghane 2000 (the only two studies included in our review) or they are not published studies. To assess the real cost-effectiveness of interventions for the UK NHS we prefer UK studies. In detail these are the reasons for exclusion of the studies included in your review: - Bouchier-Hayes: study from Australia, costs only, not clear what components were considered in the calculation. - Stovsky: study from USA, assumption was that KTP was performed as a daycase procedure and TURP as an inhospital procedure. The authors had financial interest or relationship with Laserscope. - Goh: only published as an abstract, costs only. - Tugcu: study from Turkey, costs only, not clear what components were considered in the calculation. - Liatsikos: only published as an abstract, costs only. After careful consideration we have decided not to consider your cost model because it was not based on RCT studies and it did not evaluate the effectiveness of interventions. In addition, some important cost components (i.e. cost of equipment) were missing. Despite the fact that the cost of KTP might have been underestimated, your cost analysis shows virtually no difference between the two interventions in terms of costs. In conclusion, we do not think KTP should be recommended as an alternative to TURP.

SH	American Medical Systems, UK-Ltd.	17	Full	282	1	Statement - "If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer laser vapourisation, bipolar TUVP or monopolar or bipolar transurethral vapourisation resection of the prostate (TURVP) as part of a clinical trial" Comment – Based on the ample research already published supporting similar clinical efficacy, safety and cost-effectiveness between KTP laser vapourisation and TURP (see comment #3), and we recommend that KTP laser vapourisation be offered as part of the surgical management for BPE without the restriction of clinical trials. Similar clinical efficacy, improved safety, proven durability, decreased catheterization and hospital times, and fast learning curve have all led to the worldwide adoption of KTP laser vapourisation (See comments #5, #13, #14). We suggest that the most efficient means for acquiring additional country specific cost-effectiveness data would be from conducting a cost analysis of existing cases done in the UK at sites performing both TURP and GreenLight laser vapourisation (See comments #2 and #15).	Thank you for this comment. After careful consideration we do not agree that there is sufficient evidence to justify changing this recommendation. A cost-utility analysis alongside an RCT is the best way to assess the cost-effectiveness as it is less subject to bias.
SH	American Medical Systems, UK-Ltd.	18	Appendix H – IPSS symptom score sheet	718		Statement - "A recent NCCHTA commissioned systematic review suggests that TURP should remain the standard of care and specifically that green Light laser was unlikely to be cost-effective in the economic model and thereby arguing against its unrestricted use in the NHS until further evidence of effectiveness and cost-reduction is obtained." Comment – The references for this statement include the following: 1. Armstrong N, Vale L, Deverill M, Nabi G, McClinton S, N'Dow J, Pickard R. Surgical treatments for men with benign prostatic enlargement: cost effectiveness study. BMJ. 2009 Apr 16;338:b1288. (Guideline Ref	Thank you for your comment. The GDG has decided to consider laser vaporisation techniques as a single intervention and therefore we have not analysed different types of laser techniques separately.

						ID:ARMSTRONG2009). 2. Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R et al. Systematic review and economic modeling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement. Health Technology Assessment 2008;12(35):iii-169. (Guideline Ref ID: LOURENCO2008B) 3. Lourenco T, Pickard R, Vale L, Grant A, Fraser C, MacLennan G, N'Dow J, Benign Prostatic Enlargement Team. Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomized controlled trials. BMJ 2008 Jun 30;337:a449. (Guideline Ref ID: LOURENCO2008) 4. Lourenco T, Pickard R, Vale L, Grant A, Fraser C, MacLennan G, N'Dow J, Benign Prostatic Enlargement Team. Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systemative review of randomized controlled trials. BMJ 2008 Jun 30;337:a449. (Guideline Ref ID: LOURENCO2008A) Based on the critique of the Lourenco analysis (LOURENCO2008) presented in comment #15 and the attached review, the flaws of this study are carried over into the Armstrong analysis (ARMSTRONG2009). In addition, the Armstrong analysis biases the outcome by: • Treated urinary incontinence was the only complication included in the cost analysis • Only randomized studies were included with a lack of consideration for all other comparative and single-arm studies (See comment #3) • A generalization of conclusions for laser vapourisation to KTP laser vapourisation based primarily on Nd-YAG data which is inappropriate based on the arguments	

						provided in comment #2 Thus the conclusions of the clinical and cost-effectiveness of KTP laser vapourisation should not be based upon these analyses as the data applies more specifically to Nd-YAG results than to KTP. The information provided demonstrates that any conclusion for laser vapourisation must be made specific to the technology and not generalized to lasers as a group.	
SH	American Medical Systems, UK-Ltd.	19	Appendix H – IPSS symptom score sheet	718		Statement - "Proposed research can be carried out in a realistic timescale and at an acceptable cost. There are no ethical issues." Comment –According to personal communication with sites, current randomized trials are facing challenges enrolling patients such as in similar government funded trials (i.e. France and Canada) because patients do not want to be randomized and prefer KTP laser vapourisation therapy once fully informed about the risks of surgical complications.	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree that randomisation will be a problem. We appreciate in every RCT there are difficulties in recruiting but we still think it is important to have reliable and unbiased evidence to make strong recommendations in the future. We think no other type of study could provide evidence of sufficiently high quality to be able to compare the relative effectiveness and risk of procedures.
SH	American Medical Systems, UK-Ltd.	20	Full	General		Attachments: one is a review of the literature detailed in the guidance and the second is a cost model of GreenLight Laser Vapourisation vs. TURP. We have added these two documents as attachments following our comments. We have also included the Greenlight bibliography as a separate document.  American Medical Systems UK.doc  Greenlight product bibliography.doc	Thank you for your comment and submitted documents. After careful consideration of your own clinical and economic reviews and your cost model we have decided that they do not meet our inclusion criteria. Your clinical review included six studies which do not meet our inclusion criteria (preliminary results only or non-randomised studies and therefore subject to bias) and one foreign language paper. The other paper (Horasanli) was included in our review. The studies in your economic review were excluded because they were not as well conducted as Lourenco 2008 and Keoghane 2000 (the only two studies included in our review) or they are not published studies.

							To assess the real cost-effectiveness of interventions for the UK NHS we prefer UK studies. In detail these are the reasons for exclusion of the studies included in your review: - Bouchier-Hayes: study from Australia, costs only, not clear what components were considered in the calculation. - Stovsky: study from USA, assumption was that KTP was performed as a daycase procedure and TURP as an in hospital procedure. The authors had financial interest or relationship with Laserscope. - Goh: only published as an abstract, costs only. - Tugcu: study from Turkey, costs only, not clear what components were considered in the calculation. - Liatsikos: only published as an abstract, costs only. After careful consideration we have decided not to consider your cost model because it was not based on RCT studies and it did not evaluate the effectiveness of interventions. In addition, some important cost components (i.e. cost of equipment) were missing. Despite the fact that the cost of KTP might have been underestimated, your cost analysis shows virtually no difference between the two interventions in terms of costs. In conclusion, we do not think KTP should be recommended as an alternative to TURP.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	1	FULL	GENERAL		The ACA would like some clarity on who should be providing initial assessment as feedback from the implementation meeting suggested that this would be done by GP's rather than primary care continence	Thank you for your comment. We have used the term 'initial assessment' as a generic term. We feel that it does not matter which healthcare provider performs this assessment

						services and the association is concerned that GP's will not be able to devote the time required to do these assessments adequately (even with training) which will result in unnecessary secondary referral, financial wastage and poor care.	provided that they are competent to do so. For the majority of men, this may indeed be their general practitioner but this responsibility may vary depending upon local healthcare provision. Details on service provision are outside the scope of this guideline. However, we have added 'initial' and 'specialist assessment' definitions to the glossary and the NICE version to clarify what we mean by these terms.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	2	FULL	62	20	Providing containment products at initial assessment runs the risk of giving the patient the subliminal message that their incontinence is untreatable with containment being the only option and may reduce rather than enhance QOL. Assessment for appropriate products is also time consuming and must be got right to avoid unnecessary financial wastage and provide dignified options. Pads are not currently prescribable items and with budgets for these currently with PCT's the provision for financing this would have to be carefully considered as PCT's will not relinquish monies to be managed elsewhere .	Thank you for your comment. We agree and have amended the recommendation to read: Offer men with storage LUTS (particularly incontinence) temporary containment products (for example, pads or collecting devices) to achieve social continence until a diagnosis and management plan has been discussed.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	3	FULL	96	1 4.10. 4	ACA are concerned that not providing patients with a post void residual volume assessment at initial assessment will result in unnecessary misdiagnosis and potential complications e.g. when anticholinergic are prescribed for OAB and some degree of retention is present, where undiagnosed MS or missed congenital problems might be the course of the LUTS. To some extent this links back to the first point of clarity around initial assessment but it was felt that this should not be left until secondary referral.	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree that this should be changed. There was no evidence to support that these tests provide any additional benefit at initial assessment.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	4	FULL	96	1 4.10. 4	Where patients report voiding difficulties ACA feel that flow studies should be offered before secondary referral as this does add important information to the whole assessment picture and compliment the findings of DRE and I-PSS' as many patients have difficulty completing scores sheets accurately .	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree that this should be changed. There was no evidence to support that flow studies are useful tests at initial assessment.
SH	ASSOCIATION FOR	5	FULL	63	22	Are you recommending DRE at initial assessment for	Thank you for your comment. We are

	CONTINENCE ADVICE (ACA)					all men over 18yrs or will this be age related?	recommending that all men over 18 years presenting with LUTS should have a digital rectal examination.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	6	FULL	66	9-26	ACA would like to see some advice regarding the risks associated with catheterisation at his point as the current guidance implies that catheters are simple options. We are pleased, however, to see intermittent catheterisation recommended over indwelling catheterisation.	Thank you for your comment. We agree that it is important to highlight the risks involved with catheterisation. After careful consideration we came to the conclusion that this is adequately covered in recommendation 1.3.13, which states that 'If offering long-term indwelling catheterisation, discuss the practicalities, benefits and risks with the man and, if appropriate, his carer'. It would be expected that anyone involved in discussing or carrying out the procedure should have received training, including information about the risks involved.
SH	ASSOCIATION FOR CONTINENCE ADVICE (ACA)	7	FULL	GENERAL		There were many aspects of this document which ACA support wholeheartedly. A guideline on LUTS in men is long overdue and we would like to thank the development group for their hard work.	Thank you for your comment.
SH	Association of Chartered Physiotherapists in Women's Health (ACPWH)	1	Full	63 3.2.2	25	Please add "and teach a strong contraction of the pelvic floor muscles after voiding" (Dorey, 2001)	Thank you for your comments. After careful consideration the GDG came to the conclusion that they do not agree. We do not think that teaching contraction of pelvic floor muscles after voiding will reduce post-micturition dribble for all patients, and there is no good quality evidence to suggest the use of this technique for this indication. The GDG considers published peer reviewed RCT evidence and where evidence is lacking, makes a decision based on consensus. Some of the factors considered by the GDG when recommending post void milking include the ease of teaching the technique and the immediate benefit to patients without significant inconvenience, harms or costs.

SH	Association of Chartered Physiotherapists in Women's Health (ACPWH)	2	Full	116 5.6.1	116	Post void milking: contract pelvic floor muscles strongly after voiding to eliminate post-micturition dribble. Dorey G, 2001 "Conservative treatment of male urinary incontinence & erectile dysfunction", Whurr Publishers, London	Thank you for your comments. After careful consideration we came to the conclusion that we do not agree. We do not think that teaching contraction of pelvic floor muscles after voiding will reduce post-micturition dribble for all patients, and there is no good quality evidence to suggest the use of this technique for this indication. The GDG considers published peer reviewed RCT evidence and where evidence is lacking, makes a decision based on consensus. Some of the factors considered by the GDG when recommending post void milking include the ease of teaching the technique and the immediate benefit to patients without significant inconvenience, harms or costs.
SH	Association of Chartered Physiotherapists in Women's Health (ACPWH)	3	Full	73 Algorithm 3 Storage symptoms		Stress urinary incontinence. Change to "offer PFMT +/- containment" (not PFMT or containment)	Thank you for your comment. We agree. We have amended the algorithm accordingly.
SH	Astellas Pharma Ltd	1	NICE	6		Recommend including in 'Key priorities for implementation' a section on Drug Treatment. Currently as it reads it appears that drug treatment is not a key priority in the management, whereas the vast majority of LUTS patients, whether the underlying cause is BPE or OAB, are managed through drug treatment.	Thank you for your comments. After careful consideration we came to the conclusion that we do not agree. The priorities are for implementation and not treatment priorities. As the drug treatments recommended are already in widespread use we think that other recommendations carried higher priority for implementation.
SH	Astellas Pharma Ltd	2	NICE	11		Sections 1.3.2 and 1.3.3 These two sections appear to be very similar statements. Suggest merging into one statement.	Thank you for your comment. We have considered your suggestion but feel that the recommendations would be weakened by amalgamation. We wish to emphasise that patients should not only be offered products to

							manage their incontinence, they should also have a choice of products to ensure that an appropriate product is available for them.
SH	Astellas Pharma Ltd	3	NICE	11	28	Section 1.3.4 Astellas recommend editing to read: ……if needed, containment products until a definite management plan has been agreed.	Thank you for your comments. We had considered your suggestions carefully, and decided that we prefer the original wording of the recommendation.
SH	Astellas Pharma Ltd	4	Appendix C			Algorithm 3 In the box underneath 'Overactive Bladder', that reads: Advise on fluid intake, offer supervised bladder training, lifestyle advise, behavioural and containment products. Astellas think that the use of containment products should only be temporary at this stage until a definitive management plan is agreed	Thank you for your comments. We have amended the wordings in the algorithm to reflect the exact wording of the recommendation. It is now changed to "…if needed, containment products".
SH	BAUS		Full	117	16	The explanation of urethral milking for post micturition dribbling needs more detail for implementation. They recommend it, but the data shows just 1 study of 50 men in each arm with "severe limitations/severe imprecision".	Thank you for your comments. We agree that there are severe limitations in the RCT for urethral milking. There were only 15 men in each arm, and the methods and analysis had severe limitations. These were detailed in the full version of the guideline. The GDG was composed of multidisciplinary experts and patient representatives who agreed on the recommendations by consensus in areas where evidence is unavailable or has severe limitations. For urethral milking, it was decided that this method should be recommended because it is very easy to learn with immediate benefits to the patients. The benefits largely outweigh the harms. Information about urethral milking is available in the full version of the guideline. In addition, we have also added a footnote to indicate where further information could be found on the web in response to your comments.

SH	BAUS	1	Full	General		The guideline sets out to address “Variations in practice to allow equitable and appropriate treatment for all men” which is clearly a laudable objective. We do not think there is too much here to object to. Necessarily some of the detail is a bit thin, but it is still an remarkably comprehensive work for which the authors should be congratulated.	Thank you for your comment.
SH	BAUS	2	Full	General		The selection of studies for analysis follows a very rigid framework which will itself influence the outcome and introduces a bias towards well funded randomised control studies (RCTs), usually from the Pharmaceutical industry. Devices, phytotherapy and other interventions tend to be disadvantaged.	Thank you for your comments. The protocol for review follows the NICE Guidelines Manual 2007. For every clinical question, we seek the highest level of evidence available, which is evidence with the most rigorous methodology and lowest risk of bias. It is important that we follow a systematic protocol set a priori, both to ensure a systematic evaluation of evidence and efficient use of resources. For intervention studies, the ideal design is a double blinded randomised controlled trial. We understood that this may not be practical or feasible for surgical or devices. Therefore, non-blinded studies were included. We also made some exceptions in situations where no double blinded trials are found to include non-blinded studies. Therefore, we do not think our strategy have disadvantaged devices, phytotherapy or other interventions. We cannot apply different standards in appraising and evaluating evidence, as this would inevitably introduce biases into the review. If the industry believe that they have a clinically effective product, it should be demonstrated in a well designed trial.
SH	BAUS	3	Full	Gene		The economic studies chosen exclude “non-UK cost	Thank you for your comment. We chose to

				ral		analysis". It seems a pity to miss out on the rest of the world's economic data and have to repeat it in the UK before we can adopt new ideas. Surely other economic data could be adjusted for UK purposes. A point for future assessments.	exclude the non-UK studies reporting a simple cost analysis when better evidence was available (full economic evaluations or cost analyses from the UK NHS perspective). As for the clinical evidence, every study is appraised in terms of quality and applicability. A study that does not meet the criteria for inclusion is very unlikely to inform recommendations.
SH	BAUS	4	Full	General		Who should be doing the assessing – GPs, primary care nurses, secondary care nurses, urologists? What training and accreditation should they have?	Thank you for your comment. Details on service provision are outside the scope of this guideline.
SH	BAUS	5	Full	General		There are at least 2 off label recommendations (diuretics and Desmopressin), which few would disagree with and many try. Some guidance probably needs to be added. "– I think the use of desmopressin should be more cautious eg - < 65 years and no cardiovascular co-morbidity"	Thank you for your comments. We only consider making recommendations about off label usage if we are satisfied based on evidence presented or clinical experience that if the treatment is used cautiously and correctly the benefits will most likely outweigh the harms and no other satisfactory treatment options are available to help certain patient groups. After careful considerations, the GDG agreed that it is important to add precautions to the recommendation. However, we do not think we should emphasise on age alone, as this may not always correspond really well with the actual level of health or physiological age of a patient. We have amended the recommendation to read: "Consider offering oral desmopressin [Foot note 1] for men with nocturnal polyuria if other medical causes [Foot note 2] have been excluded and they have not benefited from

							other treatments. Measure serum sodium 3 days after the first dose". Foot note 1: At the time of publication July 2009 desmopressin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Consult the summary of product characteristics for the contraindications and precautions. Foot note 2: Medical conditions that can cause nocturnal polyuria symptoms include diabetes mellitus, diabetes insipidus, adrenal insufficiency, hypercalcaemia, liver failure, polyuric renal failure, chronic heart failure, obstructive apnoea, dependent oedema, pyelonephritis, chronic venous stasis, sickle cell anaemia. Medications that can cause nocturnal polyuria symptoms include calcium channel blockers, diuretics, selective serotonin reuptake inhibitors (SSRI) antidepressants.
SH	BAUS	6	Full	General		Some minor changes to the Algorithms might improve them.	Thank you for your comment. We have made some amendments to algorithm 2, 3 and 4.
SH	BAUS	7	Full	63	8	What are 'LUTS maintenance products'?	Thank you for your comments. We have amended the recommendation to "containment products", which would include absorbent products such as pads and also collecting devices. An example of the containment products are listed in the conservative recommendations and a glossary is provided in the full guideline. We hope that the amendment improves the clarity of the recommendation.
SH	BAUS	8	Full	63	32	What about men with family history of CaP and life expectancy?	Thank you for your comment. After careful consideration we came to the conclusion that

							we do not agree. These risk factors would only be considered if diagnosing prostate cancer.
SH	BAUS	9	Full	84	9	(Section 4.3.3) PSA and LUTS: NICE GL includes the use of PSA testing. Clinical opinion does vary between those who would avoid PSA testing due to the risk of it leading to other investigations and treatment for prostate cancer and those who regard PSA as a legitimate test to allow BPH risk categorisation. On balance we support PSA as a legitimate test to allow BPH risk categorisation.	Thank you for your comment. There was no clinical evidence and the recommendation was based on expert opinion. The group decided the recommendation should give the patient the necessary information to make this decision.
SH	BAUS	10	Full	63	44	What about men with proteinuria to correspond to CKD guidelines.	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree. This recommendation is specific to risk factors for LUTS that might be associated to renal impairment and not proteinuria.
SH	BAUS	11	Full	72	Algorithm 2	It is not clear what “surveillance” should involve for men with non-bothersome chronic urinary retention (CUR). We need more detail here for the implementation process.	Thank you for your comment. We agree. We have amended the algorithm to include that surveillance includes post void residual, upper tract imaging and serum creatinine.
SH	BAUS	12	Full	75	Algorithm 3	Surely men with moderate symptoms scores but more bothersome symptoms, especially IPSS closer to 19 could also be considered for medical treatment directly rather than having to go through active surveillance or conservative therapy. What is “conservative therapy”? We need more detail for implementation.	Thank you for your comments. Algorithm 4 is on page 75 rather than algorithm 3 referred to in the comment. We have answered this comment in reference to algorithm 4 which we think the comment is in reference to. We have amended the algorithm to improve clarity. The classification of symptom scores has been removed from this algorithm so all men are offered active surveillance and then conservative management before medical treatment. The healthcare professional will decide whether active surveillance/ conservative management are appropriate before medical treatment depending on the individual patient’s symptoms.

							The algorithm has been amended to state that conservative options include bladder training and catheters. We hope this clarifies this point.
SH	BAUS	13	Full	76	6	Desmopressin. "– … the use of desmopressin should be more cautious - < 65 years and no cardiovascular co-morbidity"	Thank you for your comments. After careful considerations, the GDG agreed that it is important to add precautions to the recommendation. However, we do not think we should emphasise on age alone, as this may not always correspond really well with the actual level of health or physiological age of a patient. We have amended the recommendation to read: "Consider offering oral desmopressin [Foot note 1] men with nocturnal polyuria if other medical causes [Foot note 2] have been excluded and they have not benefited from other treatments. Measure serum sodium 3 days after the first dose". Foot note 1: At the time of publication July 2009 desmopressin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Consult the summary of product characteristics for the contraindications and precautions. Foot note 2: Medical conditions that can cause nocturnal polyuria symptoms include diabetes mellitus, diabetes insipidus, adrenal insufficiency, hypercalcaemia, liver failure, polyuric renal failure, chronic heart failure, obstructive apnoea, dependent oedema, pyelonephritis, chronic venous stasis, sickle

							cell anaemia. Medications that can cause nocturnal polyuria symptoms include calcium channel blockers, diuretics, selective serotonin reuptake inhibitors (SSRI) antidepressants.
SH	BAUS	14	Full	68	16	Spelling! Should it be vaporisation or vapourisation? US or UK?	Thank you for your comments. This should be vaporisation. We have checked that this has been spelt as 'vaporisation' consistently throughout the guideline.
SH	BAUS	15	Full	69	2	It is sacral nerve stimulation NOT sacral nerve root stimulation.	Thank you for your comment. We agree. We have amended the wording accordingly.
SH	BAUS	16	Full	71	Algorithm 1	what is the evidence of planning treatment on the basis of voiding versus storage symptoms?	Thank you for your comment. We did not search for evidence on planning treatment by voiding or storage symptoms. We think that dealing with these symptoms separately was the most logical and systematic approach.
SH	BAUS	17	Full	76	6	The laser vapourisation (agree spelling!) treatment including KTP/green light. BAUS input to Implementation mtg: GDC should consider using the term "vapourising laser" for this group of high energy, relatively tissue removing laser methods rather than using trademarked descriptions. This has been made a priority area for research. GDC conclude, "The evidence base is inadequate to give clear guidance" and later (p282, L1) recommend that many of the "minimally invasive" options should be offered only as part of a trial. p282, L1+: "The GDC felt they could not recommend these procedures outside of research". This seems to apply to all vapourising lasers. Appendix H on page 718 shows in section 10.4 a possible study outline. However, it is not clear what constitutes "a trial"	Thank you for this comment. We have changed this research recommendation to include all laser vaporisation techniques. We agree that laser vaporisation techniques should only be used in the context of an RCT and we have changed the recommendation 1.5.7 to reflect this.

						anymore, particularly after the NICE experience with HIFU and prostate cancer. Would a “registry” be sufficient? Many UK urology units (management and clinicians) will have invested in a green light laser or similar as the only means of managing an increasing patient workload with reducing resources of beds and main operating theatre time. Clearly the evidence is not sufficiently compelling for NICE and was not for many in BAUS but in many centres the investment has been made, patient workload has been redirected and simply returning to the previous situation is very difficult. Many centre suggest reasonable outcomes in a “natural experiment”. In the absence of a nationally funded study (unlikely but possible if NICE facilitated some state/HTA funding) then some form of sponsored national study or at least registry with careful follow up and report on outcome would be a pragmatic solution. Ideally there should be a state funded RCT of vapourising laser versus TURP with 2 to 5 year follow up built in, but that will need a lot of funding and that may be unrealistic in the current and future economic climate for the NHS. It is very unlikely that the foreign based manufacturers would fund such a study now. Perhaps they or their UK distributors would contribute to the costs. We do not think BAUS should be financially liable for such a study. Matters are complicated because NICE itself has approved the KTP laser earlier (IPG120, March 2005) – “current evidence appears adequate to support KTP laser on safety and short term efficacy grounds”. Comments included: 1 “A more pragmatic method of assessing newer ablative techniques may need to be adopted. Much of the benefit lies in improved pathways of care – hospitals stay for TURP now averages at < 3 days. Use of ‘tracker’ and patient/physician preference trials would seem to be a lower cost option and a more	

						inclusive methodology than RCTs." 2"I think it unrealistic to recommend that Greenlight PVP is only performed as part of randomised trial when many centres have established services with excellent outcomes, albeit there is not the same published evidence as there is for HoLEP. Surely a more pragmatic recommendation would be that all PVP should be carefully audited by BAUS or be undertaken in an RCT until evidence that it is equivalent to TUVP emerges."	
SH	BAUS	18	Full	76	23	The GL states that the main cause for increasing numbers of men presenting with voiding difficulties or chronic retention of urine is due to radical prostatectomy and then aging. It might be better to put aging first! We feel this is much the greater cause.	Thank you for your comments. We agree. We have edited this to put aging first. It now reads "The number of patients in this group is steadily increasing as the population ages and more radical prostatectomies are carried out."
SH	BAUS	19	Full	82	1	"RBC detection is not a sensitive or specific test to detect bladder cancer, urinary tract infection or urinary calculi". That is worth publicising to the non-urological world! It might help reduce the currently overwhelming tendency for anyone with microscopic haematuria and pain to be admitted under urology!	Thank you for your comment.
SH	BAUS	20	Full	86	3	DRE and pelvic examination are necessary! The old challenge about education of GPs in how to do a DRE/pelvic examination with particular reference to assessing prostate size and prostatic health (benign or malignant) will need to be re-explored. This was debated at the first implementation meeting and NICE now appreciate that a major educational effort will be required. Probably will be a challenge in the absence of incentives such as the QoF points process (which is linked to GP income). This recommendation also implies the need for a major educational programme for GPs and primary care assessors.	Thank you for your comments. We agree that this is an important issue. We will pass these suggestions to the implementation team at NICE.

						BAUS input to Implementation mtg: GDC will consider recommending that NICE propose DRE be included in the QoF process in future so would earn points and therefore income!	
SH	BAUS	21	Full	89	1	GDC recommend a frequency volume chart in primary care, but say the IPSS (p86) is "time consuming and did not add much to the history". Many of us would disagree but that is probably an issue for primary care to resolve, as specialist units will almost certainly do both. *BAUS input to Implementation mtg: GDC will reconsider encouraging use of the IPSS (and Qof L score) as a means of recording symptoms and bother to help stratification into treatment categories.*	Thank you for your comments. After careful consideration we came to the conclusion that we do not agree this should be changed. We think that the IPSS score should be used to assess symptoms change rather than the decision whether to treat.
SH	BAUS	22	Full	97	24	GDC recommend "consider offering multi-channel cystometry for men with LUTs considering surgery" though show no evidence for this, so is presumably is opinion. There are other forms of less invasive urodynamic measurement. There is, of course, considerable data out there, which they may not have wanted to plough through. It seems reasonable to accept since the key word is "consider" and not "do"! Urologists therefore have discretion about whether they operate with or without pressure flow studies. *Comments included: "Due to the concentration of RCT evidence for treatment effects, I feel that that newer diagnostic tests with established worth such as bladder wall thickness and non-invasive bladder pressure measurement (cuff test) have been excluded. It seems to me to be inconsistent that newer unlicensed therapies such as NSAIDs and PDE-5 inhibitors are included but newer tests are not."*	Thank you for your comments. There was no evidence for multi-channel cystometry and the recommendation was based on expert opinion. We have added more detail to the linking evidence to recommendation section. The bladder wall thickness and cuff test assessments were not prioritised for review by the guideline group for this guideline.
SH	BAUS	23	Full	115	15	Recommendation: LUTs OAB men should be given advice on diet – but p119, L5 and L6 gives no clinical or economic studies. Once again opinion, although fits in with general urological practice, we suspect.	Thank you for your comments. The GDG was composed of multidisciplinary experts and patient representatives who agreed on the recommendations by consensus in areas

							where evidence is unavailable. This recommendation is consistent with the general and urological practice.
SH	BAUS	24	Full	124	17	The same applies to p124, L17 where supra pubic catheters “may provide benefits long term” but with no evidence shown. Once again, fits with general urological practice. On p126, L2 GDC recommend supra pubic rather than indwelling catheterisation.	Thank you for your comments. The GDG was composed of multidisciplinary experts and patient representatives who agreed on the recommendations by consensus in areas where evidence is unavailable.
SH	BAUS	25	Full	123	12	The GDC “review alpha blockers” but did not include Silodosin or Naftopidil although there is extensive Japanese and recent US evidence available on efficacy and safety and Silodosin will be available in the UK in 2010. It seems a pity to have missed out new agents, which may have advantages and are likely to have a role in the management of male LUTs almost immediately in UK practice.	Thank you for your comments. As documented in the full guideline, “the GDG decided to review only doses and formulations which are licensed in the UK for the treatment of LUTS”. It is not standard practice to consider drugs which do not have a license except under exceptional circumstances (e.g., there are no licensed options for an indication, or where a drug has been widely used.) There are a number of agents in the alpha-blockers class and we reviewed those which are commonly used (Alfuzosin, Doxazosin, Tamsulosin and Terazosin).
SH	BAUS	26	Full	141	1	The economic review of alpha blockers suggests “they are less costly and more effective than 5 ARIs” but this surely depends on the man’s particular views on trading off symptoms against the possibility of avoiding future problems as well. A problem here is that GDC often refer to an effect “in the general population” by which they appear to mean men without much obvious enlargement of the prostate. For instance, p149, L1 states that 5 ARIs are not cost effective in the general population, but on p186 and p191 they give more detail and are more reasonable and suggest that cost effectiveness is more likely in men with prostatic enlargement.	Thank you for your comment. When quality of life measures are considered in the economic analysis, patient’s preference for health states as defined by LUTS or side effects is already captured. We appreciate there are exceptions, such as men with larger prostates, and in fact we have made a separate recommendation for that group.

SH	BAUS	27	Full	145	4	The text suggests there is no statistical difference between PDE-5Is and ABs for SS or QMax at 3 months. Most experts report no flow rate changes with PDEIs in our experience. Also, p154 says "No statistically significant difference between PDE-5Is and placebo in improving Qmax" but p136 reports ABs increase QMax more than placebo, section 8". Circular but inconsistent data.	Thank you for your comments. The evidence statements are only meant to provide a very short summary of the conclusions of the evidence found. Readers can find out more information about the limitations of these conclusions in the "Clinical Study Characteristics" and "Clinical Summary of Findings" in the preceding pages In these tables, the limitations for each outcome is clearly displayed and foot notes are provided to point out the limitation of these studies. There is also an overall quality of evidence next to the results. On page 154, evidence of *moderate* quality showed that there is no statistical significance between placebo and PDE5-I in improving Qmax. On page 134, *moderate* quality evidence showed that alpha blocker improved Qmax. Page 145 showed that there is no difference between alpha blocker and PDE5- I in improving Qmax based on *very low* quality evidence. As outlined in section 2.6.2 (Table 2-6). *Very low* quality evidence indicates that any estimate of effect is very uncertain, whereas *moderate* quality indicates that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. Taking into the account the quality of the evidence, it will not be inconsistent to conclude that although the study had shown no difference between PDE5-I and alpha blocker, we are not confident with these estimates at all. On the other hand, we are more confident that alpha blockers significantly improve Qmax whereas

							PDE5-I do not.
SH	BAUS	28	Full	199	22	GDC state that it is particularly important that surgeons are able to give their own outcomes data for their treatment for LUTs/BPH surgery. May be a role for BAUS or Section of Endourology.	Thank you for your comment. We agree that these suggestions are a good idea and will pass these suggestions to the implementation team at NICE.
SH	BAUS	29	Full	204	5	HoLEP versus TURP. The GDC have not given much consideration to the issue of morcellation. Is morcellation is still an issue with the latest morcellating devices? Since the GL is supportive of HoLEP (though to be performed in special centres) we need to be sure on this point.	Thank you for this comment. We agree that morcellation remains an issue with this technique and have amended the introduction to make this clear.
SH	BAUS	30	Full	278	1	Under "other considerations" the GL suggests, "National organisations should investigate ways of facilitating the expansion of this service (HoLEP) with the appropriate training and mentoring process in place". There may be an advisory role for BAUS if there was funding available for BAUS. GDC would clearly like to see "HoLEP Centres".	Thank you for your comment. We agree that these suggestions are a good idea and will pass these suggestions to the implementation team at NICE.
SH	BAUS	31	Full	325	2	"Do not offer homeopathy, phytotherapy or acupuncture for treatment of LUTs in men". *Comments: "There appears to be too much emphasis on experimental drugs used outside their licence such as PDE-5 inhibitors and NSAIDs. Inclusion of these options legitimises their uncontrolled use."*	Thank you for your comment. This guideline did not recommend the use of PDE5I or NSAIDs for the treatment of LUTS. Instead, research recommendations were made for these agents to prevent their uncontrolled use. The GDG shared your concerns about the unlicensed use of PDE5-I and NSAIDs for LUTS. Therefore a decision was made to search and review whether there is any evidence to support the use of these agents. Our review had showed that there is a lack of evidence to support the use of any PDE5-I or NSAIDs for LUTS, although some preliminary studies with small sample size and high risk of bias suggest some potential benefits.

							Therefore the GDG had made research recommendations for NSAIDs and PDE5-I. This means these agents should not be used for the treatment of LUTS, except as part of a randomised control trial. This would prevent the uncontrolled use of these agents.
SH	BAUS	32	Full	328 329	25	Evidence statement: Interactive multi media programmes are more costly and did not generate better outcomes. There has been a lot of interest in DVD based projects (particularly in East Anglia) but perhaps this now needs review and resource re-allocation. The GL may need to recommend more clearly and strongly against such projects	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree that this should be changed. We are satisfied with the recommendations as they stand because there was not enough strong evidence to recommend against these projects.
SH	Boehringer Ingelheim Limited	1	Full	75		Algorithm 4. The algorithm currently shows that for a man with mild to moderate IPSS scores active surveillance is indicated and if conservative management fails to then continue forward to medical treatment. We believe that this box should be amended to read active surveillance or active intervention as per full description on page 196 for consistency. Here active surveillance is described as reassurance, and lifestyle advice and active intervention as conservative management or drug treatment. This would dispel any confusion between the algorithm and the supporting text in the full document	Thank you for your comment. We have amended the algorithm to improve clarity. We have amended the box with active surveillance to contain discussion of active surveillance, conservative, medical or surgical options.
SH	Boehringer Ingelheim Limited	2	Full,	Gene ral		We wish to make NICE aware that Tamsulosin has received positive comments from the CHM, and is currently being reviewed by the MHRA for reclassification from a POM to Pharmacy only medication under the brand name of Flomax Relief MR so that it can be sold appropriately to men with LUTS under the strict supervision of a pharmacist. We believe it is important for the document to reflect this as patients will be able to obtain supply at the pharmacy but must see their GP for assessment of their LUTS prior to completing six weeks of treatment with Tamsulosin. This fits in very well with the advice	Thank you for your comments. It is outside the remit of the guideline to comment on service implementation such as where or how patients obtain their medications.

						given within the full guideline as it stands	
SH	British Nuclear Medicine Society	1	Full	General		Most of the guideline is related to clinical management of this condition and therefore out with the remit of the BNMS to comment.	Thank you for your comment.
SH	British Nuclear Medicine Society	2	Full	90 91		The BNMS however would like to comment on page 90 and 91 of the guidelines, section 4.8 – renal function. The guideline states "however more exact glomerular filtration rate estimation can be obtained when needed by measuring the creatinine clearance". As many of these patients will either have incomplete voiding or urinary incontinence or both, the measurement of creatinine clearance using the twenty four hour total urine is notoriously unreliable. We would suggest that the committee consider including isotopic GFR measurement either with 51-Cr EDTA or 99m-Tc DTPA using the blood clearance method (reference: BNMS Guidelines for the Estimation of Glomerular Filtration Rate http://www.bnmsonline.co.uk/procedures.) as the preferred method of obtaining more exact glomerular filtration rate. The radiation dose from this investigation is low (in the region of 0.06mSv (99m-Tc) – 0.006mSv (51-Cr) depending on the method used). Reference Administration of Radioactive Substances Advisory Committee (ARSAC) notes for Guidance. http://www.arsac.org.uk/guidelines	Thank you for your comments. After careful consideration we came to the conclusion that we do not agree that this should be changed. We think that it is adequately covered with the current wording and additional detail is not required at this level.
SH	British Nuclear Medicine Society	3	Full	71		We would also suggest that if assessment of renal function is required that the isotopic GFR would be the standard when there is clinically suspected renal impairment, in the algorithm of diagnosis on page 71. We would suggest in the serum creatinine test box after plus eGFR "calculation and/or isotopic clearance measurements if appropriate" be added.	Thank you for your comments. After careful consideration we came to the conclusion that we do not agree that this should be changed. We think that it is adequately covered with the current wording and additional detail is not required at this level.
SH	British Nuclear	4	Full	99		In the imaging section 4.13, page 99 and 100 there is	Thank you for your comments. These nuclear

	Medicine Society			100		no mention of radioisotopic estimation of relative renal function or assessment of the dilated upper tract to distinguish true obstruction from dilatation. These tests are not routinely used in men with lower urinary tract symptoms but they are sometimes used following specialist assessment, and can be used to assess the functional significance of any findings. Whilst it is agreed that Nuclear Medicine investigations such as dynamic renography or DMSA scans have no role in the routine uncomplicated patient with lower urinary tract symptoms, the BNMS would however submit that it may have a role in patients undergoing specialist assessment for LUTS particularly where renal impairment precludes contrast studies, or the initial investigations are equivocal. As these tests are normally performed as second line investigations we would understand the committee may not wish to include them in this current guideline. However if any other second line investigations are included following consultation, these Nuclear Medicine tests should be given consideration.	medicine tests were not included in the scope for this guideline because they are not routinely used in men with LUTS. .
SH	Cambridge University Hospitals Foundation Trust	1	Full	general		Generally well written and easy to follow	Thank you for your comment.
SH	Cambridge University Hospitals Foundation Trust	2	Full	general		Laser terminology is inconsistent and in some cases too non specific. Examples listed below. The following clarification may help in understanding the terminology issues: There are 3 laser techniques used currently • Laser Enucleation: HoLEP • Laser resection: Holmium Laser Resection of the Prostate (HoLRP) and Thulium Vaporesection of the Prostate • Laser Vaporisation: Holmium Laser Ablation of the Prostate (HoLAP), Thulium Laser Vaporisation of the Prostate and Greenlight Photoselective Vaporisation of the Prostate (PVP)	Thank you for your comment. We agree. We have amended the laser terminology to clarify which specific intervention we refer to in every section of the guideline. In places the reference to laser vaporisation technologies or laser coagulation technologies is necessarily generic – where the reference is to a specific modality this has been made clear.

SH	Cambridge University Hospitals Foundation Trust	3	Full	199	31	There are several of the above laser procedures that were considered in the guidance but are not listed here. Laser resection of the prostate (both Holmium laser resection of the prostate and thulium vaporesection of the prostate) are mentioned in the guidelines but not mentioned in this summary list	Thank you for your comment. We agree. We have added the missing descriptions in Chapter 8.1.
SH	Cambridge University Hospitals Foundation Trust	4	Full	200	21	Only greenlight PVP is mentioned under the heading of laser vaporisation. HoLAP should also be mentioned as it too is a laser vaporisation procedure and technically identical to greenlight PVP. HoLAP has been mentioned elsewhere in the guidelines	Thank you for your comment, We agree. We have amended the section accordingly
SH	Cambridge University Hospitals Foundation Trust	5	Full	208	3	Reference 81 is described as relating to HoLEP when in fact this paper relates to HoLRP (Holmium resection of the prostate). This is an important distinction as the economic analysis in this paper does not include the costs of morcellation which is used in HoLEP but not in HoLRP	Thank you for your comment. We have decided to consider HoLRP, HoLEP and Thulium in the same group and we have made this clear in the guideline. We have also made clear that the study Fraundorfer2001 was about HoLRP.
SH	Cambridge University Hospitals Foundation Trust	6	Full	238	1	Table 8-120: Title is HoLAP vs laser vaporisation. As noted above HoLAP is 1 of several laser vaporisation procedures and therefore this title is confusing. It should be HoLAP vs Greenlight PVP	Thank you for your comment. We agree. We have amended the wording accordingly.
SH	Cambridge University Hospitals Foundation Trust	7	Full	252	3	Confusing use of laser terminology: Paragraph 8.6.3: “TURP vs laser”. Laser on it’s own is too generic too be useful. Laser what? It could be vaporisation, resection or enucleation or any 1 of these. Please clarify	Thank you for your comment. After careful consideration we have decided to keep the term ‘laser’ generic in the title as we are referring to all types of laser. We have added a description of each type of specific laser included in the review under the clinical evidence section for this comparison.
SH	Cambridge University Hospitals Foundation Trust	8	Full	278	1	8.15. Given the fact that the Holmium User Group coordinates a national training programme for HoLEP and that a number of centres are introducing HoLEP and wider dissemination of the technique is being recommended in the guidelines, it would be reasonable to consider the following modification in bold: “Perform HoLEP at a centre specialising in the technique, or with mentorship arrangements in place”	Thank you for your comment. We agree. We have amended the recommendation accordingly.

SH	Cambridge University Hospitals Foundation Trust	9	Full	279	3	The justification given for recommending open prostatectomy rather than HoLEP for prostates > 80g is that 1 small study has shown QOL is better at 3 months with OP compared to HoLEP. It is then stated that the working group is uncertain about these results. There are a number of published HoLEP case series consistently suggesting that the outcomes of IPSS, QOL, flow rate, and complications of transfusion and reoperation are not significantly different in men with prostates > 80g compared to those < 80g. (I can provide references if helpful). Given the uncertainty about the validity of the single small study mentioned and the findings of the unmentioned HoLEP papers that all consistently suggest that HoLEP is a size independent procedure, perhaps the recommendation that OP be considered rather than HoLEP for larger prostates should be omitted. For prostates >80g HoLEP should only be performed in specialised centres.	Thank you for this comment. We have recommended OP as an alternative to TURP/HoLEP/TUVP for men with large prostates. We are still recommending HoLEP as well as OP. We have amended the algorithm and recommendation to make this clearer.
SH	Cambridge University Hospitals Foundation Trust	10	Full	282	1	“Laser vaporisation” mentioned here appears to relate only to greenlight PVP. What about Thulium vaporisation and HoLAP? They are all the same technique. The only difference is the laser wavelength used	Thank you for this comment. We agree that the recommendation should apply generically to all laser vaporisation techniques and we have amended the recommendation accordingly.
SH	Cambridge University Hospitals Foundation Trust	11	Full	284		8.18. Research recommendations. Terminology is inconsistent. The term greenlight prostatectomy is used, where previously greenlight PVP has been used. The research question should include all laser vaporisation wavelengths currently used. ie Greenlight PVP at 120 Watts as well as HOLAP at 100 Watts and thulium vaporisation	Thank you for this comment. We agree that the research recommendation should apply to laser vaporisation techniques in general and we have amended the research recommendation accordingly.
SH	Cambridge University Hospitals Foundation Trust	12	Full	General		Inconsistency in terminology for Greenlight PVP throughout the document. It is referred to as: • KTP laser vaporisation eg Pg 284 footnote and Pg 237 line 1	Thank you for your comment. We agree. We have amended the terminology and used ‘KTP laser vaporisation’ to indicate this specific modality.

						• Greenlight laser prostatectomy eg Pg 284, line 6 • Laser photoselective vaporisation eg Pg 237, 7 • Laser vaporisation eg Pg 227 line 1 and Pg 238 line 1 • Photoselective vaporisation eg Pg 225 line 2 and 233 line 13 • There may be other examples. • This degree of variation in describing a single procedure is very confusing. Uniformity of terminology would be appreciated please	
SH	Cambridge University Hospitals Foundation Trust	13	Full	General		The use of the meaningless term “laser” which could refer to a number of different techniques. Eg. Pg 229, line 5; Pg 230, line 1; Pg 231, line 1; Pg 232, lines 6 and 11. There may be more examples Please be more specific	Thank you for your comment. We agree. We have kept the title as ‘laser’ as we are referring to all types of laser. However, in the clinical evidence section we have added details of each type of laser included in the section.
SH	Cambridge University Hospitals Foundation Trust	14	Full	278	1	There is a national training program for HoLEP organised via the Holmium User Group which has successfully mentored surgeons in HoLEP in the UK. In view of this it might be worth rewriting this paragraph to read something like, “ Few centres in the UK are currently able to offer HoLEP routinely and appropriate mentored training is necessary to learn how to perform the procedure. There is a learning curve associated with HoLEP” The Holmium User Group is exploring the possibility of establishing a national HoLEP database via the BAUS data and audit program. Perhaps the statement “A national audit should be established to monitor expansion of this service”, could be included here to help improve knowledge of how HoLEP is being implemented nationally. The sentence “It involves learning to coagulate and resect tissue using…..not recommended routinely by this guideline” is not true and should be deleted	Thank you for this comment. We agree and we have amended the wording accordingly. We are grateful for the expert advice that there is no need to learn resection and ablation prior to enucleation and have removed it from the text.
SH	Cambridge University Hospitals Foundation Trust	15	Full	310	1	The outcome of surgery in men with chronic urinary retention is not at all poor (references can be provided), and in fit men TURP/HoLEP should be the	Thank you for your comment. We agree that surgery should be considered before intermittent self catheterisation. We are

						standard. The evidence that ISC is acceptable or good treatment for the man in CUR who is fit for surgery seems to be confined to a single RCT (Pg 302, line 16). Perhaps a stronger lean towards surgery rather than ISC should be considered?	satisfied that this is supported by the recommendation which states that is an alternative to surgery if there is impaired bladder function.
SH	Cambridge University Hospitals Foundation Trust	16	Full	general		In the glossary CUR is defined as residual volume > 1 litre. In other places the text refers to a palpable bladder. The work done in elucidating the pathophysiology of CUR is not presented (references can be provided). This work shows that upper tract dilatation can occur in men with high pressure CUR with a residual volume < 1 litre. Perhaps Creatinine +/- upper tracts should be checked if RV > 1 litre or in the presence of a palpable bladder	Thank you for your comments. We agree. We have amended the chapter introduction and the recommendation accordingly.
SH	Department of Health	1	Full	General		the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
SH	Ferring Pharmaceuticals Ltd	1	Full	General	General	My comments are as follows: Ferring believe that this version of the guidelines overlook some strong evidence suggesting that oral desmopressin is effective in significantly reducing the bothersome symptoms associated with nocturnal polyuria. The only evidence cited for desmopressin use in nocturia is a small, low-quality study using a desmopressin nasal formulation. The guidelines in their current form recommend oral desmopressin but only cite one study involving a nasal preparation. These studies are referred to specifically in later comments (comments 4 and 5). Due to this additional clinical evidence we believe that desmopressin should have a higher place in therapy than diuretics (see algorithm 3). In addition - the most recent International Consultation on Incontinence (ICI) Guidelines (2005) describes oral desmopressin as having ‘level 1’ evidence and a ‘Grade A’ treatment option (highly recommended) for	Thank you for your comments. Thank you for submitting a list of publications for considerations. Unfortunately, all these studies had been excluded from the review because they did not meet the inclusion and/or quality criteria. We looked through the ICI document and we have not missed any studies which could meet our inclusion and quality criteria from our review. Where evidence is lacking or unavailable, the GDG made decisions based on consensus or expert opinion of the GDG. Decisions are not based on other guidelines, but they may be taken into considerations. Similarly, recommendations will not be made based on the registrations in other countries or studies which are not completed and published in a peer review journal. The study using nasal preparations of

						nocturia. Diuretics are not recommended in these guidelines. Other than the evidence presented in these guidelines, clinical studies examining diuretics in the treatment of nocturia are lacking and of low-quality. Oral desmopressin is licensed for use in nocturia in a number of countries worldwide including Canada, France, Germany, Ireland, New Zealand and Sweden. Ferring have recently submitted an application to the FDA for the use of the desmopressin melt formulation in nocturia. Two additional randomised, placebo controlled trials were conducted to support this application. Although not published yet more details can be found at the following links. http://clinicaltrials.gov/ct2/show/NCT00615836?term=desmopressin&rank=7 http://clinicaltrials.gov/ct2/show/NCT00477490?term=desmopressin&rank=6	desmopressin has a lot of limitations – these are documented in the full guidelines and considered when recommendations are made. We had specifically discussed the indirectness of evidence because different dosage forms may produce different efficacy and side effects profiles. The GDG had considered the recommendations involving desmopressin and diuretics very carefully. We made the decision that desmopressin should not have a higher place than diuretics because of safety concerns with desmopressin. A large proportion of patients with nocturnal polyuria are elderly or have comorbidities that can put them at great safety risk with desmopressin. The GDG had noted that complications from desmopressin can be life – threatening, especially among the elderly, and at the dose used for nocturnal polyuria, diuretics are probably safer. Therefore we had amended the recommendations to further clarify that oral preparations of desmopressin should only be considered if patients do not have other conditions that put them at risk and other treatment options have failed.
SH	Ferring Pharmaceuticals Ltd	2	Full	63 3.2.3	6	My comments are as follows: Ferring agree that the oral form of desmopressin should be recommended over nasal forms; however, the evidence listed in this guideline for desmopressin use in nocturia consists of one lower quality study with a nasal formulation. We believe that higher-quality; randomised, controlled studies involving use of the oral	Thank you for your comments. We had to consider the indirect evidence obtained using the intranasal formulation because no RCT using the oral form met the inclusion criteria of this guideline and passed the quality assessment.

						formulations of desmopressin have been omitted. We believe that these studies offer strong evidence for advocating the use of oral desmopressin in nocturnal polyuria. These are highlighted below in comment numbers 4 and 5. While Ferring acknowledge the quoted incidence figures of hyponatraemia being lower for the oral than the spray, we suggest the reason for use of the oral version is due to the published evidence base and licenses in other countries.	The list of papers which you had provided had been excluded during the review process because of these issues. Please refer to our response to your comments where main reason(s) for excluding each study are listed. We had specified the oral form should be used because of concerns about the safety of the nasal formulation. We do not make recommendations to offer a particular therapy based on licensing in other countries.
SH	Ferring Pharmaceuticals Ltd	3	Full	70 3.3 Algorithm 3	Algorithm	My comments are as follows: We suggest that oral desmopressin as a treatment option for confirmed nocturnal polyuria should be placed higher than diuretics in the treatment the treatment algorithm. According to the ICI Guidelines, desmopressin has level 1 evidence for use in nocturia and is a grade A treatment recommendation. Similar robust evidence does not exist for diuretics and on this basis believe that oral desmopressin should have a higher place in the treatment algorithm (algorithm 3).	Thank you for your comments. We have carefully considered your suggestions and discussed this extensively. We came to the conclusion that we do not agree. There are a large proportion of patients who are elderly, and the side-effects from desmopressin are potentially life threatening in the presence of other comorbidities. Therefore, oral desmopressin should only be considered when other treatment options have failed, and there are other medical conditions are excluded. There is no additional evidence from the ICI guideline which could meet our review criteria but had been missed.
SH	Ferring Pharmaceuticals Ltd	4	Full	155 6.8.1.1	2	My comments are as follows: Ferring believe that a number of robust studies have been omitted from the clinical evidence category. The study included in the guidelines by Cannon et al (1999) involves use of the nasal formulation; the	Thank you for your comments. For intervention studies, we only included randomised controlled trials which met the inclusion and quality control criteria of the review. Studies which are at a high risk of bias would be excluded. Please refer to

						recommendation in these guidelines is for oral desmopressin. The following studies examining oral desmopressin in nocturia are as follows: Data for men Only: - Mattiasson P et al. Efficacy of desmopressin in the treatment of nocturia: a double-blind, placebo controlled study in men. BJU International 2002, 89:855-862. - Lose G et al. Clinical experiences with desmopressin for long-term treatment of nocturia. Journal of Urology 2004, 172; 1021-1025. Data for men and women: - van Kerrebroeck P et al. Desmopressin in the treatment of nocturia: A double-blind, placebo controlled trial. European Urology 2007, 52; 221-229. - Apslund R, Sundberg B et al. Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebo controlled randomized exploratory study. BJU International. 1999, 83; 591-595.	section 2.6.1 of the full version of the guideline for more details. The four studies which you have suggested had been excluded from the review because they did not meet our inclusion criteria and/or quality control criteria. Specifically; ▪ Mattiasson P et al 2002: In this study, all patients had three weeks of treatment prior to randomisation. Non responders (<20% reduction in nocturnal diuresis) were excluded from the randomisation into the study. This could bias the outcomes – favouring the desmopressin over placebo. ▪ Lose G et al was not a randomised controlled trial. Studies which had a mixture of men and women were excluded, unless the results for males and females were reported separately. In addition ▪ Van Kerrebroeck 2007 excluded non responders (<20% reduction in nocturnal enuresis) from the randomisation. ▪ Asplund1999 was a very small study (n=17).
SH	Ferring Pharmaceuticals Ltd	5	Full	155 6.8.1.3	3	My comments are as follows: Although the study examined in the current guideline does not demonstrate a clinical significance of desmopressin nasal formulation over placebo, the more robust studies referred to in the comments above differ. The studies by Mattiasson and Lose (above) all demonstrate that oral desmopressin is significantly	Thank you for your comments. The four studies which you have suggested had been excluded from the review because they did not meet our quality control criteria or inclusion criteria. Please see the response to your suggestion of these studies.

						better than placebo in terms of decrease in nocturnal voids relative baseline, number of voids, duration of first sleep period, rate of diuresis and urine volume. No significant differences in adverse events are observed.	Mattiasson P et al 2002 excluded all non-responders (<20% reduction in nocturnal diuresis) from the randomisation. This could strongly bias the outcomes to favour desmopressin over placebo. Lose G et al was not a randomised controlled trial.
SH	Ferring Pharmaceuticals Ltd	6	Full	193 6.15	4	My comments are as follows: This summary recommendation places desmopressin as a last resort where other treatments have failed. Due to the efficacy demonstrated in nocturia, and safety data gathered from the other countries where Ferring do have the license, we believe that desmopressin should have a higher place in therapy than diuretics.	Thank you for your comments. We have carefully considered your suggestions and discussed this extensively. We came to the conclusion that we do not agree. There are a large proportion of patients who are elderly, and the side-effects from desmopressin are potentially life threatening in the presence of other comorbidities. Therefore, oral desmopressin should only be considered when other treatment options have failed, and there are other medical conditions are excluded. We only consider marketing approvals obtained in the UK.
SH	GlaxoSmithKline	1	Full	general		The CombAT 4yr data manuscript was accepted for publication on 15th September 2009 by the European Urology journal and has been available online from 13th October 2009. *Roehrborn CG et al. The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study. [Online]* Eur Urol (2009), doi:10.1016/j.eururo.2009.09.035. *Available from: URL: http://www.europeanurology.com* The CombAT 4 year study (see reference above) is the first major study to consider the role of a 5-alpha	Thank you for your comment. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results did not add anything new and

						reductase inhibitor (5-ARI) and alpha-blocker combination in patients with moderate to severe benign prostatic hyperplasia (BPH) who are at risk of disease progression. GSK believes that this study adds important evidence for the role of a 5-ARI and alpha blocker combination. GSK is hopeful that NICE will therefore be able to update the literature search prior to completing the guidelines to ensure that these data are included in the relevant clinical evidence summaries of the guidelines.	would not change the conclusions and subsequent recommendations.
SH	GlaxoSmithKline	2	Full	159 -163		The evidence presented in section 6.10, does not distinguish between studies considering a sub-population of men with moderate to severe BPH who are at risk of disease progression and those including a wider range of BPH patients. In light of the findings of the CombAT 4 year study, GSK believes that the evidence base for use of combination therapy amongst patients with moderate to severe BPH who are at risk of disease progression is much stronger than the evidence drawn from the wider BPH population. GSK believes that the population of patients with moderate to severe BPH who are at risk of disease progression should be reviewed separately since this sub-population derives particular benefit from combination therapy.	Thank you for your comments. Among the studies considered in this section, only one study had specifically recruited men with moderate to severe LUTS and larger prostate sizes and this was annotated in the foot notes for all outcomes reported at 2 years (foot note (d) after Tables 6-61 and Table 6-65) The GDG were presented with forest plots (Appendix E, Figures E54 to E60), and the results from the large prostate study could be clearly seen. This aspect was extensively discussed in the GDG and as a result, the GDG made a recommendation for using alpha blocker and 5-alpha reductase inhibitors specifically in men with bothersome moderate to severe LUTS with large prostates or with PSA >1.4ng/ml. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The

							ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results did not add anything new and would not change the conclusions and subsequent recommendations.
SH	GlaxoSmithKline	3	Full	159 -163		In the clinical evidence section 6.10 - Combination therapy (Alpha blockers plus 5-alpha reductase inhibitors) there is no mention of the possibility of patients requiring BPH-related surgery. This is an important and common outcome for men with moderate to severe BPH. In the CombAT study at 4 years both acute urinary retention (AUR) and the need for BPH-related surgery were significantly reduced amongst patients treated with dutasteride and tamsulosin, compared to those who received tamsulosin alone. GSK therefore believe that BPH-related surgery should be included in section 6.10.	Thank you for your comment. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results would not change the conclusions and subsequent recommendations. BPH related surgery was discussed but not identified as a primary outcome for the review protocol. We think that this outcome is not standardised and dependent on both patients' and doctors' views. The criteria for performing surgery are not reported in the studies and we were uncertain how these rates can be comparable between different studies. The full 4 year data could be included in future updates of the guideline.
SH	GlaxoSmithKline	4	Full	185 -187		Section 6.13 - Recommendations and link to evidence. GSK suggests that the sub-population of patients with moderate to severe BPH who are at risk of disease progression should be considered separately within this section.	Thank you for your comments. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that

						The CombAT 4 year study shows that the combination of dutasteride and tamsulosin was more effective in terms of symptom improvement from month 3 onwards when compared with dutasteride alone and from month 9 onwards when compared with tamsulosin alone. This evidence supports the contention that men with moderate to severe BPH who are at risk of disease progression should routinely be started with 5-ARI and alpha-blocker combination therapy, rather than 5-ARI monotherapy.	it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results did not add anything new and would not change the conclusions and subsequent recommendations. We had carefully considered your suggestion carefully. We believe our current recommendation has addressed the balance of symptom control and long term risk of progression adequately. Patients at a risk of progression are offered a 5-alpha reductase inhibitor. If the patients find the LUTS bothersome and it is moderate or severe, the recommendation is to consider offering a combination treatment. The evidence we reviewed showed that 5ARI are effective in reducing risk of progression and the additional benefits of combination in prevention of progression should be considered against 5-alpha reductase inhibitor monotherapy. We have decided to keep “consider offering” level of recommendation for combination treatments based on the balance between additional effectiveness versus additional risk of adverse events.
SH	GlaxoSmithKline	5	Full	66	42-44	Men who have a prostate volume of >30g and who have a prostate-specific antigen (PSA) > 1.4ng/mL are known to be at elevated risk of progression, regardless of other risk factors. GSK suggests that the guidelines should be re-worded to “Offer a 5-alpha reductase inhibitor to men with moderate to severe LUTS considered to be at high risk of progression (i.e. men	Thank you for your comments. Factors such as prostate size and PSA levels were considered by the GDG. We have recommended “Offer a 5-alpha reductase inhibitor to men with LUTS who have prostates estimated to be larger than 30 g or

						who have a prostate volume of >30g and who have a PSA greater than 1.4ng/ml). The CombAT study included men over the ages of 50 with prostate volume ≥30g and PSA ≥1.5ng/mL In this study men treated with alpha blockers alone had a 6.8% risk of AUR and a 7.8% risk of BPH surgery over 4 years. These risks were reduced by 68% and 71% respectively with the combination of 5ARI and alpha-blocker.	PSA greater than 1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men)." The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results would not change the conclusions and subsequent recommendations. The GDG believed it is important to consider the additional benefits versus the additional risks of adverse events when offering combination treatments for each patient. In terms of progression, the additional benefits of combination therapy should be considered against the efficacy of 5alpha reductase inhibitor monotherapy. We believe our current set of recommendations have addressed the issues of symptom control and prevention progression adequately and well balanced.
SH	GlaxoSmithKline	6	Full	137	1	In Table 6-39 the 2 year outcomes in this table incorrectly refers to the reference 224 instead of 225. This reference is for *Roehrborn CG et al, The Effects of Dutasteride, Tamsulosin and Combination Therapy on Lower Urinary Tract Symptoms in Men With Benign Prostatic Hyperplasia and Prostatic Enlargement: 2-Year Results From the CombAT Study. Journal of Urology 2008 179 (2):616-621*	Thank you for your comments. We had double checked the referencing for the 2 year outcomes and it was correct. Reference 224 in the full guideline referred to *Roehrborn CG et al, The Effects of Dutasteride, Tamsulosin and Combination Therapy on Lower Urinary Tract Symptoms in Men With Benign Prostatic Hyperplasia and Prostatic Enlargement: 2-Year Results From the CombAT Study. Journal of Urology 2008 179 (2):616-621.*

							There is a separate list of references for the full guideline and the accompanying appendix in the documents which went out to consultation.
SH	GlaxoSmithKline	7	Full	137	1	In Table 6-39, it Is stated that there is “serious imprecision” for the Qmax(ml/s) at 2 years. GSK suggests that this should state “No serious imprecision”	Thank you for your comments. We agree and have changed this to “no serious imprecision” in Table 6-39 and the quality of evidence to “High” for the corresponding outcome in Table 6-40. Although the change of Qmax was statistically significant, -1.0 [95% CI -1.33 to -0.67] this difference is less than the predetermined MID. This outcome would be considered as “imprecise” but not clinically significant. Therefore, there is high quality evidence that there is statistically significant (but not clinically important) difference between the two treatment arms.
SH	GlaxoSmithKline	8	Full	137	1	In Table 6-39 the need for BPH related surgery is not included in this table as an adverse event (AE) outcome. GSK considers that this should be considered as an AE in the same way as urinary retention.	Thank your for your comment. To ensure consistency, the outcomes are determined prior to the systematic review, as discussed in Section 2.4.3 of the full guideline. BPH related surgery was discussed but not identified as an outcome for in the review protocol. We think that this outcome is not standardised and dependent on both patients' and doctors' views. The criteria for performing surgery are usually not reported in pharmacological studies and we were uncertain how these rates can be comparable between different studies.
SH	GlaxoSmithKline	9	Full	139	1	In Table 6-40 the mean difference (MD) and confidence intervals for Qmax at 2 years are incorrectly reported as negative values. These values should be reported as positive as the ‘within treatment’ increases from baseline seen at 2 years were	Thank you for your comments. As a higher value of QMax is the desired outcome, a negative value for the mean difference between different treatment arms

						significantly greater for dutasteride compared with tamsulosin.	indicates this outcome favours the control (dutasteride) arm, as shown in Forest Plot Figure E-18. The improvement in Qmax is better with dutasteride and therefore, the reporting was correct.
SH	GlaxoSmithKline	10	Full	139	1	In Table 6-40 the need for BPH related surgery is not included in this table as an AE outcome.	Thank your for your comment. To ensure consistency, the outcomes are determined prior to the systematic review, as discussed in Section 2.4.3 of the full guideline. BPH related surgery was discussed but not identified as an outcome for in the review protocol. We felt that this outcome is not standardised and dependent on both patients' and doctors' views. The criteria for performing surgery are usually not reported in pharmacological studies and we were uncertain how these rates can be comparable between different studies.
SH	GlaxoSmithKline	11	Full	159	19	In Table 6-61 for the symptom score at 2 years the draft guidelines state “serious imprecision (c)”. It is unclear why this is the case as the sample size was large and a significance difference was observed.	Thanks you for your comments. We agree and have changed this to “no serious imprecision” in Table 6-61 and the quality of evidence to “High” for the corresponding outcome in Table 6-62. Although the change of symptom score was statistically significant, i.e. - 1.90 [95% CI –2.31 to –1.49], this difference is less than the predetermined MID. This outcome would not be considered as “imprecise” but it is still not clinically significant. Therefore, there is high quality evidence that there is statistically significant (but not clinically important) difference between the two treatment arms.
SH	GlaxoSmithKline	12	Full	161	1	In this section there is no mention of the requirement for BPH-related surgery. In the CombAT study at 4 years both AUR and the need for BPH-related surgery were significantly reduced with dutasteride and	Thank you for your comment. BPH related surgery was not identified as a primary outcome for the systematic review.

						tamsulosin combination compared with tamsulosin alone.	The 2-year data from the CombAT study published by Roehrborn et al in 2008 was included in the systematic review. Unfortunately, this study did not report acute urinary retention (AUR). Because the CombAT 4 year was published online on 19th September 2009 (after our cut off date for literature search -17th June 2009), we would not routinely include such data. Nevertheless, we reviewed this study to ensure that it did not provide new results that are important and would change our recommendations. The GDG discussed this study and agreed that we would not need to include it.
SH	GlaxoSmithKline	13	Full	162	13	The National Clinical Guideline Centre (NCGC) Combination Model is in men with moderate LUTS with a normal prostate size. As the CombAT 4 year study is now published and given the strength of evidence for combination therapy amongst men with moderate to severe BPH who are at risk of disease progression (ie. Men with larger prostates (>30cc) and higher PSA values (>1.4ng/ml)) GSK believes it is important that a separate economic model which takes into account the results from this study, including the reductions seen in AUR and BPH related surgery, is included. GSK acknowledges the note in the Discussion section 10.4.10 of Appendix E referring to a population of men with large prostates that "A specific model for that population could be built once good data are available."	Thank you for your comment. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results would not change the conclusions and subsequent recommendations.
SH	GlaxoSmithKline	14	Full	163	1	2nd Paragraph – It should be noted that although it was not the primary endpoint, the CombAT study did also show greater improvements from baseline with dutasteride/tamsulosin combination compared with tamsulosin alone in symptom score at 1 year.	Thank you for your comments. For combination studies, we only included the final end points in the meta-analysis. Before formulating recommendations the GDG was presented with the trend of the studies and were aware of when the different treatments show improvements over baseline.

BSH	GlaxoSmithKline	15	Full	163	1	2nd Paragraph – It should be noted that although it was not the primary endpoint, the CombAT study did also show greater improvements from baseline with dutasteride/tamsulosin combination compared with tamsulosin alone in Qmax at 6 months and 1 year.	Thank you for your comments. For combination studies, we only included the final end points in the meta-analysis. Before formulating recommendations the GDG was presented with the trend of the studies and were aware of when the different treatments show improvements over baseline.
SH	GlaxoSmithKline	16	Full	163	1	8th Paragraph – GSK would point out that in the CombAT study, acute urinary retention and BPH related surgery were significantly reduced with dutasteride/tamsulosin combination compared with tamsulosin alone.	Thank you for your comment. BPH related surgery was not identified as a primary outcome for the systematic review. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we would not need to include it as the results would not change the conclusions and subsequent recommendations. However, we have included the publication of the 2-year data from the CombAT study by Roehrborn et al in 2008. Unfortunately this study did not report acute urinary retention.
SH	GlaxoSmithKline	17	Full	163	1	Economic statement. Given the CombAT 4 year data (now published), GSK considers that the statement "alpha blockers are more cost-effective compared with a combination of alpha-blockers and 5-ARIs" due to the impact on costs of the reduction in AUR treatment and BPH related surgery with dutasteride, should be revised. This will require additional economic modelling.	Thank you for your comment. The cut off date for our literature search was 17th June 2009. The CombAT 4 year was published online on 19th September 2009. We reviewed this study even though it was outside our search cut off date to ensure that it did not provide new important results. The ComBAT 4 year results were similar to the 2 year results that had been included in the guideline. The GDG discussed this study and agreed that we

							would not need to include it as the results did not add anything new and would not change the conclusions and subsequent recommendations.
SH	GlaxoSmithKline	18	Full	167	10	2nd Paragraph – It should be noted that although it was not the primary endpoint in the CombAT study [255], there was a statistical difference between combination therapy and dutasteride in Qmax at 6 months, with a significantly greater mean increase seen in the combination arm.	Thank you for your comments. For combination studies, we only included the final end points in the meta-analysis. Before formulating recommendations the GDG was presented with the trend of the studies and were aware of when the different treatments show improvements over baseline.
SH	GlaxoSmithKline	19	Full	186		Recommendation statement – GSK suggests the wording as in row 5 above	Thank you for your comments. As detailed in the response to your previous comments the GDG believed it is important to consider the additional benefits versus the additional risks of adverse events when offering combination treatments for each patient. In terms of progression, the additional benefits of combination therapy should be considered against the efficacy of 5alpha reductase inhibitor monotherapy. We believe our current sets of recommendations have addressed the issues of symptom control and prevention progression adequately and well balanced.
SH	GlaxoSmithKline	20	Full	186		There is some missing text in sentence 2 of the section on relative values of different outcomes. It currently reads “The reduction of LUTS progression and risk of retention or need of surgical intervention”.	Thank you for your comment. There was some missing text and we have amended the sentence to read: “The reduction of LUTS progression and risk of retention or need of surgical intervention” were considered important outcomes.
SH	GlaxoSmithKline	21	NICE	13	1.4.5	GSK suggest a change to the text to read “Offer a 5-alpha reductase inhibitor to men with moderate to severe LUTS considered to be at high risk of progression (i.e. men who have a prostate volume of >30g and who have a PSA greater than 1.4ng/ml)	Thank you for your comments. After careful considerations and discussion, we disagree. We believed that the current set of recommendations offer the best balance for symptoms control and minimising risk of progressions.

							The additional benefits from combination therapy should be considered against the additional risks and these should be considered individually for each patient.
SH	GlaxoSmithKline	22	Appendices	696	24-25	The text states "We could not find any studies reporting the proportion of successful treatment where success was defined as an improvement of at least 3 points of IPSS". In the CombAT 2 yr study [225], although not the primary endpoint, responders were categorised as men with a 3-point or greater improvement in IPSS score at month 24. The proportion of responders in the dutasteride/tamsulosin combination group was significantly greater than in the tamsulosin group.	Thank you for your comment. Our model evaluated a general population of men with LUTS while participants in the CombAT study had a prostate size larger than normal. For this reason data on IPSS change from this study were not used in the model. We have amended the Combination Model chapter, Appendix F to make this clearer.
SH	GlaxoSmithKline	23	Appendices	697	1	Table 15 only considers success up to one year, however in the clinical evidence section 6.10.2, International Prostate Symptom Score (IPSS) are reported up to 4 years.	Thank you for your comment. The 2 year and 4 year data in the clinical evidence section refer respectively to the CombAT {ROEHRBORN2008} and MTOP study{MCCONNELL2003} which were conducted on men with enlarged prostates. As our model tries to evaluate strategies in the average population, IPSS change data reported in these studies were not used in the model. We have amended the text in the Combination Model chapter, Appendix F to make this clearer.
SH	GlaxoSmithKline	24	Appendices	702	2	Text should state "see 10.3.11" not "see 10.5.11"	Thank you for your comment. We have amended the text accordingly.
SH	GlaxoSmithKline	25	Appendices	703	1, 2, 6	All references to 10.5 should be 10.3	Thank you for your comment. We have amended the text accordingly.
SH	Medtronic UK	1	Full	286	21	We feel that the document should make clearer that this use of botulinum toxin is currently out with the licensed indication for the product. The only notice that makes this clear is currently is a footnote on page 290. We believe that wherever botulinum toxin or Botox™ is	Thank you for your comment. We have added the detail from the footnote to the trade off between clinical benefits and harms section. The unlicensed use of botulinum toxin is also detailed under other considerations.

						mentioned it should be made clear when it is outside of its licensed indication.	
SH	Medtronic UK	2	Full	286	32	The trial use use of botulinum toxin will remove the chance for neuromodulation to be tried for a period of up to 6 months while the botulinum toxin paralysis wears off. This is the case *even* if the botulinum toxin has had no discernable effect on the detrusor overactivity. We suggest that the guideline makes this clear and suggests that patients who are being considered for Neuromodulation have a trial of Neuromodulation prior to botulinum toxin using the PNE technique described in line 41	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree. Percutaneous tibial nerve stimulation (neuromodulation) was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Medtronic UK	3	Full	287	1	We would wish to add that the cost of the PNE test is comparatively small and that the availability of a test such as this which shows clearly which patients will respond to full implantation of a sacral nerve stimulator is of real value as it offers the possibility of a NNT of 1 for implantation.	Thank you for your comment. Percutaneous tibial nerve stimulation was not prioritised as a clinical question and has not been included in the guideline and therefore an economic analysis is not necessary. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Medtronic UK	4	Full	289	23	We feel that the study inclusion criteria is not suitable for application in Sacral Nerve Stimulation. The anatomy of the detrusor muscle and sacral nerves is similar in both men and women and so mixed studies should be acceptable without precise split out of male and female results. Understandably procedures which are anatomy dependant such as male slings, injectibles, artificial sphincters etc do require male specific studies.	Thank you for comment. The GDG agreed that mixed populations of men and women in which the results were not analysed separately did not meet our inclusion criteria. These were not included as men and women differ with regards to bladder outlet obstruction and stress urinary incontinence.

SH	Medtronic UK	5	Full	290	2	We feel the recommendation should include the warning that trial of botulinum toxin will preclude trial of sacral nerve stimulation for 5-6 months while botulinum toxin wears off irrespective of if a desired clinical effect is seen from the toxin. Suggest trial of neuromodulation in patients considered suitable prior to botulinum toxin as a successful trial of SNS is a reversible procedure that will not preclude or delay other treatment options.	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree. Percutaneous tibial nerve stimulation (PTNS) (neuromodulation) was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under IP 822 (percutaneous tibial nerve stimulation for overactive bladder syndrome).
SH	Medtronic UK	6	Full	291	1	We would suggest the recommendation is modified to reflect the need to try neuromodulation before a trial of botulinum toxin	Thank you for your comment. Percutaneous tibial nerve stimulation (PTNS) (neuromodulation) was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Medtronic UK	7	Full	291	1	We object to the phrase “the long term consequences of implantation are unknown” and recommend its removed. Sacral nerve stimulation has been in practice for 25 years and patient cohort follow up has now reached 11 years. Sacral Nerve Stimulation is a well established procedure with long term outcome data. We would invite you to review: “Results of Sacral Neuromodulation Therapy for Urinary Voiding Dysfunction: Outcomes of a Prospective, Worldwide Clinical Study” Kerrebroeck,*,† Anco C. van Voskuilen et al – Journal Of urology Vol. 178, 2029-2034, November 2007. This paper shows a 5 year follow up of a patient cohort of male and female patients “Sacral Nerve Stimulation for Voiding Dysfunction: One	Thank you for your comments. After careful consideration we have amended the wording slightly to: there are no high quality data on long term consequences. The GDG agreed that mixed populations of men and women in which the results were not analysed separately did not meet our inclusion criteria, and therefore these studies were not included in the guideline.

						Institution's 11-Year Experience" Sutherland, Lavers et al - Published online inWiley InterScience (www.interscience.wiley.com) DOI 10.1002/nau.20345 This paper shows an 11 year follow up of a patient cohort "Sacral neuromodulation for treating the symptoms of overactive bladder syndrome and non obstructive urinary retention: > 10 years of clinical experience" Kastler - 2 0 07 B J U I N T E R N A T I O N A L | 101 , 4 1 7 – 4 2 3 | doi:10.1111/j.1464-410X.2007.07233.x	
SH	Medtronic UK	8	Full	291	1	The phrase "No clinical or economic evidence was identified". Many studies exists which provide evidence in this field which we would be delighted to supply for review. Draft paper awaiting publication is available for review on request but is subject to confidentiality. Several examples from a list of many that we would invite consideration of include: Sacral Neuromodulation: Cost Considderations and Clinical Benefits – Aboseif, Kim, Reider et Al – J. Urology 2007.07.073	Thank you for your comment. For intervention studies, we only included randomised controlled trials which met the inclusion and quality control criteria of the review. Studies which are at a high risk of bias would be excluded. Please refer to section 2.6.1 of the full version of the guideline for more details. The study by Abseil you have suggested had been excluded from the economic review because it did not meet our inclusion criteria. Specifically it was a mixed population of men and women and the results were not analysed separately.
SH	Medtronic UK	9	Full	295	9	We would request that as a licensed treatment with extensive experience plus the availability of an inexpensive predictive test for efficacy that the phrase could be redrafted to "Consider offering sacral nerve root stimulation to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments excluding botulinum toxin Due to the need to wait 5 – 6 months post botulinum toxin treatment (irrespective of the outcome	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree. Percutaneous tibial nerve stimulation (PTNS) (neuromodulation) was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for

						of the toxin) a reversible trial with sacral nerve stimulation should be undertaken prior to botulinum toxin in suitable patients"	overactive bladder syndrome) so there will be advice on this procedure.
SH	Medtronic UK	10	Full	291	1	We object to the phrasing regarding high cost in the economic section. Although the treatment has a high up front acquisition cost it is only implanted in patients who have a positive predictive test (which is inexpensive) and thus the intervention itself has a NNT of 1. The acquisition costs should be balanced against the life of the device and the reduction in consumption of other health care resources by the patient during the life of the device. References can be provided to show a decrease in consumption of healthcare resources during the life of a device. The average battery life of a sacral nerve stimulator device is 6-7 years which is referenced in the study below: "Long Term Results of Neuromodulation by Sacral Nerve Stimulation for Lower Urinary Tract Symptoms: A Retrospective Single Center Study" van Voskuilen, Oerlemans et al – European Urology 2006	Thank you for your comment. We agree there might be future savings associated with this intervention. We have changed "high costs" with "high acquisition costs" as per your comment. We have added some considerations on possible future savings dependent on the intervention success.
SH	Medtronic UK	11	Full	253	1	Comment (a) about concealment does not seem applicable to the randomization in clinical studies for instrumental therapies like TUNA	Thank you for your comments. Randomisation concealment is still relevant in instrumental therapies such as TUNA, particularly if the studies are not blinded or masked. If the allocation concealment is adequate, those responsible for enrolling patients are not aware of the group to which the next enrolled patient will be allocated to. This prevents investigators from selectively enrolling patients, and results in patients who are more likely to benefit from treatment being randomised to it. In fact, we believed that it is even more important in cases where the participants and/or investigators are not blinded.
SH	Medtronic UK	12	Full	254	2	TUNA patient selection is an alternative to medical management, not surgery gold standard like TURP. In this respect, we believe that cost comparison should	Thank you for your comment. We agree that TUNA should also be compared to medical management and we did include this

						be made vs drugs, not TURP (See Naslund MJ, J Urol. 2005 Jun;173(6):2090-3)	comparison in our review. However we did not find any RCT or economic study comparing TUNA with medical management.
SH	Medtronic UK	13	Full	255	8.7.1 .3	Due to the lower side effects profile of TUNA (especially of sexual kind, like erectile and ejaculatory dysfunction) vs TURP, we believe that patient preference should be taken into account when deciding therapy choice	Thank you for this comment. The importance of patient preference in making surgical decisions has been mentioned in the recommendation 1.5.1 which suggests 'discuss the alternatives to and outcomes from surgery'.
SH	Medtronic UK	14	Full	286	41	In line with the section beginning on line 21 where the available brand names are mentioned we would request that the line 41 is modified to "…permanently implantable sacral nerve stimulators such as InterStim™ [Medtronic Ltd]"	Thank you for your comment. After careful consideration we came to the conclusion that it is not appropriate to use specific brand names. In order to be consistent we have removed other brand names from the guideline.
SH	Medtronic UK	15	Full	286	41	We request that the sentence in line 41 is modified to reflect the available brand names ie: "Patients first undergo a percutaneous nerve evaluation (PNE) in which a needle is inserted through the sacral foramina under local anaesthetic - InterStim™Test Stimulation Kit [Medtronic]"	Thank you for your comment. After careful consideration we came to the conclusion that it is not appropriate to use specific brand names. In order to be consistent we have removed other brand names from the guideline.
SH	Medtronic UK	16	Full	287	2	Request sentence is modified to "Those who show satisfactory response to the PNE, may then proceed to a permanent InterStim™ implant"	Thank you for your comment. After careful consideration we came to the conclusion that it is not appropriate to use specific brand names. In order to be consistent we have removed other brand names from the guideline.
SH	Medtronic UK	17	Full	287	9	Suggest including a sentence in line with page 286 line 32 that reads "All the evidence in this guideline refers to InterStim™ and the InterStim™ Test Stimulation kit both Medtronic Ltd"	Thank you for your comment. After careful consideration we came to the conclusion that it is not appropriate to use specific brand names. In order to be consistent we have removed other brand names from the guideline.
SH	Medtronic UK	18	Full	290	1	In the section regarding trade offs it would be helpful to make clear that botulinum toxin therapy requires repeated regular treatments every few months meaning ongoing costs and procedures are necessary to maintain the effect.	Thank you for your comment. We have added more detail to the link section: This is an apparently low risk day case procedure that can be performed under local anaesthetic. The benefits are short to medium term, and

							possible long term harms are unknown at present. We have amended the economic considerations to incorporate your comment:: This intervention is associated with high acquisition costs and ongoing costs for repeated regular treatments.
SH	Medtronic UK	19	Full	291	1	In the section regarding trade offs it would be helpful to clarify the statement regarding the inevitable need for battery replacement with the fact that the average battery life for an InterStim (Medtronic) implant is 6-7 years.	Thank you for your comment. After careful consideration we came to the conclusion that it is not appropriate to use specific brand names. In order to be consistent we have removed other brand names from the guideline.
PR	NETSCC 1	1	Full	general	general	I could not spot any major methodological flaws in this review.	Thank you for your comment.
PR	NETSCC 1	2	Full	81	23	NPV and PPC quoted as 92.4% and 9.4% respectively, yet the appendices (page 48) give these as 98.6% and 4.3% respectively. Please confirm.	Thank you for your comment. We agree. We have amended the text accordingly.
PR	NETSCC 1	3	Full	83	4	Summary of findings for Roehborn 2006, analysis "…using logistic regression expressed as hazard ratios". Logistic regression yields odds ratios not hazard ratios.	Thank you for your comment. We have checked Roehrborn 2006 to confirm the analysis carried out. The study reports the influence of baseline PSA on the risk of deterioration in IPSS using Cox regressions. Results of the logistic regression were expressed as hazard ratios.
PR	NETSCC 1	4	Full	95	11	Diagnostic information for Oelke 2007, unable to find this information in the appendices. Page 66 of the appendices is where I believe this information should lie, but this page is blank.	Thank you for your comment. The study Oelke (2007) reports data used in two clinical questions (diagnostic accuracy of uroflowmetry and post void residual). The evidence table can be found in the appendix on page 62 under evidence table 3 for diagnostic accuracy of uroflowmetry. The next clinical question's evidence tables for post void residual are on page 66 but the Oelke study is cross-referenced to the earlier version

							on page 62 rather than repeating the table.
PR	NETSCC 1	5	Full	120	9	Table 5-30. Slightly odd way to report the confidence intervals – would suggest the authors use standard notation here. If the MD is negative then the confidence should include this negative value.	Thank you for your comments and pointing out this inconsistency. We have updated the confidence interval reporting to be consistent with the rest of the guideline. A negative sign is used to denote lower values for the control group.
PR	NETSCC 1	6	Full	149	1	First clinical statement should include time points; 3 and 6 months.	Thank you for your comments and pointing out these errors. We had added the appropriate time points to the statements.
PR	NETSCC 1	7	Full	149	1	Similarly, the 5th clinical statement "5-alpha reductase inhibitors are more effective than placebo in reducing prostate volume", this is at 1 year follow-up and this should be stated or combine this with the 6th clinical statement.	Thank you for your comments. The 5th clinical statement referred to prostate volume. When two or more follow up periods (1 and 2 years) are available and these showed a statistical significance favouring 5-ARI over placebo. We prefer not to state all the individual time points available when the results are consistently beneficial/harmful/ not different across all time points. The 6th clinical statement referred to PSA values. We prefer not to combine the clinical effectiveness outcomes in one statement.
PR	NETSCC 1	8	Full	153	9	Table 6-54: would recommend listing the studies in the same order as they are referenced in Table 6-53.	Thank you for your comment. We agree and have amended this accordingly.
PR	NETSCC 1	9	Full	160	1	Table 6-68. the figures regarding vertigo, I don't see how they get these numbers. They do not tie in with the corresponding table in the appendices on pages 132-135, according to that table they should be 8/286 (2.8%) and 3/269 (1.1%)	Thank you for your comments. We agree that there is an error and corrected the values in the table and the corresponding forest plots.
PR	NETSCC 1	10	Full	177	1	Table 6-74. Urgency episodes/24h, Absolute effect reads -1.4, shouldn't this be -0.4 if the figures on the corresponding table in the appendix (page 129) are correct.	Thank you for your comment. We agree and have amended the values for urgency episodes in Table 6-74 to -0.4.
PR	NETSCC 1	11	Full	179	1	Table 6-76. Symptom score at 3 months, MD is	Thank you for your comment.

						reported as -0.9, I believe this should be -1.9 if the figures in the corresponding table in the appendix (pages 129-131) are to be believed.	We have rechecked this section and this should be -1.8. We have updated the appendix table accordingly after double checking the publication.
PR	NETSCC 1	12	Full	179	1	Table 6-76. Qmax at 3 months. The authors report a p-value of 0.003, is this correct? In the corresponding table in the appendix (pages 129-131) this is ”NS”.	Thank you for your comment. The information in the evidence table was correct. This should have been not statistically significant. We have also added an evidence statement to reflect this change.
PR	NETSCC 1	13	Full	249	15	4th clinical statement, state time points for Qmax.	Thank you for your comment. We agree. We have amended the evidence statement accordingly.
PR	NETSCC 1	14	Full	320	1	The last 5 clinical statements starting “There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing urinary retention”. There is no information on these in Table 14-174.	Thank you for your comment. The primary adverse event outcomes reported for the complementary chapter are urinary retention and incontinence. We have removed the evidence statements concerning other secondary outcomes in line with the evidence provided in Table 14-174.
PR	NETSCC 1	15	Full	144	1	The authors say there is no statistical significant differences between anticholinergics and alpha blockers in patients with headache. RR=0.22 with 95% CI 0.05 to 1.01, this is very borderline.	Thank you for your comments. We agree that the confidence interval was very wide and borderline. However, we had to adhere to the cut off points that had been set priori to the analysis and reporting. Forest plots are shown (As in Figure E-39 in Appendix E) and the confidence intervals and analysis results were discussed with the GDG. The GDG would have taken into account borderline or imprecise results when formulating recommendations.
PR	NETSCC 1	16	Full	144	1	Similarly (as above), constipation is also borderline, RR=2.46 with 95% CI 0.97 to 20.4.	Thank you for your comments. We agree that the confidence interval was very wide and borderline. However, we had to adhere to the cut off points that had been set priori to the analysis and reporting.

							Forest plots are shown (As in Figure E-39 in Appendix E) and the confidence intervals and analysis results were discussed with the GDG. The GDG would have taken into account borderline or imprecise results when formulating recommendations.
PR	NETSCC 1	17	Full	163	1	4th clinical statement on QMAX. The authors report alpha-blockers plus 5-alpha combinations are more effective than alpha blockers in improving Qmax at 2 and 4 years follow-up. Qmax at 4 years isn't presented.	Thank you for your comments. We have made the amendments in the evidence statements.
PR	NETSCC 1	18	Full	177	5	The authors reported no statistical significant differences between combination treatment of alpha-blockers plus anticholinergics compared to anticholinergics in headaches yet the RR=6.72 with a 95% CI reported as 1.55 to 29.22	Thank you for comment. We agree and have amended the evidence statements accordingly.
PR	NETSCC 1	19	Full	177	5	The authors reported no statistical significant differences between combination treatment of alpha-blockers plus anticholinergics compared to anticholinergics in nasal congestion yet the RR=20.16 with a 95% CI reported as 1.19 to 342.	Thank you for your comment. We agree and have amended the evidence statement accordingly.
PR	NETSCC 1	20	Full	232	17	3rd clinical statement states TUVP was more effective than lasers in improving quality of life at 5 years post-op. The results in the corresponding table 8-110 do not support this.	Thank you for your comment. We agree and have amended the evidence statement accordingly.
PR	NETSCC 1	21	Full	232	17	6th clinical states no statistical difference between laser and TUVP in retrograde ejaculation, yet the RR=0.28 with 95% CI 0.18 to 0.45 is reported in table 8-110.	Thank you for your comment. We agree. We have amended the evidence statements accordingly.
PR	NETSCC 1	22	Full	249	15	2nd clinical statement. TURP is more effective than TUCP in improving quality of life at 6 months and 3 years follow up. Yet the data reported in table 8-130 do not support this for the 6 month time point, in fact the opposite is true, in that TUVP is more effective than TURP in improving quality of life (MD=0.48 95% CI 0.14 to 0.82).	Thank you for your comment. We agree. We have amended the evidence statements as TURP is more effective at improving quality of life score than TUVP at 6 months but TUVP is more effective than TURP at 3 years.

PR	NETSCC 1	23	Full	225	2	Minor. Table 8-103. Row labelled “TUR” is labeled “TUR syndrome” in the corresponding table 8-104.	Thank you for your comment. We agree and have amended the text accordingly.
PR	NETSCC 1	24	Full	241	6	Combine the first two clinical statements.	Thank you for your comment. We agree. We have combined the evidence statements.
PR	NETSCC 1	25	Full	268	16	Table 8-150. column headings. Instead of intervention and control as heading titles, for consistency and to aid clarity would be useful to have this as TEAP and TURP.	Thank you for your comment. We agree. We have incorporated this into the table.
PR	NETSCC 1	26	Full	271	2	Table 8-152. as above	Thank you for your comment. We agree. We have incorporated this into the table.
PR	NETSCC 1	27	Full	274	1	Table 8-156. as above	Thank you for your comment. We agree. We have incorporated this into the table.
PR	NETSCC 1	28	Full	316	4	3rd clinical statement refers to “saw palmetto”, for consistency it would be better if this was kept the same as what was reported and presented in the accompanying table 14-170 i.e. “Serenoa repens”.	Thank you for your comments. We have amended this wording for consistency within the guideline.
PR	NETSCC 2	1	Full	General		Overall the work fulfilled the declared intentions.	Thank you for your comment.
PR	NETSCC 2	2	Full	General		The work appears to be of high quality and validity in terms of the methods and their applications. My expertise is in health economics so my comments will mainly apply to the economic evaluation sections of the report. However, I have noted issues as I read through the rest of the report to provide the perspective for the economic modeling work.	Thank you for your comment.
PR	NETSCC 2	3	Full	General		In the scope there was particular reference to “older men and men who are of black origin” but I did not see any specific reference to them as I read the document. I may have missed it as I went through but I assumed they were highlighted for a specific reason.	Thank you for your comment. The scope identified that men of black origin and older men have a higher prevalence or may be at higher risk of LUTS. Age is identified as a risk factor in one of the recommendations (1.4.5). We did not find any studies with comparative data on men who are of black origin. The guideline development group considered treatment options for men with larger prostates, making specific recommendations for this patient group.

PR	NETSCC 2	4	Full	General		In the methodology section there was no description of economic methods as it mainly focused on clinical aspects.	Thank you for your comment. We disagree as we have described the general economic methods in paragraphs 2.5.2, 2.6.3, and 2.7.2. In addition a thorough description of the methods used in the economic modelling can be found in Appendix F.
PR	NETSCC 2	5	Full	74		In the 4th algorithm there was a part of the diagram that I was not sure what it meant the arrow to active surveillance to specialized treatment to medical treatment appears to be incomplete.	Thank you for your comment. The algorithm has been amended to make this clearer.
PR	NETSCC 2	6	Full	62	4	Probably a typo you have selection criteria A,B,C,F(should be E?)	Thank you for your comment. We have amended this typo error.
PR	NETSCC 2	7	Full	200	24	States that requires similar anaesthesia as TURP but the type is not stated in the TURP section. Is it possible to be consistent in the description of the type of anaesthesia for all the surgical procedures, a few of them do not have it.	Thank you for your comment. After careful consideration we decided the level of details is adequate and we prefer to mention anaesthesia only where it is relevant.
PR	NETSCC 2	8	Full	General		Overall the methods used to develop the economic models generate data to populate the model and the analyses adhered closely guidelines. However, there is some additional information that may be required to understand the methods and appropriateness of choices made.	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree. We think that the methods are adequately covered in Appendix F.
PR	NETSCC 2	9	Full	677	2	Figure 236 (Appendix F) under the model structure you have stated The health states are represented by the six blue circles on the top right corner. Does this mean that the bottom two circles (brown or orange color) are different?	Thank you for your comment. The two bottom circles do not represent full health states but only a dimension of it. In fact, men going to the orange circles also have LUTS and their states will be completely defined by the two circles (LUTS+Incontinence and LUTS+AUS) on the top right corner.
PR	NETSCC 2	10	Full	674		The authors have indicated that the perspective of cost analysis was based on that of a health service provider. However, some of the containment products may not be provided the NHS. Was it assumed that the NHS would provide all the containment products? The decision not to use a societal perspective in the	Thank you for your comment. Health economics is part of NICE Guidelines because we aim to achieve efficiency in the use of the NHS budget. This justifies adopting the NHS perspective rather than societal, as stated in the NICE reference case. In our cost analysis we included only the costs

						analysis should be justified.	borne by the NHS and the Personal and Social Services, assuming they would provide containment products.
PR	NETSCC 2	11	Full	688		In the probabilistic sensitivity analysis, no probability distributions were attached to the costs of some of the variables. However, costs of consumables and equipment usually vary due to the different agreements that trusts and manufacturers make. Can the authors justify this lack of variation?	Thank you for your comment. No data were available to define credible distributions on cost of equipment and consumables. So it was not possible to vary these parameters in the probabilistic sensitivity analysis. However, our model concludes that there is a high uncertainty around the cost-effectiveness of HoLEP versus TURP, and this conclusion would not be altered if a probability distribution on cost of equipment and consumables was added to our analysis.
PR	NETSCC 2	12	Full	690		Table 11 Appendix F page 690 the fourth row from the top is this a word missing it is not clear what this means	Thank you for your comment. We have amended the table.
PR	NETSCC 2	13	Appendix F	General		Appendix F needs to be proof read as there was reference to section 10.5.1-12 and 10.6.1-? that I could not find where they were.	Thank you for your comment. We have amended the text accordingly.
PR	NETSCC 2	14	Full	695	13	Figure 239 Maybe a personal preference for choice of words but could you use circles in the description instead of round boxes	Thank you for your comment. We have amended the wording accordingly.
PR	NETSCC 2	15	Full	703		Table 22 has some information that has been reported in tables 15 and 16 is it possible to put the values here as this table is a good summary of the parameters used. There is a huge blank space and also it is possible to explain why no probability distribution is attached to these parameters.	Thank you for your comment. We agree. We have added the information in Table 22 as well. Probability distributions were not attached directly to those parameters because in the model they are functions of IPSS changes for which distributions were assigned. Probability of success was therefore varied in the probabilistic sensitivity analysis according to the distribution of IPSS change. We have amended Table 22 to make this clear.
PR	NETSCC 2	16	Full	General		In the economic models I did not see any mention of the two groups of men that had been singled out in the scope. It is possible to explain why these two groups	Thank you for your comment. The economic models were based on the systematic review of clinical evidence. In the clinical studies

						were not focused on in the economic analysis.	included in our systematic review there was no subgroup analysis for the two groups identified in the scope. Therefore a subgroup analysis in the economic models was not possible.
PR	NETSCC 2	17	Full	General		The recommendations are based on the findings and are justified given the evidence and all the aspects of the evidence are complete	Thank you for your comment.
PR	NETSCC 2	18	Full	General		Yes important limitations of the evidence have been clearly described and discussed.	Thank you for your comment.
PR	NETSCC 2	19	Full	General		Given the substantial volume of work presented in this report, it is well presented and readable. However, the document would benefit from some further proofing especially the numbers of title headings.	Thank you for your comment. We agree. We have completed further proof reading of the document.
PR	NETSCC 2	20	Full	General		The research recommendations are clearly stated based on the evidence gathered in the study	Thank you for your comment.
SH	NHS Direct	1	Full	General		Guidance welcome by NHS Direct. No specific comments related to content.	Thank you for your comment.
SH	Royal College of Nursing	1	Full	General	General	The RCN welcomes this guideline. Excellent attention to detail has been given with respect to continence products devices and advice.	Thank you for your comment.
SH	Royal College of Nursing	2	Full	general	general	The guideline has been long awaited in the hope that it would clarify what interventions can be completed in primary care under the direction of the GP. There is no mention of nurse led clinics and the recommended parameters of practice. The NICE Urinary Infection in women is specific in primary care and secondary care interventions.	Thank you for your comment. Service provision was outside the scope of the guideline. We have made recommendations on diagnosis at initial and specialist assessment and this provision should be organised locally.
SH	Royal College of Nursing	3	Full	General	General	As the document does not clarify the distinction between primary and secondary services, commissioners are most likely to use the Urology Commissioning guidance (copy attached) which states that all LUTS should have a urology consultant lead. We are aware that in some areas, urology consultants stopped the primary care LUTS clinics as they felt it would destabilise the acute urology services if the	Thank you for your comment. Service provision was outside the scope of the guideline. We have made recommendations on diagnosis at initial and specialist assessment and this provision should be organised locally.

						income was lost. This reduces options for community based services.	
SH	Royal College of Nursing	4	full	80	3	It is not made clear who should be doing the initial assessment, either a urologist, specialist nurse etc. Properly trained specialist nurses within the community are best placed to assess and medically manage these patients, with of course access to secondary care where necessary. This is the most cost-effective way of managing these patients, which also addresses issues of choice, access and care closer to home, freeing up the urologists' time to deal with more urgent and fast-track referrals.	Thank you for your comment. Service provision is outside the scope of this guideline. We have used the term initial assessment as a generic term. We feel that it does not matter which healthcare provider performs this assessment provided that they are competent to do so. For the majority of men, this may indeed be their general practitioner but this responsibility may vary depending upon local healthcare provision. We have added 'initial' and 'specialist assessment' definitions into the glossary and in the NICE version to clarify what we mean by these terms.
SH	Royal College of Nursing	5	full	94 4.10.4	1	We feel that though there may be limited evidence to support scanning a patient at the initial assessment, in practice it seems to be a logical and necessary part of an assessment for LUTS.	Thank you for your comment. After careful consideration, we came to the conclusion that we do not agree. As there is no evidence available we think that imaging is unnecessary at initial assessment. However, we have amended the recommendation to 'do not routinely offer' as in some specific cases it may be appropriate.
SH	Royal College of Nursing	6	full	96	4.10.4	As per our comments above, specialist assessment is undertaken by a number of specialist nurse-led community based Bladder and Bowel Services which include flow rate/post void residual. There should be a distinction about specialist services and where they are carried out in community care by specialist nurses linked but not part of a urology dept i.e. then they can make direct referrals, but clinics do not come under the urologists codes. This should be classed as specialist clinics run by specialist nurses. This keeps costs down, where Acute Trust and consultants HRG4 are expensive and under	Thank you for your comment. Service provision is outside the scope of this guideline.

						Transforming Community Services means that patients are seen closer to home…this is especially important in areas that are very rural.	
SH	Royal College of Nursing	7	full	96	4.10.4	There should be a general statement that where there are specialist nursing led clinics that are supported by urologists that these should be 1st referral to initial specialist services rather than secondary care….but only where they are fully supported and where staff have training that has been supervised by the local urologists and where there are partnership agreements.	Thank you for your comment. Service provision is outside the scope of this guideline.
SH	Royal College of Pathologists	1	FULL	General		The management of lower urinary tract symptoms (LUTS) in men is essentially clinical and does not usually require pathological evaluation of tissues at the time of diagnosis. The initial assessment of men with LUTS should occur at the level of Primary Care. In this respect, completion of a Urinary Frequency Volume Chart could become a routine procedure before an individual patient is referred to an Urologist for specialist management. Part of this recommendation might be to raise awareness, at Primary Care level, of the value of Urinary Frequency Volume Charts. Measurements could be handled by trained nurse-specialists before referral to the Primary Care Physician.	Thank you for your comment. We agree. We have recommended that men with bothersome LUTS should be offered a urinary frequency volume chart at initial assessment.
SH	Royal College of Pathologists	2	FULL	General		LUTS most commonly occurs in men of the same age-group as that in which prostate cancer is common. The two diagnoses are not physiologically related since LUTS is not a normal sequel to prostate cancer and neither is long-standing LUTS an aetiological factor in the causation of prostate cancer.	Thank you for your comment. We agree that evaluating prostatic carcinomas is an interesting question but it is outside of the scope of this guideline.

						Since part of the later management of LUTS may require transurethral prostatic resection (TURP), it is not infrequent that a previously occult prostatic carcinoma becomes pathologically evident. At the time of its diagnosis, it is imperative that pathological evaluation is made by an experienced urological pathologist who establishes whether the carcinoma is central (transition zone) in origin or is a peripheral carcinoma that, through local invasion, impinge on the peri-urethral tissues being resected. In this respect, there is an onus on pathologists to recognise the morphological differences between transition zone and peripheral carcinomas since these are behaviourally distinct.	
SH	Royal College of Pathologists	3	FULL	General		Biomarkers are now available (e.g. HSP-27)[1,2] with which to assess the probable phenotypic behaviour of prostatic carcinomas. These should be used in the management of any newly-diagnosed prostate cancer so that the patient, now treated for his LUTS, is not turned into a "cancer victim". Wherever biologically appropriate, patients with newly-diagnosed prostate cancer should be reassessed and managed conservatively until appropriate indications for active intervention.	Thank you for your comments. The management and detection of prostate cancer is beyond the scope of the current guideline. Please refer to the NICE guidance on Prostate Cancer: diagnosis and management on the NICE website.
SH	The Prostate Cancer Charity	1	Full	General		The Prostate Cancer Charity welcomes this guideline and believes it will make a valuable contribution to the management of men with Lower Urinary Tract Symptoms (LUTS). The Charity also believes it will provide excellent information that will help both the organisation's Information and Helpline Teams provide quality information to men who want to know more about LUTS.	Thank you for your comment.

SH	The Prostate Cancer Charity	2	Full	82 (4.3)	15	The guideline states that prostatitis is “also known as chronic pelvic pain syndrome”. Strictly speaking that is only true of chronic prostatitis.	Thank you for your comment. We agree. We have clarified this in the text by referring to ‘chronic prostatitis’ rather than ‘prostatitis’.
SH	Uromedica, Inc	1	Full	53 2.9.1	3	My comments are as follows: In the Recommendation section on intramural injectables, implanted adjustable compression devices and male slings, “other considerations”, mention is made of the NICE interventional procedure (256), considering male slings a safe and efficacious procedure. As you state on page 288, lines 1-3, there are a wide range of techniques, concepts and materials ion this area, making evaluation of “slings” as a group difficult. With this in mind it is difficulty to understand that the adjustable compression devices are not also considered to be safe and efficacious (based on IPG 224). The amount of evidence published in peer reviewed journals on this technique (which does not consist of a wide range of techniques, concepts and materials) equals that published on male slings (which is however based on a multitude of different products. WE would suggest that it is time to review the earlier IPG 224 and update this based on material published since 2007. All articles demonstrate that this is a minimally invasive procedure (less invasive than male slings) with good outcomes (also in the longer term). The procedure is considered safe, with complications tending to be mild and easily managed, procedure is easily reversible, which can not be said of male slings.	Thank you for your comment. Updating interventional procedures are outside the remit of this guideline. We will pass your comments onto NICE.
SH	Uroplasty	1	Full	69	6	My comment is as follows. Include: “Consider offering peripheral Percutaneous Tibial Nerve Stimulation (PTNS) a minimally invasive peripheral neuromodulation therapy to manage detrusor overactivity to men whose symptoms have not responded to conservative management and drug treatments before offering more invasive surgery”.	Thank you for your comment. Percutaneous tibial nerve stimulation (PTNS) was not prioritised as a clinical question and has therefore not been included in the guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for

						Rationale: There are numerous articles that demonstrate clinical effectiveness for Percutaneous Tibial Nerve Stimulation (PTNS) with a very low adverse events profile for both male and female patients. None of the published studies include ONLY male patients so would not have been found in a gender specific literature search. There are also no specific studies on implantable Sacral Nerve Stimulation for only male patients. The International Consultation on Incontinence Paris, 2008 recommended grade D for neuromodulation in male, due to lack of evidence. The recent publication on PTNS by Peters, K. et al (*Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: Results from the Overactive Bladder Innovative Therapy Trial. J Urol 2009; 182: 1055-1061*) shows that success rates of PTNS treatment for overactive bladder symptoms is comparable to and with respect to adverse events are better than drugs. This reference was outside the timeframe of the literature search, and includes both female and male subjects, so it would not have been found with a search criteria of "male only studies." Other publications also support PTNS effectiveness in the treatment of overactive bladder symptoms (*MacDiarmid SA, Staskin DR, Percutaneous tibial nerve stimulation (PTNS) A literature-based assessment. Current Bladder Dysfunction Reports 2009; 4: 29-33*). This publication includes a meta-analysis 244 patients in 7 studies with 71% of the patients responding with statistically significant improvements in daily voids, nighttime voids, voided volume, incontinence episodes, quality of life measures. Most of the published studies present data for female and male subjects with the consequence that these	overactive bladder syndrome) so there will be advice on this procedure. In addition the cut off date for our literature search was 17 June 2009 and in order to be consistent and systematic we will not consider papers after this date. Also, the papers mentioned do not meet the inclusion criteria agreed by the GDG as they are mixed male and female studies.

						studies would also have been excluded from the review if a “male only study” search criterion was used. The success rates of PTNS was reported by gender in an abstract presented at EAU 2007, Eur Urol 2007; Suppl 6(2):141 This also not reviewed in this consultation. The results show efficacy of PTNS for treatment of OAB symptoms in both men (45%) and women (66%).	
SH	Uroplasty	2	Full	73	1	In the algorithm 3: Storage symptoms, the box with: “If treatment fails (possible detrusor overactivity), arrange multichannel cystometry with a view to discussing bladder wall botulinum, implanted sacral nerve root stimulation, and cystoplasty.” My comment is as follows: Per the rationale of comment 1, percutaneous tibial nerve stimulation should be added as the most minimally invasive option with the lowest adverse event profile compared to the other treatments currently listed: If treatment fails (possible detrusor overactivity), arrange multichannel cystometry with a view to discussing *percutaneous tibial nerve stimulation*, bladder wall botulinum, implanted, sacral nerve root stimulation, and cystoplasty.	Thank you for your comment. Percutaneous tibial nerve stimulation (PTNS) was not prioritised as a clinical question and has therefore not been included in the guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Uroplasty	3	Full	286	37	The sentence: “This can be done by the application of external electrodes to appropriate dermatomes, temporary implantation of electrodes e.g. posterior tibial nerve stimulation, or by permanent implantation” My comment is as follow: This can be done by the application of external electrodes to appropriate dermatomes, temporary implantation of electrodes e.g. peripheral percutaneous tibial nerve stimulation, or by permanent implantation.”	Thank you for your comment. Percutaneous tibial nerve stimulation was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.

SH	Uroplasty	4	Full	291	1	My comment, based on the rationale of comment 1 , is to include a new recommendation to chapter 9.3 as follows: *Recommendation* Consider offering peripheral Percutaneous Tibial Nerve Stimulation (PTNS) to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments before offering more invasive surgery." Relative values of different outcomes Symptom score, relief of incontinence, adverse events and quality of life as primary outcomes demonstrate statistically significant improvements with PTNS therapy. Economic considerations This intervention is associated with significantly lower costs and should be offered before more invasive and expensive surgical treatments. Quality of evidence Numerous peer reviewed publications provide compelling clinical evidence of PTNS efficacy. Other considerations This intervention is already in widespread use for both female and male patients without the risks associated with more major and complex surgery.	Thank you for your comment. Percutaneous tibial nerve stimulation (PTNS) was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Uroplasty	5	Full	292	1	The sentence: "Consider offering urinary diversion to manage intractable urinary tract symptoms only to men who symptoms have not responded to conservative management and drug treatments, and if cystoplasty, , or sacral root stimulation are not appropriate or unacceptable." My comment is as follows: "Consider offering urinary diversion to manage intractable urinary tract symptoms only to men whose symptoms have not responded to conservative management,drug treatments, or percutaneous tibial nerve stimulation and if, cystoplasty, or, sacral root stimulation are not	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree. Percutaneous tibial nerve stimulation was not prioritised for inclusion in the scope of this guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.

						appropriate or unacceptable."	
SH	Uroplasty	6	NICE	16	1.6.5	My comment is as follows. Include based on the rationale of comment 1: "Consider offering peripheral Percutaneous Tibial Nerve Stimulation (PTNS) to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments before offering more invasive surgery".	Thank you for your comment. After careful consideration we came to the conclusion that we do not agree. Percutaneous tibial nerve stimulation (PTNS) was not prioritised as a clinical question and not included within the guideline. Please note that NICE is currently evaluating PTNS for its safety and efficacy under their Interventional Procedure Programme (IP 822 percutaneous tibial nerve stimulation for overactive bladder syndrome) so there will be advice on this procedure.
SH	Welsh Assembly Government	1	NICE	5 "Patient-Centred Care"	6-9	The text currently reads: *"If men do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk)."* Could the following text be added to reflect that similar guidance has been issued in Wales: *"In Wales, healthcare professionals should follow the guidance issued by the Welsh Assembly Government in 2008* – 'Reference Guide for Consent to Examination and Treatment' (*available from www.wales.nhs.uk/consent)"*	Thank you for your comment. We agree. We have added text to the NICE versions "Patient Centred Care" section to reflect that similar guidance has been issued in Wales.