The management of lower urinary tract symptoms in men

Appendices F – H

DRAFT FOR CONSULTATION

APPENDICES

Produced by the National Clinical Guidelines Centre for Acute and Chronic Conditions

Contents

Appendices A–E are in separate files.

Appendix F - Cost-effectiveness analysis

1.1 Introduction

Two original cost-effectiveness analyses were carried out to answer the clinical questions on transurethral resection of the prostate (TURP) vs. laser (Chapter 8), and the clinical question on Alpha-blockers (AB) alone or in combination with 5-Alpha Reductase-Inhibitors (5-ARI) (Chapter 6). Throughout the guideline we refer to these two analyses respectively as 'NCGC Surgery Model' and 'NCGC Combination model'.

1.2 Methods

A review of the literature was conducted followed by economic modelling of the cost-effectiveness of the listed interventions in England and Wales. The literature search and review methods can be found in Chapter 2.

Our aim in constructing the models was to determine the most cost-effective strategy in men considering respectively surgery and medical treatment. Those would be mainly men with moderate to severe lower urinary tract symptoms (LUTS).

We found a number of economic evaluations in the published literature (Chapters 6 and 8), among which a Health Technology Assessment (HTA) model of good quality[150]. However the Guideline Decisional Group (GDG) felt that they needed an original model with slightly different assumptions and data in order to make a recommendation with confidence.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- We followed the methods of the NICE reference case[186]. Therefore costs were calculated from a health services perspective. Health gain was measured in terms of quality-adjusted life-years (QALYs) gained. Both future costs and QALYs were discounted at 3.5%.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained.
- The model was peer-reviewed by another health economist at the NCGC.

1.2.1 Software

The cost-effectiveness analyses were conducted using TreeAge Pro 2008.

1.3 NCGC Surgery model

1.3.1 General method

We based the model on two of the main outcomes considered in our systematic review of the clinical evidence (Chapter 2.4): mean IPSS change from baseline and adverse events. We chose IPSS change because it better expresses the change in quality of life as felt by the patient compared to other clinical measures such as Qmax. Consequently, it was easier to find data linking utility values to levels of symptoms.

Since LUTS are a lifelong condition, we built a Markov model with a life time horizon and we changed this in a sensitivity analysis. The cycle length is three months, as this was deemed the minimum clinically meaningful time interval to detect differences in patients undergoing surgery.

All the probabilities, costs and health utilities were converted in order to reflect the three-month values.

The treatments compared in our analysis are TURP and Holmium Laser Enucleation of Prostate (HoLEP). TURP is the current standard practice and HoLEP was one of the alternative treatments that were significantly effective as compared to TURP. Transurethral electrovaporisation of prostate (TUVP) was another effective treatment as compared to TURP but the available economic evidence was considered sufficient to prove it cost-effective.

Patients in the studies included in our clinical review had a moderate-to-severe level of symptoms. Therefore patients in our model were defined as men with moderate-to-severe LUTS who are suitable for either TURP of HoLEP.

Both arms of the model have the same structure (Figure 237): after the intervention, the patient can either have a significant remission of symptoms (success) or no remission/minor remission (failure).

Short-term complications identified in the clinical review (see Appendix E) were assumed to be resolved within 3 months (the cycle length) and could occur with a probability independent from the success. Incontinence is the only long-term adverse event and in some cases it requires an artificial urinary sphincter (AUS). If the man still has storage LUTS together with incontinence, he will not undergo further de-obstructive surgery, therefore he will remain in this health state throughout the model.

Men who initially had a successful outcome can have deterioration in symptoms and end up with residual LUTS state. Some of them will undergo further de-obstructive surgery if incontinence is not present, and some will be medically treated. The second surgery is always TURP, even in the HoLEP arm, as the experts in the GDG believe that HoLEP is unlikely to be performed twice. We

varied the structure between the two arms in a structural sensitivity analysis where we assumed TURP was not possible after HoLEP either.

The list of the health states that are part of the model is reported in Table 1.

Table 1 - Health states

HEALTH STATES
(Moderate-to-Severe) LUTS
Remission
LUTS + Incontinence
LUTS + Incontinence AUS
Incontinence
Incontinence AUS

The experts of the GDG members have defined a significant remission of symptoms after surgery as a change in IPSS greater than five. This was agreed after considering that the minimally important difference is estimated as 3 points (Barry1998) but a more consistent improvement is expected after an invasive intervention. It was agreed that a change by 5 points would constitute a treatment success.

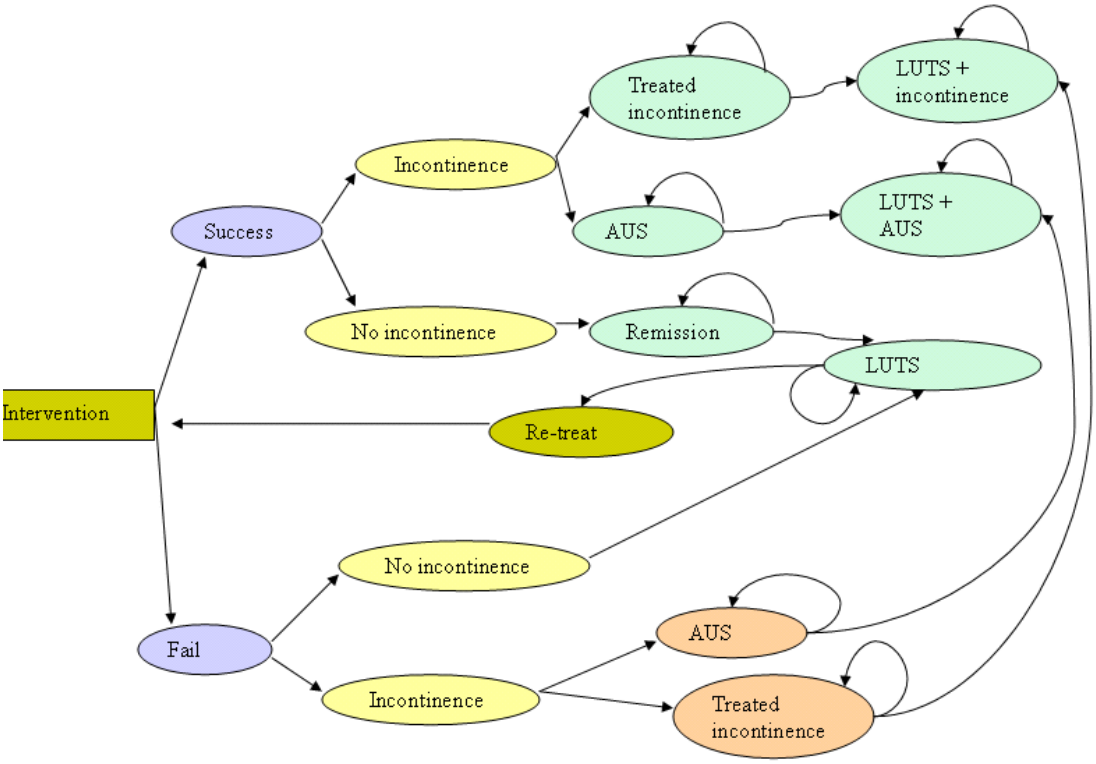

Figure 1 - Model structure. The health states are represented by the six blue circles on the top right corner. The arrows represent the possible transitions from a state to another or to the same state.

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each state and then multiplying them by the proportion of patients who would be in that state as determined by the strategy taken.

We performed a probabilistic sensitivity analysis (SA) to test the robustness of the results against the imprecision of these estimates and the other model parameters, and to obtain more accurate estimates of expected costs and QALYs.

We identified sensitive parameters with a threshold analysis and then conducted multi-way sensitivity analyses on those parameters at decision point.

1.3.2 Key assumptions

The experts in the GDG were consulted in order to make the following assumptions:

a) After a relapse in symptoms, only 5% of patients will undergo a second TURP. The remaining 95% are treated medically.

b) The probability of success of the same intervention when performed a second time is 75% the probability of success when performed for the first time.

c) The proportion of men with incontinence after surgery/laser requiring an AUS is 5%. The remaining 95% are treated medically or with incontinence products (catheters, pads, etc).

1.3.3 Probability of success - TURP

We searched for an RCT which reported the probability of success of either TURP or HoLEP as defined in our model (change in IPSS≥5). We found only one large multicentre RCT[83] where 120 of the randomised patients received TURP while the other 115 received TUVP. Data from this study[83] that were used in the model are reported in Table 2.

Table 2 - Data on TURP used in the model (a)

	Data used in the model
IPSS at baseline (IPSS pre)	20.7 (SD 6.9)
IPSS at 6 months (IPSS post)	6.9 (SD 5.5)
Probability of success of TURP at 6 months	85.4%
Probability of success of TURP at 24 months	84.0%

(a) From Fowler et al. (2005)[83]

1.3.4 Probability of success - HoLEP

We could not find similar data for HoLEP so we adopted an alternative approach, linking the probability of success of the two interventions using the IPSS change data from our clinical review.

Table 3 - Effectiveness from meta-analysis

	HoLEP vs. TURP
Weighted Mean Difference (WMD) from baseline IPSS at 6 months	- 0.52
WMD from baseline IPSS at 24 months	- 0.80

1.3.4.1 Setting up the precondition

IPSSpost is the mean IPSS after the intervention and it is equal to:

I IPSSpost = Psuccess * IPSSsuccess + (1-Psuccess) * IPSSfail

Where IPSSfail and IPSSsuccess are respectively the mean IPSS in the group of patients whose treatment has failed and the mean IPSS in the group of patients whose treatment was successful.

By assuming that IPSSfail is the same for both TURP and HoLEP and also that IPSSsucess is the same for both, we can estimate the success rate for HoLEP.

1.3.4.2Deriving IPSS after a TURP failure

II IPSSfail = IPSSpre - ΔIPSSfail

Where ΔIPSSfail is the change in IPSS in patients for whom the intervention has failed. By definition this must be ≤4. Assuming in some patients the symptoms might have deteriorated, we can consider the range -1 to 4, and use the central value 1.5, which is then varied in a sensitivity analysis. Substituting this value in II and using the data from TURP we get IPSSfail = 20.7 – 1.5 = 19.2

1.3.4.3Deriving IPSS after a successful TURP

We can rearrange equation **I** as

III IPSSsuccess = (IPSSpost- (1-Psuccess)xIPSSfail)/P(success)

Using data from Table 2 and our result for IPSSfail from 10.5.4.2 we get:

IV IPSSsuccess = (6.9 –14.6%*19.2)/85.4% = 4.8

1.3.4.4Deriving IPSS after HoLEP

The mean difference in change in IPSS from baseline to 6 months was -0.52 compared with TURP (Chapter 8.3.1). The IPSS 6 months after HoLEP is simply the IPSS at 6 months for TURP plus this difference:

V IPSSpost=6.9-0.52=6.4

1.3.4.5Calculating the probability of HoLEP success at 6 months

We rearranged equation **I** to give us:

VI Psuccess= (IPSSpost-IPSSfail)/(IPSSsuccess-IPSSfail)

Substituting the values derived above (10.5.4.2, 10.5.4.3, 10.5.4.4) we get:

VII Psuccess = (6.4-19.2)/(4.8-19.2) = 88.9%

1.3.5 Probability of relapse

According to the data reported in Fowler et al (2005)[83], TURP was more effective after 6 months than after 24 months, as only 84% of patients had an improvement in symptoms by at least 5 points at 24 months compared to 85.4% of patients at 6 months Table 2. To mimic what happens in real practice, where a relapse in symptoms sometimes follows an initial improvement, it was necessary to incorporate a time-dependant probability of relapse after an initial success.

The probability of relapse between these two intervals (6 months and 24 months) is calculated as follows:

VIII (P success 6 months – P success 24 months)/P success 6 months

Which in case of TURP is equal to (85.4% - 84%)/85.4% = 1.6%

We converted the probability of relapse of TURP over 18 months into a 3-month rate, which is the cycle length of the model, by using the formula:

IX 1 - exp((ln(1- relapse18months))/6)

We used the same probability of relapse for HoLEP (a conservative assumption).

1.3.6 Probability of complications

Several complications of HoLEP and TURP were identified in the systematic review (Appendix E). In our economic model we only included those that would require additional treatment and generate additional costs.

To calculate the probability of complications following TURP (Table 4), we aggregated data from the TURP arm in every study included in our review, excluding the duplicates. We then compared the incidences of adverse events after TURP with those reported in the AUA[11] and we found no considerable difference.

The incidence of complications following HoLEP (Table 4) was estimated by multiplying their probability after TURP by the risk ratio (RR) of HoLEP compared to TURP.

Table 4 - Probability of complications

	TURP	**HoLEP**	
	Probability	RR vs. TURP	Probability
Incontinence	4.0%	1.19	4.8%
Blood transfusion	6.2%	0.27	1.8%
Acute urinary retention (AUR)	3.9%	0.71	2.8%
Urinary tract infections	6.9%	0.45	3.1%
Transurethral syndrome	2.0%	0.31	0.6%
Strictures	7.2%	0.69	5.0%

All the adverse events were assumed to occur within three months after the intervention, and so within the same cycle in the model. All of them have associated one-off costs (see 10.5.11) and no detriment in quality of life with the exception of incontinence which has a lifetime cost and disutility (10.5.8).

1.3.7 Life expectancy

The mean age of the men when entering the model was 71 as this was the mean age of men in the diagnosis-related group 'Hyperplasia of prostate' in the Hospital Episode Statistics 2006/07.

Life expectancy in patients with LUTS was assumed to be the same as the general population in England and Wales. The remaining life expectancy for men aged 71 is 12.99 years, as reported in the Life Tables for the general

population of England and Wales in the year 2005-2007 from the Government Actuary Department (http://www.gad.gov.uk/Documents/Demography/EOL/ILT%202005-07/wltewm0507.xls).

1.3.8 Quality of life

The utility scores in Table 5 are a measure of the quality of life associated with LUTS and incontinence. A systematic search for quality of life in men with LUTS and with incontinence was performed (Appendix C). Studies were included if they reported utility values for the states of LUTS or incontinence.

Studies reporting utilities specific to non-compared interventions were excluded.

Two studies[18,173] were excluded because the values were obtained from consensus rather than from patients or general public.

Kok et al (2002)[130] reported utility values according to the obstructive and irritative dimension of IPSS. However, using this study to estimate an average utility score for LUTS would have required further assumptions on the nature of the symptoms.

Ackerman et al (2000)[6] assessed the preference of 13 patients to health states with the standard gamble technique. We excluded this study due to the small sample size but we used it as an alternative source of data in the sensitivity analysis.

Trueman et al (1999)[256] designed a survey to collect EQ-5D scores by symptoms severity in 1115 men in the UK. The results of this study[256] were used in our model and are reported in Table 5. Although the population in the model is made of men with moderate-to-severe LUTS we used the utility value for severe LUTS as 20.7 was the average IPSS of this population.

We found a UK study[50] reporting the deterioration in quality of life caused by incontinence. A multivariate analysis of EQ-5D scores, found that after controlling for age, gender and body mass index, incontinence was associated with a reduction in the EQ-5D score by 0.11 (SE 0.026). This value was subtracted from the remission and LUTS utility scores for the health states respectively characterised by symptoms remission and Incontinence and LUTS and Incontinence. The values thus obtained are reported in Table 5.

Among patients with incontinence, 5% require an artificial urinary sphincter while the remaining 95% are treated pharmacologically or with incontinence products. The utility score does not differ for these two subgroups.

Other adverse events were assumed to be negligible in terms of quality of life because they could be promptly treated.

Table 5 - Utility values

	Utility score
Remission (a)	0.91
LUTS (a)	0.71
Remission + Incontinence (a, b)	0.80
LUTS + Incontinence (a, b)	0.60

(a) *Source: Trueman at al (1999)*[256]
(b) *Source: Currie et al (2006)*[50]

1.3.9 Calculating QALYs gained

For each strategy, the expected QALYs in each cycle are calculated as follows:

X **Expected QALYs = Σ (U_i x P_i)**

where

U_i = the utility score for health state i

P_i = the proportion of patients in health state i

and where health state i could be any of the health states reported in Table 1.

The proportion of patients in each health state depends on the effectiveness of the treatment, in terms of symptoms improvement and incontinence, and on the proportion of patients still alive, which falls as the number of cycles and therefore age increases.

The overall *lifetime expected QALYs* are given by the sum of QALYs calculated for each cycle. The *incremental QALYs gained* associated with a treatment strategy are calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

1.3.10 Cost of interventions

We adopted a bottom-up approach to calculate the intervention cost as differentiating the total costs for the two intervention was not possible by using national sources (NHS Reference Costs or Tariffs) or published evidence. In fact, no UK study could be found which reported the cost of HoLEP as this is performed only in a few UK centres only while TURP is a widespread technique. For this reason we decided to include only the capital cost of the HoLEP equipment as the TURP equipment is already present in every Urology centre. Only disposables used in TURP were included in the calculation.

We contacted the UK supplier of HoLEP equipment (SIGMACON) to obtain precise data on the cost of the machine and the cost and number of uses of disposables. We assumed the life span of the machine is 10 years. As we want to estimate the cost of the machine per patient, the GDG had to estimate the number of patients per centre undergoing surgery for LUTS in a year.

We found the cost of TURP disposables in a study[83] and the GDG estimated the number of uses. The data thus collected are reported in Table 6.

In addition to the cost of equipment, other factors influencing the total costs are the operating theatre cost, the length of stay after the intervention, and the complications. The costs of operating theatre and hospital stay are reported in Table 6 while the costs of complications are described in 10.5.11.

Table 6 – Resources used and costs

	HoLEP	Source
Cost of HoLEP machine	£150,000	UK supplier (SIGMACON)
Lifespan of HoLEP	10 years	Assumption
Number of patients per year per HoLEP machine	280	Expert opinion
Cost of morcellator blades (HoLEP)	£595 each	UK supplier (SIGMACON)
Number of uses per blade	10	UK supplier (SIGMACON)
Cost of fibres (HoLEP)	£550 each	UK supplier (SIGMACON)
Number of uses per fibre	20	UK supplier (SIGMACON)
Cost of loops (TURP)	£47	Expert opinion
Number of uses per loop	10	Expert opinion
Operating time TURP	60 minutes	Systematic review (Appendix E) (a)
Operating time HoLEP	75 minutes	Systematic review (Appendix E) (a)
Cost of urology operating theatre	£9 per minute	Local cost estimate
Median length of hospital stay after TURP (b)	3 days	Hospital Episode Statistics 2006/07
Median length of hospital stay after HoLEP (b)	2 days	Hospital Episode Statistics 2006/07
Mean cost per bed day	£204	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG LB25C

(a) *Mean number of times reported in Gupta et al (2006)[97] and Montorsi et al (2004)[177].*
(b) *The median was used as an estimate of the mean to exclude outliers probably due to complications.*

The annual cost of the HoLEP machine is a function of the capital cost of the machine, its life span and the discount rate according to the formula:

XI $E = K*r/[1-(1+r)^{-n}]$

where E = annual cost of the machine

K = capital outlay (cost of purchasing the machine)

r = discount rate / interest rate = 3.5%

n = lifespan

The total cost of a single intervention can be represented by the formula:

XII $TCi = E/np + cDisp_i + opT_i*cTheatre + cComp * pComp_{A-i}$

Where TC_i = total cost of the intervention i

E = annual cost of machine (only HoLEP)

np = number of patients using the machine per year

$cDisp_i$ = cost of disposables of intervention i

opT_i = operating time of intervention i

cTheatre = cost of theatre per minute

$cComp_A$ = cost of treating complication A (Table 7)

$pComp_{A-i}$ = probability of complication A after intervention i (Table 4)

where i is either TURP or HoLEP and A is any complication described in Table 7.

1.3.11 Cost of complications

The complications included in the model and their probabilities are reported in 10.5.6. The GDG estimated the resources used to treat each complication as shown in Table 7 with the exception of acute urinary retention for which we used a UK economic study[14]. When a procedure could be performed as a daycase or inpatient, we checked this proportion in the Hospital Episode Statistics 2006/07 [2].

Table 7 - Cost of complications

	COST	SOURCE
Blood transfusion	£635 (a)	Varney et al (2003)[266]
Stricture	£706 (b)	National Schedule of Reference Costs 2006-07 – HRG code LB30B
Acute urinary retention	£2,029 (c)	Annemans et al (2005)[14]
Trans-urethral syndrome	£1,710 (d)	National Schedule of Reference Costs 2006-07: 1) High Dependency Unit – 0 organs supported XC07ZHDU; plus 2) Excess bed day - HRG LB25C
Urinary tract infections	£742 (e)	National Schedule of Reference Costs 2006-

		07– HRG code LA04C

(a) *cost of a transfusion of red blood cells*
(b) *weighted cost - £509 x 54%(daycase) + £938 x 46%(inpatient)*
(c) *cost of the most cost-effective intervention to treat AUR in the study*
(d) *cost of tow days in HDU and two days in normal ward*
(e) *weighted cost - £376 x 10%(daycase) + £783 x 90%(inpatient)*

Incontinence is a complication but it is also a health state in the model so its cost is calculated separately in 10.5.12.

1.3.12 Cost of health states

The possible health states in which a patient could be in the model are listed in Table 1. By collecting information on the resources used while in these states from the GDG experts, we calculated the costs reported in Table 8.

When the patient has a remission of symptoms, we assumed no further treatment would be necessary and this state has no cost associated.

If after the intervention a patient still has LUTS, he would undergo urodynamic studies to investigate the cause of the intervention failure. He would then be treated with either anticholinergics or alpha-blockers and be recalled for a visit every six months. We assumed that 50% would be treated with anticholinergics and 50% with alpha-blockers. The details of the cost calculations are reported in Table 8.

Table 8 - Cost of residual LUTS state

Resources used	Proportion of patients using the resource	Unit cost of resource	Total cost per month per patient
Alpha-blockers	50%	£0.35 (a)	£5.32
5mg Oxybutynin twice daily	25%	£0.39 (b)	£5.93
Other Anticholinergics	25%	£1.05 (c)	£15.97
One visit every 6 months	100%	£75 (d)	12.50
TOTAL			**£39.72**
Urodynamic studies (one-off)	100%	£165 (e)	**-**

(a) *Average cost per day of Alfuzosin, Tamsulosin, Doxazosin, and Prazosin (BNF 57)*
(b) *Cost of treatment per day (BNF 57)*
(c) *Average cost per day of Darifenacin, Solifenacin, Tolterodine, Trospium, Propiverine and Fesoterodine (BNF 57)*
(d) *From National Schedule of Reference Costs 2006-07– Consultant led follow-up attendance – outpatient face-to-face – Urology*
(e) *From National Schedule of Reference Costs 2006-07 - Outpatient procedure LB42Z*

To estimate the cost of incontinence in men treated with drugs or products we searched for UK cost-of-illness studies excluding those studies conducted in women. We did not find any so we estimated the resources and their costs with the help of experts from the GDG (Table 9).

Table 9 - Cost of incontinence in men treated with products or drugs

Resources used	Proportion of patients using the resource	Unit cost of resource	Total cost per month per patient (f)
3 ISC catheters per day	25%	£1.30	£29.66
1 indwelling catheter every 6 weeks	25%	£6.00	£1.08
5mg Oxybutynin twice daily	50%	£0.39 (a)	£5.93
Other anticholinergics	50%	£1.05 (b)	£15.97
1 pad a day	25%	£0.34	£2.58
1 leg bag per week	25%	£2.50	£2.71
1 overnight bag per night	25%	£0.10	£0.76
1 bag support, leg sleeve and Stalock Bard per week	25%	£6.00	£6.50
Sheath appliances	25%	£40.00 (c)	£10.00
1 district nurse visit per week	100%	£21.00 (d)	£91.00
1 specialist nurse visit every 6 months	100%	£66.00 (e)	£11.00
TOTAL			**£177.19**

(a) Cost of treatment per day (BNF 57)
(b) Average cost per day of Darifenacin, Solifenacin, Tolterodine, Trospium, Propiverine and Fesoterodine (BNF 57)
(c) Estimate on cost per month rather than number of items.
(d) From Curtis (2008)[51] – cost of district nurse per home visit including travel, excluding qualification
(e) From Curtis (2008)[51] – cost of specialist nurse per hour of client contact, excluding qualification
(f) These figures account for the proportion of patients who use that resource

In the model, 5% of the men with incontinence have an AUS implanted. The costs associated with this intervention are the one-off cost of urodynamic studies, the cost of implanting the AUS and the recurrent visits. The AUS needs to be re-implanted on average every ten years and this is taken into account in the model with a recurrent cost of the operation (Table 10).

Table 10 - Cost of artificial urinary sphincter (AUS)

Resources used	Frequency	Unit cost of resource	Source of cost
AUS implant	10 years	£4,137	National Schedule of Reference Costs 2006-07– HRG code LB21Z
Urology visit	6 months	£75	National Schedule of Reference Costs 2006-07– Consultant led follow-up attendance – outpatient face-to-face – Urology
Urodynamic studies	One-off	£165	National Schedule of Reference Costs 2006-07 - Outpatient procedure LB42Z

The costs associated with the 'LUTS + Incontinence' state are similar to the costs of the Incontinence state, while the 'LUTS + Incontinence AUS' state generates the same costs as the 'LUTS+Incontinence AUS' state with the addition of the anticholinergics (in 50% of the men) and alpha-blockers (in the other 50%).

For each strategy, the expected cost per cohort of patients is calculated as follows:

XIII Expected cost $= C_s + \sum_{j=1}^{40} \sum_{i=1}^{6} C_i P_{ij}$

where

C_s = cost of the initial strategy (TURP or HoLEP)

C_i = cost of health state i

P_{ij} = proportion of patients in health state i in cycle j

and where health state i could be any stage in Table 1.

The proportion of patients in a health state depends on the magnitude of the improvement in symptoms specific to each treatment, its probability of causing incontinence, and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected costs are given by the sum of costs calculated for each cycle. The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

1.3.13 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the model results to plausible variations in the model parameters.

Probability distributions were assigned to each model parameter, where there was some measure of parameter variability (Table 11). We then re-calculated the main results 10000 times, and each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random.

Table 11 - Parameters and distributions used in the probabilistic sensitivity analysis

Description of variable	Mean value	Probability distribution	Parameters	Source
IPSS post treatment with TURP after 6 months	6.9	Normal	SD = 0.5102	Fowler et al (2005)[83]
IPSS post treatment with TURP after 2 years	7.5	Normal	SD = 0.6633	Fowler et al (2005)[83]
Initial IPSS	20.7	Normal	SD=0.6633	Fowler et al (2005)[83]

IPSS change when treatment fails	1.5	Triangular	Min=0 Likeliest=1.5 Max=3	Assumption
Weighted mean difference of IPSS at 6 months	0.52	Normal	SD=0.4235	Systematic review of clinical effectiveness
Weighted mean difference of IPSS at 2 years	0.8	Normal	SD=0.9847	Systematic review of clinical effectiveness
Capital cost of HoLEP	£150,000	None		UK Supplier SIGMACON
Lifespan of HoLEP machine (years)	10	Gamma (a)	$\alpha = 61.46$ $\lambda = 6.146$	Assumption
Number of patients per year	280	Gamma (a)	$\alpha = 61.46$ $\lambda = 0.2195$	Assumption
Cost of each blade	£595	None		UK Supplier SIGMACON
Cost of each fibre	£550	None		UK Supplier SIGMACON
Cost of each loop	£47	None		Experts opinion
Number of uses of a blade	10	Triangular (b)	Min=5 Likeliest=10 Max=15	UK Supplier SIGMACON
Number of uses of a fibre	20	Triangular (b)	Min=15 Likeliest=20 Max=25	UK Supplier SIGMACON
Number of uses of a loop	10	Triangular	Min=5 Likeliest=10 Max=15	Experts opinion
Cost of operating theatre per minute	£9	Gamma (a)	$\alpha = 61.46$ $\lambda = 6.829$	Local cost estimate
Operating time – HoLEP (minutes)	75	Triangular	Min=55 Likeliest=75 Max=95	Gupta at al (2006)[97] and Montorsi at el (2004)[177]
Operating time – TURP (minutes)	60	Triangular	Min=45 Likeliest=60 Max=75	Gupta at al (2006)[97] and Montorsi at el (2004)[177]
Cost bed day	£204	Gamma (c)	$\alpha = 4.925$ $\lambda = 0.0241$	National Schedule of Reference Costs 2006-07 Excess Bed Day HRG code LB25C
Hospital stay after HoLEP (days)	2	Triangular (d)	Min=1 Likeliest=2 Max=3	Hospital Episode Statistics 2006/07

Hospital stay after TURP (days)	3	Triangular (d)	Min=2 Likeliest=3 Max=4	Hospital Episode Statistics 2006/07
Cost of residual LUTS state	see 10.5.12	None		NCGC calculations
Cost of incontinence per three months (see 10.5.12)	£510	Gamma (a)	α = 61.46 λ = 0.1205	NCGC calculation of cost of health states
Cost of AUS	£4,137	Gamma (c)	α = 7.089 λ = 0.0017	National Schedule of Reference Costs 2006-07 HRG code L25 – LB21Z
Cost of treating AUR	£2,029	Gamma (a)	α = 61.46 λ = 0.0303	Annemans2005[14]
Cost of treating TUR	See Table 7			
Cost of HDU per day	£651	Gamma (c)	α = 5.096 λ = 0.0078	National Schedule of Reference Costs 2006-07 HDU – 0 organs supported XC07ZHDU
Cost of multichannel cystometry	£165	Gamma (c)	α = 4.094 λ = 0.0248	National Schedule of Reference Costs 2006-07 Outpatient procedure LB42Z
Cost of treating strictures – daycase	£509	Gamma (c)	α = 4.055 λ = 0.008	National Schedule of Reference Costs 2006-07 non elective LB30B
Cost of treating strictures – inpatient	£938	Gamma (c)	α = 3.344 λ = 0.0036	National Schedule of Reference Costs 2006-07 non elective LB30B
Cost of blood transfusion	£635	Gamma (a)	α = 61.46 λ = 0.0968	Varney et al (2003)[266]
Cost of treating UTI – daycase	£376	Gamma (c)	α = 3.926 λ = 0.0104	National Schedule of Reference Costs 2006-07 LA04C
Cost of treating UTI - inpatient	£783	Gamma (c)	α = 3.079 λ = 0.0039	National Schedule of Reference Costs 2006-07 LA04C
Cost of urology visit	£75	Gamma (c)	α = 7.898 λ = 0.1053	National Schedule of Reference Costs 2006-07 Consultant led follow-up attendance, face-to-face - Urology
Number of visits every 3 months	0.5	Triangular	Min=0.25 Likeliest=0.5 Max=1	Experts opinion
Probability of AUR after TURP (see 10.5.6)	3.9%	Beta	α = 88 β = 2184	Systematic review of clinical effectiveness

Proportion of patients with incontinence requiring an AUS	5%	Triangular	Min=2.5% Likeliest=5% Max=7.5%	Experts opinion
Probability of incontinence after TURP (see 10.5.6)	4.0%	Beta	α = 84 β = 2036	Systematic review of clinical effectiveness
Probability of strictures after TURP (see 10.5.6)	7.2%	Beta	α = 180 β = 2316	Systematic review of clinical effectiveness
Proportion of treating strictures inpatient: daycase	0.46 : 0.54	None		Hospital Episodes Statistics 2006-07
Probability of success at 6 months after TURP	85%	Beta	α = 88 β = 15	Fowler et al (2005)[83]
Probability of success at 2 years after TURP	84%	Beta	α = 63 β = 12	Fowler et al (2005)[83]
Probability of blood transfusion after TURP (see 10.5.6)	6.2%	Beta	α = 197 β = 2977	Systematic review of clinical effectiveness
Probability of TUR after TURP (see 10.5.6)	2.0%	Beta	α = 29 β = 1454	Systematic review of clinical effectiveness
Probability of UTI after TURP (see 10.5.6)	6.9%	Beta	α = 111 β = 1488	Systematic review of clinical effectiveness
Proportion of treating UTI inpatient: daycase	0.9 : 0.1	None		Hospital Episodes Statistics 2006-07
Proportion of patients being re-operated after a first failure	5%	Triangular	Min=0% Likeliest=5% Max=10%	Experts opinion
Relative Risk of AUR – HoLEP vs. TURP	0.72	Log-normal	SD=0.157	Systematic review of clinical effectiveness
Relative Risk of incontinence – HoLEP vs. TURP	1.26	Log-normal	SD=0.106	Systematic review of clinical effectiveness
Relative Risk of strictures – HoLEP vs. TURP	0.69	Log-normal	SD=0.175	Systematic review of clinical effectiveness
Relative Risk of blood transfusion – HoLEP vs. TURP	0.27	Log-normal	SD=0.304	Systematic review of clinical effectiveness
Relative Risk of TUR – HoLEP vs. TURP	0.31	Log-normal	SD=0.809	Systematic review of clinical effectiveness
Relative Risk of UTI – HoLEP vs. TURP	0.45	Log-normal	SD=0.319	Systematic review of clinical effectiveness
Utility of severe LUTS	0.71	Beta	α = 80.23 β = 32.77	Trueman et al (1999([256]

Utility of Remission	0.91	Beta	α = 33.67 β = 3.33	Trueman et al (1999([256]
Disutility from incontinence	0.11	Normal	SD = 0.026	Currie et al (2006)[50]
Effectiveness when procedure is performed the second time compared to first time	*75%*	Triangular	Min=50% Likeliest=75% Max=100%	Experts opinion
Discount rate (cost and QALYs)	3.5%	None		

(a) We approximated the standard error (SE) of the mean by assuming the width of the 95% CI was 50% of the mean using the following equation: SE=0.25 x mean / $Z_{0.0975}$
(b) Based on experts opinion
(c) We used the interquartile range (IQR) to approximately estimate the SE of the mean using the following equation: SE=0.5 x IQR / $Z_{0.75}$
(d) Based on the range from HES 2006/07

1.3.14 Results of the cost-effectiveness analysis

We analysed the data deterministically (Table 12) and probabilistically (Table 13 - Probabilistic SA results - HoLEP vs. TURP). We found that the results of the model were sensitive to various parameters and this is reflected in the extreme confidence intervals obtained with the probabilistic SA.

In the base case analysis HoLEP is more cost-effective than TURP but this result is overthrown by minimal changes in variables (Table 12).

Table 12 - HoLEP vs. TURP - Results of base case analysis

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained (HOLEP vs. TURP)	Sensitivity analysis
TURP	2,479	6.2315	-	TURP is cost-effective if: - cost of treating AUR<£1,000; - cost of bed day <£190; - cost of incontinence over three months >£575; - cost of operating theatre per minute >£10; - length of stay after HoLEP >2; - length of stay after TURP<3; - operating time of HoLEP >77minutes; - operating time of TURP <58minutes; - probability of incontinence TURP >4%; - utility values; - TURP is not possible after HoLEP.
HoLEP	2,480	6.2523	48	

The instability of this conclusion is even more evident from the results of the probabilistic SA (Table 13).

Table 13 - Probabilistic SA results - HoLEP vs. TURP

Mean incremental cost/mean QALYs gained	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
HoLEP dominates (a)	HoLEP dominates	TURP dominates	HoLEP 55% TURP 45%

(a) HoLEP dominates means that HoLEP is both more effective and less costly. Hence the ICER cannot be calculated.

The probability of HoLEP being cost-effective (55%) is very close to the probability of TURP being cost-effective (45%) at a willingness to pay of £20,000/QALY (the NICE threshold). The probabilities are very similar for other willingness to pay thresholds (Figure 238).

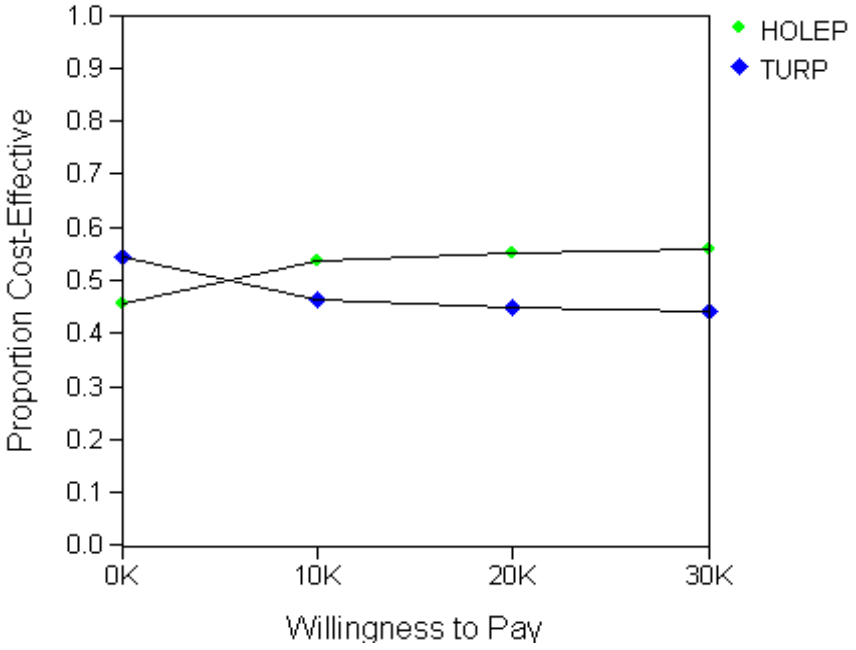

Figure 2 - Acceptability curve of HoLEP and TURP

The uncertainty can also be graphically represented by plotting the results of the incremental analysis for all the 10,000 simulations into a cost-effectiveness plane (Figure 239). Each point represents the ICER of TURP vs. HoLEP for each simulation. The dotted line represents the £20,000/QALY threshold while the ellipse delimits the 95% confidence interval.

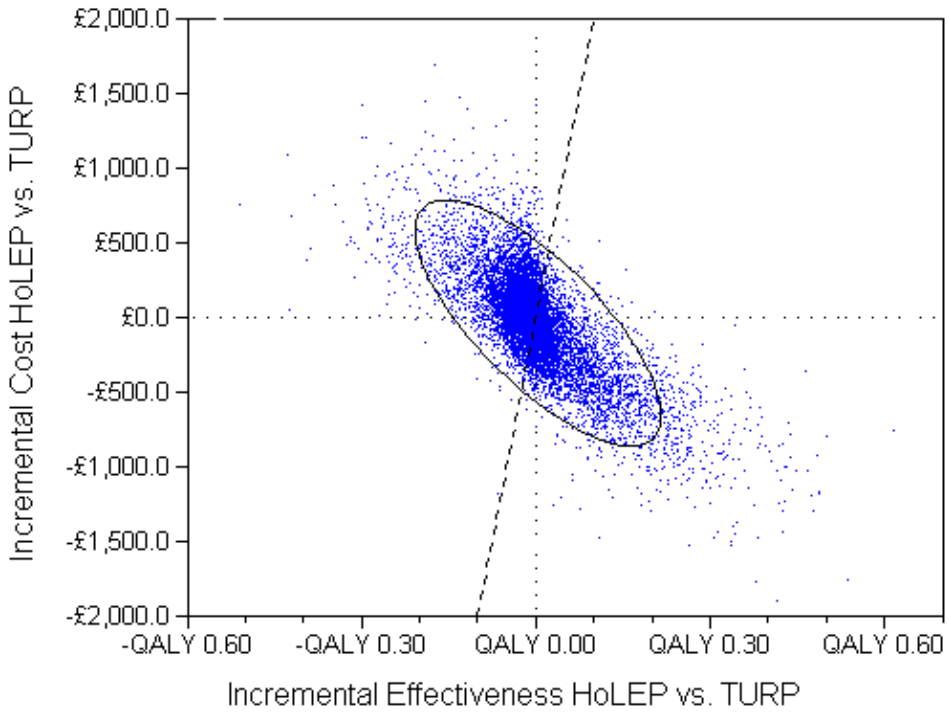

Figure 3 - Incremental cost-effectiveness scatterplot

1.3.15 Discussion

HoLEP and TURP could be equally cost-effective.

TURP is the current standard of care in the UK while HoLEP is a relatively new technique practiced in a small number of UK centres. Although our analysis shows that HoLEP is at least as cost-effective as TURP, careful considerations should be given to recommending its widespread use.

The cost-effectiveness of HoLEP seems to be associated with the skills of the surgeons. For example the operating time was a parameter to which results were sensitive. Also the probabilities of complications depend on the expertise of the surgeon performing the operation. The probabilities as reported in the studies included in our clinical review, where HoLEP was performed by specialised surgeons, might be largely different from the actual events following an operation performed by a trainee surgeon. Therefore we might have overestimated the effectiveness of HoLEP.

Another overestimation might be due to the blood transfusion rate after TURP as estimated from our review of clinical studies. Some of the included studies[127] reported a blood transfusion rate after TURP higher than the average.

The major limitation of our model is the arbitrary definition of success (IPSS change of at least 5 points). Although other authors[83] have adopted this definition, it is still debatable whether a change of 5 points could be considered a remission in symptoms. Other authors[150] have used an improvement by 10% in IPSS as a proxy for success but this was judged to be even more optimistic by

our experts, as this would equate to 2 points of improvement when the baseline score is 20.

The results of our study are based on trial data for men with moderate-to-severe symptoms with a mean baseline IPSS of 20.7. For men with less severe symptoms, TURP might be more cost-effective as it is less costly, while for men with more severe symptoms HoLEP might be more cost-effective as it is more effective than TURP at improving symptoms.

We compared the results of our study with the economic analysis from the HTA[150] included in our review and we found similar results and conclusions. In this study[150], HoLEP was more effective and less costly than TURP but the results were highly sensitive to several parameters. Unlike this study[150] our model takes into account the capital cost of HoLEP which might explain the higher cost of HoLEP compared to TURP.

From an NHS perspective, the results of our study would suggest training new surgeons in HoLEP could improve outcomes and save costs if performed correctly. However, a shift from TURP to HoLEP would have to be gradual for it to be cost-effective since purchasing the new equipment might not warrant the improved outcomes which were marginal. It is important to note that there is still inadequate long-term data for HoLEP. However, if a centre has to replace old equipment and surgeons trained in HoLEP are available, HoLEP could be an efficient option.

In conclusion, given the learning curve associated with the new technique and the cost of purchasing the new equipment, the GDG felt it was reasonable to recommend HoLEP only in centres specialised in the technique.

1.3.16 Conclusions

- HoLEP and TURP are similarly cost-effective
- In settings where HoLEP is not currently performed, TURP is more cost-effective because of the capital cost and the learning curve

1.4 NCGC Combination model

An economic model comparing Alpha-Blockers (AB) with a combination of AB and 5-Alpha-Reductase Inhibitors (Comb) was developed further to the exclusion of any economic evidence focusing on this comparison. The main outcomes considered were the change in IPSS from baseline and the treatment adverse events which were expressed in quality of life measures. Patients in this model are men who have moderate lower urinary tract symptoms and are selected for medical treatment.

We built a Markov model with a lifetime horizon (Figure 240) and we chose a cycle length of six months as it was the shortest follow up period in our clinical review of effectiveness (Chapter 6.10.1). All the probabilities, costs and health utilities were converted in order to reflect the six-month values. The time horizon was shortened to 5 years in a sensitivity analysis.

After a treatment period of six months, men can have either a meaningful improvement in IPSS (treatment success) or a negligible/no improvement (treatment failure). During this period they can also experience various adverse events which are independent from the treatment success. However, a proportion of those men experiencing adverse events will discontinue treatment, going back to the LUTS state. Men who had a treatment failure to start with will go to the LUTS state (with or without adverse events) but they can still have an improvement in the following six month cycle. Some men in the LUTS state will undergo TURP and they will feed into the TURP model (10.5).

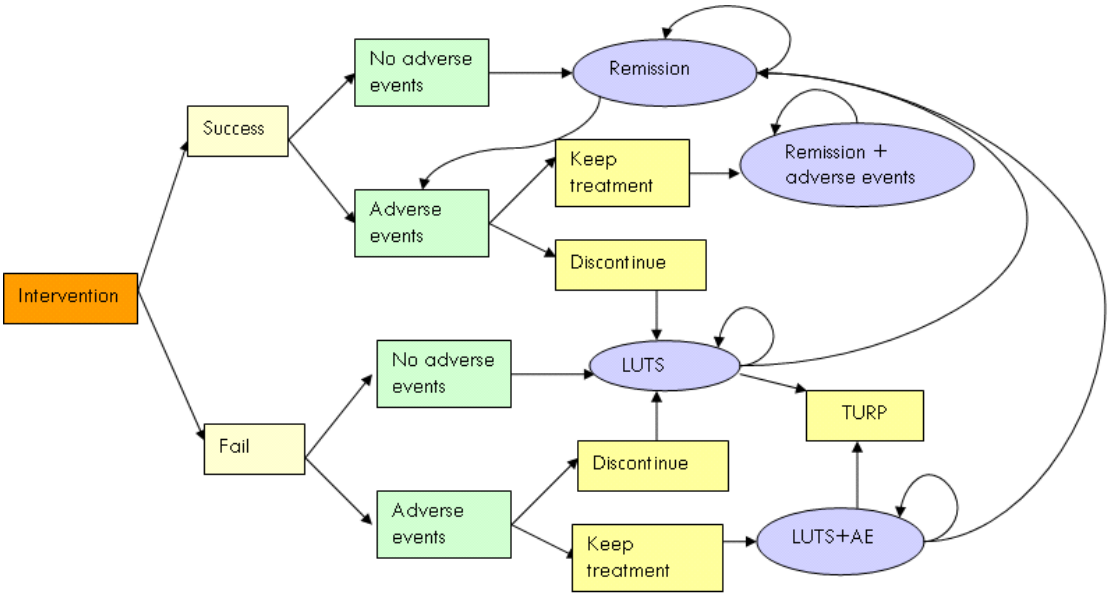

Figure 4 - Structure of the combination model. The squared boxes represent the chance nodes in the model while the round boxes are the possible health states.

The list of the health states that are part of the combination model is reported in Table 14.

Table 14 - Health states of combination model

HEALTH STATES
(Moderate) LUTS
Remission
LUTS +adverse events
Remission + adverse events
TURP

While in the Surgery model a significant remission of symptoms was a change in IPSS greater than five, in the Combination model we used the 3 point estimate by Barry et al (1995)[21].

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each state and then multiplying them by the proportion of patients who would be in that state as determined by the strategy taken.

We performed a probabilistic sensitivity analysis (PSA) to test the robustness of the results against the imprecision of these estimates and the other model parameters, and to obtain more accurate estimates of expected costs and QALYs.

1.4.1 Key assumptions

The experts in the GDG were consulted in order to make the following assumptions:

a) Patients are kept on treatment for all their life if the treatment is effective and there are no adverse events.

b) If the treatment does not work (i.e. IPSS improves by less than 3 points) the treatment is kept for one year then it is discontinued.

c) 50% of the patients who discontinue the treatment after one year undergo TURP.

d) If adverse events have not occurred during the first two years, they will never occur.

The following assumption was based on the conclusions of our clinical review:

a) After the first year the treatment effectiveness is stable (no improvement or deterioration in IPSS are possible).

1.4.2 Probability of success

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. We assumed that the IPSS change was normally distributed and we used the standard deviation (SD) from the mean to obtain the proportion of cases within the 3-point cut-off (Table 15). This was calculated as:

Success rate=1- $\Phi_{\mu\sigma 2}$(IPSS) where IPSS=3,

where μ=mean IPSS, σ^2=IPSS variance= IPSS SD squared (Table 15), 3 is the IPSS cut-off for success and where $\Phi_{\mu\sigma 2}$(IPSS) gives the cumulative distribution function for a normal distribution with mean μ and variance σ^2.

Table 15 - Probability of treatment success when the cut-off is 3 points

	Mean IPSS change (a)	SD of IPSS change (a)	Proportion of treatment success
AB – 6 months	6.3	5.8	72%
Comb – 6 months	6.1	7.4	66%
AB – 12 months	7.1	5.7	76%
Comb – 12 months	7.3	5.8	77%

a) Source: clinical review.

As the figures in Table 15 suggest, treatment success is more likely achieved at 12 months than 6 months. Therefore men in the model for whom treatment has failed in the first six months can still experience a remission in the following 6 months. The probability of remission is simply the difference between the probability of success at 12 months and the probability of success at 6 months (Table 16).

Table 16 - Probability of symptoms remission at 12 months

	P success 6 months	P success 12 months	P remission between 6 and 12 months (a)
AB	72%	76%	14.3%
Comb	66%	77%	16.6%

a) (P success 12 months – P success 6 months)/(1- P success 6 months)

We changed the definition of success in sensitivity analyses where we defined success as an improvement by at least 5 or at least 8 points.

1.4.3 Probability of adverse events and withdrawals

We looked for RCT data on adverse events and withdrawals due to adverse events. We realised it was not feasible to estimate the incidence of specific adverse events and their specific probability of causing withdrawals from treatment. Consequently we adopted a three-step approach:

1. estimate the overall probability of a man experiencing a drug-related adverse event with AB and with combinations
2. estimate the probability of an adverse event leading to treatment discontinuation with AB and with combination
3. once an adverse event occurs, estimate the probability of specific adverse events

We found a large RCT[225] reporting both drug related adverse events and drug-related adverse events leading to study withdrawals. With these data (Table 17) we were able to perform step 1 and 2 (Table 17).

Table 17 - Probability of discontinuation in patients with adverse events*

	Number of drug-related adverse events x	Number of drug-related adverse events leading to withdrawal y	Probability of drug-related adverse events	Probability of discontinuation in patients with adverse events z=x/y
AB	258	48	16%	18.6%
Comb	386	80	24%	20.7%

** From Roehrborn et al (2008)[225]*

Figure 241 and Figure 242 illustrate how these values were used in the model.

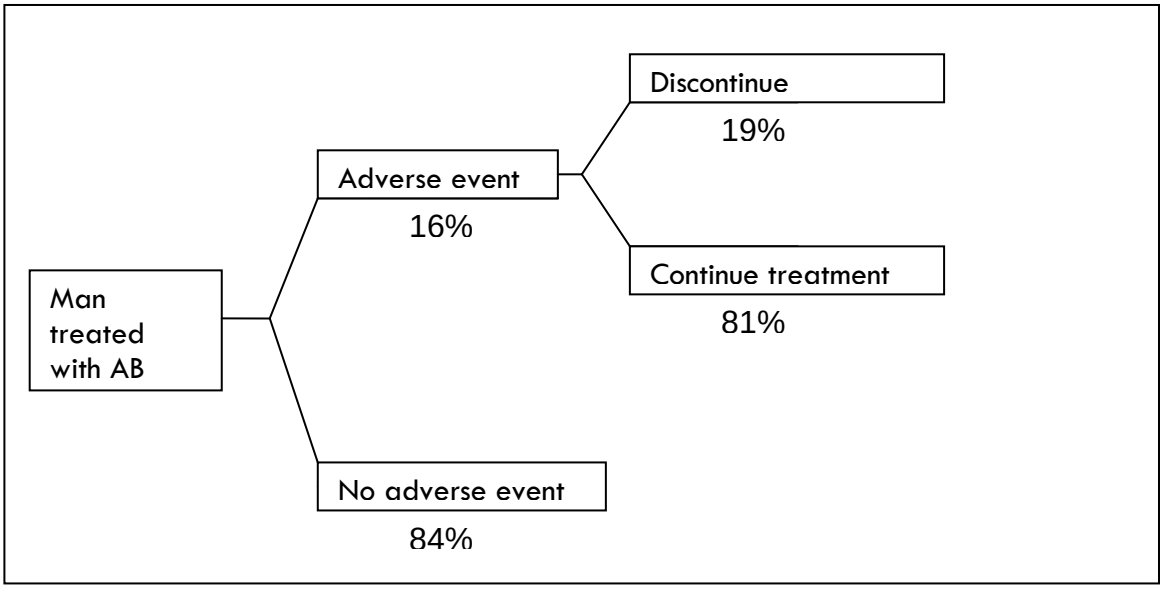

Figure 5 - Adverse events in the AB arm of the model

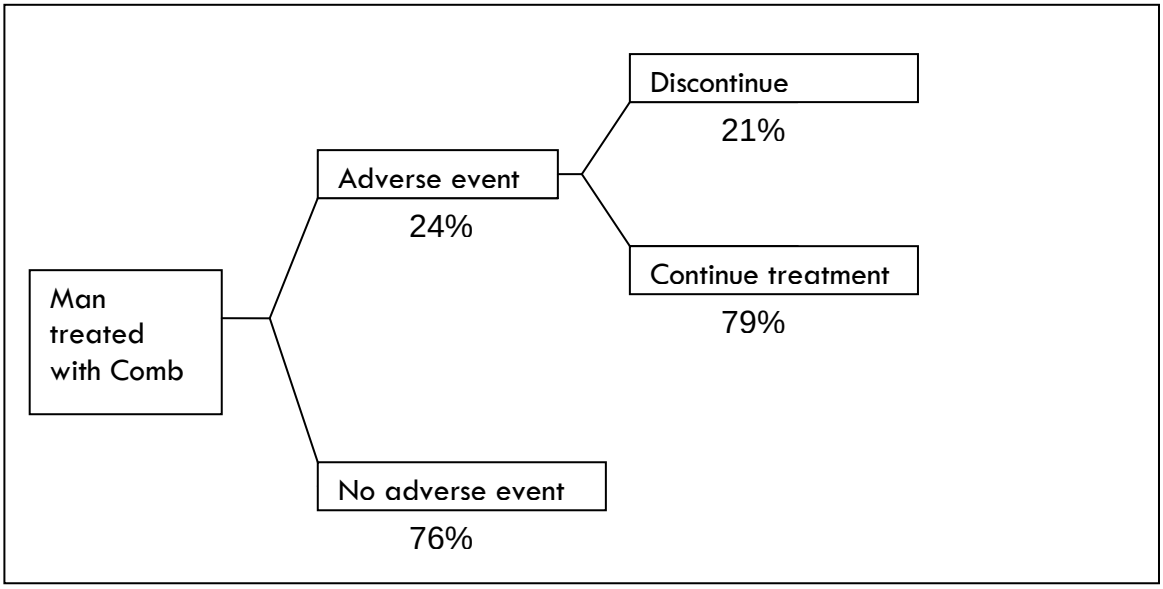

Figure 6 - Adverse events in the combination arm of the model

For step 3 we used the evidence from the review of clinical effectiveness (Chapter 6.10.1). Various adverse events were reported in the included studies and in order to avoid double-counting we grouped those adverse events that could be similar in symptoms. The most common adverse event was used to represent the group (Table 18). Therefore whilst in the clinical review postural hypotension, headache, syncope and dizziness are all reported, it is likely to be an overlap of those symptoms and just dizziness (the most frequent one) is reported as part of that group. Similarly decreased libido was grouped together with impotence or erectile dysfunction.

In our model we did not use the incidences reported in the included studies (Chapter 6.10.1) but these were used to calculate the probability of each type being the adverse event occurring (Table 18).

Table 18 - Incidence and proportion of adverse events

	Incidence		Proportion of adverse events	
	AB X_i	Comb Y_i	AB $X_i/\sum X_i$	Comb $Y_i/\sum Y_i$
Dizziness	4.8%	4.3%	22%	16%
Fatigue	3.6%	4.2%	17%	16%
Rhinitis	6.6%	7.8%	31%	29%
Ejaculatory abnormality	0.6%	3.0%	3%	11%
Impotence/erectile dysfunction	3.0%	5.9%	14%	22%
Breast enlargement	1.8%	1.4%	8%	5%
Acute urinary	1.0%	0.4%	5%	1%

retention (AUR)				
TOTAL	*21.4%*	*27.0%*	*100%*	*100%*

The probability of each adverse event group was used in the model to estimate the detriment in quality of life and additional costs due to adverse events (see 10.6.5 and 10.6.7).

1.4.4 Life expectancy

Men in the Combination Model were assumed to be on average 60 years old.

Life expectancy in patients with LUTS was assumed to be the same as the general population in England and Wales. The remaining life expectancy for men aged 60 is 21.22 years, as reported in the Life Tables for the general population of England and Wales in the year 2005-2007 from the Government Actuary Department (http://www.gad.gov.uk/Documents/Demography/EOL/ILT%202005-07/wltewm0507.xls).

1.4.5 Quality of life

The same sources used in the Surgery Model for quality of life estimates of the residual LUTS and remission states were used in the Combination Model (10.5.8). However, while men in the Surgery Model had on average severe symptoms, in the Combination Model men have moderate symptoms.

The health states 'Remission + Adverse events' and 'LUTS + Adverse events' are made of the Remission or LUTS utility value and the disutility (decrease in utility) due to adverse events.

Being the spectrum of adverse events in the AB arm different from that in the combination arm (10.6.3), the adverse events health states will also have different utility values in the different arms.

The utility value of the LUTS + adverse events state for intervention y will be calculated as:

XIV $uLUTS\text{-}AE_y = uLUTS + \sum(disutilityAE_i * pAE_{iy})$

where uLUTS is the utility values of Moderate LUTS reported in Table 19,

disutilityAEi is the disutility of the adverse event i where i is any of the adverse events reported in Table 18,

and pAEi,y is the proportion of the adverse event i for the intervention y, where y could be either AB or combination.

From equation **XIV** it can be deduced that the utility of these health states depend on the intervention being the proportion of adverse events the variable parameter.

We conducted a search in the CEA Registry (https://research.tufts-nemc.org/cear/default.aspx) to find quality of life values associated with the adverse events reported in Table 18.

Two studies[248,267] were found which reported the one-day disutilites deriving from dizziness, fatigue and rhinitis. We assumed that those symptoms were experienced half the time; therefore the original value was halved in our analysis (Table 19) but this assumption was varied in sensitivity analyses.

One study[206] reported the disutility due to breast enlargement.

In a study by Dedhia et al (2008)[62] patients with LUTS were interviewed and their time-trade off scores for various adverse events collected. The utility values reported in this study were 0.71 for ejaculatory abnormality and 0.73 for erectile dysfunction in men with LUTS. If we assume that the utility decrements are additive, we can calculate the disutility due to these adverse events as the difference of the utility of LUTS and the utility of adverse event in presence of LUTS:

XV $\text{disutilityAE} = \text{uLUTS} - \text{uLUTS+AE}$

By substituting the values from the study[62] in formula **XV** we obtain the disutilities reported in Table 19.

Table 19 - Utility values used in the Combination Model

	Utility score	Source
Remission	0.91	Trueman et al (1999)[256]
Moderate LUTS	0.78	Trueman et al (1999)[256]
Disutility breast enlargement	- 0.05	Penson et al (2005)[206]
Disutility dizziness (a)	- 0.11	Vera-Llonch et al (2008)[267]
Disutility ejaculatory abnormality	-0.07	Dedhia et al (2008)[62]
Disutility fatigue (a)	-0.125	Vera-Llonch et al (2008)[267]
Disutility impotence	-0.05	Dedhia et al (2008)[62]
Disutility rhinitis (a)	-0.095	Sullivanet al (2004)[248]
Disutility AB adverse events	- 0.088	Weighted average of above disutilities
Disutility Comb adverse events	- 0.086	Weighted average of above disutilities

(a) Assuming symptoms are experienced half the time.

The disutility due to Acute Urinary Retention (AUR) was not included in the model as this complication was assumed to be treated and resolved within six months.

The cost associated with this adverse event is already explained in the Surgery Model (see 10.5.11).

1.4.6 Calculating QALYs gained

See 10.5.9.

1.4.7 Cost of interventions and health states

The cost components of the health states in the model are made of the continuous cost of drug therapy and the cost of visits (Table 20). During the first six-month cycle men are treated with either AB or Combination and have a follow-up visit. The cost of the initial treatment is kept for at least another cycle unless there is a discontinuation due to adverse events. If the treatment is discontinued only the cost of a visit is included in the cost of a cycle.

Table 20 - Resources used in the health states of the model

HEALTH STATE	RESOURCES USED
Moderate LUTS - initial	Drugs (AB or Comb) + 1follow-up visit
Moderate LUTS - residual	1 follow-up visit
Remission	Drugs (AB or Comb)
LUTS +adverse events	1 follow-up visit
Remission + adverse events	Drugs (AB or Comb)

The cost details of the resources used in the health states are reported in Table 21.

Table 21 - Cost of resources used

Resource	Total cost per patient over six months	Source
Alpha-blockers	£65	BNF 57 (a)
Combination (5-ARI+AB)	£186	BNF 57 (b)
Follow-up visit	£75	National Schedule of Reference Costs 2006-07– Consultant led follow-up attendance – outpatient face-to-face – Urology

a) Based on the average cost per day of Alfuzosin, Tamsulosin, Doxazosin, and Prazosin =£ 0.35
b) Based on the cost of AB and on the average cost per day of Dutasteride and Finasteride = £0.66

In addition, some costs are associated with particular events in the model: the cost of treating AUR when adverse events occur (adjusted by the proportion of AUR in the adverse events) and the cost of TURP if the therapy fails and the man considers surgery. In this event the model feeds directly into the Surgery Model

described in 10.5 where the cost components are the same ones described in 10.5.10 and 10.5.11 for the TURP strategy.

1.4.8 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the model results to plausible variations in the model parameters.

The same method described for the Surgery Model (10.5.13) was used for the Combination Model. The same parameters used in the TURP arm of the Surgery Model were used in the Combination Model when men undergo TURP after a treatment failure. All the other parameters and their distributions are listed in Table 22.

Table 22 - Parameters and distributions used in the probabilistic sensitivity analysis

Description of variable	Mean value	Probability distribution	Parameters	Source
Mean IPSS change at 6 months – AB	6.3	Normal	SD= 5.8	Systematic review of clinical effectiveness
Mean IPSS change at 6 months – Comb	6.1	Normal	SD=5.6	Systematic review of clinical effectiveness
Mean IPSS change at 12 months – AB	7.1	Normal	SD=5.7	Systematic review of clinical effectiveness
Mean IPSS change at 12 months – Comb	7.3	Normal	SD=5.8	Systematic review of clinical effectiveness
Probability of success at 6 months – AB	See Table 15			
Probability of success at 6 months - Comb	See Table 15			
Probability of success at 12 months – AB	See Table 15			
Probability of success at 12 months - Comb	See Table 15			
Probability of remission at 12 months – AB	See Table 16			
Probability of remission at 12 months - Comb	See Table 16			
Cost of Alpha-blockers treatment over 6 months	£65	None		BNF 57
Cost of combination treatment over 6 months	£186	None		BNF 57

Cost of urology visit	£75	Gamma (a)	α = 7.898 λ = 0.1053	National Schedule of Reference Costs 2006-07 Consultant led follow-up attendance, face-to-face - Urology
Cost of treating AUR	£2,029	Gamma (b)	α = 61.46 λ = 0.0303	Annemans et al (2005)[14]
Probability of adverse events - AB	16%	Beta	α = 258 β = 1353	Roehrborn et al (2008)[225]
Probability of adverse events - Comb	24%	Beta	α = 386 β = 1224	Roehrborn et al (2008)[225]
Probability of discontinuing in men with adverse events - AB	18.6%	Beta	α = 48 β = 210	Roehrborn et al (2008)[225]
Probability of discontinuing in men with adverse events - Comb	20.7%	Beta	α = 80 β = 306	Roehrborn et al (2008)[225]
Proportion of breast enlargement/adverse events AB	8%	Dirichlet	0.08, 0.22, 0.17, 0.03, 0.14, 0.31, 0.05 where each parameter refers to proportion of each type of adverse event	Systematic review of clinical effectiveness
Proportion of dizziness/adverse events AB	22%	Dirichlet		Systematic review of clinical effectiveness
Proportion of fatigue/adverse events AB	17%	Dirichlet		Systematic review of clinical effectiveness
Proportion of ejaculatory abnormality/adverse events AB	3%	Dirichlet		Systematic review of clinical effectiveness
Proportion of impotence/adverse events AB	14%	Dirichlet		Systematic review of clinical effectiveness
Proportion of rhinitis/adverse events AB	31%	Dirichlet		Systematic review of clinical effectiveness
Proportion of AUR/adverse events AB	5%	Dirichlet		Systematic review of clinical effectiveness
Proportion of breast enlargement/adverse events - Comb	5%	Dirichlet	0.05, 0.16, 0.16, 0.11, 0.22,	Systematic review of clinical effectiveness
Proportion of dizziness/adverse events - Comb	16%	Dirichlet		Systematic review of clinical effectiveness
Proportion of fatigue/adverse events – Comb	16%	Dirichlet		Systematic review of clinical effectiveness

Proportion of ejaculatory abnormality/adverse events AB	11%	Dirichlet	0.29, 0.01 where each parameter refers to proportion of each type of adverse event	Systematic review of clinical effectiveness
Proportion of impotence/adverse events – Comb	22%	Dirichlet		Systematic review of clinical effectiveness
Proportion of rhinitis/adverse events – Comb	29%	Dirichlet		Systematic review of clinical effectiveness
Proportion of AUR/adverse events – Comb	1%	Dirichlet		Systematic review of clinical effectiveness
Proportion of men undergoing TURP after treatment failure	50%	Triangular	Min=0% Likeliest=50% Max=100%	Experts opinion
Utility of Moderate LUTS	0.78	Beta	$\alpha = 80.23$ $\beta = 32.77$	Trueman et al (1999([256]
Utility of Remission	0.91	Beta	$\alpha = 33.67$ $\beta = 3.33$	Trueman et al (1999([256]
Disutility from breast enlargement	0.05	Beta	$\alpha = 23.7$ $\beta = 450.3$	Penson et al (2005)[206]
Disutility from dizziness	0.11	Beta	$\alpha = 6.22$ $\beta = 50.32$	Vera-Llonch et al (2008)[267]
Disutility from fatigue	0.125	Beta	$\alpha = 6.097$ $\beta = 42.681$	Vera-Llonch et al (2008)[267]
Disutility from ejaculatory abnormality	0.07	Beta	$\alpha = 14.81$ $\beta = 196.76$	Dedhia et al (2008)[62]
Disutility from impotence/erectile dysfunction	0.05	Beta	$\alpha = 6.706$ $\beta = 127.406$	Dedhia et al (2008)[62]
Disutility from rhinitis	0.19	Beta	$\alpha = 20.604$ $\beta = 87.836$	Dedhia et al (2008)[62]
Discount rate (cost and QALYs)	3.5%	None		NICE Reference Case

(a) We used the interquartile range (IQR) to approximately estimate the standard error (SE) of the mean using the following equation: $se=0.5 \times IQR / Z_{0.75}$
(b) We approximated the SE of the mean by assuming the width of the 95% CI was 50% of the mean using the following equation: $se=0.25 \times mean / Z_{0.975}$

1.4.9 Results

Alpha-blockers generate less cost and more QALYs compared to combinations (Table 23).

Table 23 - Results of base case analysis - Combination vs. Alpha-blockers

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained	Sensitivity analysis
Alpha-blockers	3,824	12.4347	-	One-way SA: Combination is cost-effective if probability of adverse events with AB>29% (16% in base case). Results were not sensitive to other changes in parameters or structure.
Combination	6,411	12.4276	Dominated	

In a set of one-way sensitivity analyses, where the low and high values were respectively half or double the base case value, we identified the parameters that might have changed the results. The only variable to which the model was sensitive was the probability of adverse events with AB. We explored this uncertainty further through a two-way SA where the probability of adverse events with AB was co-varied with the probability of adverse events with combination (Figure 243).

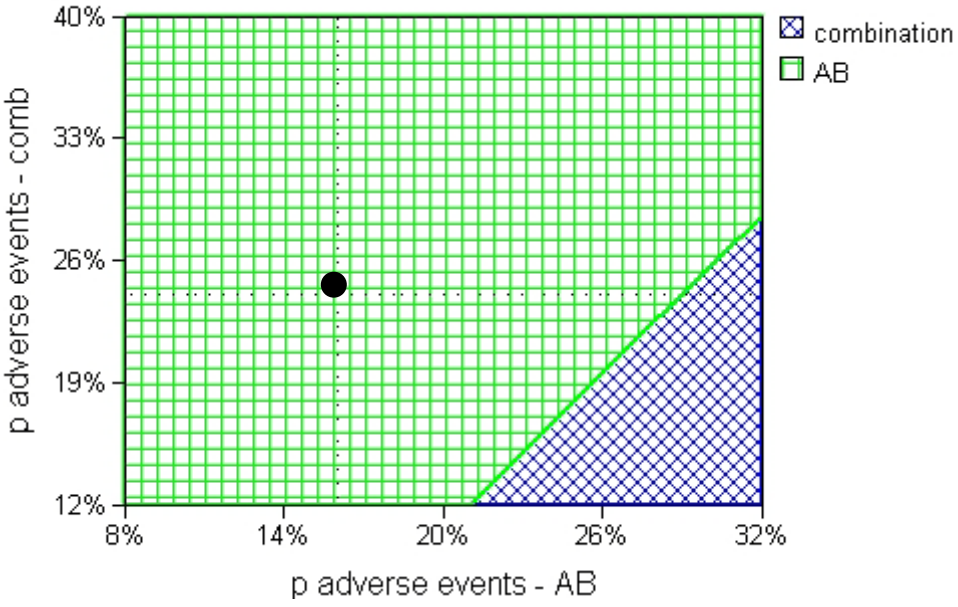

Figure 7 - Two-way SA on probability of adverse events with AB (x axis) and comb (y axis). The area in green is where AB is cost-effective, while the area in blue is where combination is cost-effective. The black dot represents the base case values.

If we consider a 95% confidence interval the base case results did not reach statistical significance (Table 24).

Table 24 - Results of probabilistic SA - Comb vs. AB

Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
Comb dominated	3,850	Comb dominated	AB 90% Comb 10%

However, at a willingness to pay of £20,000/QALY alpha-blockers have a 90% probability of being cost-effective (Figure 244).

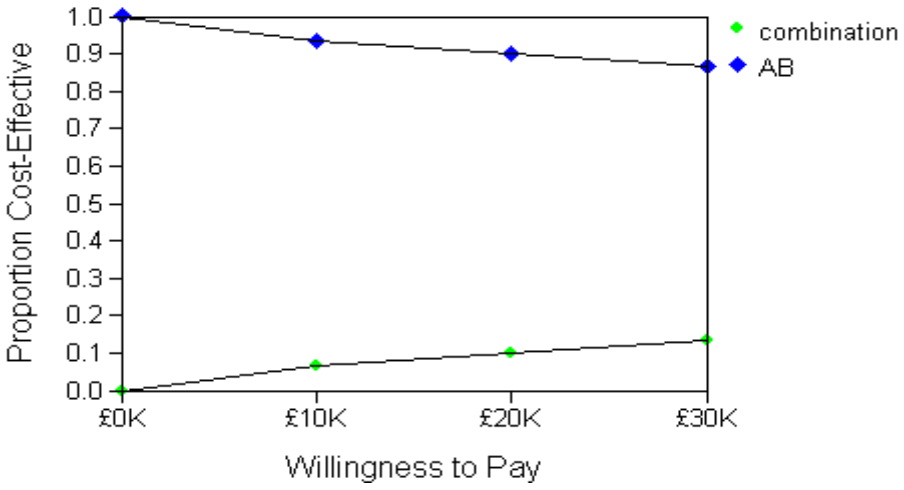

Figure 8 - Acceptability curve of AB and Comb

1.4.10 Discussion

5-ARI and AB have a different mechanism of action and the combination of the two could enhance the effectiveness on men with LUTS. Our review of clinical evidence (Chapter 6.10.1) has shown that the long-term (one year) improvement in IPSS is higher with combinations than with AB. However there are extra costs associated with the improvement and more side effects. The results of our model show that after weighting the advantages (improvement in IPSS) and disadvantages (costs and side effects) combinations are not cost-effective in a general population of men with LUTS.

We based our model on studies where men had a normal prostate size. We have deliberately excluded those studies conducted on men with large prostates as 5-ARI are believed to be more effective in this group of men. A specific model for that population could be built once good data are available.

We encountered some challenges when building our model: defining success of treatment according to an IPSS improvement by 3 points might have been arbitrary even if based on a previous study[21]; however, when we changed this definition to up to 10 points the overall results did not change.

Other assumptions were made while building the model but those did not have an impact on the conclusions.

Adverse events were a core component of the model and their incidence was the only parameter to which the results were sensitive. When we changed the probability of adverse events with AB and combinations simultaneously we noted that if the probability was lower with combination than with AB the former would have been more cost-effective than the latter. Nevertheless, as AB are part of the combination it would be very unlikely that their adverse events while used in combination would be less frequent than when they are used alone.

This is the only model which compares AB and combination using randomized data. A cost-utility analysis by McDonald et at (2004)[167] concluded that combinations were more cost-effective than Doxazosin but the clinical data were obtained from men with large prostate for one arm and men with normal prostate for the other arm. This explains the higher value-for-money of combination in this study compared to ours. Conversely the cost-utility analysis by DiSantostefano et al (2006)[63] reached our same conclusions, yet the effectiveness data on combinations were not based on RCTs but on assumptions.

1.4.11 Conclusions

- Combination of alpha-blockers with 5-ARI was not cost-effective in a general population of men with LUTS.

- Clinical data on men with large prostate might be useful to assess the cost-effectiveness in this group where combinations are presumed to be more effective.

Appendix G - Recommendations for research

1.1 Multichannel cystometry

PICO question Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO framework (patient, intervention, comparison and outcome).	Question: What is the clinical and cost effectiveness of multichannel csytometry in improving patient related outcomes in men being considered for bladder outlet surgery? Patients: Bothersome LUTS not responding to conservative therapy (catheterised patients excluded). Intervention: Pressure flow studies. Comparison: Two groups, awaiting bladder outlet surgery, randomised either to pre-operative pressure flow studies, or not Outcome: Primary outcome-patient-related outcome (IPSS, EQ5D), secondary outcomes-adverse events, flow rate, residual urine, pdetQmax.
Importance to patients or the population. What would be the impact of any new or altered guidance on the population? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	This research would clarify whether this test could improve the outcome of surgery. If the result is positive, this could improve the chance of a good outcome from surgery.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	As above, it would add to knowledge about the utility of pressure flow studies and allow them to be recommended or not recommended in future revisions of guidance.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	It would allow the NHS to know whether resources should be committed to the test or not.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	NSF for older people, Integrated Continence Services.
Current evidence base What is the current evidence base? What are the problems with the current evidence	There are currently no randomised controlled trials comparing multichannel cystometry to no intervention in men

base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews. The date on which the final literature search was undertaken should be specified.	before surgery.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	No specific consideration.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	*Design*: A randomised comparative trial of men awaiting bladder outlet surgery, to be randomised to either a pressure flow study or not, before their surgery. The results of the pressure flow study would be used in subsequent counselling of patients in a protocol-driven way, before the proposed surgery, and *might* result in surgery not being done. *Outcome*: As above.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? As part of cost-effectiveness analysis, formal value-of-information methods may also sometimes be used to estimate the value for money of additional research. Are there any ethical or technical issues?	The research would be ethically and technically feasible.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	The National Institute for Health Research (NIHR) would be an appropriate funding source. The normal service delivery cost to participants would be taken over by the research during the trial, thus relieving the service delivery budget. Since the NIHR is an NHS funded body the costs of care would simply be shifted from one NHS budget to another. Additional costs would be those associated with conducting the research itself.
Importance How important is the question to the overall guideline? The research	High. The research is essential to inform future updates of key recommendations in the guideline.

recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	

1.2 Catheterisation

PICO question Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO framework (patient, intervention, comparison and outcome)	What are the clinical and cost effectiveness and associated adverse events of intermittent catheterisation compared to indwelling suprapubic or urethral catheterisation for men with voiding difficulty and chronic retention of urine?
Importance to patients or the population. What would be the impact of any new or altered guidance on the population? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	The number of men judged unfit to undergo de-obstructing surgery is steadily increasing given the increasing proportion of older men in the population. Current practice varies widely across the UK with no established standard for long term management and no systematic review of practice. The research could establish the best approach to management in these men in the longer term and so bring more effective treatment, better focused on each patient's need, and consequent cost-efficiency gains.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	NICE currently cannot give clear guidance on this topic because of an inadequate evidence base.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Catheters are currently used variably across the UK with no systematic approach to management except for men with spinal cord injury. The aim of catheterisation, to drain the bladder so as to protect the upper renal tracts and maintain continence may not be achieved acceptably. Evidence-based guidance on the selection of the most suitable mode of catheterisation will benefit the quality of life of patients, ensure the efficient use of skilled staff and may reduce the costs of waste of unsuitable or sub-optimal product use.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	None currently relevant.
Current evidence base What is the current evidence base? What	There is no currently no evidence for these interventions.

are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews. The date on which the final literature search was undertaken should be specified.	
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	This treatment predominantly affects older people.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	A randomised controlled study of the interventions: a) intermittent catheterisation b) indwelling suprapubic catheterisation c) indwelling urethral catheterisation Outcomes of interest: quality of life, healthcare resource utilisation, adverse events (including leakage, skin breakdown, infection, erosion and death).
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? As part of cost-effectiveness analysis, formal value-of-information methods may also sometimes be used to estimate the value for money of additional research. Are there any ethical or technical issues?	The major issues with this trial would be the identification of cases and the studying of them in a primary care environment. An adequate population of men with this problem already exists precisely because of the absence of any consensus strategy for this group.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	None.

Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High. Surgery is indicated as therapy for retention – but may not be appropriate in the presence of impaired bladder function (underactive) or where comorbidity precludes it.

1.3 Products for men with urinary incontinence

PICO question Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO framework (patient, intervention, comparison and outcome)	What is the clinical and cost effectiveness and associated adverse events of absorbent pads compared to sheath collectors for men with urinary incontinence?
Importance to patients or the population. What would be the impact of any new or altered guidance on the population? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	The number of patients in this group is steadily increasing with more radical prostatectomies and an ageing demographic. Current practise varies widely across the UK with no established standards of good practice. The research could establish the best approach to continence management in these men and so bring more effective treatment, better focussed on each patient's needs, and consequently cost-efficiency gains.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	NICE currently cannot give clear guidance on this topic because of an inadequate evidence base.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Containment products are currently used variably across the UK. It is rare that any element of bladder training or recognition and treatment of bladder dysfunction is recognised as part of the continence management problem. The aim, so often, is simply to keep the patient socially dry; and even that is not always achieved acceptably. Evidence-based guidance on the selection of the most suitable containment product and its subsequent management will benefit the quality of life of patients, use skilled nurse/career resources more efficiently and reduce the costs of waste of unsuitable or sub-optimal product use.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	There is currently no national service framework for men with LUTS and incontinence or difficulty with bladder emptying.
Current evidence base What is the current evidence base? What are the problems with the current	There is no currently no level 1 evidence for pads and sheaths.

evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews. The date on which the final literature search was undertaken should be specified.	
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	There are no equality issues.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	A randomised controlled trial to compare these interventions. Outcomes of interest would be symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? As part of cost-effectiveness analysis, formal value-of-information methods may also sometimes be used to estimate the value for money of additional research. Are there any ethical or technical issues?	The major issues with this trial would be the identification of cases and the studying of them in a primary care environment. An adequate population of men with this problem already exists precisely because of the absence of any consensus strategy for this group.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	In general, manufacturers have been reluctant to fund randomised controlled trials. Currently the D4D project is addressing unmet needs. Work with specialist and patient advocacy groups and manufacturers will be essential.
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the	High. This is a population of men who have been rendered incontinent by surgery. The impact on their quality of life is profound and there is currently only one realistic treatment option for more major incontinence namely surgery which many men find unacceptable. It is important that solutions are found for this growing number of men.

research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	

1.4 Green light laser prostatectomy

PICO question Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO framework (patient, intervention, comparison and outcome)	What is the clinical and cost effectiveness and associated adverse events of Green Light Laser prostatectomy compared to TURP in men with moderate to severe bothersome LUTS considering surgery for bladder outlet obstruction? Assessed by symptom severity, quality of life, and adverse events.
Importance to patients or the population. What would be the impact of any new or altered guidance on the population? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	The potential advantages of reduced blood loss, shorter hospital stay and earlier return to normal activities 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.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	NICE cannot give clear guidance on this intervention because the evidence base is inadequate. The proposed research will add new knowledge.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Green Light laser use in the NHS is increasing at a rapid rate with approximately 70 units in the UK using it (~ 60% NHS and ~ 40% private sector) from personal communication with representatives of American Medical Systems Inc and clinical units. This is despite a lack of clinical and cost-effectiveness data to support this practice.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	None
Current evidence base What is the current evidence base? What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews. The date on which the final literature search was undertaken should be specified.	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 [16,150-152].
Equality Does the research recommendation address equality issues? For example, does it focus	Not applicable

on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	Primary research (RCT). Comparator is TURP. Careful consideration must be given to treatment strategies within the trial design such as incorporating early versus delayed intervention.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? As part of cost-effectiveness analysis, formal value-of-information methods may also sometimes be used to estimate the value for money of additional research. Are there any ethical or technical issues?	Proposed research can be carried out in a realistic timescale and at an acceptable cost. There are no ethical issues. A potential risk is that Green Light Laser use may diminish without adequate assessment.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	NCCHTA would be the obvious funder
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High

1.5 Male slings

PICO question Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO framework (patient, intervention, comparison and outcome)	In men with mild to moderate post prostatectomy urinary incontinence (P), what is the clinical or cost effectiveness of a male sling or an extraurethral non circumferential compression device (IC), when assessed by symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events (O). **Possible interventions include:** Non compression retrobulbar sling, compressive bulbar slings, adjustable bulbar slings, extraurethral compressive support and extraurethral non circumferential compression devices. Paraurethral injections have been used but are not recommended by the recent WHO International Consultation on Incontinence.
Importance to patients or the population. What would be the impact of any new or altered guidance on the population? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	This increasingly prevalent group of men have, until recently, had no acceptable treatment option other than insertion of an artificial urinary sphincter but many men consider this treatment to be too invasive and too prone to complication or failure. A number of new interventions have been devised but there is no clarity on which of these offers the best outcomes. This research could lead to clear recommendations and effective treatment for the majority of these men.
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	NICE currently cannot give clear guidance on this topic because of an inadequate evidence base.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	This group of men currently depend on containment alone for control of their incontinence – there are likely to be cost savings from effective incontinence treatment Insertion of an artificial urinary sphincter, whilst of recognised efficacy, carries a significant cost. Guidance is needed on the most suitable surgical options for this group of men.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	There is currently no national service framework for men with LUTS or incontinence.
Current evidence base What is the current evidence base? What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the	There is currently no level 1 evidence for these surgical interventions because they are relatively new and have not been subjected to randomised controlled trials.

full guideline that describes the current evidence base, including details of trials and systematic reviews. The date on which the final literature search was undertaken should be specified.	NICE Interventional Procedures Committee has reported on Male slings (mostly "Invance") and non circumferential extraurethral compression devices.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	There are no equality issues.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	A randomised controlled trial comparing up to three current interventions; retrobulbar "non compressive" male sling (Advance) , adjustable compression sling (Argos), and extraurethral non circumferential compression device (Proact) is recommended. However other new devices are being introduced rapidly into the market place with little or no clinical data to underpin marketing.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? As part of cost-effectiveness analysis, formal value-of-information methods may also sometimes be used to estimate the value for money of additional research. Are there any ethical or technical issues?	The major issues with this trial would be the centralisation of cases into centres able to offer the surgery and the training of participating surgeons since the procedures proposed are still relatively new. An adequate population of men with this problem already exists precisely because of the absence of any really effective treatment for this group.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	In general, manufacturers have been reluctant to fund randomised controlled trials and prefer to sponsor the establishment of surgical registries. Whilst these facilitate the involvement of a greater number of surgeons and cases, the risk of bias is very high. It may be that independent registries are a better way to establish the associated risks of surgery because of the feasibility of including all patients, not just those eligible for inclusion in an RCT.
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High. This is a population of men who have been rendered incontinent by surgery which may or may not cure their cancer. The impact on their quality of life is profound and there is currently only one realistic treatment option which many men find unacceptable. It is important that solutions are found for this growing number of men.

Appendix H – IPSS score sheet

International prostate symptom score (IPSS)

	Not at all	Less than 1	Less than	About half the	More than	Almost always	**Your score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Total IPSS score	

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally	Mostly dissatisfie	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

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