Cedar

Healthcare Technology Research Centre

External assessment centre report:

The Urolift system for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia

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In Version 2 corrections were made to the original version (dated 13/2/2015). This involved changes to the figures in table 60 and to references to them in the text.

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External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the sponsor's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

Title: The Urolift system for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia

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Declared interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

Grace Carolan-Rees is employed by the NHS; the NHS has a financial interest in the guidance issued by NICE as a result of this work.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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1 Summary

Scope of the sponsor's submission

The sponsor's submission contained all published evidence available on the Urolift device, which comprised of uncontrolled before and after studies, or reports of a single sham-controlled, blinded RCT. The completeness of the sponsor's evidence submission was confirmed by an independent EAC literature search. However, the NICE scope called for evidence that included TURP or HoLEP as a comparator and this evidence does not currently exist.

Summary of clinical evidence submitted by the sponsor

The sponsor submitted a peer-reviewed systematic review by Perera et al. (2014) in place of a de novo evidence submission and synthesis. The meta-analysis within Perera et al. (2014) utilizes data from 10 studies on IPSS score, men's sexual health scores, health-related quality of life, urinary flow rate and post-void residual volume. Of the studies used in the systematic review, there were 2 published papers (McVary et al., 2014 & Roehrborn et al., 2013) on a blinded, sham controlled RCT (LIFT Study), and 8 uncontrolled before and after studies (Abad et al., 2013; Cantwell et al., 2014; Chin et al., 2012; Delongchamps et al., 2012; McNicholas et al., 2013; Shore et al., 2014 & Woo et al., 2011 & 2012) .

The meta-analysis reported pooled estimates of outcome measures at 1, 3, 6 and 12 months post-Urolift procedure. Results were shown as standardised mean gains (SMGs) rather than keeping the original units e.g. score for IPSS, ml/s for Q_{max}. Prostate symptom scores (IPSS and BPHII) are pooled and reported together, as are the sexual health scores IIEF, MSHQ-EjD and MSHQ-Bother. IPSS QoL is reported separately, as are Q_{max} and post-void residual volume (PVR). All are reported with an effect size, and a heterogeneity score.

The pooled IPSS/BPHII results presented indicate a large improvement in symptoms. The authors convert their reported SMGs into IPSS improvements as follows: -7.2 points (95% CI, -7.9 to -6.5) at 1 month, -8.3 (95% CI, -9.1 to -7.5) at 3 months, -8.7 (95% CI, -9.4 to -7.9) at 6 months and -8.0 (95% CI, -8.8 to -7.2) at 12 months. QoL measurements also improved by between 2.2 (95% CI, -2.5 to -2.0) and 2.4 points (95% CI, -2.6 to -2.2) (MG). The sexual

health scores also indicated a small improvement, SMG ranged from 0.3 (95% CI, 0.2-0.4) and 0.4 (95% CI, 0.3-0.5) .

Functional outcomes (Q_{max} and PVR) were inconsistently reported in the included studies, but Q_{max} showed a small improvement of between 3.8 ml/s (95% CI, 3.0-4.6) and 4.0 ml/s (95% CI, 3.4-4.6). The authors state that PVR results are significantly variable due to inconsitent reporting with very high heterogeneity estimates.

Summary critique of clinical evidence submitted by the sponsor

The sponsor presented a peer-reviewed systematic review (Perera et al., 2014) rather than their own literature search, data synthesis and analysis. However the systematic review included all of the studies identified as relevant by the EAC in an independent literature search.

Quality assessment of the systematic review (Perera et al., 2014) was performed by the EAC. Although some aspects of the review were reasonable there was insufficient methodological detail to fully explain their meta-analysis. Furthermore the quality of some of the included studies had a high risk of bias, 8/9 studies were uncontrolled before and after studies. Patient numbers in the analysis are not clearly explained. Perera et al., (2014) claimed that the pooled estimates were obtained from 888 to 1298 responses (depending on the score) from 452 to 680 patients. However, even if all the patients in all 10 studies listed in Table 2 are summed, this would only give 650 patients, and some of these are common to more than one study e.g. Chin et al. (2012) and Woo et al. (2012), and the two LIFT Study papers (McVary et al., 2014 & Roehrborn et al., 2013). Also the authors state that some studies were not included in the final meta-analyses, but do not clearly state which studies these are.

The results table presented gave pooled estimates of outcome measures with effect sizes, rather than using the units of individual outcome measures, which the EAC feel would be more transparent. The authors present a difference in IPSS of -7.2 and -8.7 points (a negative IPSS score is a symptom improvement). This change in IPSS is a derived number, back-calculated to IPSS scores from the effect size in the meta-analysis, which in itself is calculated from pooled IPSS and BPHII numbers. As a result, this reports a worse IPSS

improvement than in all the publications included in the meta-analysis (the EAC-calculated weighted mean IPSS score is actually around -11 points).

The potential for double-counting patients in these studies a lack of methodlogical clarity, and the somewhat short-form nature of a journal publication, means a lack of transparency in the authors' methodology for the analyses.

Summary of economic evidence submitted by the sponsor

There were no published economic studies available on the Urolift device. The sponsor's submission consisted of a very detailed de novo economic analysis and the sponsor submission was from the national NHS perspective. Data inputs for Urolift were collated from the LIFT study and expert clinical opinion. Outcome and complications costs were taken from a robust HTA (Laurenco et al. 2008).Comparators presented included TURP and HoLEP, as specified in the scope. The executable model included out-of scope-comparators such as laser resection and TUVP, which are not relevant for this assessment, but these were not included in the written submission. The time horizon was 2 years, which is appropriate, given the evidence base for Urolift.

Summary critique of economic evidence submitted by the sponsor

The sponsor's model is very thorough, and the EAC note that it actually contains too much detail e.g. out of scope comparators (laser and TUVP). The model includes before and after procedure appointments that appear to be the same for all interventions (therefore making no difference to the cost outcomesThe base case submitted actually makes Urolift slightly cost incurring (by £3 per case) versus TURP and £418 per case versus HoLEP. The sponsor's breakdown of costs for each technology showed that the equipment costs per procedure for Urolift were much greater than for the comparators. Urolift had lower clinical supplies and services costs due to the estimated shorter length of hospital stay. Sensitivity analysis was somewhat limited and a range of ±20% was insufficient for some inputs, such as LOS for Urolift, where there was considerable uncertainty.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The model is backed by robust data, comprising of Urolift data from the LIFT study and clinical opinion. Comparator data was taken from a thorough HTA authored by Laurenco et al. (2008). The EAC agreed with most of the inputs and assumptions used by the sponsor in the model.

Summary of any additional work carried out by the External Assessment Centre

For the clinical part of this assessment, the EAC designed and performed an independent literature search, and obtained a professional translation of the Spanish-language manuscript for Abad et al. 2013.

The EAC took a more simplified approach to the data presented in the studies for greater clarity. Firstly, we combined the three LIFT publications into a single set of results for the LIFT Study, and the two papers by Chin et al (2012) and Woo et al. (2012) to report from this 64-patient cohort. We present data as changes from baseline, with means and weighted means to account for cohort sizes, in order to retain the data in the original units. We provide context for the results by citing clinically important changes in each measure from published sources, where available, and also by surveying clinical experts. In order to provide some comparative context, we present changes from baseline in TURP and HoLEP from papers selected by a recent, methodologically robust systematic review (Li et al. 2014). It should be noted that this is not true comparative data, but gives an idea of improvements from baseline and complications post-TURP and HoLEP, presented in the same format as the Urolift data.

For the economic submission, the EAC checked the model inputs and corrected /adjusted them where necessary using a combination of published evidence and expert clinical opinion. We performed sensitivity and threshold analysis in order identify the key drivers of the model as the cost of the Urolift device, operating time and length of stay. The EAC present a scenario in which Urolift can be cost-saving compared to mTURP and BiTURP, but not HoLEP. This relies upon a low number of Urolift implants, a short procedure time of 30

minutes or less, adding urological operating theatre overhead costs, local anaesthetic, and a day-case procedure of 0.125 days (3 hours). Under these conditions, savings of £336 compared with mTURP and £209 compared with BiTURP are achievable. All of the inputs of the EAC scenario are supported by published sources or by clinical experts for the assessment, who are currently using the Urolift device in the UK.

Table 1 Glossary

Term	Definition
5-ARI	5-Alpha-Reductase Inhibitors
AUASI	American Urological Association Symptom Index (also known as IPSS score)
AUR	Acute Urinary Retention
AUS	Artificial Urinary Sphincter
BiTURP	Bipolar transurethral resection of prostate
BPH	Benign Prostatic Hyperplasia
BSC	Best Supportive Care
HOLEP	Holmium laser enucleation of the prostate
IPSS	International Prostate Symptom Score
LCI	Lower confidence interval
LOS	Length of stay
LUTS	Lower Urinary Tract Symptoms
MG	Mean Gain
mTURP	Monopolar transurethral resection of prostate
NHS	National Health System
NICE	National Institute for health and Clinical Excellence
PSA	Prostate Specific Antigen
PSS	Personal Social Services
PUL	Prostatic Urethral Lift
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
SHIM	Sexual Health Inventory for Men (same as IIEF-5)
SMG	Standardised mean gain
TUR	Transurethral resection
TURP	Transurethral resection of the Prostate
TUVP	Transurethral Vaporisation of the Prostate
UCI	Upper confidence interval
UK	United Kingdom
UTI	Urinary tract infection

2 Background

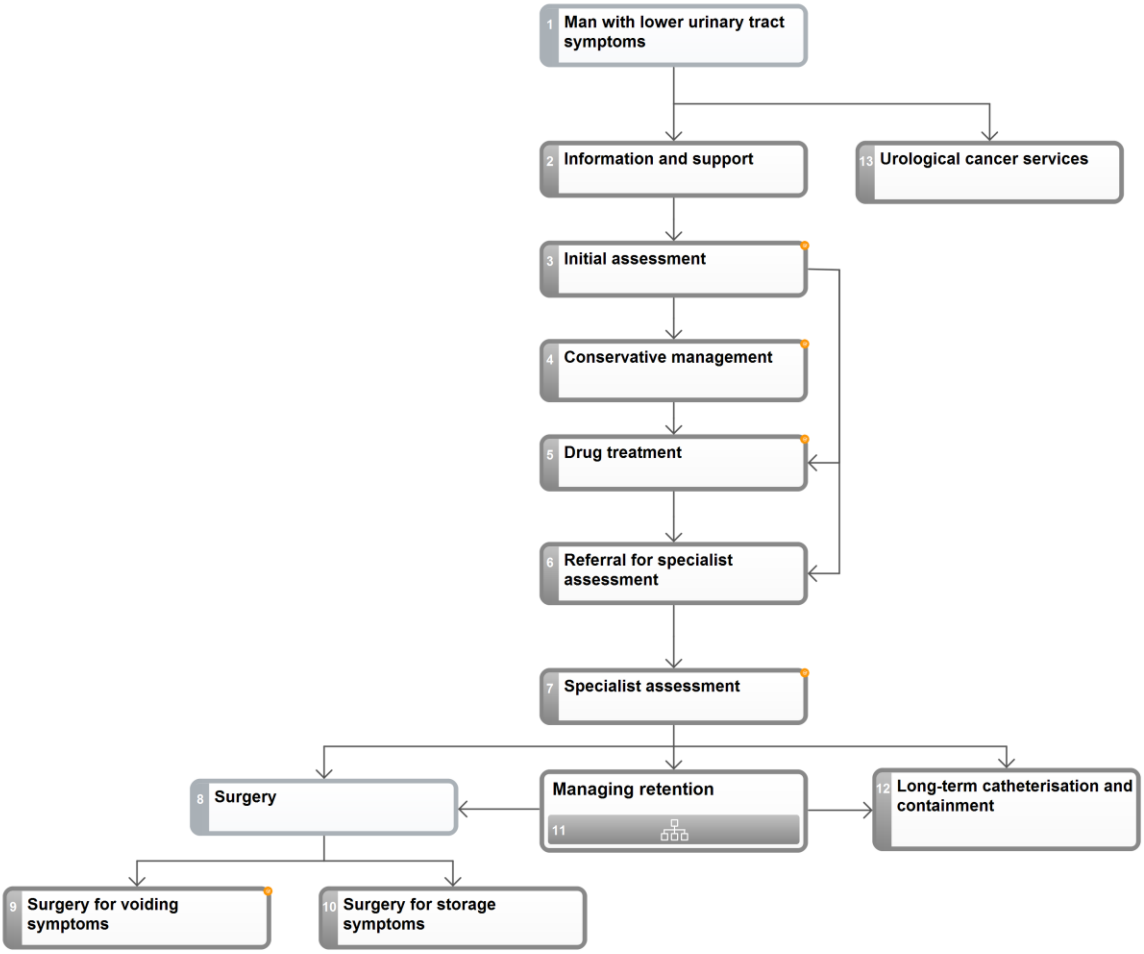
2.1 Overview and critique of sponsor's description of clinical context

The sponsor's submission outlines the clinical context well, with references from published journals to support the statements made. They describe Lower Urinary Tract Symptoms (LUTS) and the resulting decrease in quality of life that accompanies the condition. They also correctly identify that medication is the first type of therapy used to treat the condition, and that this comes with a number of unpleasant side-effects, noting that "over one quarter of patients discontinue medical therapy, often after only three months".

The sponsor refers to NICE IPG475, which has given "Normal Arrangements" for the use of prostatic urethral lift implants. It is worth noting that all the evidence in IPG475 is published data on the Urolift device, and there do not seem to be any competing devices for prostatic urethral lift.

The sponsor's submission states, "no UK clinical pathways relevant to Urolift have been published to date". However, the following overview is available on the NICE website, accompanying IPG475:

Figure 1 NICE clinical pathway for BPH



Urolift would be placed in section 9 of this pathway, as an option for "Surgery for voiding symptoms". In their submission, the sponsor specifically places Urolift in the pathway after the failure of drug management and prior to invasive surgical remedies (e.g. TURP, PVP, etc), which shows that they are aware of NICE clinical pathways and the EAC agrees that this placement of Urolift in the pathway is appropriate, as it is a minimally invasive procedure.

2.2 Overview of sponsor's description of ongoing studies

The EAC conducted an independent search of Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), and found the same ongoing clinical trials as noted by the Sponsor in their submission. Therefore, the EAC is in agreement with the sponsor's submission. The studies found were:

1) NCT01876706. Urolift System Tolerability and ReCovery When Administering Local Anesthesia (active, not recruiting)

2) NCT01533038. BPH-6: Comparison of the Urolift System to TURP for Benign Prostatic Hyperplasia (active, not recruiting)

3) NCT01294150 . The Safety and Effectiveness of Urolift: LIFT Pivotal Study (active, not recruiting).

The EAC is particularly interested in the results, or any preliminary analyses, arising from the BPH-6 trial, as it directly compares Urolift with TURP. As such, it is the only study that fully meets the scope for this assessment. However, the Clinicaltrials.gov listing denotes an end point of December 2015 for the BPH-6 trial and trial results are not available for inclusion in this report.

2.3 Critique of sponsor's definition of the decision problem

Note: The Sponsor's submission consists of a peer-reviewed systematic review by a separate group, Perera et al. (2014), rather than a de novo literature search followed by data extraction and synthesis/meta-analysis. Where possible, we will critique the Sponsor's work, and also the systematic review by Perera et al. 2014.

2.1.1 Population

The sponsor's submission contains studies that match the requirements of the NICE scope quite well. However, in table A1, the sponsor has misunderstood the table's requirements. The aim of the table is to re-state what was asked by NICE in their scope, and then give an overview of the sponsor's presented data with a rationale for any differences presented. The sponsor used the table to outline the state of BPH more generally in the UK – describing the total patient population, the number of surgical treatments per year, and the expected outcome measurements. One point the EAC would be interested in was the rationale behind the sponsor's identification of TURP alone as the comparator to Urolift, rather than also including HoLEP, as in the NICE scope. The EAC completed the table, using the studies in the presented Perera et al. systematic review:

Table 2 EAC-completed Table A1 from sponsor submission template

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) aged 50 or over, and with prostate volumes no greater than 100 cc (100 g).	None	
Intervention	The UroLift system	None	
Comparator(s)	Current practice varies and is changing as a result of which there are 2 comparators: Monopolar or bipolar transurethral resection of the prostate (TURP) Holmium laser enucleation of the prostate (HoLEP)	No comparative studies available – only one RCT vs sham control and uncontrolled before and after studies	No comparative studies available.
Outcomes	The outcome measures to consider include: -Length of hospital stay -The need for, or duration of, catheterisation -Number of post discharge follow-on consultations, both in primary and secondary care settings -Time to re-operation and re-operation rates -Symptoms of BPH (using the International Prostate Symptom Score [IPSS]) -Reduction in ejaculatory or sexual function -Time to return to normal	Only "Healthcare-associated infection" is not reported. UTIs, a device-related complication, are reported in the studies.	Data not available – not a standard outcome for urological studies.

	activities -Quality of life -Healthcare associated infection -Device-related adverse events		
Cost analysis	Comparator(s): Monopolar or bipolar TURP and HoLEP Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Sponsor's cost model also submitted comparator costs for laser (e.g. Greenlight) transurethral vaporisation of the prostate (TUVP), and bi-TUVP.	
Subgroups to be considered	Men for whom TURP or HoLEP is unsuitable because of difficulties with blood loss or sedation.	None	
Special considerations, including issues related to equality	Men who wish to preserve sexual function and fertility.	None – sexual function scores widely reported	

2.1.2 Intervention

The sponsor's submission matches the final scope issued by NICE. The submission was restricted to Urolift, the version of the device that has received CE marking and is sold in the UK.

The procedure is undertaken transurethrally with the patient under local or general anaesthesia. A pre-loaded delivery device is passed through a rigid sheath under cystoscopic visualisation. The delivery device is used to compress one lateral lobe of the prostate in an anterolateral direction towards the prostatic capsule. A needle is then advanced through the lobe and capsule, and a monofilament implant with two end pieces is deployed. One end of the implant is anchored in the urethra and the other on the outer surface of the prostatic capsule, retracting the prostatic lobe away from the urethral lumen. Multiple implants are usually inserted during each procedure (NICE IPG475).

2.1.3 Comparator(s)

The evidence submitted by the sponsor did not include any of the comparators detailed in the final scope, the scope called for comparative evidence against TURP or HoLEP. However, all studies submitted by the sponsor were either uncontrolled before and after studies or a RCT with a sham control. However, the available evidence is limited and the EAC did not find any comparative studies with Urolift vs. TURP or HOLEP in an independent literature search. The sponsor does point out that the study populations are similar, but this is still no substitute for a true comparative (preferably blinded) study, as this can be subject to selection bias, or outcomes can be interpreted differently due to detection bias in the different populations.

2.1.4 Outcomes

Primary clinical outcomes reported in the Perera et al. (2014) systematic review were:

- Prostate symptoms (IPSS – International Prostate Symptom Score, and BPHII – BPH impact Index)
- Sexual health (IIEF – International Index of Erectile Function, MSHQ – Male Sexual Health Questionnaires for ejaculatory function for ejaculatory function and Bother)
- Functional parameters (Qmax – maximum urinary flow rate, and PVR – post void residual volume)
- Procedural data (local anaesthetic, operative time and number of Urolift implants used
- Time to re-operation, reported as “progression to TURP at 12 months”
- Postoperative catheterisation

- Early postoperative complications, dysuria, haematuria, pelvic pain, urinary tract infection, incontinence)
- Device-related adverse events

The final scope listed additional outcomes, which were not reported in any of the identified studies. These were:

- Length of hospital stay
- Number of post-discharge follow-on consultations
- Time to return to normal activities

2.1.5 Cost analysis

The cost analysis presented in the sponsor's submission was a very detailed de novo economic analysis that matched the analysis specified in the scope. Costs were presented from national NHS perspective. Comparators presented included TURP and HoLEP, as specified in the scope. The time horizon is 2 years, which is appropriate, given the evidence base for Urolift, and outcome and complications are costed from a thorough HTA (Laurenco et al. 2008).

2.1.6 Subgroups

The scope specifies subgroups as men for whom, TURP or HoLEP is unsuitable because of difficulties with blood loss or sedation. Blood loss is not directly reported in the manufacturer's submission, but some of the identified studies report transfusion rates as a complication of the Urolift procedure. The EAC note that this technology may be of a benefit to groups for whom blood transfusions are not an option e.g. Jehovah's Witnesses.

Sedation data (local versus general anaesthetic) is also addressed by a number of the publications.

2.1.7 Special considerations, including issues related to equality

Special considerations in the scope were for men who wished to preserve sexual function and fertility. Several of the papers in the systematic review had contained outcomes pertaining to sexual function, which addresses this concern.

No equality issues were identified in the scope. Neither the sponsor nor the EAC have identified any further equalities issues.

3 Clinical evidence

Note: The Sponsor did not present a de novo literature search and review for their clinical submission of evidence. A systematic review by Perera et al. (2014) was presented instead. The systematic review (Perera et al. (2014) included 10 studies: two reports from an RCT and eight uncontrolled before and after studies.

3.1 Critique of the sponsor's search strategy

As noted above the sponsor did not undertake their own literature search. Instead, the sponsor described the literature search methods that were used in a recent, peer-reviewed systematic review (Perera et al. 2014). The search strategy is provided in the supplementary data that accompanies the systematic review publication. The EAC critically appraised the systematic review (Perera et al. 2013) using a checklist designed by the Support Unit for Research Evidence, Cardiff University.

The scope of the systematic review (Perera et al., 2014) lacked detail with regard to the population and comparators. The search strategy of the review was appropriate and the sources searched provided reasonable coverage for the review itself. However the review did not include a search for clinical trials, adverse events or seek to obtain unpublished data all of which are required for a submission of evidence. The sponsor attempted to seek unpublished data though this did not include contacting the authors of the included studies. The EAC designed a search strategy and performed an independent search of the literature, details in 3.9.

3.2 Critique of the sponsor's study selection

Inclusion and exclusion criteria were briefly described, and copied directly from the methods section of Perera et al. (2104). Studies reporting functional sexual outcomes following the urethral lift procedure for LUTS secondary to BPE were included. No language or sample-size restrictions were used. Conference proceedings were not included.

For publications where duplicate study populations or repeated data were identified, the publications reporting the larger sample size was used. However, due to the lack of

transparency in the methods presented by the Sponsor (specifically in the meta-analysis), the EAC took a more simplified approach to the analysis of data presented in the studies. Certain publications (Chin et al., 2012 and Woo et al., 2012, and those reporting the LIFT Study) were collated together to avoid double-reporting of results from the same patient cohorts (see section 3.9 – Additional work carried out by the EAC).

3.3 Included and excluded studies

Of 61 suitable studies, 23 conference proceedings and 28 editorials were excluded by Perera et al. (2014). One published study (Abad et al. 2013) was also excluded, as it did not report standard deviations. Nine studies were finally included:

Table 3 Included and excluded studies

Study	Country	Study Description	S quality assessment system ample size
Abad et al. 2013 (**excluded by Sponsor**)	Spain	Uncontrolled before and after study	20
Cantwell et al., 2013	,USA, Canada and Australia. 19 centre study	Before and after study to assess Urolift in patients who had previously been randomised to the sham arm of the LIFT study. After the primary endpoint comparison at 3 months, sham controls were unblinded and offered enrolment into this study.	53 (patients elected to have PUL after sham in the LIFT study)
Chin et al. , 2012 (same cohort as Woo et al. 2012 – see below)	Australia 6 centre study	Multicentre uncontrolled before and after study.	64
Delongchamps et al., 2012	France	Single centre prospective uncontrolled before and after study.	4
Roehrborn et al., 2013 (LIFT Study)	19 centre study: USA 14 Canada 2 Australia 3	RCT, 2:1 randomisation between Urolift and sham control. Sham control: patient blinded and given rigid cystoscopy, no implants used.	Urolift group: 140 Control group: 66
McVary et al., 2014 (LIFT Study)	19 centre study: USA 14 Canada 2 Australia 3	RCT, 2:1 randomisation between Urolift and sham control. Sham control: patient blinded and given rigid cystoscopy, no implants used.	Urolift group: 140 Control group: 66
McNicholas et al., 2013	7 centres in 5 countries. Not clearly stated, authors are from UK, Australia, USA, Spain, Germany,	Retrospective analysis of prospectively accrued data from consecutive multicentre uncontrolled before and after study.	102

	The Netherlands and Italy.		
Shore et al., 2014	Not reported	Uncontrolled before and after study.	51
Woo et al., 2011	Australia	Prospective, non-randomised uncontrolled before and after study, assessing safety and feasibility.	19
Woo et al., 2012 (same cohort as Chin et al. 2012 – see above)	Australia 6 centre study	Multicentre uncontrolled before and after study.	64

The EAC's independent literature search did not find any additional studies over those found by the sponsor. Alongside the systematic review by Perera et al. (2014), the sponsor also provided one additional publication: a 2-year update on the LIFT Study by Roehrborn et al. 2014. The sponsor states "the results do not materially change the meta-analysis and thus Perera et al. (2014) stands as relevant and current".

Delongchamps et al. (2012), a study published in French with only 4 patients, was excluded as it was not considered to be a pivotal study for this assessment.

Summary of the key points in each study:

Abad et al. (2013) (Not included in Sponsor's meta-analysis):

Patient population	Sample size		Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: Age ≥50, IPSS >20, Qmax <15ml/s, PSA<10 ng/ml **Exclusion criteria:** Obstructing medial lobe (observed with cystoscopy), urinary tract infection, previous surgical treatment for prostate pathology.	**Urolift group:** 20 **Withdrawals:** None **Note:** No SDs reported for baselines or results.		Spain	Mean 74.3 (range 43-90) years	IPSS 26.7, (range 20-35)	Not reported	All patients: Mean 6.9 (range 0-13 ml/s Excluding 4 patients catheterised at baseline due to chronic retention: Mean 8.6ml/s (range 3-13)	42.6 (range 19-109) cc (TRUS)	Not reported	Retrospective uncontrolled before and after study. Primary endpoints: evaluate the effectiveness of Urolift and the number and intensity of side effects post-procedure **Follow-up:** IPSS, BPHII and Qmax at 4 weeks, 3, 6 and 12 months.

Cantwell et al. (2013):

Patient population	Sample size	Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: ≥50 years old, provided informed consent, no prior surgical BPH treatment, washed out or naive to α-blockers or 5 α-reductase inhibitors. IPSS ≥13, Qmax ≤12ml/s with a voided volume of 125ml. Prostate volume of 30-80ml, without an obstructing median lobe. **Exclusion criteria:** Retention, post-void residual volume (PVR) >250ml, active infection, PSA >10ng/ml unless negative biopsy, cystolithiasis within 3 months, bacterial prostatitis within 1 year.	53 patients elected to have PUL after sham in the LIFT study. **Withdrawals:** None	19 centre study, USA, Canada and Australia.	64±8.0, range 50-79) years	IPSS 23.3±5.5, (range 13-34) IPSS QoL 4.5±1.2 (range 2-6) BPHII (n=52) 6.3±3.0 (range 1-12)	IIEF (n=53) 12.8±8.3, (range 1-25) MSHQ-EjD (n=42) 9.5±10.0 (range 3-14)	.8±4.2 (range 2.0-30.0) ml/s	40.3±9.9 (range 30-68) mls	67.8±66.44 (range 0-262) mls	Before and after study to assess Urolift in patients who had previously been randomised to the sham arm of the LIFT study. Primary endpoints were symptom scores, QoL and sexual health questionnaire scores. **Follow-up:** IPSS, IPSS QoL BPHII, IIEF-5 and MSHQ were 2 weeks, 1, 3, 6 and 12 months. Qmax and PVR at 3 and 12 months. Safety was assessed at each follow-up visit

Chin et al. (2013)

Patient population	Sample size	Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: ≥55 years of age,. Symptomatic BPH, IPSS>13, PVR<250ml, peak Qmax of 5-12ml/s. Wash-out of α-blockers for 1 week and 5 α-reductase inhibitors within 6 months of treatment. **Exclusion criteria:** PSA >10ng/ml, history of urinary retention, previous prostate surgery, compromised renal function, current infection, obstructive median lobes.	**Urolift group:** 64 **Withdrawals:** Not reported	Australia (6 different centres)	66.9 ±7.3 years (range 53-83)	IPSS: Not reported for total cohort, but varies throughout follow-up Duration of LUTS = 4.7±4.3 years (range 0.5-23)	Not reported for total cohort, but varies throughout follow-up	Not reported for total cohort, but varies throughout follow-up	51 ±23 mls (range 21-149) (TRUS)	Not reported for total cohort, but varies throughout follow-up	Multicentre uncontrolled before and after study. Primary endpoints were longer-term effectiveness of PUL in relieving LUTS **Follow-up:** 2 weeks, and 3,6,12 and 24 months IPSS results were analysed on a) the entire dataset and b) patients 26-64 only. Patients 26-64 had the most recent version of Urolift device (3 generations of device used over the total cohort) and refined method used, where implant placement formed continuous channel from bladder neck to verumontanum.

Roerhborn et al. 2013 (the LIFT Study):

Patient population	Sample size	Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria ≥50 years of age, provided consent, , no prior BPH surgical treatment, washout of 2 weeks for α-blockers, 3 months for 5-α-reductase inhibitors, 3 days for anticoagulants, IPSS>13, Qmax ≤12ml/s, 125ml voided volume, 30-80cc prostate volume (via TRUS). **Exclusion criteria:** Median lobe obstruction, retention, PVR >250ml, active infection, PSA >10ng/ml (unless negative biopsy), cystolithiasis within 3 months and bacterial prostatitis within 1 year.	**Urolift group:** 140 **Ctrl group:** 66 **Withdrawals:** 7 censored due to use of BPH medication 1 subject discontinued participation 2 exclusions due to significant protocol violations	19 centres: USA 14 Canada 2 Australia 3	**Urolift group:** 67±8.6 years **Ctrl group:** 65±8.0 years	**Urolift group:** IPSS 22.2±5.4 **Ctrl group:** Mean 24.4±5.8 **Urolift group:** IPSS QoL 4.6±1.1 **Ctrl group:** IPSS QoL 4.7±1.1 BPHII baselines not reported	**Urolift group:** IIEF 13.0±8.4 MSHQ-EjD 8.7±3.2 **Ctrl group:** IIEF 13.5±8.5 MSHQ-EjD 8.8±3.2	**Urolift group:** 8.9±2.2 ml/s **Ctrl group:** 8.8±2.2 ml/s	**Urolift group:** 44.5±12.4 mls **Ctrl group:** 40.9± 10.8 mls	**Urolift group:** 85.5±69.2 mls **Ctrl group:** 87.7± 72.4 mls	RCT, 2:1 randomisation between Urolift and sham control. Sham control: patient blinded and given rigid cystoscopy, no implants used. Primary endpoint: reduction in IPSS at 3 months after PUL procedure was at least 25% better than sham. **Follow-up:** IPSS, QoL, BPHII, IIEF and MSHQ-EjD assessed at 2 weeks, 1,3, 6,12 and 24 months.

McNicholas et al. 2013

Patient population	Sample size	Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: Prostate volume <60mls, IPSS>12, Qmax<15ml/s, PVR<350 NOTE: these are "typical inclusions" No exclusion criteria reported	102	7 centres in 5 countries. Not clearly stated, authors are from UK, Australia, USA, Spain, Germany, The Netherlands and Italy.	Mean 68±10 years	IPSS 23.2±6.1 IPSS QoL 4.7±1.0	Not reported for total cohort, but varies throughout follow-up	8.7±4.0 ml/s	48±21mls	Not reported for total cohort, but varies throughout follow-up	Retrospective analysis of prospectively accrued data from consecutive uncontrolled before and after study. Primary endpoints were to evaluate safety and efficacy with the most current Urolift device and surgical technique in day-to-day practice. **Follow-up:** 2 and 6 weeks, 3,6 and 12 months

McVary et al. 2014 (the LIFT Study):

Patient population	Sample size	Country	Mean age ±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria >50 years of age, provided consent, , no prior BPH surgical treatment, washout of 2 weeks for α-blockers, 3 months for 5-α-reductase inhibitors, 3 days for anticoagulants, IPSS ≥13, Qmax ≤12ml/s, 125ml voided volume, 30-80cc prostate volume (via TRUS). **Exclusion criteria:** Median lobe obstruction, retention, PVR >250ml, active infection, PSA >10ng/ml (unless negative biopsy), cystolithiasis within 3 months and bacterial prostatitis within 1 year.	**Urolift group:** 140 **Ctrl group:** 66 **Withdrawals:** 7 censored due to use of BPH medication 1 subject discontinued participation 2 exclusions due to significant protocol violations	19 centres: USA 14 Canada 2 Australia 3	**Urolift group:** 67 years **Ctrl group:** 65 years **Note:** SDs not reported by McVary but cohort is the same as Roerhborn et al. 2013 above.	**Urolift group:** IPSS 22 **Ctrl group:** IPSS 24 **Urolift group:** IPSS QoL 4.6 **Ctrl group:** IPSS QoL 4.7	**Urolift group:** IIEF 13.0 **Ctrl group:** IIEF 13.5	**Urolift group:** 8.9 ml/s **Ctrl group:** 8.8 ml/s	Not reported	Not reported	RCT, 2:1 randomisation between Urolift and sham control. Shame control: patient blinded and given rigid cystoscopy, no implants used. **Primary endpoint:** Change in IPSS and sexual health measures (IIEF and MSHQ) up to 12 months post-PUL **Follow-up:** QoL, BPHII, IIEF and MSHQ-EjD assessed at 2 weeks, 1,3,6,12 and 24 months.

Shore et al. 2014:

Patient population	Sample size	Country	Mean age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: ≥50 years of age, provided informed written consent, had no prior surgical BPH treatment, wased out or naive to α-blockers and 5- α-reductase inhibitors. IPSS ≥13. Qmax <12ml/s, prostate volume 30-80cc without obstructing median lobe. **Exclusion criteria:** Current urinary retention, PVR >250ml, active infection, gross haematuria, cystolithiasis, within 3 months, bacterial prostatitis within 1 year.	51	NR	66±7.6 years (range 51-85)	IPSS 21.45±5.43 (range 13-32) BPHII 6.65±3.08	IIEF 16.51±7.33 ml/s (range 2-25) MSHQ-EjD 9.95±2.59 (range 5-15)	8.22±2.18 (range 2-12.0)	41.3±11.6 cc (range 30.0-77.3)	77.05±74.92 mls (range 0-247)	Non-blinded uncontrolled before and after study. **Primary endpoint:** ascertain whether 80% of patients achieve a score of ≥80 on the Quality of Recovery Visual Analogue Scale (QoR VAS) by 1 month follow-up. **Follow-up:** 2 weeks, and 1 month

Woo et al. 2011:

Patient population	Sample size	Country	Age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: IPSS ≥13, Qmax 5-12ml/s, prostate volume 20-100ml, PVR <250ml, PSA <10ng/ml. **Exclusion criteria:** Median lobe obstruction, current infection, history of urinary retention, α-adrenergic receptor blocking medication within 1 week, or 5-α-reductase inhibitor medication within 6 months of treatment, history of significant medical co-morbidity, prior BPH surgery, or if had a known or suspected urological condition that may affect voiding function.	19	Australia	Mean 66±6 years (range 55-77)	Not reported for total cohort, but varies throughout follow-up	Not reported	Not reported for total cohort, but varies throughout follow-up	Mean 49±20 mls (range 21-97)	Not reported for total cohort, but varies throughout follow-up	Prospective, non-randomised safety and feasibility study **Primary aim:** Safety: Evaluate number and severity of SAEs up to 12 months follow-up Feasibility: deliver sutures to increase urethral lumen **Follow-up:** IPSS and QoL at 2 weeks, 3, 6 and 12 months

Woo et al. 2012:

Patient population	Sample size	Country	Age±SD	Mean baseline IPSS, or BHPII ±SD	Mean baseline IIEF or MSHQ ±SD	Mean baseline Qmax ±SD	Mean baseline prostate volume ±SD	Mean baseline PVR ±SD	Study design
Inclusion criteria: ≥55 years of age,. Symptomatic BPH, IPSS>13, PVR<250ml, peak Qmax of 5-12ml/s. Wash-out of α-blockers for 1 week and 5 α-reductase inhibitors within 6 months of treatment. **Exclusion criteria:** PSA >10ng/ml, history of urinary retention, previous prostate surgery, compromised renal function, current infection, obstructive median lobes.	**Urolift group:** 64 **Withdrawals:** Not reported	Australia (6 different centres)	66.9 ±7.3 years (range 53-83)	**IPSS:** 22.9 ±5.4 (range 14-35, n=64) **Duration of LUTS** = 4.7±4.3 years	**IIEF:** 11.7(±8.6) (range 1-25, n=58) **MSHQ-EjD:** 9.0±3.7 (range 1-15, n=46) **MSHQ-Bother:** 1.7 ±1.5 (range 0-5 , n=46)	Not reported	51 ±23 mls (range 21-149) (TRUS)	Not reported	Multicentre uncontrolled before and after study. Primary endpoint: effect of PUL on erectile and ejaculatory function **Follow-up:** 2 weeks, and 3,6, and 12 months

3.4 Overview of methodologies of all included studies

Table 4 Overview of methodologies of all studies

Study	Methods
Abad et al. 2013 (not included in Sponsor's submission)	**Primary endpoints:** Evaluate the effectiveness of Urolift and the number and intensity of side effects post-procedure **Follow-up:** IPSS, BPHII and Qmax at 4 weeks, 3, 6 and 12 months. **Statistical methods:** Changes from baseline measurements compared and Wilcoxon nonparametric test used. Significance calculated as $p<0.05$.
Cantwell et al. 2013	**Primary endpoints:** Symptom scores, QoL and sexual health questionnaire scores. **Follow-up:** IPSS, IPSS QoL and BPHII were assessed at 2 weeks, 1 and 3 months after both the sham and PUL and additionally at 6 and 12 months post-PUL. IIEF-5, MSHQ-EjD and MSHQ-Bother were also assessed at the same time-points in sexually active patients. Qmax and PVR assessed at 3 and 12 months. Safety was assessed at each follow-up visit through adverse event reporting. **Statistical methods:** Descriptive statistics used for IPSS, IPSS QoL, BPHII, Qmax, PVR, IIEF-5, MSHQ-EjD. Students t-test used to compare changes from baseline to 3 months between sham and PUL.
Chin et al. 2012	**Primary endpoints:** longer-term effectiveness of PUL in relieving LUTS **Follow-up:** 2 weeks, and 3,6,12 and 24 months **Statistical methods:** To evaluate change from baseline, a general estimating equation model was fit to each outcome parameter (IPSS, QoL, BPHII, Qmax, PVR, IIEF (SHIM) and MSHQ-EjD). To address potential effects of the device and procedural changes made during the study, IPSS results were analysed on a) the entire dataset and b) patients 26-64 only.
Roehrborn et al. 2013 (The LIFT Study)	**Primary endpoint:** Reduction in AUASI (IPSS, on an intention-to-treat basis) at 3 months after PUL procedure was at least 25% better than sham. **Follow-up:** QoL, BPHII, IIEF and MSHQ-EjD assessed at 2 weeks, 1,3,6,12 months. **Statistical methods:** The study was powered for the primary endpoint assuming a Student's *t* test comparison of mean values on an ITT basis, 0.05 2-sided type-1 error and 80% power. For per-protocol analysis to evaluate change from baseline, a general estimating equation model was fit to each outcome parameter.
McVary et al. 2013 (The LIFT Study)	**Primary endpoint:** Change in IPSS and sexual health measures (IIEF and MSHQ) up to 12 months post-PUL **Follow-up:** QoL, BPHII, IIEF and MSHQ-EjD assessed at 2 weeks, 1,3,6, and 12 months. **Statistical methods:** The study was powered for the primary endpoint assuming a Student's *t* test comparison of mean values on an ITT basis, 0.05 2-sided type-1 error and 80% power. For per-protocol analysis to evaluate change from baseline, a general estimating equation model was fit to each outcome parameter.
McNicholas et al. 2013	**Primary endpoints**: Evaluate safety and efficacy with the most current Urolift device and surgical technique in day-to-day practice. **Follow-up:** 2 and 6 weeks, 3,6 and 12 months **Statistical methods:** To evaluate change from baseline, a general estimating equation model was fit to each outcome parameter (IPSS, QoL, BPHII, Qmax, PVR, IIEF (SHIM) and MSHQ-EjD).
Shore et al. 2014	**Primary endpoint:** Ascertain whether 80% of patients achieve a score of ≥80 on the Quality of Recovery Visual Analogue Scale (QoR VAS) by 1-month follow-up. **Follow-up:** 2 weeks, and 1 month **Statistical methods:** Primary endpoint tested by calculating the one-sided 95% confidence

	limit using the Clopper-Pearson method. Descriptive statistics used for IPSS, IPSS QoL, BPHII, Qmax, PVR, IIEF-5, MSHQ-EjD. A general estimating equation model was fit to each outcome parameter.
Woo et al. 2011	**Primary aims:** Safety: Evaluate number and severity of SAEs up to 12 months follow-up Feasibility: deliver sutures to increase urethral lumen **Follow-up:** IPSS and QoL at 2 weeks, 3, 6 and 12 months **Statistical methods:** Not reported.
Woo et al. 2012	**Primary endpoints:** Effect of PUL on erectile and ejaculatory function **Follow-up:** 2 weeks, and 3,6,and 12 months **Statistical methods:** To evaluate change from baseline, a general estimating equation model was fit to each outcome parameter (IPSS, QoL, BPHII, Qmax, PVR, IIEF (SHIM) and MSHQ-EjD). To address potential effects of the device and procedural changes made during the study, IPSS results were analysed on a) the entire dataset and b) patients 26-64 only.

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor's submission contained a number of tables with critical appraisals for the studies within the Perera et. al. systematic review. The table template used was designated for randomised controlled trial (RCT) appraisal, and appropriately used for the two LIFT Study papers (Roerhborn et al. 2013 and McVary et al. 2014). All other studies are uncontrolled before and after studies and were appraised appropriately with a tool for observational studies.

Quality assessment in the systematic review by Perera et al. (2014) is described very briefly. Studies were quality assessed by two researchers, working independently, using a method based on The Cochrane Handbook for Systematic Reviews of Interventions 5.02.

3.6 Results

Table 5 Sponsor's submission meta-analysis results, as presented in Perera et al. 2014

	1 month	3 month	12 month	24 month
Prostate symptom scores (IPSS, BPHII) No of data sources, response sample size (*n*)	9 (1298)	6 (1050)	6(1022)	6 (888)
Effect size (95% CI)	-1.30 (-1.4 to -1.2)	-1.50 (-1.7 to -1.4)	-1.6 (-1.7 to -1.3)	-1.5 (-1.6 to -1.3)
Heterogeneity (τ^2)	0.1	0.1	0.00	0.00
Male sexual health scores (IIEF, MSHQ-EjD, MSHQ-Bother) No of data sources, response sample size (*n*)	13 (1042)	9 (889)	9 (908)	9 (786)
Effect size (95% CI)	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.5)	0.3 (0.2 to 0.4)
Heterogeneity (τ^2)	0.00	0.00	0.00	0.00
Health related QoL No of data sources, response sample size (*n*)	4 (628)	3 (508)	3 (496)	4 (452)
Effect size (95% CI)	-2.2 (-2.5 to -2.0)	-2.4 (-2.6 to -2.2)	-2.4 (-2.6 to -2.2)	-2.2 (-2.4 to -2.1)
Heterogeneity (τ^2)	0.2	0.1	0.1	0.00
Maximum flow rate (Qmax) No of data sources, response sample size (*n*)	3 (242)	3 (488)	1 (106)	3 (362)
Effect size (95% CI)	3.8 (3.0 to 4.6)	4.0 (3.4 to 4.6)	4.4 (3.2 to 5.6)	3.8 (3.1 to 4.4)
Heterogeneity (τ^2)	0.4	0.03	NA	0.2
Postvoid residual (PVR) No of data sources, response sample size (*n*)	2 (128)	2 (396)	1 (122) Note: this is data from a single study	2 (350)
Effect size (95% CI)	15.5 (12.6 to 18.6)	-6.2 (-10.1 to -2.8)	-11 (-13 to -9)	-4.0 (-10.5 to 2.6)
Heterogeneity (τ^2)	1732	24	NA	219

The presentation of the meta-analysis makes it difficult to elucidate which studies are being used by the sponsor, as it is not explicitly stated. The number of studies using different outcome measures varies but exact studies are not identified by name.

Raw data are not presented at all, and therefore this is difficult to discuss, as the results are presented in meta-analysis form only, with a separate table for collated complications (see Section 3.7 below).

Each study does contain the relevant patient population (elucidated by the EAC after gathering the included papers), and uses Urolift as the intervention, which is within scope.

There were no comparators (the scope required comparative studies with TURP or HoLEP, as discussed previously) because identified studies were either case series or a single RCT against a sham control. No comparative studies for Urolift against TURP or HoLEP exist at the time of writing.

The lack of detail in the results presentation in the sponsor's submission means that it is more appropriate to critique the meta-analysis by Perera et al. – see Section 3.8.

3.7 Description of the adverse events reported by the sponsor

The operative details and complications are reported in one unified table that the sponsor presented from Perera et al. (2014). Complications are not combined, but reported for each publication separately.

Operative details are:

- Local anaesthetic (incidence of use), operative time (mins), implants (meaning number of Urolift implant sutures used in the procedure), postoperative catheter (patient numbers needing catheterisation, or catheterised as per hospital protocol).

Complications reported are:

- Early postoperative complications:
    - Dysuria, haematuria, pelvic pain, UTI (urinary tract infection), Incontinence
- Progression to TURP at 12 months

The EAC feels that the adverse events reported are quite mild, with the most common complications being short-term dysuria and haematuria.

One item of greater concern is the variability in progression to TURP at 12 months – this is reported as being as low as 1.4% (LIFT Study, Roerhborn et al. 2013) but as high as 19% (Chin et al. 2012).

The authors also mention implant encrustation and quantify it in the text of the review. This is reported in one of the studies (publications by Chin et al. 2012 and Woo et al 2012), and

occurs when implants are placed too close to the bladder, exposed to static urine. Two out of fourteen encrusted implants required removal with endoscopic forceps. This is important as a Urolift-specific complication that will not arise with TURP or HoLEP. In order to get more detail on this issue, the EAC consulted clinical experts on the severity of implant encrustation. The opinions varied due to there being very little long-term data available on Urolift. Three experts stated that encrustation is a significant issue, with one detailing that they will gradually become stones over time, potentially causing an infection. Two experts did not see encrustation as a significant issue, and one further expert stated that he did not know due to lack of long-term data. The majority of experts stated that the removal of encrusted implants was a simple procedure, but one expert was concerned that a TURP or HoLEP to remove encrusted implants was more complex than a standard procedure.

The EAC were also concerned that the Urolift implants themselves may cause a problem if a patient progresses to TURP. This may be through conduction of heat or electricity from the electrosurgery loop. The EAC asked Specialist advisers about this issue, and were reassured that it is not a concern, particularly from Specialists who had performed a post-Urolift TURP in practice. One published source (Woo et al. 2011) mentions that three patients in their case series required TURP and the Urolift implants were cut without difficulty and no alteration of the TURP procedure was required. This was also the case in Chin et al. 2012, where patients were re-treated with TURP, photoselective vaporisation of the prostate or repeat Urolift procedure. Each retreatment method was performed routinely, unaffected by the presence of the Urolift implants.

Our EAC data analysis shows that not all complications are reported in the systematic review, so we will attempt to rectify this in Section 3.9.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The meta-analysis results presented by the sponsor are shown in Section 3.7 and are the only (non-complication) outcome measure results in Perera et al. (2014).

The systematic review gives insufficient methodological detail to fully explain their meta-analysis. The results table presented gives pooled estimates of outcome measures with

effect sizes, rather than using the units of individual outcome measures, which the EAC feel would be more transparent. Below are categorised notes on the meta-analysis:

Patient numbers

The authors claimed that the pooled estimates were obtained from 888 to 1298 responses (depending on the score) from 452 to 680 patients. However, even if all the patients in all 10 studies listed in Table 2 are summed, this would only give 650 patients, and some of these are common to more than one study e.g. Chin et al 2012 and Woo et al. 2012, and the two LIFT Study papers (and this despite the fact that the authors stated that some studies were not included in the final meta-analyses). The EAC has attempted to contact the authors regarding this issue but received no response.

Making an assumption of which five studies were included in the final meta-analyses gives a total number of 53 (Cantwell et al., 2014) + 140 [Lift Study (McVary et al., 2014 & Roehrborn et al., 2013)] + 51 (Shore et al., 2014) + 102 (McNicholas et al., 2013) + 64 (Chin et al. 2012) = 410 patients, much less than the numbers quoted by the authors.

Further, in Table 4, the number of studies included in the analysis in many of the cells exceeds either 5 or 6, with up to 13 studies being included for one analysis (with 1042 responses). It is not clear which studies have been included in each of the analyses.

Note that in the abstract, it is stated that 6 independent patient cohorts were included for analysis, although the conclusions state 5.

Presentation of meta-analyses

Presumably, the primary outcome of interest is the change in IPSS and whether there is a significant improvement; or, alternatively, whether the improvement is similar to that found when using other established methods, but with fewer side effects.

However, the Perera et al. (2014) present the outcome as a compound 'prostate symptom score' (IPSS and BPHII combined) in Figure 2 and Table 4, so it is difficult (if not impossible) to determine how much the IPSS itself has changed following the procedure.

The authors present in the abstract that there was a difference in IPSS of -7.2 to -8.7 points, but with no indication if this is a range, a confidence interval or at which time-point(s). In the discussion, this is stated as an improvement of -8.0 points (95% CI, -8.8 to -7.2) at 12-mo follow-up. In fact, the change in IPSS is a derived number, calculated as follows (according to *Data extraction and analysis*):

The standardised mean gain (SMG) was calculated from the pooled standard deviation of the multiple scales comprising the prostate symptom score. The SMG and its 95% CI were then multiplied by 5.5, which 'represents a typical standard deviation for the IPSS scores'. Moreover, the authors state that 'This interpretation should be considered indicative only'. This caution is not repeated in the abstract or the discussion. This method of calculation seems to be unwarranted when the actual IPSS scores, their means and overall changes, could be presented.

The usual method used to present results from a meta-analysis (using forest and funnel plots) was not used by the authors. For example, if the outcome of interest is the change in IPSS 3 months after the procedure, then (as an example) the results from McVary and Cantwell (and others) could be combined. Separately, the results are as follows:

Table 6 Calculation of 95% CI of mean change after 3 months in IPSS from two studies on PUL

Paper	Mean change (SD)	n	95% CI
McVary	-11.1 (7.67)	140	-9.8 to -12.4
Cantwell	-11.1 (7.2)	52	-9.1 to -13.1

Note that Perera et al. (2014) state that a difference in IPSS of 7 points represents a large difference. Not only is the mean change in IPSS greater than 7 in both these studies, but the whole 95% confidence interval is also greater than 7. Therefore, the results from just these two studies indicate a statistically significant and clinically important effect of the procedure on the IPSS score (in fact, not only are the mean changes statistically significantly different to zero, ruling out the null hypothesis, but they are also significantly different to 7).

Note also that the mean change is identical in both studies, although the patients are drawn from the same study population. One reason for carrying out a meta-analysis is to see if the effect of the treatment is similar in different populations, but the results from the individual studies would have to be displayed in order to provide this information. Another reason for carrying out a meta-analysis is to combine results from several underpowered studies to provide a robust estimation of the effect of a particular treatment. However, in this case, it appears that the individual studies have already demonstrated a significant effect (statistically and clinically) of the treatment.

Other (minor) comments

Most of the studies in the meta-analysis were uncontrolled studies, with a single sham-control RCT. It may not be appropriate to present effect-size data from non-comparative studies in this way, as this type of meta-analysis is typically reserved for two-armed randomised trials.

Heterogeneity is usually expressed using I^2, which varies in value between 0 and 100%. However, in this study, heterogeneity was expressed in terms of τ^2, which is usually used to express an estimate of the between-study variance in a random-effects meta-analysis.

The authors claimed that the mean operative time was comparable over the six patient series, but the values stated were 19.1 to 66 minutes, which appears to indicate a large difference between studies.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

EAC literature search

The EAC designed a search strategy in Medline (Ovid), (Appendix 1) and conducted a search of Medline and Medline In-Process. The strategy was adapted for and run in the following databases:EMBASE; The Cochrane Library; Pubmed (“epub ahead of print”); National Technical Information Service (NTIS) database; NHS Evidence and Web of Science Core

Collection. Citation tracking in Google Scholar of the studies included in the Perera et al. (2014) review was also performed.

The EAC conducted a search of the FDA MAUDE database and of the MHRA Field Safety Notices and Medical Device Alerts for adverse events and safety alerts and warnings related to Urolift, none were identified. No additional adverse events were detailed in the publications found by the EAC.

The EAC search identified all studies included in the Perera et al. (2014) review as well as editorials, conference proceedings and reviews that referenced the sponsor-submitted studies (and therefore carried no additional value, and were not included) but no other additional studies that met the inclusion criteria were identified. The sponsor also provided a more recent two-year follow-up of the LIFT Study by Roehrborn et al. 2014. Expert clinical advisers requested long-term data in this Assessment, so these results were incorporated into the EAC's analysis.

Specifically no comparative studies of Urolift vs. TURP/HoLEP were identified by the EAC, which would have more closely fit the NICE scope for this assessment. No additional adverse events were detailed in the publications found by the EAC.

We obtained the Spanish-language manuscript for Abad et al. 2013 and had it professionally translated by Languages For Business Ltd. This allowed us to include it in our simplified data analysis, using weighted mean changes/improvements from baseline in various outcome measures.

EAC synthesis and analysis

Due to the lack of transparency in the meta-analysis presented by the Sponsor, the EAC took a more simplified approach to the data presented in the studies. Firstly; the following publications results were combined, as they reported different aspects of the same series of patients:

1) Chin et al. 2012 and Woo et al. 2012 reported urological and sexual function outcomes, respectively, from the same 64-patient case series.

2) Roerhborn et al. 2013 and 2014, and McVary 2014 all report on the LIFT Study RCT. Roehrborn et al. 2013 reports 12 month urological function results, Roerhborn et al. 2014 is a 2-year follow-up report, and McVary reports sexual health outcomes for the initial 12 month follow-up on the LIFT Study.

This was important because some of the results may have been double-counted in the Perera et al. (2014) meta-analysis, if these publications were not combined into their respective studies.

Roerhborn et al. 2014 was provided by the Sponsor alongside their submission of Perera et al. 2014, but not included. Although not a separate study, this does add more long-term data (24-month follow-up) to the LIFT RCT, which the EAC felt was of value to the analysis. Two clinical advisers also requested long-term clinical data, and therefore this publication was included in light of this.

The EAC were asked to provide comparator data for TURP and HoLEP. In order to achieve this, a recent, methodologically-sound systematic review, assessed using a checklist designed by the Support Unit for Research Evidence, Cardiff University (Appendix 3), comparing TURP and HoLEP was sought out (Li et al. 2014). The source publications identified by this review were gathered and relevant outcome data extracted for TURP and HoLEP.

3.9.1 EAC data analysis

Clinically important differences

In order to provide the MTAC Committee with some context to judge the results, the EAC sought out published minimally important differences in each of the reported outcome measures. These are available for questionnaires such as IPSS and IIEF, as they go through a validation and testing process during development.

Where published sources were not available or unsuitable (PVR, for example), the clinical experts were surveyed by the EAC for their opinion on the minimum clinically significant differences in each outcome reported.

Published sources

- IPSS (Barry et al. 1995):
    - Minimum clinically important difference = 3.0 points
    - Moderate difference = 5.1 points
    - Marked difference = 8.8 points
- BPHII (Barry et al. 1995):
    - Minimum clinically important difference = 0.5 points
    - Moderate difference = 1.1 points
    - Marked difference = 2.2 points
- IIEF-5 (Rosen et al. 1999): 4 points.
    - Note: The authors/developers of IIEF-5 (Rosen et al. 1999) classify erectile dysfunction (ED) into five severity grades: no ED (SHIM total score, 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (1–7). In the published literature, there is no such reported “minimal clinically important difference”. The EAC suggested a minimal difference of four points, as this would carry a patient from one ED classification to another. The majority of clinical experts agreed this was a sensible limit to use for IIEF-5.
- Q_{max} (NICE CG97):
    - Minimum clinically important change = 2ml/s.

- "A consensus during a GDG meeting suggested that a change of 2ml/s is usually considered as important enough to guide treatment decision. The minimal clinical difference was unknown from the patient's perspective."

- PVR is assessed by NICE CG97 as having little value as a measure (or diagnostic indicator) for LUTS because of poor sensitivity and positive/negative likelihood ratios, stating that "elevation of PVR may reflect poor detrusor function as much as obstruction". This was also mentioned to the EAC by one of the specialist clinical advisors. It also does not have questionnaire-style validation, as it is a functional urological measurement.

Table 7 Clinical expert survey for clinical differences

	Expert 1	Expert 2	Expert 3	Expert 4 (drug treatments)	Expert 4 (surgical treatments)
IPSS	3.00	2.50	3	3 to 5	7 to 15
IPSS QoL	1.00		2	1 to 1.5	1.5 to 3
BPHII	2.00			1 to 2	2 to 5
IIEF	3.00		4	6.00	6.00
MSHQ-EjD	1.50				
MSHQ-Bother	1.00				
Qmax (ml/s)	2.50	4.00	5		10-15
PVR (ml)			50		

Blank spaces indicate that a reply was not received, or the expert did not know/was unable to give a clinically significant difference for the outcome measure.

Outcome measures overview – EAC calculations

Table 8 collates all EAC-calculated outcome measures (using weighted means) published studies in the sponsor's submission, as a quick results overview. The outcomes reported are IPSS, IPSS QoL, BPHII, IIEF, MSHQ-EjD, MSHQ-Bother, Qmax and PVR. This is shown for 1, 3, 12 and 24 month follow-up points, as reported. Each individual outcome measure has its own table below that, with individual studies reporting changes from baseline, the number of patients in the study, and significance values (*p*).

Table 8 Overview of EAC-calculated results at 1, 3, 12 and 24 months post-Urolift from baseline (from studies in the Perera et al. (2014) meta-analysis)

	1 month	3 month	12 month	24 month
IPSS (Negative score is improvement)	-10.35	-11.82	-10.49	-9.22
IPSS QoL (Negative score is improvement)	-2.27	-2.48	-2.31	-2.22
BPHII (Negative score is improvement)	-3.29	-3.96	-3.95	-3.76
IIEF (Positive score is improvement)	0.52	1.34	0.80	
MSHQ-EjD (Negative score is improvement)	1.82	1.47	0.83	
MSHQ-Bother (Negative score is improvement)	-0.67	-0.79	-0.91	
Qmax (Positive is improvement)	4.16	3.78	3.52	4.15
PVR (Negative is improvement)	-7.00	-10.34	-5.72	

Outcome measures from all studies

The tables below show mean changes from baseline for each study (Abad et al., 2013; Cantwell et al., 2013; Chin et al. 2012 and Woo et al. 2012 combined cohort study; LIFT combined study results (Roerhborn et al. 2013 and 2014 and McVary 2014), McNicholas et al. 2013; Shore et al. 2014 and Woo et al. 2011), with the number of patients in the analysis, mean results and weighted mean results at 1, 3, 12 and 24 months, where reported.

IPSS score: IPSS scores were widely reported and mean improvements from baseline over 12 months ranged from -9.22 to -11.59 points. All improvements were statistically significant where reported. A higher score is worse, so negative score means a symptom improvement.

Table 9 Mean difference changes in IPSS score in each included study

	IPSS Change from baseline: mean ±SD, (n, *p* value)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013 (no SDs reported for mean change)	-10 (n=20) *p*=0.001)	-9.9 (n=17 *p*<0.001)	-11 (n=9 *p*=0.008)	
Cantwell 2013	-10.9±6.9 (n=53 *p*<0.001)	-11.1±7.2 (n=52 *p*<0.001)	-8.7±7.5 (n=48 *p*<0.001)	
Chin and Woo 2012 (no SDs reported for mean change)		-13.6 (n=62 *p*<0.001)	-10.4 (n=55 *p*<0.001)	
LIFT Study	-9.91±7.08 (n=138 *p*<0.001)	-11.13±7.68 (n=139 *p*<0.001)	-10.63±7.44 (n=126 *p*<0.001)	-9.22±7.57 (n=106 *p*<0.001)
McNicholas 2013 (no SDs reported for mean change)	-10.7 (n=95 *p*<0.001)	-12.6 (n=82 *p*<0.001)	-12.3 (n=51 *p*<0.001)	
Shore 2014	-10.47±7.35 (n=51 *p*<0.001)			
Woo 2011		-11.2±5.7 (n=15 *p*<0.001)	-8.6±7.8 (n=13 *p*=0.002)	
Mean	-10.396	-11.58833333	-10.27166667	-9.22
Weighted mean	-10.3522409	-11.81735695	-10.48701987	-9.22

IPSS QoL: IPSS QoL score mean improvements from baseline ranged from -2.22 to -2.584 points. All improvements were statistically significant where reported. This is to be expected, as QoL is a sub-question of the IPSS, so where IPSS improvement is seen in the table above, there should also be a corresponding QoL improvement. A higher score is worse, so negative score means a symptom improvement.

Table 10 Mean difference changes in IPSS QoL in each included study

	IPSS QoL change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013				
Cantwell 2013	-2.2±1.8 (n=53 *p*<0.001)	-2.3±1.7 (n=52 *p*<0.001)	-2.0±1.7 (n=48 *p*<0.001)	
Chin and Woo 2012 (no SDs reported for mean change)		-2.8 (n=62 *p*<0.001)	-2.4 (n=55 *p*<0.001)	
LIFT Study	-2.01±1.74 (n=138 *p*<0.001)	-2.22±1.78 (n=139 *p*<0.001)	-2.3±1.59 (n=126 *p*<0.001)	-2.22±1.71 (n=106 *p*<0.001)
McNicholas 2013 (no SDs reported for mean change)	-2.9 (n=138 *p*<0.001)	-2.8 (n=65 *p*<0.001)	-2.6 (n=43 *p*<0.001)	
Shore 2014	-2.12±1.94 (n=51 *p*=0.001)			
Woo 2011		-2.8±1.7 (n=15 *p*<0.001)	-2.2±1.9 (n=13 *p*<0.001)	
Mean	-2.3075	-2.584	-2.3	-2.22
Weighted mean	-2.266031746	-2.47981982	-2.30947	-2.22

BPHII: BPHII score mean improvements from baseline ranged from -3.384 to -3.854 points. All improvements were statistically significant where reported. A higher score is worse, so negative score means a symptom improvement.

Table 11 Mean difference changes in BPHII in each included study

	BPHII change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013 (no SDs reported for mean change)	-3.3 (n=20 *p*=0.001)	-3.1 (n=17 *p*=0.001)	-3.4 (n=9 *p*=0.006)	
Cantwell 2013	-3.1±3.3 (n=53 *p*<0.001)	-3.3±2.9 (n=52 *p*<0.001)	-3.1±3.1 (n=48 *p*<0.001)	
Chin and Woo 2012 (no SDs reported for mean change)		-4.6 (n=53 *p*<0.001)	-4.1 (n=46 *p*<0.001)	
LIFT Study	-2.81±3.46 (n=138 *p*<0.001)	-3.96±3.21 (n=139 *p*<0.001)	-3.97±3.26 (n=126 *p*<0.001)	-3.76±3.45 (n=106 *p*<0.001)
McNicholas 2013 (no SDs reported for mean change)	-4.3 (n=68 *p*<0.001)	-4.2 (n=65 *p*<0.001)	-4.7 (n=47 *p*<0.001)	
Shore 2014	-3.41±3.57 (n=51 *p*<0.001)			
Woo 2011				
Mean	-3.384	-3.832	-3.854	-3.76
Weighted mean	-3.28603	-3.961779141	-3.94609	-3.76

IIEF: IIEF score mean changes ranged from +0.483333 to +1.4 points. The majority of changes from baseline were positive, indicating a symptom improvement (a better score indicates better sexual function). However, many of the measurements were not statistically significant, which supports the claim that Urolift does not affect sexual function, and no results indicated a worsening of sexual function post-Urolift.

Table 12 Mean difference changes in IIEF score in each included study

	IIEF change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013				
Cantwell 2013	0.5±4.6 (n=34 *p*=0.51)	0.7±9.2 (n=40 *p*=0.66)	0.9±5.7 (n=33 *p*=0.30)	
Chin and Woo 2012 (no SDs reported for mean change)		2.2 (n=33 *p*=0.004)	1.8 (n=26 *p*=0.01)	
LIFT Study (no SDs reported for mean change)	0.6 (77 *p*=0.309)	1.3 (80 *p*=0.021)	0.4 (73 *p*=0.013)	
McNicholas 2013				
Shore 2014	0.35±4.76 (n=34 *p*=0.67)			
Woo 2011				
Mean	0.483333	1.4	1.033333	
Weighted mean	0.517931	1.337255	0.800758	

MSHQ-EjD: MHSQ-EjD score mean changes ranged from +0.466667 to +1.696667 points. All changes from baseline were positive, indicating a symptom improvement (a higher score indicates better sexual function). Some of the changes from baseline were statistically significant and others were not, however there was only a mean worsening of MHSQ-EjD scores in one time-point of one study (12 month follow-up, Chin and Woo et al. 2012), which does not change the overall mean improvement or weighted mean improvement seen across studies.

Table 13 Mean difference changes in MSHQ-EjD in each included study

	MSHQ-EjD change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013				
Cantwell 2013	1.4±2.3 (n=34 *p*<0.001)	0.3±4.6 (n=39 *p*=0.98)	0.8±2.8 (n=33 *p*=0.62)	
Chin and Woo 2012 (no SDs reported for mean change)		1.6 (n=28 *p*<0.001)	-0.7 (n=22 *p*=0.7)	
LIFT Study (no SDs reported for mean change)	2.1 (n=77 *p*<0.001)	1.8 (n=80 *p*<0.001)	1.3 (n=75 *p*<0.001)	
McNicholas 2013				
Shore 2014	1.59±2.75 (n=34 *p*=0.002)			
Woo 2011				
Mean	1.696667	1.366667	0.466667	
Weighted mean	1.816276	1.470068	0.834615	

MSHQ-Bother: MSHQ-Bother score mean changes from baseline over 12 months ranged from -0.65333 to -0.76667 points. A higher score is worse, so negative score means an improvement. Some of the changes from baseline were statistically significant and others were not. None of the results indicated a worsening of sexual function post-Urolift.

Table 14 Mean difference changes in MSHQ-Bother in each included study

	MSHQ-Bother change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013				
Cantwell 2013	-0.5±1.1 (n=34 *p*=0.008)	-0.4±2.3 (n=37 *p*=0.44)	-0.4±1.4 (n=33 *p*=0.23)	
Chin and Woo 2012 (no SDs reported for mean change)		-0.7 (n=28 *p*<0.001)	-0.7 (n=22 *p*=0.002)	
LIFT Study (no SDs reported for mean change)	-0.7 (n=77 *p*<0.001)	-1 (n=80 *p*<0.001)	-1.2 (n=75 *p*<0.001)	
McNicholas 2013				
Shore 2014	-0.76±1.39 (n=34 *p*=0.003)			
Woo 2011				
Mean	-0.65333	-0.7	-0.76667	
Weighted mean	-0.66717	-0.78897	-0.91231	

Qmax: Qmax mean improvements from baseline ranged from +3.456 to +4.166666667 ml/s. All improvements were statistically significant where reported, with $p<0.05$, so the evidence supports Urolift's ability to increase maximum urine flow rates.

Table 15 Mean difference changes in Qmax in each included study

	Qmax ml/s change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013 (no SDs reported for mean change)	4.5 (n=20 *p*=0.006)	4.8 (n=17 *p*=0.003)	4.2 (n=9 *p*=0.042)	
Cantwell 2013		2.5±5.3 (n=40 *p*=0.002)	2.5±5.0 (n=37 *p*=0.005)	
Chin and Woo 2012 (no SDs reported for mean change)		2.4 (n=46 *p*<0.001)	2.6 (n=39 *p*<0.001)	
LIFT Study		4.24±5.13 (n=124 *p*<0.001)	3.98±4.92 (n=105 *p*<0.001)	4.15±5.05 (n=98 *p*<0.001)
McNicholas 2013 (no SDs reported for mean change)	4.7 (n=67 *p*<0.001)	4.3 (n=80 *p*<0.001)	4 (n=41 *p*<0.001)	
Shore 2014	3.3±4.5 (n=50 *p*<0.001)			
Woo 2011				
Mean	4.166666667	3.648	3.456	4.15
Weighted mean	4.159854015	3.784234528	3.522077922	4.15

PVR: PVR changes from baseline ranged from -3.0575 to -10.55 mls. No changes were statistically significant.

Table 16 Mean difference changes in PVR in each included study

	PVR ml change from baseline: mean ±SD, (n)			
Study	**1 month**	**3 month**	**12 month**	**24 month**
Abad 2013				
Cantwell 2013 (no SDs reported for mean change)		-13.23 (n=51 *p*=0.241)	-11.23 (n=46 *p*=0.262)	
Chin and Woo 2012 (no SDs reported for mean change)		-4 (n=61 *p*=0.7)	8 (n=8 *p*=0.4)	
LIFT Study (no SDs reported for mean change)		-11 (n=137 *p*=0.146)	-12 (n=120 *p*=0.1111)	
McNicholas 2013 (no SDs reported for mean change)	-7 (n=48 *p*=0.775)	-14 (n=41 *p*=0.082)	3 (n=29 *p*=0.299)	
Shore 2014				
Woo 2011				
Mean	-7	-10.55	-3.0575	
Weighted mean	-7	-10.3386	-5.71832	

Note: In order to utilise the results from as many of the studies as possible, results here are not displayed with 95% CIs (This is not done above due to inconsistent reporting of SDs). In Appendix 2 we present these results with 95% CIs.

Comparison with sham control at 3 months (t-test) (from Roerhborn et al. 2013)

The table below is taken from the LIFT Study RCT, comparing Urolift implants to the sham procedure, which involves rigid cystoscopy. This is the only comparative data available for Urolift, and the EAC feels it is of value, as there is a known "sham effect" (Roerhborn et al. 2013) where there is an improvement in IPSS and BPHII after the sham treatment. This is seen below in the "Control ITT group), as there is **some** improvement in these measures. The authors recognise this phenomenon and attribute to a combination of placebo, dilation and regression. However, most importantly, it is only around half of the improvement seen with Urolift; with a statistically significant difference from sham control improvements. Sexual health measures are not significantly different, which supports the Sponsor's claims that Urolift does not affect sexual function in these patients.

Table 17 Intention-to-treat comparison of Urolift and sham control from Roerhborn et al. (2013)

	Urolift-ITT group. Mean±SD (n)			Control ITT group. Mean±SD (n)			
	Baseline	**3 months**	**Change**	**Baseline**	**3 months**	**Change**	***p* Value**
IPSS	22.2±5.48 (140)	11.2± 7.65	-11.1±7.67	24.4±5.75 (66)	18.5±8.59	-5.9±7.66	0.003
IPSS QoL	4.6±1.1 (140)	2.4±1.7	-2.2±1.8	4.7±1.1 (66)	3.6±1.6	-1.0±1.5	0.005
BPHII	6.9±2.8 (140)	3.0±3.1	-3.9±3.2	7.0±3.0 (66)	4.9±3.2	-2.1±3.3	<0.001
IIEF	13.3±8.4 (132)	13.4±9.2	0.1±5.8	13.7±8.5 (65)	15.2±8.5	1.5±6.4	0.139
MSHQ-EjD	8.7±3.1 (94)	10.9±3.2	2.2±2.5	8.8±3.1 (50)	10.5±3.5	1.7±2.6	0.283
MSHQ-Bother	2.4±1.7 (117)	1.6±1.7	-0.8±1.5	2.2±1.7 (60)	1.5±1.7	-0.7±1.6	0.595
Qmax ml/s	8.02±2.43 (126)	12.29±5.4	4.28±5.16	7.93±2.41 (56)	9.91±4.29	1.98±4.88	0.005
PVR ml	85.5±69.2 (140)	75.8±83.9	-9.7±85.5	85.6±70.8 (65)	63.4±64.0	-22.2±70.7	0.306

TURP and HoLEP Comparator data

Note: These "comparative" results must be considered carefully. There are no comparative studies with Urolift vs TURP or HoLEP, and therefore the patient populations may vary and outcome measure improvement e.g. IPSS scores, are highly dependent upon the patients' baseline scores. These numbers are provided by the EAC in order to provide some comparative context to the MTAC committee.

None of the studies in the sponsor's submission are comparative with TURP or HoLEP, as requested in the NICE scope document, and no such studies were identified by the EAC in our independent literature search. Therefore, the EAC performed a rapid pragmatic data synthesis in order to provide some comparative outcome data for these technologies.

The EAC's solution was to find a TURP vs HoLEP systematic review, and extract relevant outcome data from their identified sources. A systematic review search led to the selection of a review by Li et al. 2014, for the following reasons:

- This is a very recent systematic review, published in July 2014, and contains the most recent RCTs – namely a paper by Sun et al., also published in 2014.
- The protocol for this review is published on the PROSPERO website at The University of York Centre for Reviews and Dissemination (CRD) – protocol number CRD42014007334
- Baseline patient characteristics (age, prostate volume, IPSS score and Qmax) are similar to those seen in the Urolift studies in the sponsor's submission:

Table 18 Baselines comparison between Urolift studies and TURp vs HoLEP RCTs from Li et al. (2014)

Outcome measure	Urolift studies	TURP/HoLEP RCTs
Age (years)	64 - 74	65.1 - 72.2
IPSS	21.45 - 26.7	21.9 - 26.4
Prostate volume (mls)	41.3 - 51	36.5 - 77.8
Q_{max} (ml/s)	6.9 – 8.85	4.9 - 8.9

The patient age and IPSS baselines all fall within the same range. The prostate volume range is wider in the TURP/HoLEP RCT studies, particularly skewed slightly towards men with larger prostates. Similarly, the Q_{max} baselines are skewed slightly towards slower flow rates in the baselines of the TURP/HoLEP RCTs.

The EAC critically appraised the systematic review (Li et al. 2014) using a checklist designed by the Support Unit for Research Evidence, Cardiff University.

Results are presented as weighted mean changes from baseline. Negative IPSS, IPSS QoL and PVR results represent an improvement from baseline. Positive Q_{max} results represent an improvement from baseline. The number of studies contributing to the weighted mean results is shown in brackets.

Table 19 Notes on TURP vs HoLEP RCT studies identified by Li et al. (2014)

Study	Notes
Ahyai et al 2007	Replaces Kuntz et al. 2004, as this contains 2-year follow-up results.
Eltabey et al 2010	
Gilling et al 1999	4 year results published, but not usable – dropout rates not reported for each patient group.
Gupta et al 2006	
Mavuduru et al 2009	Only reports results up to 9 months post-procedure.
Montorsi et al 2004	
Sun et al 2014	
Tan et al	2 year and 7 year results published, but not usable – dropout rates not reported for each patient group.

Table 20 EAC-calculated TURP and HoLEP improvements in mean from baselines

TURP	Weighted mean change from baseline (number of studies reporting)			
	1 month	3 month	12 month	24 month
IPSS	-17.34 (5)	-19.70 (2)	-18.13 (7)	-17.50 (1)
IPSS QoL	-2.99 (3)	-2.80 (1)	-3.18 (4)	NR (0)
Q_{max}	14.58 (5)	14.11 (2)	16.69 (7)	23.20 (1)
PVR	-137.43 (3)	-89.34 (1)	-127.29 (3)	-196.10 (1)

HoLEP	Weighted mean change from baseline (number of studies reporting)			
	1 month	3 month	12 month	24 month
IPSS	-17.68 (5)	-20.88 (2)	-19.29 (7)	-20.40 (1)
IPSS QoL	-2.64 (3)	-3.00 (1)	-3.24 (4)	NR (0)
Q_{max}	15.29 (5)	18.25 (2)	17.78 (7)	23.10 (1)
PVR	-160.23 (3)	-78.00 (1)	-161.47 (3)	-231.40 (1)

Notes on these comparative outcome results:

- Both TURP and HoLEP give much better improvement in IPSS scores (including QoL, as these scores are linked) at all time-points:
    - Urolift: -9.22 to -11.82
    - TURP: -17.34 to -19.70
    - HoLEP: -17.68 to -20.88
- Q_{max} improvements are also higher at all time points with both TURP and HoLEP:
    - Urolift: +3.53 to +4.16 ml/s
    - TURP: +14.11 to +23.20 ml/s
    - HoLEP: +15.29 to +23.10 ml/s
- TURP and HoLEP also give better improvements in PVR, but this is less widely reported in both the Urolift studies and the TURP/HoLEP studies. It may be worth noting that one Specialist Clinical Adviser questioned the importance of PVR as an outcome measure for Urolift, and presumably other surgical treatments for BPH

- BPHII scores are not reported in the TURP and HoLEP studies, but as a prostate symptom score, it should give general improvements in agreement with IPSS scores. IPSS is the standard measure of BPH symptom improvement, which may explain the lack of BPHII results with TURP and HoLEP

- Sexual function is poorly reported in the TURP and HoLEP papers (their aim is symptom improvement, so sexual function is secondary, and a complication), and therefore it is difficult to ascertain the impact of these interventions on erectile and ejaculatory function

    - A clinical adviser pointed out that it is difficult to get reliable data on erectile function for the comparator interventions, but recommended the GOLIATH Study (Bachmann et al. 2015) for IIEF-5 reporting post-TURP up to 12 months. GOLIATH patients were measured as **13.7±7.2 at baseline**, and **14.1±8.2 at 12 months post-TURP**, showing no significant changes in a cohort of 119 patients.

    - Two further clinical advisers stated a **5% rate for new erectile dysfunction** and **70-80% retrograde ejaculation rate**, post-TURP.

    - One clinical advisor recommended the 6-year follow-up on HoLEP by Gilling et al. (2008) for sexual function post-HoLEP; and a **76% retrograde ejaculation rate** is reported, which is similar to that quoted by our clinical experts for TURP. IIEF improvement from baseline is not reported.

Complications and procedural data from all Urolift studies

Complications are reported in detail as in all publications. As with outcome data, complications were collated where multiple studies reported on the same patient cohort e.g. the three LIFT study papers. Complications are quantified per study and presented as percentages of total patients, with an overall and 95% CI for each. Complications are grouped according to type: pain and sexual complications, urological, and other (including infections). Procedural data is presented below complications.

Table 21 Urolift complications; pain, haematuria, sexual function

Study	Sample size	Erectile dysfunction		Retrograde ejaculation		Dysuria		Haematuria		Irritative symptoms		Penile pain		Pelvic pain/discomfort		Unspecified pain	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abad et al. 2013	20	0	0%	0	0%	14	70%	6	30%	8	40%						
Cantwell et al. 2013	53	0	0%	0	0%	20	38%	14	26%					11	21%		
Chin et al. 2012 and Woo et al. 2012	64																
LIFT Study	140	0	0%	0	0%	49	35%	37	26%					27	19%		
McNicholas et al. 2013	102					25	25%	16	16%								
Shore et al. 2014	51					27	53%	38	75%			2	4%	8	16%		
Woo et al. 2011	19	2	11%			11	58%	12	63%	9	47%	1	5%	1	5%	1	5%
Overall (95% CI)			1% (0% to 2%)		0% (0% to 1%)		38% (25% to 51%)		31% (27% to 36%)		44% (29% to 60%)		5% (1% to 11%)		18% (14% to 23%)		5% (1% to 25%)

Table 22 Urolift complications; urological

Study	Sample size	Weak stream		Urinary frequency		Urine flow decreased		Incontinence		Retention		Urgency		Spraying		Incomplete voiding	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abad et al. 2013	20									2	10%						
Cantwell et al. 2013	53							2	4%	4	8%	7	13%				
Chin et al. 2012 and Woo et al. 2012	64																
LIFT Study	140							6	4%	1	1%	13	9%				
McNicholas et al. 2013	102									3	3%	10	10%				
Shore et al. 2014	51			0	0%	0	0%	2	4%	3	6%	4	8%				
Woo et al. 2011	19	1	5%					3	16%	3	16%			2	11%	1	5%
Overall (95% CI)			5% (1% to 25%)		0% (0 to 7%)		0% (0 to 7%)		5% (3% to 8%)		4% (2% to 6%)		10% (7% to 4%)		11% (3% to 31%)		5% (1% to 25%)

Table 23 Urolift complications; other

Study	Sample size	Bladder spasm		Prostatitis		Orchitis/ epidiymitis		Urinary tract infection		Rigor	
		n	%	n	%	n	%	n	%	n	%
Abad et al. 2013	20					1	5%				
Cantwell et al. 2013	53	3	6%								
Chin et al. 2012 and Woo et al. 2012	64			1	2%	1	2%	7	11%	1	2%
LIFT Study	140	6	4%					4	3%		
McNicholas et al. 2013	102					3	3%	3	3%		
Shore et al. 2014	51										
Woo et al. 2011	19	3	16%	1	5%			1	5%		
Overall (95% CI)			6% (3% to 9%)		4% (1% to 10%)		3% (1% to 6%)		5% (3% to 7%)		2% (0% to 8%)

Table 24 Urolift complications; procedural data

Study	Sample size	Reoperation rate		Procedure time (mins)		Local anaesthesia		Return to normal activity (days)		Catheter required		Catheter duration (hrs) [1]		Encrusted implants		Encrusted implants removed	
		n	%	mean	SD	n	%	mean	SD	n	%	mean	SD	n	%	n	%
Abad et al. 2013	20	1	5%	19.1		0	0%			2	10%			0	0%		
Cantwell et al. 2013	53	1	2%	53	15.0	46	87%	6.5	6.8	26	49%	33					
Chin et al. 2012 and Woo et al. 2012	64	13	20%							34	53%	20		0	0%		
LIFT Study	140	11	8%	66.2	23.8	139	99%	8.6	7.5	40	29%	21.6		10	7%	6	4%
McNicholas et al. 2013	102	4	4%	57.8	15.8					54	53%						
Shore et al. 2014	51			52	22.0	50	98%	5.1	5.8	10	20%	16					
Woo et al. 2011	19	3	16%							13	68%			0	0%		
Overall (95% CI)			8% (5% to 11%)	59.6 (57.5-61.7)	20.2		93% (89% to 96%)	7.4 (6.7-8.2)	5.9		39% (35% to 44%)	22.3			3% (1% to 6%)		4% (2% to 9%)

[1]Catheter duration was not always reported with SDs, so 95% CIs could not be calculated.

Length of stay data was only reported by Abad et al. 2013, at 2.6 hrs (range 3-72). Otherwise, Shore et al. report "All patients were treated as day cases, there were no overnight stays", but this is not quantifiable.

It is also worth noting the 100% general anaesthesia use by Abad et al. in their protocol, and the markedly shorter procedure time. This may be a facet of having a patient under general anaesthetic, but the publication does not clarify this. However, the shorter procedure time in the Abad et al. (2013) study does not impact the weighted mean greatly due to the low patient number in this case series. The EAC asked clinical advisers about Urolift procedure times, and many said that it could be done in 30 minutes (from their own practical experience), and that 60 minutes was under "trial conditions".

Complications and procedural data from all TURP vs HoLEP studies

Table 25 TURP complications; pain, haematuria, sexual function

Study	Sample size	Dysuria		Irritative symptoms	
		n	%	n	%
Ahyai et al 2007	88				
Eltabey et al 2010	40			8	20%
Gilling et al 1999	59				
Gupta et al 2006	50	1	2%		
Mavuduru et al 2009	15	3	20%		
Montorsi et al 2004	48	13	27%		
Sun et al 2014	82				
Tan et al 2003	30				
Overall (95% CI)			13% (0% to 36%)		20% (10% to 35%)

Table 26 TURP complications; urological

Study	Sample size	Incontinence		Retention	
		n	%	n	%
Ahyai et al 2007	100	1	1%		
Eltabey et al 2010	40	12	30%		
Gilling et al 1999	59	1	2%		
Gupta et al 2006	50				
Mavuduru et al 2009	15	0	0%		
Montorsi et al 2004	48	18	38%	1	2%
Sun et al 2014	82				
Tan et al 2003	30	11	37%		
Overall (95% CI)			11% (0% to 30%)		2% (0% to 11%)

Table 27 TURP complications; other

Study	Sample size	Urinary tract infection		Transfusion		TUR Syndrome		Bladder neck contracture		Urethral stricture		BPH recurrence	
		n	%	n	%	n	%	n	%	n	%	n	%
Ahyai et al 2007	100			2	2%			3	3%	3	3%	0	0%
Eltabey et al 2010	40			3	8%					2	5%		
Gilling et al 1999	59			4	7%					6	10%		
Gupta et al 2006	50			1	2%	1	2%			2	4%		
Mavuduru et al 2009	15			1	7%								
Montorsi et al 2004	48					1	2%			4	8%		
Sun et al 2014	82				11%		21%			4	5%		
Tan et al 2003	30	2	7%	1	3%					2	7%		
Overall (95% CI)			7% (2% to 21%)		6% (4% to 8%)		9% (0% to 24%)		3 (1% to 8%)		6% (4% to 9%)	0% (0% to 4%)	

Table 28 TURP complications; procedural data

Study	Sample size	Reoperation rate		Procedure time (mins)		Length of stay (hrs)		Catheter required		Catheter duration (hrs)	
		n	%	mean	SD	mean	SD	n	%	mean	SD
Ahyai et al 2007	100	7	7%	73.8	24.00	85.8	39.10	5	5%	43.4	21.10
Eltabey et al 2010	40			73.6	22.30	91.2	38.40			50.4	26.40
Gilling et al 1999	59	4	7%			47.5	17.37	8	14%	37.2	15.92
Gupta et al 2006	50			64.1	13.10			3	6%	45.7	12.70
Mavuduru et al 2009	15			43	9.36			1	7%	78.2	17.84
Montorsi et al 2004	48	1	2%	57	15.00	85.8	18.90			57.78	17.50
Sun et al 2014	82			62.91	27.52	283.68	81.84			127.43	75.93
Tan et al 2003	30	2	7%			49.9	5.60	4	13%	44.9	5.60
Overall (95% CI)			6% (4% to 10%)	65.9	16.4	122.3	47.2		8% (5% to 12%)	62.7	37.4

Table 29 HoLEP complications; pain, haematuria, sexual function

Study	Sample size	Dysuria		Irritative symptoms	
		n	%	n	%
Ahyai et al 2007	100				
Eltabey et al 2010	40			10	25%
Gilling et al 1999	61				
Gupta et al 2006	50	5	10%		
Mavuduru et al 2009	15	1	7%		
Montorsi et al 2004	52	33	63%		
Sun et al 2014	82				
Tan et al 2003	30				
Overall (95% CI)			31% (0% to 80%)		25% (14% to 40%)

Table 30 HoLEP complications; urological

Study	Sample size	Incontinence		Retention	
		n	%	n	%
Ahyai et al 2007	100	1	1%		
Eltabey et al 2010	40	8	20%		
Gilling et al 1999	61				
Gupta et al 2006	50	1	2%		
Mavuduru et al 2009	15	2	13%		
Montorsi et al 2004	52	26	50%	3	6%
Sun et al 2014	82				
Tan et al 2003	30	15	50%		
Overall (95% CI)			14% (0% to 38%)		2% (0% to 11%)

Table 31 HoLEP complications; Other

Study	Sample size	Urinary tract infection		Transfusion		TUR Syndrome		Bladder neck contracture		Urethral stricture		BPH recurrence	
		n	%	n	%	n	%	n	%	n	%	n	%
Ahyai et al 2007	100							3	3%	4	4%	1	1%
Eltabey et al 2010	40			0	0%					1	3%		
Gilling et al 1999	61	3	5%	0	0%					6	10%		
Gupta et al 2006	50			0	0%					1	2%		
Mavuduru et al 2009	15												
Montorsi et al 2004	52					0	0%			1	2%		
Sun et al 2014	82				1%		6%			3	4%		
Tan et al 2003	30	0	0%	0	0%					1	3%		
Overall (95% CI)			3% (0% to 8%)		1% (0% to 2%)		3% (0% to 12%)		3% (1% to 8%)		4% (3% to 7%)		1% (0% to 5%

Table 32 HoLEP complications; procedural data

Study	Sample size	Reoperation rate		Procedure time (mins)		Length of stay (hrs)		Catheter required		Catheter duration (hrs)	
		n	%	mean	SD	mean	SD	n	%	mean	SD
Ahyai et al 2007	100		7%	94.6	35.10	53.3	15.90	0	0%	27.6	10.40
Eltabey et al 2010	40			72.8	21.70	62.4	28.80			36	33.60
Gilling et al 1999	61	1	2%			26.1	11.71	5	8%	20	11.39
Gupta et al 2006	50			75.4	22.80			2	4%	28.6	20.50
Mavuduru et al 2009	15			53	9.84			1	7%	46.42	14.25
Montorsi et al 2004	52	1	2%	74	19.50	59	19.90			31	13.00
Sun et al 2014	82			70.17	29.51	272.88	94.32			113.63	50.61
Tan et al 2003	30	0	0%			27.6	2.70	5	17%	17.7	2.70
Overall (95% CI)			4% (2% to 7%)	72.1	20.5	97.8	47.4		4% (0% to 11%)	44.2	26.8

Notes on complications comparison between Urolift, TURP and HoLEP studies

As with the clinical outcome measures being compared earlier, these results should be interpreted cautiously and in knowledge that there are no true comparative studies between Urolift and TURP or HoLEP. One weakness of this type of comparative approach is that the Urolift studies report a different set of complications than those reported for TURP vs HoLEP RCTs, and with good reason: Urolift complications seem to be typically mild, such as transient dysuria or haematuria. Presumably, dysuria and haematuria are expected occurrences with TURP and HoLEP. Therefore, these are not as widely reported in the TURP vs HoLEP RCTs, in part due to them being so normal and their mild nature. Similarly, implant encrustation is not an event that can occur with TURP or HoLEP, but where seen, the implants can easily be removed with forceps without further issue. This was largely supported by when the EAC asked the clinical advisers, and the majority did not see implant encrustation as a significant issue.

Other complications comparisons (of those most widely reported):

- Incontinence was less prevalent with Urolift (5%, CI 3% to 8%) compared to TURP (11%, CI 0% to 30%) and HoLEP (14%, CI 0% to 38%)
- Reoperation rates were slightly higher with Urolift (8%, CI 5 % to 11%) compared to TURP 4% (2% to 7%) and HoLEP (6%, CI 4% to 10%)
- Procedure time is shorter with Urolift (59.6 mins ± 20.2) compared to TURP (72.1 mins ± 20.5) and HoLEP (65.9 mins ± 16.4). The EAC asked clinical advisers about the Urolift procedure time, in their experience. The majority said that the procedure could be done in 30 minutes, and that 60 minutes was under “trial conditions”.

Additional notes:

- Length of stay was poorly reported in the Urolift studies, which means a comparison cannot be made to TURP and HoLEP. The EAC asked clinical advisers about the Urolift length of stay, and the majority said that it was done as a daycase procedure, with very few patients needing an overnight stay.

- Erectile function, urinary tract infection, prostatitis, orchitis and bladder spasm were poorly reported in the TURP vs HoLEP RCTs, which means a comparison cannot be made to Urolift. The EAC asked the clinical experts about this:
    - One clinical adviser pointed out that it is difficult to get reliable data on erectile function for the comparator interventions, but recommended the GOLIATH Study (Bachmann et al. 2015) for IIEF-5 reporting post-TURP up to 12 months. GOLIATH patients showed no significant changes in IIEF-5 post-TURP.
    - Two further clinical advisers stated a **5% rate for new erectile dysfunction** and **70-80% retrograde ejaculation rate**, post-TURP.
    - Another clinical advisor recommended the 6-year follow-up on HoLEP by Gilling et al. (2008) for sexual function post-HoLEP; and a **76% retrograde ejaculation rate** was reported, which is similar to that quoted by our clinical experts for TURP. IIEF improvement from baseline is not reported.
- Catheterisation rates vary due to local procedures (e.g. some hospitals seem to catheterise post-procedurally as a matter of course) so this is a difficult comparison to make. Post-procedure catheterisation times were shorter for Urolift (22.3 hrs, no SDs reported) compared to TURP (62.7 hours ± 37.4) and HoLEP (44.2 hours ± 26.8). However, this again could be decided by local procedures rather than patient need, or a genuine difference between the surgical procedures.

The mild complications of the Urolift procedure may be enough to for some patients, concerned about blood loss or TUR syndrome, to prefer Urolift if it was offered to them as an alternative to TURP and HoLEP by their urologist.

3.10 Conclusions on the clinical evidence

The sponsor's submission uses pooled effect sizes to show mean changes from baseline in a number of key areas: prostate symptom score measures (IPSS, BPHII), health-related quality of life (IPSS QoL), male sexual health (IIEF, MSHQ-EjD, MSHQ-Bother) and urological function (Q_{max} and PVR) up to 12-months post-Urolift. The presented meta-analysis indicates a large improvement in prostate symptom scores and QoL, a small improvement (but not negative

impact) on sexual health. The authors note that Q_{max} and PVR were inconsistently reported, leading to a higher heterogeneity score in their meta-analysis, which made true effects difficult to assess.

The EAC considers that this meta-analysis does show that Urolift is clinically effective, but is not a clear representation of the data. The methodology in the systematic review paper was short and lacked transparency, certain patients from some of the publications could have been double-counted (multiple publications covered some of the cohorts involved, but again, this is not clearly stated in the methods) and effect sizes are less clear than simply using the units of the outcome measures themselves. The EAC attempted to address this in our analysis by maintaining the original units of the outcome measures of each study, rather than converting to effect sizes, and taking a more simplified approach of reporting the mean change from baseline in each outcome measure reported.

Overall, the studies used in the sponsor's submission show that Urolift is a clinically effective device for the treatment of BPH. However, this relies upon context. Using the IPSS score as a primary outcome for symptom improvement, the published minimally important change in IPSS score is 3 (Barry et al. 2005), and Urolift delivers a weighted mean IPSS improvement of between 9.22 – 11.82 points. These Urolift improvements are also larger than the published "marked improvement" in IPSS score of 8.8 (Barry et al. 1995). Therefore, in light of the published evidence on the IPSS tool, Urolift delivers very satisfactory clinical results.

However, the EAC comparison using papers selected by a recent TURP vs. HoLEP systematic review (Li et al. 2014) showed that patients with a similar range of baselines (age, IPSS score, prostate volume, Q_{max}) made much better improvements in IPSS with both TURP and HoLEP. A similar effect is seen in IPSS QoL, Q_{max}, and PVR: although improvements are made with Urolift, all symptom-related measures improve more dramatically with both TURP and HoLEP.

Sexual function is poorly reported in the TURP and HoLEP RCTs (the study aims are mostly based around symptom improvement, so sexual function impact is secondary outcome, and a complication), and therefore it is difficult to ascertain the impact of these interventions on erectile and ejaculatory function. The evidence shows that Urolift does not negatively affect

these outcomes, but small improvements are achieved, however these are not always statistically significant.

The mild complications of the Urolift procedure (mainly dysuria and haematuria) may be of interest to some patients, specifically those wishing to avoid blood loss or TUR syndrome. These were either not reported as a complication of Urolift, or are not possible with Urolift, respectively. Furthermore, the clinical improvements of IPSS (discussed above) may also be enough to satisfy patients with severe BPH, as a 10 point improvement would carry a patient from “severe BPH” (20-35 points) to “moderate BPH” (8-19 points) (British Association of Urological Surgeons).

Therefore, the evidence may support Urolift being used an alternative, based upon patient preference, for symptom relief lower than that of TURP or HoLEP, but at reduced risk of the more dangerous complications.

Table 33 Overview of outcome measures

	Published or clinical expert opinion – minimally important change	Urolift	TURP	HoLEP
IPSS (Negative score is improvement)	Minimum = 3.0 Moderate = 5.1 Marked change = 8.8 (Barry et al. 1995)	1 month -10.35 3 month -11.82 12 month -10.49 24 month -9.22	1 month -17.34 3 month -19.70 12 month -18.13 24 month -17.50	1 month -17.68 3 month -20.88 12 month -19.29 24 month -20.40
IPSS QoL (Negative score is improvement)	Minimum = 1-3 (Clinical expert opinion)	1 month -2.27 3 month -2.48 12 month -2.31 24 month -2.22	1 month -2.99 3 month -2.80 12 month -3.18 24 month N/A	1 month -2.64 3 month -3.00 12 month -3.24 24 month N/A
BPHII (Negative score is improvement)	Minimum = 0.5 Moderate = 1.1 Marked changed = 2.2 (Barry et al. 1995)	1 month -3.29 3 month -3.96 12 month -3.95 24 month -3.76	N/A	N/A
IIEF (Positive score is improvement)	Minimum = 4 (Clinical expert opinion)	1 month +0.52 3 month +1.34 12 month +0.80 24 month N/A	N/A	N/A
MSHQ-EjD (Negative score is improvement)	Minimum = 1.5 (Clinical expert opinion)	1 month +1.82 3 month +1.47 12 month +0.83 24 month N/A	N/A	N/A
MSHQ-Bother (Negative score is improvement)	Minimum = 1.0 (Clinical expert opinion)	1 month -0.67 3 month -0.79 12 month -0.91 24 month N/A	N/A	N/A
Qmax (ml/s) (Positive is improvement)	Minimum = 2ml/s (NICE CG97)	1 month +4.16 3 month +3.78 12 month +3.52 24 month +4.15	1 month +14.58 3 month +14.11 12 month +16.69 24 month +23.20	1 month +15.29 3 month +18.25 12 month +17.78 24 month +23.10
PVR (ml) (Negative is improvement)	Minimum = 50 ml (Clinical expert opinion)	1 month -7.00 3 month -10.34 12 month -5.72 24 month N/A	1 month -137.43 3 month -89.34 12 month -127.29 24 month -196.10	1 month -160.23 3 month -78.00 12 month -161.47 24 month -231.40

4 Economic evidence

4.1 Published economic evidence

4.1.1 Critique of the sponsor's search strategy

The sponsor has combined the search for relevant economic studies with a search for evidence to inform model inputs. Therefore the search is broader than the PICO in the scope, for example including studies that evaluate interventions/procedures other than Urolift. The search terms used were:

(Benign prostatic hyperplasia OR benign prostatic enlargement) AND Cost

The use of 'AND cost' is overly restrictive, since some studies may include other terms such as economic, or variations on this. The clinical terms are also restrictive and more terms should have been included, such as LUTS and variations on this.

NHS EED was searched for economic evidence. The NHS EED database is populated by a search of CINAHL, Embase, MEDLINE, PsycINFO and PubMed, which already incorporates an economic filter, therefore there was no need to include 'AND cost'. If possible a search of EconLit would have made the search for evidence more thorough. The sponsor's submission also included a search of the manufacturer's internal literature databases and reference list checking of all relevant study publications. The search for evidence did not include citation tracking of included studies or contacting authors of the included studies

Grey literature was searched using Google and there was a search of the NICE website.

The EAC conducted a search in the following databases: Cost Effectiveness Analysis; EcoLit; HEED and NHS EED for economic evidence concerning Urolift. This was in addition to the searches for clinical evidence described in 3.1, which would have also identified economic evidence. The EAC search identified 40 citations.

4.1.2 Critique of the sponsors study selection

The sponsor provided a flow chart to describe the study selection process. Studies were excluded if they:

- Did not take a UK perspective
- Did not look solely at BPH
- Were focused on specific sub-groups
- Evaluated non-BPH treatments

4.1.2 Included and excluded studies

None of the studies included by the sponsor included Urolift. They were all economic studies of the comparators, including comparators in the scope and others outside the scope. Therefore none of the studies are appropriate for inclusion, although some may include useful data for inputs to the model regarding the comparators.

The EAC conducted a thorough search for economic studies relevant to the scope, described in 4.1. No relevant economic studies were identified.

4.1.3 Overview of methodologies of all included economic studies

N/A

4.1.4 Overview and critique of the sponsor's critical appraisal for each study

The sponsor carried out a critical appraisal for each economic study, but as these were not relevant to the scope, this was not required.

4.1.5 Does the sponsor's review of economic evidence draw conclusions from the data available?

The sponsor noted that 'no cost-effectiveness analysis comparing these technologies in the NHS is currently available' and this is the rationale for the de novo model.

4.2 De novo cost analysis

Patients

The population considered in the model is men with LUTS secondary to BPH aged ≥ 50 years, and with prostate volume no greater than 100cc. This accords with the population in the scope.

Technology

The technology in the model is Urolift, in accordance with the scope. The results for Urolift are presented alongside the comparators.

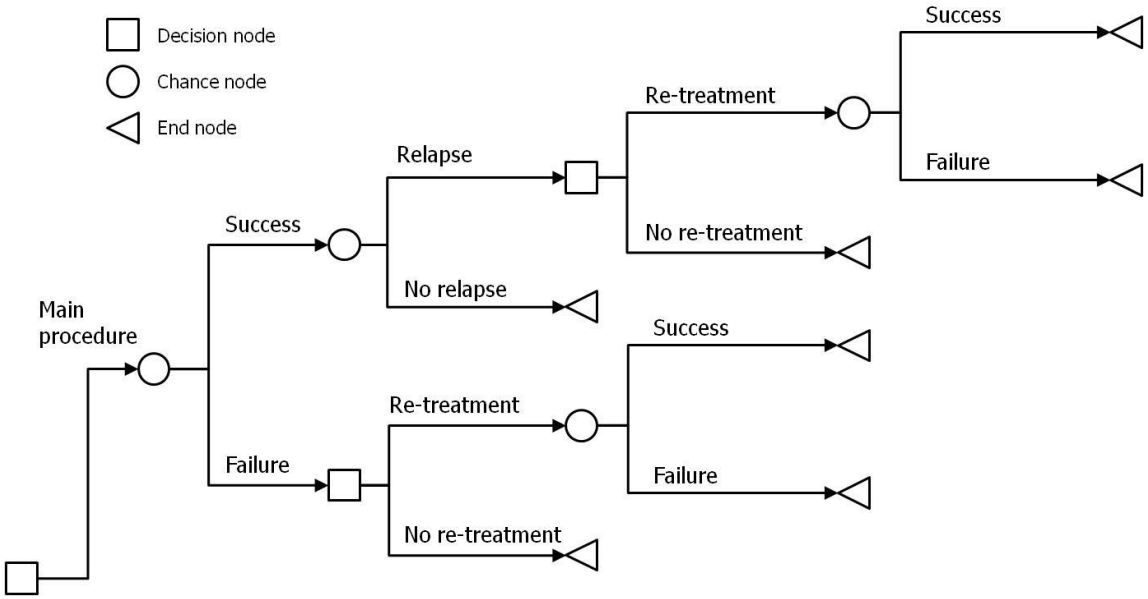
Comparator(s)

In the model the sponsor included TURP and HOLEP as comparators in agreement with the scope. The executable model also included Bipolar TURP, laser vapourisation (e.g. KTP laser) TUVP, and Bipolar TUVP as comparator arms but in the sponsor submission only the comparators in the scope are presented.

Model structure

The model structure is a decision tree, with seven executable arms, one for each technology or comparator. Following treatment the outcomes are success or failure. The success category then has options for relapse or no relapse. The relapse option then has success or failure outcomes. The failure outcome has options for re-treatment (with success or failure outcomes) or no re-treatment.

Figure 2 Flow diagram of sponsor's de novo economic model



There are three possible perspectives to be selected in the executable model:

1. Hospital (1 year timeframe)
2. Primary Care Trust (1 year timeframe)
3. National (NHS) 2 year time horizon

The sponsor submission refers only to the NHS perspective and 2 year time horizon. The two year time horizon was chosen to be long enough to assess the majority of differences in outcomes, treatment related adverse events and re-interventions. It is also the maximum length of follow-up available in the published evidence for Urolift.

The overall structure of the model is cumbersome because of the inclusion of comparators outside the scope, pre-operative and post-operative tests which are the same regardless of the intervention and options for additional perspectives not referred to in the submission.

The model includes detailed costing for complications. For example, incontinence includes the costs of drugs, incontinence bags and pads and nurse visits. The costs are taken from reliable sources.

Model assumptions

The sponsor provided a comprehensive list of 21 assumptions in the model together with a justification for each. The list is reproduced below in Table 35, together with EAC comments.

Table 34 Model assumptions

Assumption	Justification	EAC comment
The initial procedure is either successful or not. Failure is defined as failure to achieve ≥10% improvement in IPSS score relative to baseline within 30 days of procedure	In clinical practice a percentage change of less than 10% in IPSS is most often used to define insufficient improvement (Lourenco 2008)	Accept
In the base case, the proportion of patients who decide to undergo retreatment is the same for patients who have failed the initial treatment, and patients who had an initially successful procedure but then experience relapse		Accept
The mean IPSS score post treatment of patients who have failed is the same as the mean IPSS score pre-treatment, i.e. there is no change in mean IPSS score for failed patients:		Accept

The probability of retreatment after failure is equal to the probability of retreatment after relapse. I.e. patients with an unsatisfactory treatment result after the initial procedure have the same probability of retreatment regardless of the reason (initial failure, or subsequent relapse after a successful result)		Accept
The success rate for subsequent procedures is lower than for primary procedures. The relative success of a subsequent procedure compared to a primary procedure is assumed to be 0.75.	This value was used in the model was estimated from clinical expert opinion (Lourenco 2008).	Accept. Agrees with NICE CG97.
In the base case, retreatment is carried out using TURP for all patients except for those who have HoLEP as the initial procedure, for whom there is no surgical option	TURP represents the 'gold standard' of surgical treatments for BPH. Patients who have undergone a HoLEP procedure would not be eligible for further surgical treatment due to the enucleation of tissue in the prostate.	Accept
The operation time for UroLift is assumed to be 30 minutes	Assumption based on clinical expert opinion	Based on weighted mean in studies, EAC considers 60 minutes is the best available published data. This should be explored in sensitivity analysis.
The operation time for TURP is assumed to be 60 minutes	Assumption based on clinical expert opinion	Weighted mean of published studies is 66 minutes.
The operation time for HoLEP is assumed to be 76.96 minutes	Calculated as the summation of operating time by TURP and the weighted mean difference obtained from a meta-analysis (Lourenco 2008)	77 minutes is used in the sponsor's model
The operation time for HoLEP is assumed to be 58.38 minutes	Calculated as the summation of operating time by TURP and the weighted mean difference obtained from a meta-analysis (Lourenco 2008)	I think this refers to KTP laser rather than HoLEP
Length of hospital stay = 0.5 days for UroLift	Assumption based on clinical expert opinion	EAC clinical experts consider Urolift to be a day case procedure.
Length of hospital stay = 3.03 days for TURP	Weighted average of HRG4 codes LB25A, LB25B, LB25C (HSCIC 2013)	EAC weighted mean = 5.08 days However this includes a study with unusually high number of TUR syndrome cases. Accept sponsor value.
Length of hospital stay = 1.98 days for HoLEP	Calculated as the summation of operating time by TURP and the weighted mean difference obtained from the meta-analysis (Lourenco 2008)	EAC weighted mean = 4.08 days. However this includes one study with an unusually long LOS. Accept sponsor value.
Length of hospital stay = 2.33 days for Bipolar TURP	Calculated as the summation of operating time by TURP and the weighted mean difference obtained from the meta-analysis ((Lourenco 2008)	Accept
The total capital costs of equipment for TURP = 0.	It was assumed that equipment for TURP is already available in the NHS	EAC includes a capital cost of £10 per patient for TURP equipment
No. of cystoscopy sets used per procedure =1	Clinical expert opinion	Accept
The number of pre- and post-operative tests and healthcare visits does not differ between any of the surgical interventions	Clinical expert opinion	Agree but the sponsor claimed 'significantly lower number of post discharge follow-on visits' for Urolift. One clinical expert agreed that complications were lower with Urolift than TURP/HoLEP so fewer post-procedure visits needed. One clinical expert stated that more post-procedure visits were needed in the short term because Urolift is new and lacks data.

Each treatment is associated with the same levels of operating staff (1 consultant surgeon, Consultant anaesthetist, 1 band 5 nurse and 1 healthcare assistant	Clinical expert opinion	Clinical advisers suggested an additional laser operator is needed for HoLEP.
For all procedures excluding UroLift, there is risk of permanent incontinence	The risk of incontinence from each procedure were derived from the identified from meta-analyses (Lourenco 2008). For UroLift no cases of permanent incontinence post-procedure have been reported for any patient receiving the procedure to date. Clinicians also indicated that the procedure was very safe and had no effect on incontinence	Accept
Mortality is excluded from the model	There is no evidence to suggest that treatments for BPH influence overall survival. Hence, due to the short time horizon of the model, mortality was excluded from the model.	Agree
Costs were discounted at 3.5%	This is the rate recommended by NICE technology evaluation programme (NICE 2011)	Agree

The EAC did not identify any additional model assumptions.

Clinical parameters and variables

Data sources used for clinical parameters for Urolift were the papers by Lourenco 2008, Chin 2012 and Woo 2011 and unpublished data from Roehrborn 2014.

Table 35 Probability of success per procedure (>10% improvement in IPSS within 12 months)

UroLift	TURP	HoLEP	Bi-TURP
89.08%	94.00%	96.71%	94.00%

Table 36 Probability of relapse after successful procedure (long term)

UroLift	TURP	HoLEP	Bi-TURP
0.00%	0.17%	0.32%	0.99%

The probability of relapse for Urolift after successful procedure (long term) is based on limited data since only one study extended to 2 years and all other studies stopped at 12 months post procedure. Therefore it is difficult to be confident that there is zero chance of relapse. The EAC has looked at the effect of increasing the probability to 0.2% on the results of the model, and this increases the cost of Urolift by £4.

Table 37 Probability of re-treatment within 31 days (short term)

UroLift	TURP	HoLEP	Bi-TURP
0.75%	0.31%	0.21%	0.45%

Table 38 Probability of adverse effects per procedure (%)

	UroLift	TURP	HoLEP	Bi-TURP
Incontinence	0.00%	3.00%	2.91%	1.77%
Urinary retention	5.71%	5.00%	3.55%	8.55%
UTI	1.40%	6.00%	5.88%	6.00%
Stricture	0.00%	7.00%	5.88%	9.66%
TUR syndrome	0.00%	3.00%	0.93%	3.00%
Decrease in erectile function	0.00%	9.15%	9.06%	9.15%
Increase in erectile function	0.00%	3.42%	4.32%	3.42%
Ejaculation dysfunction	0.00%	37.45%	33.44%	37.45%

The EAC found the weighted mean for incontinence to be 5% (CI 3% to 8%), but this included stress and urgency incontinence. No permanent incontinence was reported for Urolift, therefore the EAC accepts the sponsor value.

The EAC calculates UTIs as 5% (CI 3% to 7%) for Urolift from the published studies, which is actually higher than claimed and similar to comparators. Considering that the operation time is similar, sterility of components is the same; we might expect similar UTI rates. Perhaps the lack of irrigation in Urolift could reduce the UTI rate.

The model doesn't specifically include:

- 3% (CI 1% to 10%) prostatitis
- 3% (CI 1% to 6%) orchitis/epididymitis

It is possible that these are included in UTI in the model, but these are not clearly reported in the published literature.

The EAC considered the erectile and ejaculatory function for Urolift is fine at 0%. There was actually a small mean improvement in IIEF (although not statistically significant), for example.

Procedural variables in the model including hospital LOS (0.5 days) and procedure time (30 minutes) for Urolift were based on clinical opinion of three experts. Procedure time was quite well reported in the literature, and the EAC calculated weighted mean was 59.6 minutes. One paper (Abad 2013) reported a 19 minute procedure time under general

anaesthetic, but this was a small study and all of the other studies showed close agreement for a procedure time with a range from 52-66 minutes.

None of the studies reported LOS for Urolift, therefore it is reasonable to use expert opinion to inform the base case. However, the sensitivity analysis needs to be across a broad range of values as there is considerable uncertainty around this estimate. LOS could be longer than 0.5 days, particularly since patients are reported to be catheterised for a weighted mean of 22.3 hours (this assumes that patients were not sent home with catheters *in situ*).

The EAC consulted clinical experts regarding LOS and operative time for Urolift. The responses were varied, but the majority classed Urolift as a true day case procedure. One adviser commented that the operative time in the published literature (59.6 minutes) may reflect trial conditions and that practical experience confirmed a 30 minute procedure time was normal.

Resource identification, measurement and valuation

The number of Urolift devices is a key driver of the model and in the base case the sponsor has used 4 as the number of devices per procedure. The reference given for this value is Chin 2012 and in the executable model it states this was also validated by clinical experts. The EAC agrees that Chin 2012 reported the mean number of devices per procedure to be 4, but published studies reported using between 2 and 9 devices per procedure. The EAC calculated the weighted mean number of implants from all of the clinical studies and found this to be 4.4 devices per procedure. We suggest that this is a more representative value for this parameter.

The cost of blood transfusion has been overestimated by the sponsor as £862.17 per transfusion. The data source (NICE CG97) references Varney and Guest (2003) and in this paper the authors conducted a top down cost analysis of transfusion services. It was assumed that a transfusion would increase LOS by 1 day and this was included in the cost of transfusion (£635 in 2003 inflated by the sponsor to current value of £826.17). The LOS for the comparators in the model is based on data from Lourenco (2008) and would include any

increase in LOS for blood transfusion. Therefore the sponsor is double counting 1 extra day LOS for patients having blood transfusion. The EAC estimates the cost of blood transfusion as £329. 1 unit standard red cells = £ 121.85 (NHS Blood and Transplant price list 2014/15. The mean number of units per transfusion is estimated to be 2.7 units of red blood cells (Varney and Guest 2003). Therefore the EAC calculates 2.7 x £121.85 = £329 per transfusion.

Although blood transfusion only occurs in 8% of patients undergoing TURP and fewer patients having HoLEP procedure (relative risk for HoLEP compared with TURP = 0.27), the probability of blood transfusion for Urolift in the model is 0, therefore this change reduces the cost of the comparators, but not Urolift.

The unit cost of hospital stay has been taken from published Scottish data for Urology specialty in-patient costs, divided by the average length of stay (3.3 days) to give the unit cost per day in hospital. The excess bed day cost used in the model is calculated from the HRG code for TURP, minus the procedure costs included in the model. It is not very clear which procedure costs have been subtracted. The result is £331 in 2012 prices which is inflated to £344 current price. The cost used in the model for hospital stay (0.5 days) for Urolift is calculated from 0.5 x £344 = £172. For comparison the EAC found the cost of an excess bed-day from the National Schedule of reference costs 2013-14 to be £294 (Excess bed day LB25F).

Technology and comparators' costs

The list price of Urolift implants is given as £330 excluding VAT per device by the sponsor.

Table 39 Consumables included in the sponsor's model

	Details	Cost per procedure	EAC comment
Urolift	4 implants @ £330	£1320	This is the largest component in the cost of Urolift.
mTURP	1 loop electrode @ £52.50	£52.50	Assume use of 1 loop electrode & 1 roller/ball in 100% of cases. Based upon NHS Supply Chain list of diathermy equipment costs: Covidien E7506 Diathermy plate standard (solid) with leadwire = £4.04 Loop electrode (models suitable for mTURP = £26.40 Roller/ball electrode (models suitable for mTURP = £26.40 Total = £56.84
HoLEP	Reusable fibre @ £614.37 (20 uses) Reusable morcellator @ £664.63 (10 uses)	£97.18	EAC investigated single use fibre @ £368.61 from NHS supply chain
Bi-TURP	1 loop electrode @ £52.50	£52.50	Change to £56.84 as above

The sponsor includes in the model the option to not re-use the HoLEP consumables, but there is no adjustment in the price of these. Selecting this option increases the cost of HoLEP from £1924 per procedure to £3106, making Urolift cost saving compared with HoLEP. The EAC considers that single use consumables would be offered at a lower price than multi-use consumables. It is unlikely that hospitals would dispose of multi-use consumables after a single use, so we consider this option unrealistic. The EAC looked at the result of using single use laser fibres @ £368.61 from NHS supply chain catalogue price, but we retained the re-usable morcellator blade as we did not find a cost for these from NHS supply chain or a manufacturer.

Table 40 Capital costs of equipment used in the sponsor's model

	Capital cost (assumed lifespan of equipment of 10 years, and used for 250 patients/year)	Cost per procedure
Urolift	£5199	£2.50
mTURP	£0	£0
HoLEP	£167,555	£80.60
Bi-TURP	£0	£0

There is an option in the model to replace the purchase of the capital equipment with a contract for a number of consumables over a time period. If this option is selected for Urolift the capital cost of the equipment (£5199) is excluded from the model. However nothing else changes in the model, so selecting this option for Urolift has the effect of simply subtracting £2.50 from the cost per patient of the procedure. Therefore it has minimal effect on the outcome of the model. For HoLEP where the capital equipment costs are significant (£167,555), choosing this option has the effect of reducing the cost of HoLEP from £1924 to £1843 per patient, the difference being £81, which is the cost per procedure of the capital equipment. The EAC considers it likely that manufacturers would charge a higher price per consumable item if such a contract were agreed in order to recoup the capital cost of the equipment. The EAC consulted clinical advisers about this, but we were unable to obtain specific details of negotiated contracts, which may vary between manufacturers and NHS organisations.

Sensitivity analysis

Since the base case shows Urolift to be more costly than the comparators, sensitivity analysis is of great importance. The sponsor has identified the key drivers in the model based on the sensitivity analysis. For Urolift the model is driven by the cost of the device and the number of devices used for each patient.

The results of sensitivity analysis were not saved in the executable version of the model, so it was necessary to change each parameter in turn, run the model and record the results.

For parameters investigated in sensitivity analysis the upper and lower values used were ±20% of base case values. This is reasonable when the variable is known with some certainty, but where the parameter is based on opinion of a small number of clinicians or on poor quality data, it would be more robust to allow the parameters to take a wider range.

Hospital length of stay was not identified as a key driver for Urolift in the model, but as there was no published data on LOS for Urolift, the sponsor relied on clinical opinion (3 clinicians) for the estimate of 0.5 days. Sensitivity analysis considered this variable, and it was varied by ±20%, so the range considered was 0.4 days to 0.6 days.

For the length of operation, which is estimated to be 30 minutes for Urolift it would be helpful to see a more robust sensitivity analysis, rather than a standard ±20% variation.

In the sensitivity analysis the sponsor has assumed in the base case that the HoLEP consumables (laser fibre and morcellator) are re-used 20 and 10 times respectively. An additional scenario was analysed in which reuse of HoLEP consumables was not permitted. The EAC found that NHS supply chain offer both single use and reusable laser fibres for HoLEP, and the reusable fibres are more expensive. For example Cook Medical multi-use fibres cost £1207.42 each, but their single use fibres cost £368.61. The sponsor has used the same price for single use and multi-use fibres and morcellators. Based on the source of the data these appear to be multi-use fibres. The sponsor appears to suggest that hospitals are disposing of multi-use consumables after a single use and the EAC considers this to be an unlikely scenario.

4.3 Results of de novo cost analysis

Base-case analysis results

The sponsor's base case results are shown in Table 9.2.5 taken from the sponsor's submission and this matches the results in the executable model. The sponsor also presented the incremental costs for Urolift (Table 9.2.6 in the sponsor's submission) . The EAC has combined these tables below, in T able 41.

Table 41 Sponsor's base case results

Intervention	Total cost per patient	Incremental cost of Urolift
UroLift	£2 342	-
TURP	£2 339	+£3
HoLEP	£1 924	+£ 418
Bipolar TURP	£2 302	+£40

The threshold at which Urolift becomes cost neutral compared with mTURP is reached when each Urolift device falls in price from £330 to £329. The sponsor also included a breakdown of costs by category reproduced below in Table 27. It is evident from this table that Urolift has much greater equipment costs per procedure than the comparators, but lower clinical supplies and services costs due to the estimated shorter length of hospital stay.

Table 42 Sponsor's breakdown of costs

Item	UroLift	TURP	HoLEP	Bi-TURP
Medical [1]	£342	£423	£457	£410
Nursing	£64	£113	£137	£105
Drugs[2]	£22	£21	£20	£21
Clinical supplies and services [3]	£549	£1,358	£923	£1,222
Equipment cost per procedure	£1,325	£56	£97	£56
Other[4]	£40	£369	£290	£487
TOTAL	£2,342	£2,339	£1,924	£2,302
[1]Consultant staff costs, [2]Cost of anaesthetic doses, saline, and antibiotics, [3]Includes cost of tests pre- and post- procedure and hospital bed day costs, [4]Includes costs of complications and capital costs				

Sensitivity analysis results

The results of sensitivity analysis are not presented very clearly by the sponsor and so the EAC has calculated the results of sensitivity analysis undertaken by the sponsor and these are presented in Table 43 below.

Table 43 Results of sponsor's sensitivity analysis

Parameter		UroLift	TURP	HoLEP	Bi-TURP
Base case		**£2342**	**£2339**	**£1924**	**£2302**
UroLift device cost per procedure	+20%	£2606			
	-20%	£2078			
12 month failure probability	+20%	£2389	£2362	£1926	£2322
	-20%	£2295	£2319	£1922	£2282
Duration of operation	+20%	£2373	£2404	£2003	£2359
	-20%	£2311	£2274	£1845	£2239
Length of stay	+20%	£2376	£2560	£2061	£2432
	-20%	£2308	£2120	£1786	£2044

Other parameters tested in sensitivity analysis are listed in Table 44 below. These had a uniformly small impact on the model (less than 1%) for all procedures.

Table 44 Other parameters tested in the sponsor's sensitivity analysis

Probability of incontinence after TURP
Probability of blood transfusion after TURP
Probability of urinary retention
Probability of UTI
Probability of stricture
Probability of TUR syndrome after TURP

Subgroup analysis

No subgroup analysis was undertaken by the sponsor. A sub-group of interest identified in the scope was ‘Men for whom TURP or HoLEP is unsuitable because of difficulties with

blood loss or sedation'. No evidence was found for this sub-group on which to base a model scenario.

Model validation

The sponsor states that the model was subject to internal quality checking. No published studies comparing Urolift with TURP or HoLEP were found, therefore the model could not be validated against any published results. The sponsor noted that in respect of the comparators, the results were consistent with published models, showing HoLEP is less costly than TURP.

4.4 Interpretation of economic evidence

The sponsor cites the lack of comparative efficacy data between Urolift and TURP or HoLEP as a weakness of the submission. The sponsor identifies a resource saving of 27 minutes of operating room time. In the model the reduction in operating time only included a reduction in staff time. There was no cost of the operating theatre included. The EAC have accounted for this in section 4.5, Table 48 Effect of adding theatre overhead costs to the sponsor's model.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC sought to verify the sponsor's estimate for length of hospital stay for Urolift patients with clinical advisers. There was some variation in the responses, but all confirmed that the Urolift procedure can be considered day case, and that length of stay would be measured in hours rather than days. All EAC changes to the model were also accompanied by threshold analysis, where the cost per Urolift implant could be altered to allow Urolift to become cost neutral compared to mTURP.

Based on the weighted mean of studies reporting the number of Urolift implants used per procedure, the EAC substituted the sponsor's estimate of 4 with the weighted mean of 4.4. This had the effect of increasing the cost of Urolift by £132. The threshold analysis at which Urolift achieves cost neutrality with mTURP under these conditions is £299 per implant.

Table 45 Effect of changing the number of Urolift implants

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
No of Urolift implants	Sponsor	4	£2342	£2339	£1924	£2302
	EAC	4.4	£2474	£2339	£1924	£2302

The EAC changed the sponsor's estimate of 30 minutes for the operation time for Urolift to 60 minutes based on the weighted mean of reported operation time from published studies. This had the effect of increasing the cost of Urolift by £154. The threshold analysis at which Urolift achieves cost neutrality with TURP under these conditions is £291 per implant.

Table 46 Effect of changing the procedure time for Urolift

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Operation time for Urolift	Sponsor	30 minutes	£2342	£2339	£1924	£2302
	EAC	60 minutes	£2496	£2339	£1924	£2302

The EAC changed the mTURP procedure time from the sponsor's 60 minutes to the weighted mean of 66 minutes taken from the EAC comparator studies. This increased the cost of mTURP so that Urolift became cost saving, by £26 per patient. Threshold analysis shows that Urolift implants would cost £337 each in order to make them cost neutral with mTURP.

Table 47 Effect of changing the procedure time for mTURP

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Operation time for mTURP	Sponsor	60 minutes	£2342	£2339	£1924	£2302
	EAC	66 minutes	£2345	£2371	£1924	£2302

The sponsor claims that Urolift can save 27 minutes of operating theatre time, but the EAC could not find operating theatre time cost accounted for in the model. We took the cost of a urology operating theatre from NICE CG97, stated at £9 per minute. For an hour's operation this is £540. We inflated this to 2015 values and then subtracted the staff costs from the sponsor's model, leaving an operating theatre overhead cost of £314 (£5.23 per minute). We validated this by comparison with another economic analysis by Noble et al. (2002), who give an inflation-adjusted cost for urological theatre time of £280 per hour (separate from staff costs). There is nowhere in the model to include theatre overheads, but we used £314 per hour as a theatre overhead cost, and inserted £5.23 per minute into the line titled "Band 5 nurse (second)" in the sponsor's economic model. This gives a per-minute cost to account for the theatre time in the model. This produces a cost saving of £139 compared to mTURP and £79 compared to BiTURP.

Table 48 Effect of adding theatre overhead costs to the sponsor's model

Model input		Values	Urolift (30 mins)	mTURP (60 mins)	HoLEP (76.96 mins)	BiTURP (55.44 mins)
Theatre overheads	Sponsor	£0	£2342	£2339	£1924	£2302
	EAC	£5.23 per minute	£2532	£2671	£2372	£2611

Some clinical experts advised that TURP may need an extra band 5 nurse over Urolift to handle irrigation fluid, so the EAC changed this. This was done for mTURP and BiTURP. These staffing changes made Urolift cost saving over mTURP, by £78, and BiTURP by £34.

Table 49 Effect of adding an additional band 5 nurse to mTURP and BiTURP

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Band 5 nurse	Sponsor	1 band 5 nurse	£2342	£2339	£1924	£2302
	EAC	2 band 5 nurses	£2351	£2429	£1924	£2385

The EAC changed the cost of blood transfusion in the model from £862.17 which includes double counting of 1 additional day in hospital to the EAC estimate of £329. This had the effect of reducing the cost of the comparators such that Urolift costs £44 more than mTURP, compared with £3 more in the base case. Threshold analysis shows that under these new conditions, Urolift implants would have to be priced at £319 per implant to achieve cost neutrality with mTURP.

Table 50 Effect of changing the blood transfusion cost

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Cost of transfusion	Sponsor	£862.17	£2342	£2339	£1924	£2302
	EAC	£329	£2338	£2294	£1913	£2255

The EAC included a £10 per procedure cost for capital equipment for TURP (total capital cost £20,799 used both mTURP and biTURP) as the sponsor did not include the capital cost in the base case. This had the effect of increasing the cost of the TURP comparators such that Urolift became cost saving compared with mTURP by £7 per patient.

Table 51 Effect of including the capital equipment costs for TURP

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Cost of mTURP and BiTURP capital equipment	Sponsor	£0	£2342	£2339	£1924	£2302
	EAC	£10	£2343	£2349	£1924	£2312

mTURP procedures use a roller or ball electrode in addition to the loop electrode in up to 100% of cases. mTURP also requires a return electrode plate. The EAC found costs for these electrodes from NHS supply chain catalogue. Our total consumables cost for mTURP comes to £56.84, which is slightly higher than the cost used by the sponsor. The effect on the model is to make Urolift cost neutral compared to mTURP. This was also done for BiTURP consumables, but did not make Urolift cost saving when compared to BiTURP

Table 52 Effect of changing the cost of mTURP and BiTURP consumables

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Cost of mTURP consumables	Sponsor	£52.50	£2342	£2339	£1924	£2302
	EAC	£56.84	£2343	£2343	£1924	£2306

The HoLEP fibres are priced differently when they are single-use. In light of this, the EAC took a price of £368.61 for single-use HoLEP fibres from NHS Supply Chain, and limited them to single use in the sponsor's model. Under these conditions, Urolift was still cost incurring compared to HoLEP, by £80 per patient.

.Note: The EAC were unable to find a cost for single-use morcellator blades (either through Supply Chain or by contacting a manufacturer, Lumenis (Versacut)) and this means they may not be available or widely used. Therefore, we retained the sponsor's original figures for re-useable morcellator blades.

Table 53 Effect of changing the HoLEP fibres to single-use

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
HoLEP fibres	Sponsor	£614.27, 20 uses	£2342	£2339	£1924	£2302
	EAC	£368.61, single use	£2342	£2339	£2262	£2302

Some clinical experts advised that HoLEP may need an extra band 5 nurse as a laser operator, so the EAC changed this. Urolift was still cost incurring compared to HoLEP under these conditions, by £309 per patient. Urolift becomes cost saving with this change when the price of the Urolift implants falls to £252 each.

Table 54 Effect of adding an additional band 5 nurse (laser operator) to HoLEP

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
Band 5 nurse	Sponsor	1 band 5 nurse	£2342	£2339	£1924	£2302
	EAC	2 band 5 nurses for HoLEP	£2342	£2339	£2033	£2302

When all EAC changes are incorporated in the model simultaneously, Urolift is cost incurring compared with all other options.

Table 55 Effect of all EAC changes to the model

Model input	Urolift	mTURP	HoLEP	BiTURP
Base case	£2342	£2339	£1924	£2302
All EAC changes	£2979	£2707	£2762	£2579
Incremental cost of Urolift (negative if Urolift is cost saving)		£272	£217	£400

Threshold analysis for all the EAC conditions shows that each Urolift implant would have to cost £268 in order to achieve cost neutrality with mTURP.

There is remaining uncertainty in the LOS for Urolift which is based on clinical opinion. The EAC has contacted clinical advisers and there is consensus that Urolift is a truly day case procedure. The sponsor sensitivity analysis considered LOS in the range 0.4 to 0.6 days. The EAC considers this too narrow and looked at the range 0.25 to 1 days LOS. At 0.25 days, Urolift is cost saving against mTURP by £83, and threshold analysis gives a Urolift implant cost of £351 per implant. At 1 day's LOS, Urolift is cost incurring compared to mTURP by £175, and threshold analysis shows that cost neutrality would require a cost of £286 per implant.

Table 56 EAC sensitivity analysis on LOS

Model input		Urolift	mTURP	HoLEP	BiTURP
Base case LOS	0.5 days	£2342	£2339	£1924	£2302
Urolift LOS EAC sensitivity	0.25 days	£2256			
	1 day	£2514			

The cost of a bed-day used in the model is based on an in-patient stay. The definition of day surgery in the UK is that 'the patient must be admitted and discharged on the same day, with day surgery as the intended management'. Several patients per day may be admitted to the same trolley space in a dedicated day unit, providing greater efficiency than can be achieved for a day case in a general ward (AAGBI Day Case and Short Stay Surgery Guideline 2011). Therefore, the actual length of stay for Urolift procedures is of great importance in a dedicated day surgery unit.

We were also able to perform sensitivity analysis for reusable HoLEP fibres, at a cost of £1207.42 (NHS Supply Chain). This was used as an upper-limit sensitivity analysis for this input. Table 57 below shows that even at this increased cost, the high number of uses for these fibres means that it makes very little impact on the cost of HoLEP.

Table 57 EAC sensitivity analysis for reusable HoLEP fibres

Model input		Values	Urolift	mTURP	HoLEP	BiTURP
HoLEP fibres	Sponsor	£614.27, 20 uses	£2342	£2339	£1924	£2302
	EAC	£1207.42, 20 uses	£2342	£2339	£1954	£2302

The model includes an option via a drop-down list to select Urolift performed under local anaesthetic. However, when selected there is no change in the result of the model and the EAC determined that this element of the model is not functioning.

4.5.1 EAC scenario

Based on responses from clinical advisers to EAC questions the EAC has identified an optimistic but realistic scenario in which Urolift is cost saving compared with mTURP. In our scenario, we see the Urolift procedure undertaken within a dedicated day surgery unit.

Table 58 EAC scenario inputs and conditions

Input	Conditions	Source/notes
Length of stay	0.125 days (3 hrs)	Clinical expert advice
Urolift procedure time	30 mins	Clinical expert advice/sponsor's model
Number of Urolift implants	4*	Sponsor's model
Local anaesthetic used for Urolift procedure	Remove consultant anaesthetist cost from model	Clinical expert advice
Theatre overhead cost	5.23 per minute	Added to model as Nurse Band 5 (second)
mTURP procedure time	66 mins	EAC weighted mean from clinical section of this Assessment Report
Cost of blood transfusion	£329	EAC figure (sponsor's original input was too high)

Table 59 EAC scenario cost results

	Urolift	mTURP	HoLEP	BiTURP
Sponsor base case	£2342	£2339	£1924	£2302
EAC scenario	£2355	£2691	£2315	£2564
Incremental cost of Urolift (negative if Urolift is cost saving)		-£336	£40	-£209

In the scenario, Urolift is cost saving by £336 compared with mTURP and by £209 compared with BiTURP.

*if the EAC figure of 4.4 Urolift implants is used (which accounts for the range of implant numbers required, reported as 2-9 in the Urolift studies), Urolift is still cost saving compared to mTURP and BiTURP under these conditions.

4.6 Conclusions on the economic evidence

The sponsor's submission relies on a de novo cost model. The model is comprehensive and somewhat overly complex as it includes pre- and post-procedure elements that are the same for the intervention and all comparators. The executable model also includes comparators not in the scope. The model options produce scenarios that the EAC considers unrealistic, such as the option for removing the capital equipment costs, but not changing the cost of consumables.

The major limitation of the model is that the base case shows that Urolift is not cost saving against any of the comparators, although it is close to cost neutral compared with mTURP (+£3). There are limited opportunities to improve this position because the cost per procedure for Urolift is strongly driven by the large cost per procedure of the implants. The costs of the comparators are strongly driven by LOS, which is well reported in the literature. The EAC has made changes to the model, some of which are in favour of Urolift, but the overall effect of EAC changes is to worsen the position of Urolift compared with mTURP and BiTURP.

Remaining uncertainties concern the LOS for Urolift, which is 0.5 days in the base case and is based on clinical opinion. The sensitivity analysis only considers a narrow range from 0.4 days to 0.6 days. The EAC has increased this range from 0.25 days to 1 day because of the uncertainty in the value. If the LOS were 0.25 days, the cost per procedure for Urolift changes from £2342 to £2256, and Urolift becomes cost saving against mTURP and BiTURP. If the LOS for Urolift is increased to 1 day, the cost per procedure for Urolift increases to £2514 per procedure and Urolift remains the most costly of the interventions and comparators. After consulting clinical advisers regarding the LOS for Urolift, the EAC devised a scenario for Urolift undertaken in a dedicated day surgery unit, which was cost saving for Urolift compared with mTURP, with a £336 compared with mTURP and by £209 compared with BiTURP.

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4.6.1 Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The impact of the EAC changes on the results of the model are summarised in Table 39 below. Shaded rows of the table are results when Urolift becomes cost saving.

Table 60 Impact of EAC changes on the model

	Urolift	mTURP	HoLEP	BiTURP
Sponsor base case	£2342	£2339	£1924	£2302
No of Urolift implants = 4.4	£2474	£2339	£1924	£2302
Operation time for Urolift = 60 minutes	£2496	£2339	£1924	£2302
Operation time for mTURP = 66 minutes	£2345	£2371	£1924	£2302
Addition of urological theatre overhead costs	£2532	£2671	£2372	£2611
Cost of transfusion = £329	£2338	£2294	£1913	£2255
Cost of mTURP and BiTURP capital equipment per patient = £10	£2343	£2349	£1924	£2312
Cost of TURP consumables = £56.84	£2343	£2343	£1924	£2306
HoLEP fibres single use @ £368.61	£2342	£2339	£2262	£2302
Additional band 5 nurse for HoLEP	£2342	£2339	£2033	£2302
All above changes	£2979	£2707	£2762	£2579
EAC scenario	**£2355**	**£2691**	**£2315**	**£2564**

If all EAC changes are incorporated in the model, Urolift becomes cost saving compared with mTURP when the price for each Urolift device falls to £268.

Urolift becomes cost saving compared with mTURP in the following circumstances, accepting the sponsor model, and making any one of the following changes only:

- Increasing the operation time for mTURP from 60 to 66 minutes
- Including the capital cost of equipment for mTURP £10 per patient
- Decreasing the LOS for Urolift from 0.5 days to 0.25 days

- One additional band 5 nurse for mTURP
- Including operating theatre overheads
- The cost of a Urolift implant decreases from £330 to below £329

Urolift becomes cost saving compared with BiTURP in the following circumstances, accepting the sponsor model and making any one of the following changes:

- Decreasing the LOS for Urolift from 0.5 days to 0.25 days
- Including operating theatre overheads
- Additional band 5 nurse for BiTURP
- The cost of a Urolift implant decreases from £330 to below £320

Urolift becomes cost saving compared with HoLEP in the following circumstances, accepting the sponsor model and making one change:

- The cost of a Urolift implant decreases from £330 to £225 or below

5 Conclusions

Overall, the studies used in the sponsor's submission show that Urolift is a clinically effective device for the treatment of BPH, giving IPSS score improvements from baseline greater than that deemed a "marked improvement" by the original developers of the IPSS score (Barry et al. 1995). However, the scope of this assessment called for comparative studies with Urolift versus TURP or HoLEP, and none such publications currently exist. In order to provide comparative context, the EAC used before-and-after data from papers selected by a recent TURP vs. HoLEP systematic review (Li et al. 2014). This pragmatic comparison shows that Urolift is out-performed by TURP and HoLEP in terms of IPSS, QoL and Qmax improvements from baseline, in patients with similar baseline characteristics.

However, Urolift appears to have the advantage in terms of minimal and mild complications, and this may be of great interest to certain patients and urologists. The clinical evidence shows that Urolift is associated with slight improvements in sexual function, and although not statistically significant, it certainly does not adversely affect these outcomes. The EAC's comparative exercise for TURP and HoLEP show that sexual function is not well reported in

many TURP and HoLEP RCTs (their main focus is IPSS and urological improvements), and this led to consultation of the clinical experts. The experts agreed on a 5% erectile dysfunction rate and 70-80% retrograde ejaculation rate post-TURP and HoLEP. The most serious of the TURP and HoLEP-related complications, are either not possible with Urolift (TUR syndrome) or not a risk due to the nature of the Urolift procedure (blood transfusion). The evidence may support Urolift being used an alternative, based upon patient preference, for symptom relief lower than that of TURP or HoLEP, but at reduced risk of the more dangerous complications.

The economic case for Urolift was made using a very detailed and thorough de novo cost model. Inputs to the model were well-researched and relied upon a robust HTA for TURP and HoLEP comparator and cost data (Laurenco et al. 2008) as well as Urolift outcome data from the LIFT Study. The model also had a lot of irrelevant data, such as results for TUVP, which was outside of the NICE scope for this assessment.

The base case posed by the sponsor placed Urolift at almost cost-neutral (£3 cost incurring) compared to TURP and £418 cost incurring compared to HoLEP. Sensitivity analysis showed that the key drivers of the model were the cost of the Urolift device and length of stay post-procedure. It was difficult to overcome the initial cost of the Urolift implants, even with the length of stay and complications savings made post-procedure. The EAC identified a number of conditions which changed the sponsor's model result for Urolift from cost incurring to cost saving for each comparator. Against HoLEP, Urolift was only cost saving if the price of the Urolift implants was reduced to less than £225.

The EAC present a scenario in which Urolift can be cost-saving compared to TURP, but not HoLEP. This relies upon a low number of Urolift implants, a short procedure time of 30 minutes or less, adding urological operating theatre overhead costs, local anaesthetic, and a day-case procedure of 0.125 days (3 hours). Under these conditions, savings of £336 compared with mTURP and £209 compared with BiTURP are achievable. All of the inputs of the EAC scenario are supported by published sources or by clinical experts for the assessment, who are currently using the Urolift device in the UK.

6 Implications for research

There is currently no published data directly comparing Urolift with TURP or HoLEP, as specified in the scope of this assessment. The logical response would be to suggest a truly comparative, preferably randomised, two- armed trial with at least one of these comparator technologies, or a three-armed trial with both TURP and HoLEP as comparators. This would ensure a single, defined patient population and eliminate baseline characteristics differences. Collecting resource use data as part of this trial would also strengthen the economic data available for decision makers regarding Urolift.

The BPH-6 trial, currently active but not recruiting, will go some way to addressing this research need. Although it only uses TURP as a comparator to Urolift, TURP is the most common surgical treatment for BPH in the UK, so this is arguably the most important comparison to make. The EAC contacted the sponsor and one of the PIs for BPH-6 (who is also a clinical expert for this assessment) and were assured that preliminary data from this study would be available in March 2015. It may be possible to update this report, or supply an additional data sheet, when these results become available.

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Appendix

Appendix 1: EAC literature search strategies

Example: Ovid MEDLINE(R) search

1) Prostatic Hyperplasia/
2) Urethral obstruction/ or urinary bladder neck obstruction/
3) Lower Urinary Tract Symptoms
4) LUTS.tw
5) (urin* adj3 tract* adj3 (sympt* or block*)).tw
6) ((urin* or urethra*) adj3 (obstruct* or block*)).tw
7) (Prostat* adj3 Hyperplas*).tw
8) (prostat* adj3 hypertroph*).tw
9) (prostat* adj3 adenoma*).tw
10) Prostatism/
11) Prostatism.tw
12) or/1-11
13) urolift.tw
14) Urologic Surgical Procedures, Male/
15) (urethra* adj3 lift*).tw
16) Prostat* adj3 lift*.tw
17) or/13-16
18) 12 and 17
19) Animals/ not humans/ exp animals/ not humans.sh.
20) 18 not 19

All other database searches were adaptations of the above.

Appendix 2: Urolift results with 95% CIs

The EAC-calculated weighted means for outcome measure results are shown in section 3.9.1 (Table 7 –Table 15). Below we present 95% CIs alongside weighted means, although it is only possible to present 95% CIs where SDs are reported. Due to inconsistent reporting of SDs in the studies, there are far fewer studies included than in the main results presented by the EAC in section 3.9.1. These results were calculated using RevMan v5.3 using the general inverse variance option. The confidence intervals account for heterogeneity, where significant, using a random effects analysis.

IPSS

	IPSS change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	53	-10.9	6.9	-10.90 [-12.76, -9.04]
LIFT Study	138	-9.91	7.08	-9.91 [-11.09, -8.73]
Shore 2014	51	-10.47	7.35	-10.47 [-12.49, -8.45]
Total				-10.25 [-11.14, -9.36]

	IPSS change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	52	-11.1	7.2	-11.10 [-13.06, -9.14]
LIFT Study	139	-11.13	7.68	-11.13 [-12.41, -9.85]
Woo 2011	15	-11.2	5.7	-11.20 [-14.08, -8.32]
Total				-11.13 [-12.13, -10.13]

	IPSS change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	48	-8.7	7.5	-8.70 [-10.82, -6.58]
LIFT Study	126	-10.63	7.44	-10.63 [-11.93, -9.33]
Woo 2011	13	-8.6	7.8	-8.60 [-12.84, -4.36]
Total				-9.80 [-11.23, -8.37]

	IPSS change from baseline 24 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
LIFT Study	106	-9.22	7.57	-9.22 [-10.66, -7.78]

IPSS QoL

	IPSS QoL change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	53	-2.2	1.8	-2.20 [-2.68, -1.72]
LIFT Study	138	-2.01	1.74	-2.01 [-2.30, -1.72]
Shore 2014	51	-2.12	1.94	-2.12 [-2.65, -1.59]
Total				-2.07 [-2.30, -1.85]

	IPSS QoL change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	52	-2.3	1.7	-2.30 [-2.76, -1.84]
LIFT Study	139	-2.22	1.78	-2.22 [-2.52, -1.92]
Woo 2011	15	-2.8	1.7	-2.80 [-3.66, -1.94]
Total				-2.29 [-2.53, -2.05]

	IPSS QoL change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	48	-2	1.7	-2.00 [-2.48, -1.52]
LIFT Study	126	-2.3	1.59	-2.30 [-2.58, -2.02]
Woo 2011	13	-2.2	1.9	-2.20 [-3.23, -1.17]
Total				-2.22 [-2.46, -1.99]

	IPSS QoL change from baseline 24 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
LIFT Study	106	-2.22	1.71	-2.22 [-2.55, -1.89]
Total				-2.22 [-2.55, -1.89]

BPHII

	BPHII change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	53	-3.1	3.3	-3.10 [-3.99, -2.21]
LIFT Study	138	-2.81	3.46	-2.81 [-3.39, -2.23]
Shore 2014	51	-3.41	3.57	-3.41 [-4.39, -2.43]
Total				-3.00 [-3.43, -2.56]

	BPHII change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	52	-3.3	2.9	-3.30 [-4.09, -2.51]
LIFT Study	139	-3.96	3.21	-3.96 [-4.49, -3.43]
Total				-3.70 [-4.33, -3.06]

	BPHII change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	48	-3.1	3.1	-3.10 [-3.98, -2.22]
LIFT Study	126	-3.97	3.26	-3.97 [-4.54, -3.40]
Total				-3.60 [-4.44, -2.76]

	BPHII change from baseline 24 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
LIFT Study	106	-3.76	3.45	-3.76 [-4.42, -3.10]
Total				-3.76 [-4.42, -3.10]

IIEF

	IIEF change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	34	0.5	4.6	0.50 [-1.05, 2.05]
Shore 2014	34	0.35	4.76	0.35 [-1.25, 1.95]
Total				0.43 [-0.68, 1.54]

	IIEF change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	40	0.7	9.2	0.70 [-2.15, 3.55]
Total				0.70 [-2.15, 3.55]

	IIEF change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	33	0.9	5.7	0.90 [-1.04, 2.84]
Total				0.90 [-1.04, 2.84]

MSHQ-EjD

	MSHQ-EjD change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	34	1.4	2.3	1.40 [0.63, 2.17]
Shore 2014	34	1.59	2.75	1.59 [0.67, 2.51]
Total				1.48 [0.89, 2.07]

	MSHQ-EjD change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	39	0.7	4.6	0.70 [-0.74, 2.14]
Total				0.70 [-0.74, 2.14]

	MSHQ-EjD change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	33	0.8	2.8	0.80 [-0.16, 1.76]
Total				0.80 [-0.16, 1.76]

MSHQ-Bother

	MSHQ-Bother change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	34	-0.5	1.1	-0.50 [-0.87, -0.13]
Shore 2014	34	-0.76	1.39	-0.76 [-1.23, -0.29]
Total				-0.60 [-0.89, -0.31]

	MSHQ-Bother change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	37	-0.4	2.3	-0.40 [-1.14, 0.34]
Total				-0.40 [-1.14, 0.34]

	MSHQ-Bother change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	33	-0.4	1.4	-0.40 [-0.88, 0.08]
Total				-0.40 [-0.88, 0.08]

Qmax

	Qmax change from baseline 1 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Shore 2014	50	3.3	4.5	3.30 [2.05, 4.55]
Total				3.30 [2.05, 4.55]

	Qmax change from baseline 3 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	40	2.5	5.3	2.50 [0.86, 4.14]
LIFT Study	124	4.24	5.13	4.24 [3.34, 5.14]
Total				3.51 [1.83, 5.19]

	Qmax change from baseline 12 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
Cantwell 2013	37	2.5	5	2.50 [0.89, 4.11]
LIFT Study	105	3.98	4.92	3.98 [3.04, 4.92]
Total				3.39 [1.97, 4.81]

	Qmax change from baseline 24 month			
Study	**n**	**Mean**	**SD**	**Mean (95% CI)**
LIFT Study	98	4.15	5.05	4.15 [3.15, 5.15]
Total				4.15 [3.15, 5.15]

PVR

No SDs reported for PVR results, therefore it was not possible to calculate 95% CIs.

Appendix 3: Critical appraisal of Li et al. (2014)

Support Unit for Research Evidence (SURE) Questions to assist with the critical appraisal of a systematic review[1]

Citation: Li 2014 Registered on Prospero http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007334

Questions ** relate to whether the methodology used is described – eg independently in duplicate

1. Does the review address a clearly focused question/hypothesis	Yes	Can't tell	No
Population/Problem?	Yes		
Intervention?	Yes		
Comparator/control?	Yes		
Outcomes? Can you identify the primary outcome?	Yes		
2. Did the authors look for the appropriate types of paper? Did the studies address the review's question and have an appropriate design?	Yes		
3. Is the search likely to have identified all the relevant evidence?	Yes generally ok but no search for clinical trials or manufacturer contact		

Sufficient range of databases searched? Date range appropriate?	
Good range of search terms (indexed terms and keywords)	
Reference list/bibliography checking?	
Hand search (journals)	
Grey literature searched (unpublished work) Websites? Contacting experts/manufacturers?	
Search terms/ strategy provided? Were they comprehensive?	
Search results provided (no of hits and final studies)? Flow diagram?	
All languages included?	
4. Are all relevant studies likely to have been included?	Yes
Are the inclusion and exclusion criteria stated?	
Is the study selection process described? **	
Multiple papers relating to same study identified?	
Is the data extraction process described? **	
5. Did the authors assess the quality (rigour) of the included studies?	Yes
Is the assessment process described? **	
6. Information about included studies Is key information provided (eg study design, population, interventions, comparators, outcomes,	Yes

areas of potential bias)?	
7. If the results of the review have been combined (meta-analysis), was this appropriate?	Yes
Were the studies sufficiently similar in design and results?	
Are the reasons for any variations discussed?	
8. Are results provided for all included studies? Do the conclusions reflect all results? Is the quality assessment of individual studies reflected in the results?	Yes
9. Were all the important outcomes considered?	Yes
10. Is any sponsorship/conflict of interest reported?	None
11. Finally…consider: Did the authors identify any limitations? Date of review – is it likely to be out of date? Are the conclusions the same in the abstract and the full text?	Ok

This checklist should be cited as:

Support Unit for Research Evidence (SURE) 2013. Questions to assist with the critical appraisal of a systematic review. Available at: http://www.cardiff.ac.uk/insrv/libraries/sure/doc/SURE_RCT_Checklist_2013.pdf

[1] Adapted and updated from the former Health Evidence Bulletins Wales (HEBW) checklist with reference to the NICE Public Health Methods Manual (2012) and previous versions of the Critical Appraisal Skills Programme (CASP) checklists.