National Institute for Health and Care Excellence

External Assessment Centre correspondence

UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Initial teleconference with NeoTract, NICE (B. Dillon) 22/12/14	Questions from Cedar email answered adequately in text response by manufacturer	See text response in appendix	None
As above	Which centres currently use Urolift?	Leciester, Lincoln, St Helens, Frimley Park, Warwick	
As above	Costing discussion – how is Urolift currently priced in tariffs and how does this compare to TURP?	TURP is priced between £1700 -£2400 per case. Urolift is currently classed as "Prostate or Bladder Neck Intermediate Endoscopic Procedure" which is costed far lower – this is dis-incentivising take-up in Trusts. New code being developed for Urolift – LB70 "other complex endoscopic prostate or bladder neck procedure". The TURP price reflects how hospitals are remunerated, not what doing a TURP actually costs. Prices have not been updated for four years, so hospitals undertake TURP at a financial loss.	Noted for future reference. Rates of remuneration should not be an issue for the economic analysis which should estimate real resource use & associated costs.

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As above	What is the expected key variable in the economics?	Length of hospital stay – Urolift is a day procedure and TURP is around 3 days, HoLEP around 2 days (according to HRG codes). Also procedure time – Urolift is only 30 mins.	None – noted for future reference
As above	Follow-up questions on performing a TURP after Urolift has been used – does it interfere with TURP or cause patient injury?	Urolift comprises a polymer suture with a metal cap. During a TURP post-Urolift, the electrosurgery loop will melt through the polymer suture, this causes no injury to the patient. Catching the metal end piece will feel (to the surgeon) like hitting a stone, and in the prostate tissue washed out from the TURP, you can see metal fragments that have been cut by the loop. Again, this does not cause patient injury as you are already injuring the tissue with the loop. The metal end pieces do not conduct heat or electricity.	None
As above	Given that Urolift procedure is performed under local anaesthetic, how is this done, and is it well-tolerated by patients?	In the US, there have been around 1000 Urolift procedures since it was cleared by the FDA. Typically, patients are given an oral sedative for comfort (xanax or	Noted. Pain scores will be assessed by EAC as an outcome measure in this report.

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		vicadin). Liquid lidocaine is then introduced transurethrally to the bladder. No Transrectal block is used. During the LOCAL study, Shore et al gave VAS pain scales throughout the procedure. Urolift scored around as painful as a non-flexible cystoscopy, but more painful than a flexible cystocopy.	
Second NICE catch-up meeting, A. Higgins and B. Dillon present from NICE, G. Carolan-Rees also present from Cedar	Catch-up meeting to discuss progress. Data extraction and meta-analysis plan, with publications unified into Studies in data extraction e.g. 3 publications on LIFT (Roerhborn 2013 and 2014, and McVary 2013 unified into single data extraction)	NICE require data and meta-analysis on comparator too. EAC have suggested using results from recent peer-reviewed systematic for key outcome measures e.g. expected improvements in IPSS and IIEF, expected complications with TURP and HoLEP	Check MAGEC Assessment Report for York's approach to the same issue. Look for systematic reviews on TURP and HoLEP
Section 3.9, additional work by the EAC	Dr Claus Roehrborn and Dr Ted Lamson, authors of the LIFT study papers 2013 and 2014: One of the most important publications in my meta-analysis is your 2014 publication on the 2-year follow-up from the LIFT Study. I am extracting the data from your table in this publication but had a question about the table's contents, example below:	Dr Lamson: Yes, you are correct. These represent the 95% CI lower and upper limits. As a quick check, you could look at the error bars in Figure 3 that show the 95%	

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	AUA-SI* Mean ±SD No Patients (paired) 138 Baseline 22.22±5.51 (21.30, 23.15) Follow-up 17.98±7.83 (16.66, 19.30) Change (95% CI) -4.25±7.63 (-5.53,-2.96) % Change (95% CI) -17.3±7.6 (-23.1,-11.6) I have highlighted the contents of the brackets next to the mean baseline and follow-up results. Are these also 95% CIs? This doesn't seem to be labelled in the table, or in the accompanying text. I also checked your 12 month follow-up paper on the LIFT study from 2013 and these bracketed values are not presented. If you could let me know what these values represent that would be greatly appreciated. Sorry if this seems like a trivial question, or I have misunderstood the table, I hope you can clarify this for me.	CI of the AUASI at each follow up time point	

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Critique of submission section 2	Justin Hall of Neotract (sponsor) contacted with request for CE mark related documents including declaration of conformity.	Documents supplied.	
Economics section 4.5	Contacted Sigmacon (distributor for Versacut) about re-usable HoLEP morcellator blades Could you let me know how many times you can re-use the blades in your morsellator system?	The morcellator blades on average last 10+ procedures. The length of use depends on the size of each prostate/prostatic lobes to be morcellated and the fibrotic nature of the prostatic tissue. Hence the variables which determines the speed at which the morcellator blades lose their sharp edge. One final issue is in reprocessing of the blade sets, if CSSD are clumsy then blades can be damaged or bent. This is entirely outside of Lumenis and the surgeon's control.	Confirmed model input
Sections 2.2 and 4.6.1	Contacted Justin Hall at Neotract (sponsor) and Neil Barber (clinical adviser) about availability of BPH-6 study interim results.	Mr Neil Barber: "Yes - I was national PI for BPH-6. The first results will be presented at the European Association of Urology annual meeting in March in Madrid and will be published as an abstract in European Urology - they will be further presented at the American Urological Association meeting in May in	Informed NICE of timelines for interim results and made note of these replies in the EAC report.

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		New Orleans and will be published in abstract form in the Journal of Urology" Justin Hall: "I have a query outstanding on the level of data you require because these results are not summarized yet and it will be some time before the full analysis is complete. A concern I have is that what do we do if the finding s of the trial impact the model as we do not have the resources to reshape all of the previous work we have done or a level one meta-analysis."	

Table 2

Correspondence with clinical advisers – clinical issues

Expert	**Minimal clinically significant measures for IPSS, QoL, BPHII, IIEF, MSHQ-EjD, MHQ-Bother, Qmax and PVR?**	**Encrusted Urolift implants: Are these a significant issue for Urolift? Is the removal complex or dangerous for the patient?**	**Are there any safety concerns regarding TURP post- Urolift, specifically electrosurgery with the metal or polymer suture components?**	**I understand that with this condition, 3 months and 12 months post-procedure are key time-points for follow up. In light of this, I plan to base my meta-analysis around these time points for key outcomes such as IPSS, QoL, BPHII, IIEF(SHIM), and MSHQ. Do you agree with this approach?**	**IIEF: It can be inferred that a change from one classification to the other needs a 4-point change: e.g. 25 decreased to 21 moves a patient from "No ED" into "Mild ED". I may include this as a minimum clinically important difference. Would you agree with this approach?**
Prof. Raj Persad consultant urological surgeon, North Bristol NHS Trust	Typical Medications / Typical Surgery IPSS 3-5 / 7-15 IPSS QoL 1-1.5 / 1.5-3 BPHII 1-2 / 2-5 IIEF-5 (SHIM) 6 or more is thought to be a detectable change. MSHQ-EjD Threshold not well understood MSHQ-Bother Threshold not well understood		I believe it is very safe indeed to do a TURP after a Urolift though i have never had to do this. The implant is easily removed if	As regards the time points of follow-up, I think the ones you mentioned	

	Qmax Qmax is a surrogate measure to determine how thoroughly obstruction has been addressed in surgical resection/vaporization/enucleation. There is, however, no minimum Qmax change that is required per se. Surgical Goal: Qmax is used to judge how thorough a resection/vaporization is at removing tissue. For TURP, one typically looks for a mean increase on the order of 10-15 mL/sec. For medications or minimally invasive procedures, Qmax change is not well understood, and therefore IPSS is the validated clinical goal. PVR Minimum PVR change sought depends entirely on baseline conditions. If PVR is very high (>350 mL), one would expect to reduce it significantly through treatment to avoid progression toward acute urinary retention. If PVR<350 mL, a criterion of many clinical studies, it has been shown that changes in PVR have too high a variability to be a clinical marker. The basic geometry of the bladder floor and natural variation in emptying creates too high a noise to detect a reliable therapeutic goal.		necessary with a endoscopic biopsy forceps by grasping and using gentle traction. It is easily and gently withdrawn fromm its position, as easily as a ureteric stent would be and without any traumata speak of.	would be acceptable standard time points.	
Mr Gordon Muir consultant urological surgeon, King's College Hospital NHS Found Trust	IPSS: 3, IPSS QoL:1, BPHII:2, IIEF-5:3, MSHQ-EjD:1.5, MSHQ-Bother:1, Qmax: 15% or 2.5 ml/s PVR: very hard to say - see our review http://onlinelibrary.wiley.com/doi/10.1111/bju.2012.110.issue-11/issuetoc. If you must have a number for pvr then perhaps a 20% reduction but it's not a proven outcome measure although all studies tend to include it.	Not a problem so far. If it did occur it would be a simple removal - have had a couple of misplaced implants in my learning curve and these were easily removed and replaced (during the initial	No concerns about safety at all. The anchors are tiny and wash out through the telescope.	I think your time points are very reasonable.	I would not agree that 4 points are needed across the scale. A man who never has a problem with erections will never think about it. A man in whom the

		procedure) with no problem and no harm to patient			erections fail occasionally may have an IIEF score of 23 but will still worry about performance . Similarly a difference between, say, 15 and 18 may well be the trigger for a man taking medication regularly compared to trying most times without.
Mr Frank Keeley consultant urological surgeon, North Bristol NHS Trust	[Recommended Mr Hashim Hashim as an adviser for this question]	The short answer is that I don't know. As you said it is not reported but is a theoretical concern. We do not have enough experience using it yet.	My understanding is that this is not an issue - I would not expect it to be noticeable.	Yes with one caveat: it is distinctly possible that this procedure may not be long-lasting	

				due to erosion of the clips or overgrowth of the prostate. There is not much literature out beyond a year with this new device. You might like to focus on any deterioration from 3 to 12 months. There is also a distinct effect of cystoscopy alone on urinary symptoms, which is more likely to have worn off by 12 months. You also will need to compare any need for	

				further procedures	
Mr Hashim Hashim consultant urological surgeon, North Bristol NHS Trust	Please find below a paragraph from the NIHR-funded clinical trial which I am currently conducting. I am not aware of MPCs for the other parameters you have mentioned. 'The literature is generally scarce in defining what clinically important differences are and in measuring the "minimum perceptible changes (MPC)". For the International Prostate Symptom Score (IPSS), a change of 3 points [3] has been used in drug trials and by NICE for pharmaceutical interventions for LUTS. The previous trial of TURP versus thulium laser used a minimally important difference of 2.0 units on the IPSS [2] (observed difference 0.4 units) which we have also utilised in this trial design. This is approximately commensurate with one category on the scale of global improvement from marked symptoms to moderate, slight, no change and worse [3]. Our previous trial (the CLasP study) of laser versus TURP versus conservative treatment used a minimally importance difference of 3.5 IPSS units [4]. Therefore, we have selected 2.5 IPSS units to reflect the expected small difference between the interventions and the NICE threshold of 3.0 units for pharmaceutical equivalence. No minimal clinically important change in flow rate is accepted in the literature. Discussions between clinicians, both in the trial team and with other urologists, were used to reach a consensus that the maximum acceptable differences between ThuVARP and TURP that would represent clinical equivalence, where a maximum flow rate of 4ml/s, and 2.5 points or less for the IPSS.'	I suspect they are a late complication as used to happen with urethral stents. They should not be difficult to remove. It would involve doing a TURP to cut the intraurethral part and string. The bit that stays outside the capsule presumably stays there but we do not know what happens to it. If a capsule forms around it, it should stay in position, otherwise there is a potential for migration. Not aware of any data in this.			Seems very reasonable
Prof. Tom McNicholas consultant urological surgeon, East & North Herts NHS Trust	As to the other scores you asked about: I am only really confident about IPSS. A recent proposal was to use IPSS cut offs of 3, 5 and 9 point changes which I quite like (pdf Blanker 2014 attached).		[It] Is safe to do TURP or laser after urolift if necessary. Designe	I agree 3mo and 12 mo assessments	These divisions for IIEF are somewhat

	Qmax is not as imp[ortant] as IPSS. Very few men complain of a slow flow. Furthermore I feel PVR is useless as an outcome as is so variable and too dependent on how it is done.		d to be so.		arbitrary. I think subdivision of the total IIEF into smaller versions is itself fraught with difficulty. Have you found any study where anyone asked patients what they perceived as an improvemen t or a minimally important difference? Otherwise4 points may well do but it is all very arbitrary and that would need to be

					explicit in any report.
Mr Andrew Thorpe consultant urological surgeon, Freeman Hospital, Newcastle Hospitals NHS Found Tru st		Encrustation is a significant problem – the makers of Urolift claim it will not happen but there is no long term data to support this – it is not a short term problem and happens over time but if the device did encrust it would involve wither a TURP or holmium laser to excise the encrusted device, so it would involve a fairly complex procedure, and so far as I am aware this has not yet been reported	I am not sure if there is any evidence on safety of TURP after Urolift - certainly some of the component of Urolift is metallic so there is the theoretical possibility of current conduction through the metallic components	I terms of time points follow up needs to be as long as possible - if there is any 5 year data that would be very useful - when we council for TURP we give 10 year re-operation rates quoted at 16%. I agree with all the key outcomes you are going to use	I think that would be fine, and I think the reasoning behind it is sound.
Mr Neil Barber, consultant urological surgeon, Frimley Park Hospital NHS Found Trust		I too am not aware of major issues regarding encrustation. I have had none so far. Generally the metal tab on the urethral	There are no safety concerns regarding the performing of a TURP, a HoLEP or Greenlight laser prostatectomy (PVP) after urolift -	I think that the time lines you are looking at would be very reasonable in	

		side is covered over with urothelium so does not get encrusted. i have had 3 cases where the tabs have probably been placed too close to the bladder neck and i have removed and replaced them more than 6 months down the line - removal is very easy and in itself poses little or no risk to the patient	indeed the metal tab on the prostatic urethral surface can easily be removed anyway should anyone have concerns (which they shouldn't)	terms of overall symptom improvement, however, part of the attractiveness for patients in selecting a urolift over TURP etc is the much faster improvement in symptoms so adding in 3 or 4 weeks post op data might be useful.	
Prof. Mark Emberton, Professor of Interventional Oncology, Division of Surgery and Interventional Science, UCL Clinical Director, Clinical Effectiveness Unit, Royal College of Surgeons of England		The great worry about this technology is that you leave something behind. Whenever we have done this before it has ended in tears. Whether the same will occur with this is not	NOT on face value as the area of implantation should be resected. However, there is obviously uncertainty in this area as we have limited data	Yes I would [Agree]. They are both sensible time points.	

		known. Encrustation is the beginning of a stone which willing time enlarge, block and get infected. So yes it is an inherent issue. [As to whether] the removal complex or dangerous for the patient? I don't think so but of course we don't know.			
Mr Mark Speakman, consultant urological surgeon, Musgrove Park Hospital, Taunton & Somerset NHS Found Trust President of BAUS	The MIDs used in CG97 and in this update are: IPSS- 3 point change, , IPSS QoL – 0.5 point change, Qmax – 2mL/min changeFor all other continuous outcomes, the standard MID of 0.5 standard deviation change was used, as per GRADE working group recommendations.No information was identified for the relevant dichotomous outcomes. Therefore, for all dichotomous outcomes in this systematic review, the thresholds suggested by the GRADE Working Group were adopted (RRR or RRI of 25%: 0.75 or 1.25). The MIDs were assessed for each outcome as the differences between groups at follow-up, using either change or final scores.				

Correspondence with clinical advisers – economic issues

Expert	Could you provide a length of stay, in days, for a typical Urolift patient?	Does Urolift differ significantly in the staff members involved in TURP and HoLEP?	In your experience, what is the operating time for Urolift?	What are the erectile and ejaculatory dysfunction rates for TURP and HoLEP?	It seems there are two options for Urolift and HoLEP: you can buy the device upfront, or take a contract where the device is free and the consumables (Urolift sutures, morcellator blades and fibres for HoLEP) are paid over the course of the contract. Do you know if the consumables are more expensive under this contract arrangement?	There is a claim that Urolift requires fewer post-procedure visits than TURP or HoLEP. Is this correct in your experience, or are they all similar?
Prof. Raj Persad consultant urological surgeon, North Bristol NHS Trust						
Mr Gordon Muir consultant urological surgeon, King's College Hospital NHS Found Trust	About 3 hours post op. Can be done under IV sedation rather than full general anaesthetic.	All require: 1 Consultant surgeon, 1 anaesthetist, 1 operating department assistant or	59 minutes is in trial setting. Real life time less that 15 minutes total surgical time. We	80% dry orgasm and 5% new erectile dysfunction	There is no device cost for Urolift except the disposable device used for each patient so no capex cost.	

		anaesthetic nurse,1 Band 5 nurse. TURP and HoLEP also need a Healthcare assistant, but Urolift does not.	schedule 35 minutes total theatre time.		A holmium laser box is about £90k to buy. The morcellator is between £25- £35k. Consumables per holep case depend on whether the instruments are single use or not - depends on local practice (some reuse fibres and blades , some don't) and caseload volume. Anything between £120 - £700. All ex vat.	
Mr Frank Keeley consultant urological surgeon, North Bristol NHS Trust	Usually a daycase.	I agree that it requires the same number of staff as any other surgical procedure. NHS theatre staffing is pretty much standard				
Mr Hashim Hashim consultant urological surgeon, North Bristol NHS Trust	Usually a daycase.	Urolift and TURP are the same, but not with HoLEP, as that would need a laser operator as well	Procedure time depends on size of prostate. Also depends on what you would consider the procedure time: is it from the time the patient enters operating room, time patient	There are published papers in European Urology with percentages. There is also the EAU guidelines which you can access on Uroweb.org which gives percentages	Not sure as there is only one NHS trust that has managed to use it in the country on the NHS, as far as I am aware. We would have to ask the company for these figures.	Follow-up depends on hospital policy. In general we give patients a call for their histology after a TURP to make sure they are well. With Urolift, i would

			is asleep, time the cystoscope is inserted. I would say 30-40 mins if you are just looking at the time of insertion of the scope to removal. Also depends on number of clips inserted.			suggest that they would need a flow test 3 months after and a review in clinic to see if symptoms have improved as we do not have long term data and it is a new procedure. However with time I would suspect that they would all be the same.
Prof. Tom McNicholas consultant urological surgeon, East & North Herts NHS Trust	All my cases have been planned as day cases. (Two cases kept overnight because of long travel distances.)	TURP needs one extra circulating nurse for irrigation fluid. Urolift can be done under light sedation, so can remove one nurse. If done under local anaesthetic, no anaesthetist needed. Urolift can also be done in an endoscopy room rather than an expensive operating theatre.				
Mr Andrew Thorpe consultant urological surgeon, Freeman Hospital, Newcastle Hospitals NHS Found Trust	Should be a daycase or even outpatient procedure – this is what the company and the clinicians who use it claim.	There would be no difference in theatre staffing for the procedures, but anaesthetic staff would include 1 anaesthetist PLUS anaesthetic assistant theatre staff – 1 urologist, 1		ED to be about 5% following TURP, Retrograde ejaculation is about 70%	It normally varies in the number of consumables that you use over the year if you are renting the equipment – there are ceiling's eg 20, 50	

		scrub nurse and in most theatres 2 other nurses. There would also be a porter present to lift the patient to and from the theatre table. Nurse banding would vary from hospital to hospital.			,100 cases per year. However the Holmium fibres work out very cheaply as they are reusable and can be use for a large number of cases – it would certainly be a lot cheaper than the Urolift – I think you would have to enquire from the Urolift company what they would charge. Most units buy the Holmium laser as it is not particularly expensive, and this laser is now dual use – it can also be used for stone cases as well so it makes it incredibly economical	
Mr Neil Barber, consultant urological surgeon, Frimley Park Hospital NHS Found Trust	This is a day case.	There should be an operating department practitioner as well for all cases involving a general anaesthetic. If the Urolift is performed under local anaesthetic then no anaesthetist or ODP is required.	Operating time for Urolift is less than 30 mins all in (operating time for me is 7 - 15 mins) - probably 45 mins to an hour or longer all in for TURP/ HoLEP	You will struggle to get good data on change in erectile function after these procedures - it has been badly measured and captured mainly in single centre series -	The uroloft device requires no more than a cystoscope and the disposables - it is a different cystoscope than generally used - but there is no further investment needed.	I think the claim is that urolift patients will have less unscheduled visits post procedure - ie attendances to A and E or urgent OPA. This is

				certainly as regards HoLeP. Take a look at the GOLIATH 6 month and 1 year data published 2014/ 15 in European Urology and Journal of Urology - IIEF was captured in an a high quality way and you will have the TURP arm from that trial	HoLEP requires a special cystoscope and a morcellator which must be purchased. Beyond that there is the cost of the 100w Holmium:YAG laser and laser fibres - I do not know of what deals exist but from what I understand, purchase of the scopes, morcellator and laser machine are usually required. there may be deals on the fibres which maybe multiuse	probably a very reasonable claim. Although unpublished in 2013 at my UK DGH, about 10% of patients were readmitted with complications via A and E
Prof. Mark Emberton, Professor of Interventional Oncology, Division of Surgery and Interventional Science, UCL Clinical Director, Clinical Effectiveness Unit, Royal College of Surgeons of England	A day case. Very few overnight stays					
Mr Mark Speakman, consultant urological surgeon, Musgrove Park Hospital, Taunton & Somerset NHS Found Trust President of BAUS	60% daycase, 40% after one night.	All require a consultant surgeon, HoLEP and TURP always require an anaesthetist. ~75% Urolift are done under general anaesthetic. In theory, a local anaesthetic list could be set up to do them without an			Urolift I think is a fairly fixed price with the only variable being the number of implants that are used typically between 3 and 5 -	

		anaesthetist. Operating theatres need a minimum of a trained nurse and a healthcare assistant but HoLEP needs to be another nurse who is laser trained (band 5 or above).			usually 4 HoLEP there are a variety of options to buy the equipment up front and the running costs are then very low or lease in the equipment and pay each time you use it. I think for HoLEP you would need to request the relative costs from the companies to compare them as I don't have access to these figures	

Appendix 1

EAC Questions prior to initial teleconference on 22/12/14:

1) ***On Page 16 it says "The Urolift system has been available in the UK for more than a year on a clinical trial basis and for use in evaluation at a very limited number of selected NHS Trusts due to a classification and coding error". What does this mean? The IP Guidance gives "normal arrangements".***

The procedure has been miscoded as a bladder neck procedure, attracting a tariff which is half that of a TURP or other respective/ablative procedure. This lack of funding has impeded the 40 or so trusts who wish to adopt the procedure from doing so on financial grounds.

2) ***We do not have a current CE mark certificate for Urolift. Could the manufacturer please provide this? It says [attached] on the submission, but we do not have it.***

Done.

3) ***Does Urolift ever need repeating (after 12, 24, 36 months, etc)? It seems to treat the symptoms rather than the condition, which is unlike TURP, or HoLEP, which remove excess prostate tissue.***

Retreatment for continued lower urinary tract symptoms after UroLift system treatment has been well studied. In the large randomized study, this was shown to be 5% at one year, rising to a cumulative total of 7.5% by 2 years. This validates prior open label studies that showed retreatment rates of 6% at 1 year and 8% at 2 years. Data to 3 years will be reported in 2015, and the protocol goes to 5 years. Because symptom response and flow rate does not show deterioration from 6 to 12 to 24 months, one is not anticipating a trend toward unduly high retreatment. Retreatment for LUTS has been either a UroLift "touch up", which entails applying implants to obstructive areas of the prostate that may not have been appreciated at time of index procedure, or moving onto a TURP, whether conducted traditionally or with a laser technique. All retreatment techniques have been conducted safely

and without incident. The implant is designed to allow for normal TURP technique, should it be desired.

It is of course important to set this rate of re-intervention in context with the standard of care, TURP. TURP is associated with a 5.8% to 12.5% rate of secondary procedures at 1 year and a 12.3% to 17% at 5 years.[Roehrborn, Urol Practice] Of these secondary procedures, 5.8% to 9.7% are actually re-treatment for residual LUTS, and the other procedures are to address complications. Clearly, the secondary procedure rate for the UroLift system treatment is as low or lower than the standard of care, TURP.

The question of whether UroLift addresses the underlying condition, rather than the symptoms, is another good point that perhaps requires some historical context. TURP was introduced in 1930's to replace surgical enucleation (blunt dissection of the glandular tissue of the prostate conducted with a gloved index finger). Enucleation is the most definitive removal of all glandular tissue, while TURP is an approximate removal of most tissue. As such a "good TURP" was one that removed the most tissue. This was and is measured by the grams of tissue removed, the volume remaining in situ per ultrasound, and the maximum flow rate achieved after tissue is removed. The urinary flow achieved after TURP, surgical enucleation or transurethral laser enucleation (so called HoLEP) is superphysiologic, in other words at a much higher rate than a normal man in that age group and health status. It is important to appreciate that a patient's objective is not tissue removal nor superphysiologic flow, but improvement in flow adequate enough to mitigate his bothersome symptoms.

UroLift system treatment has been shown to very significantly mitigate LUTS and to also "normalize" urinary flow with a statistically significant and highly repeatable 50% average improvement in peak urinary flow. With less fluid resistance, higher flow rate, and most importantly, significant reduction in symptoms associated with obstruction, UroLift system treatment has been indeed demonstrated to address the underlying condition of obstruction due to enlarged prostate.

a. Does this also mean that the prostate volume doesn't decrease post-procedurally?

It is a correct assumption that UroLift implant treatment does not reduce prostate volume, nor does it interrupt the natural ageing phenomenon of continued prostate growth. The novel objective of installing the UroLift implants is to mechanically render this growth to be irrelevant. Benign tissue growth of the prostate is, by its definition, benign. It is merely the symptomatology associated with urinary obstruction that is the clinical problem. The implants are installed such that a continuous channel is created through the anterior aspect of the prostate, often riding "above" large coapting lobes. This theoretically allows the prostate to open

more easily upon micturition and importantly allows the prostate to remain open until the bladder has more fully emptied. The prostate can continue to grow at its documented 2% per annum, as long as the mechanical aspects of growth are no longer linked to obstruction. One might ask why this channel remains patent or why the lobes continue to open more easily over several years. We believe the answer may have been found in animal studies submitted for FDA approval. Histologic analysis of the prostate tissue shows that the area originally compressed by the implant then remodels into an atrophic or far less cellularly active zone. In such a way, tissue hyperplasia continues around the channel created by the implants but preferentially not in the area of the channel. These data will be assembled into a publication late in 2015, but they remain hypothetical, as there is no way to measure a correlation between the effect and symptoms or flow in the animal model, as it does not physiologically resemble the human.

4) ***There appears to be a certain number of Urolift cases in most studies (in Perera et al) where TURP was necessary at 12 months. This is between 1-5% in Abad, Cantwell, LIFT and McNicholas but as high as 16-19% in the Woo and Chin studies. How does this compare to TURP re-procedure rates?***

This question was addressed in the answer to question 3. The higher rate seen in Woo and Chin et al, particularly in the first 25 subjects of the 64 patient series, was, as described in the manuscript, due to the fact that the lift procedure was significantly altered to the current technique starting with patient 26. The retreatment rate for subjects 26-64 was reported to be 8% at 2 years, very close to the 7.5% later reported for the 2 year randomized study. What is not described in the manuscripts is exactly what that change was. It was to limit the procedural objective to achieving a channel through only the anterior aspect of the prostatic fossa. Prior to that, the investigators were effectively attempting to "pin back" all the tissue of the prostate, and this would create an irregular shape that might or might not have a continuous channel. By selecting a single plane of implants and inspecting for opening from bladder neck to veru montanum, this created a more reliable result. And, as explained above in answer to question 3, it would appear that an anterior channel is indeed sufficient to achieve an effective and reliable result. All training materials and publications today instruct to achieve an anterior channel as the procedural objective.

5) ***Is required postoperative catheterisation as low as you claim on page 43? A quick weighted mean (calculated from the numbers in the Perera et al. study) puts this at 50.2%. Where does the 20-32% catheterisation rate with Urolift come from?***

Catheterisation is effectively and uncontrollable phenomenon and relies upon a surgeon's and medical center's standard practice. In our clinical studies, we were able to create an artificial situation by controlling the practice. Protocols for the LIFT study and the LOCAL study were written to require that patients not be catheterized at onset, but instead be retained in facility until they successfully voided. If the patient could not void comfortably, a catheter was then installed. Even in this controlled environment, several investigators chose to install a catheter prophylactically without conducting a void trial. As one might expect, this was more prevalent on Fridays than any other day. The reasoning is of course to prevent needing to come into the office or facility on a weekend to install a catheter.

In the studies across Europe, practice patterns differ greatly. In Germany almost all patients receive prophylactic catheterization because this is part of the two night stay minimum required of all hospital procedures. Unfortunately this is an unintended

consequence of the healthcare reimbursement system of that country.

Thus the rate of catheterization in the UK could be as low as 20% or lower, if indeed it were an objective to void trial each patient prior to discharge. Alternatively, it will undoubtedly be some higher percentage. Anecdotally, now with over 1,000 patients treated commercially in the USA, the catheterization rate is being reported to NeoTract at lower rates. Several centers are at 0%, some at 10%. It would appear this rate is due to effective and gentle treatment, but also center objectives in overall patient experience.

6) Does the manufacturer have a translated copy of the DeLongchamps 2012 paper cited in Perera et al?

We do not, but it is probably not worth doing. This study was a "first in France" study of four patients only, and as such, does not weigh heavily when analyzing overall UroLift system performance. The data were indeed not included in the meta analysis, since no standard deviations were calculated, etc.

EAC questions to clinical advisers following request at MTAC 19/3/15

Expert	NICE are recommending the following: "The clinical experts advised the Committee that a cystoscopy may need to be done after using the UroLift system, to check that the positioning of the prostate is appropriate" Would this be done during the procedure (requiring a cystoscopy set to be added to the economics for this), or as a separate appointment some time after the Urolift procedure? If it is simply the addition of the cystoscopy set, I wondered if you could give me an example of the set you might use for this, and if possible, do you know the price of this equipment?
Mr Gordon Muir consultant urological surgeon, King's College Hospital NHS Found Trust	Cystoscopy is done at the end of the procedure, takes 30 seconds to perform and requires no additional equipment.
Prof. Mark Emberton, Professor of Interventional Oncology, Division of Surgery and Interventional Science, UCL Clinical Director, Clinical Effectiveness Unit, Royal College of Surgeons of England	Cystoscopy is performed just after the procedure. This can be a flexi cystoscopy under local anaesthetic.
Mr Hashim Hashim consultant urological surgeon, North Bristol NHS Trust	A cystoscopy would be performed at the end of the procedure and would include a rigid cystoscope, bridge, sheath and camera. This is standard kit which should be available already. Unsure of costs, usual companies are Olympus or Storz.
Mr Frank Keeley consultant urological surgeon, North Bristol NHS Trust	Cystoscopy would be done at the end of the procedure, not separately. Many urologists would do a cystoscopy prior as well in order to rule out a big median lobe of the prostate which is considered a contraindication. Practice may be different in the US.