



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1586 – Transurethral Water Vapour Ablation (TUWA) for benign prostatic hyperplasia (BPH)

Applicant: Boston Scientific Australia Pty Ltd

Date of MSAC consideration: MSAC 79th Meeting, 28-29 July 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of transurethral water ablation (TUWA) of the prostate for the treatment of patients with benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms (LUTS) was received from Boston Scientific by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on public funding for TUWA for BPH. Although MSAC considered TUWA is likely inferior in terms of effectiveness to transurethral resection of the prostate (TURP), but may be superior in terms of safety, MSAC considered that a number of additional analyses need to be completed before it can make a recommendation. Further analyses include a clinical and economic comparison with visual laser ablation of the prostate (VLAP) and a holistic assessment of the different therapeutic approaches to BPH management that takes into account the different outcomes and costs associated with each. MSAC recognised that individual patients may have different preferences when considering the balance between side effects and long-term effectiveness.

Consumer summary

Boston Scientific applied for public funding through the Medicare Benefits Schedule (MBS) for transurethral water vapour ablation, or TUWA, a minimally invasive procedure used to treat benign prostatic hyperplasia (BPH).

BPH is a non-cancerous enlargement of a person's prostate that occurs as a natural part of ageing. This can cause lower urinary tract symptoms, such as increased frequency, urgency and/or difficulty in urinating, which can impact a patient's quality of life. TUWA works by inserting a single-use probe through the urethra and applying water vapour (steam) to

Consumer summary

decrease the size of an enlarged prostate. TUWA does not use an incision and can take as little as 20 minutes to complete. Many patients are day patients.

MSAC noted that there are other MBS funded procedures for treating BPH and that BPH is commonly treated using transurethral resection of the prostate (TURP), which involves the surgical removal of prostatic tissues through the urethra. MSAC recognised that many patients may choose TUWA over other techniques, because it is reasonably fast, safe and relieves symptoms in the short term. However, MSAC had questions about how well TUWA works in the long term compared to other MBS funded procedures. MSAC was also concerned about possible out-of-pocket costs for patients.

MSAC's advice to the Commonwealth Minister for Health

MSAC decided to defer its advice on public funding for TUWA. MSAC would like to review all the procedures used to treat prostate enlargement, and compare their advantages and disadvantages with regards to their effectiveness, safety, cost and cost-effectiveness. This will help MSAC estimate the appropriate fees for each procedure. MSAC recognised that individual patients may have different preferences when considering the balance between side effects and long-term effectiveness.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application requested MBS listing of TUWA of the prostate for the treatment of patients with BPH-related LUTS.

MSAC recalled there are MBS funded procedures available for treating BPH including TURP, VLAP, transurethral needle ablation (TUNA) and the insertion of prostatic urethral lifts (PUL). MSAC noted TUWA is different to other minimally invasive ablative procedures currently available on the MBS for treating BPH. The differences include the way that heat is produced (water vapour) and transferred (by convection, which means tissue is uniformly heated).

MSAC noted that TUWA is currently being claimed under MBS item numbers 37201/37202 for TUNA and that the application requested the fee for TUWA be at least equivalent to the current fee for TUNA. MSAC noted that TUNA is no longer recommended for BPH in clinical guidelines.

MSAC noted that the applicant nominated TURP and PUL as the main comparators to TUWA. MSAC agreed with ESC and the pre-MSAC response that TURP is the gold standard for BPH treatment and considered TURP is an appropriate comparator. MSAC noted that other MBS funded comparative procedures shown in the clinical management algorithms were not included as comparators in the ADAR. MSAC agreed with ESC that VLAP should have been included as a comparator in the ADAR, as it is also a transurethral ablative procedure that is the second most common BPH treatment used (after TURP).

MSAC noted that the comparative clinical evidence was based on three randomised clinical trials: REZUM-II (TUWA vs. sham), L.I.F.T. (PUL vs. sham) and BPH6 (PUL vs. TURP), which were used to construct indirect treatment comparisons to 3 months for TUWA versus PUL (via sham) and TUWA versus TURP (via a two-step indirect comparison). MSAC noted that the BPH6 study, used a composite endpoint to claim superiority of PUL vs. TURP,

comprised of six outcomes, with safety and erectile/ejaculatory outcomes driving the BPH6 endpoint. This biased the study against TURP. . MSAC noted that the 3 month endpoint should favour TUWA given that recovery is faster in the shorter term for minimally invasive outcomes.

Regarding safety, MSAC considered TUWA is non-inferior to PUL after 3 months. MSAC noted for TUWA versus TURP comparisons that the outcomes from the REZUM-II and BPH6 studies were not comparable and agreed with ESC that TUWA has different but likely superior safety compared to TURP. MSAC considered the reported adverse events for TUWA to be acceptable.

Regarding effectiveness, the International Prostate Symptom Score (IPSS) was considered the key clinical outcome. MSAC considered that TUWA is non-inferior to PUL at 3-month and 2-year time points. Compared with TURP, MSAC considered that TUWA is likely non-inferior after 3 months of follow-up. However, over the longer term, TUWA appears to have inferior effectiveness to TURP as patients treated with TURP showed a greater improvement in IPSS from baseline than TUWA at the 2-year time-point. MSAC noted the pre-MSAC response claimed the effectiveness of TUWA compared to TURP should be based on the 3-month time-point data only due to limitations in the long term data (i.e. naïve single arm comparisons) but MSAC did not agree.

MSAC noted that TUWA may be preferred by patients, as it appears to relieve symptoms of BPH in the short-term, the patient-reported outcomes are acceptable, and it is a quick and minimally invasive procedure. MSAC noted that there was no opportunity for testing cancer pathology with minimally invasive procedures. However, MSAC also noted that imaging was the primary modality for cancer testing. The applicant noted that a pre-procedural biopsy may be performed. MSAC also noted concerns from the Urological Society of Australia and New Zealand regarding the long-term safety and effectiveness of TUWA.

MSAC noted that the economic evaluation was a cost-comparison analysis, but MSAC queried whether a cost-effectiveness analysis may be more appropriate. MSAC noted that the intervention was claimed to be cost-saving compared to both TURP and PUL. The main drivers of the economic evaluation were length of stay and cost per loop per TURP patient, and number of Urolift® devices per procedure for PUL. MSAC also noted that the base case did not consider reintervention rates.

MSAC considered the potential out-of-pockets costs for the single use consumables used in the TUWA to be significant (\$1,950 per patient). MSAC noted the differing fee rebates for PUL, VLAP, TURP and TUWA (under TUNA), and considered it difficult to compare costs and determine appropriate fees, as each application used different assessment approaches.

MSAC noted a market share approach was used to estimate the financial implications for MBS listing of TUWA for BPH. MSAC considered the financial impact to be highly uncertain, mainly due to the uptake estimates, as it appeared to be difficult to ascertain uptake of TUWA and the proportion of substituted or displaced procedures.

MSAC considered that the treatments for BPH management required a more holistic review, and recommended that the Department, in consultation with applicants and professional and consumer stakeholders, undertake a review of the effectiveness (including short and long-term outcomes), safety, costs and cost-effectiveness of VLAP, PUL, TUWA, TUNA, TURP and any other procedures used to manage BPH.

MSAC considered this review could also usefully garner information on:

- why urologists recommended certain procedures
- what informs patient preferences for certain procedures
- long-term outcomes.

This review will allow MSAC to provide better advice to the Minister on which BPH procedures should be funded on the MBS and the appropriate fees for each procedure are.

Other discussion

MSAC noted the applicant's request that MSAC recommend listing the consumables used in the TUWA procedure on the Prostheses List (PL). MSAC noted that the role of MSAC is not to advise about the PL; this is the role of the Prostheses List Advisory Committee (PLAC).

4. Background

This is the first submission (Applicant Developed Assessment Report [ADAR] for TUWA for treatment of patients with BHP-related LUTS.

5. Prerequisites to implementation of any funding advice

The technology used to perform TUWA is currently included on the Australian Register of Therapeutic Goods (ARTG) as two components: the generator (ARTG 299127) and the cystoscopic probe (ARTG 311560; Table 1).

Table 1 Devices listed on the ARTG to conduct TUWA

Registered item	Manufacturer	ARTG number	Date of introduction	Device category
Hyperthermia system, radio frequency	NxThera Inc. (Maple Grove, MN, USA)	299127	30/01/2018	Medical Device Included Class IIb
Hyperthermia applicator, radiofrequency, intracorporeal	NxThera Inc. (Maple Grove, MN, USA)	311560	15/11/2018	Medical Device Included Class IIb

Abbreviations: ARTG = Australian Register of Therapeutic Goods.
Source: Table 5, p22 of the commentary.

6. Proposal for public funding

Since June 2018, TUWA procedures have been claimed on an interim basis under items 37201 and 37202 for TUNA of the prostate. However, MBS item 37201 and 37202 specify that patients must be found clinically unsuitable for TURP prior to the procedure. The ADAR proposed a new MBS item specific to TUWA in which the descriptor does not restrict the eligible patient population to those not medically unfit for TURP (Table 2). The applicant has requested the MBS fee for the proposed new TUWA item be at least equivalent to the TUNA items.

Additionally, there are consumable costs associated with use of the Rezūm system, estimated by the applicant to be \$redacted (see Table 65 of the ADAR). In the private hospital setting these would be borne by the insurer or patient (as out of pocket costs).

In its pre-MSAC response, the Applicant confirmed that a submission for the Rezūm system will be made to the PLAC.

Table 2 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
PROSTATE, ablation by water vapour with or without cystoscopy and with or without urethroscopy
Fee: \$842.10 Benefit: 75% = \$631.60 85% = \$715.79

Source: Table 1, pxii of the commentary.

7. Summary of public consultation feedback/consumer Issues

One response to public consultation was received from the Urological Society of Australia and New Zealand (USANZ). The response noted the benefits of TUWA, including the minimally invasive nature of the procedure and associated improvements in surgical duration, blood loss and hospital length of stay. Overall, the response was supportive of the application; however, it was noted that direct comparative evidence on TUWA and comparators and long-term safety and effectiveness data was not available.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

The proposed intervention is a transurethral procedure using water vapour to ablate the prostate for the management of LUTS caused by BPH using the Rezūm system. Superfluous prostatic tissues are ablated using water vapour delivered through the urethra. The vapour is formed using the radio frequency current created by the Rezūm generator and applied to the area through a single-use probe.

Description of Medical Condition

BPH, also called prostate enlargement, is a non-cancerous enlargement of the prostate gland, in which smooth muscle and epithelial cells proliferate, which occurs as a natural part of ageing. BPH may cause LUTS either by directly obstructing the bladder outlet or by the increased smooth muscle tone and resistance within the enlarged gland. LUTS include symptoms such as increased frequency and urgency of urination, urinating at night, and difficulty starting or stopping urination (Roehrborn 2005). This, in turn, impacts on activities of daily living, reduces patient's quality of life and interferes with sexual function (Rosen 2003, Girman 1998, Girman 1999).

Surgical therapy (including TUWA) is indicated for BPH patients with severe or high impact LUTS (Andrology Australia 2014). Thus, the proposed population for TUWA include men with severe or high impact LUTS caused by BPH.

The clinical management algorithm provided in the ADAR (Figure 1) was prepared in line with recommendations made by the National Institute for health and Care Excellence (NICE, nice.org.uk) and the urology care foundation (urologyhealth.org) for the management of LUTS caused by BPH. The intervention needs to be conducted by an urologist in a hospital or day surgery facility.

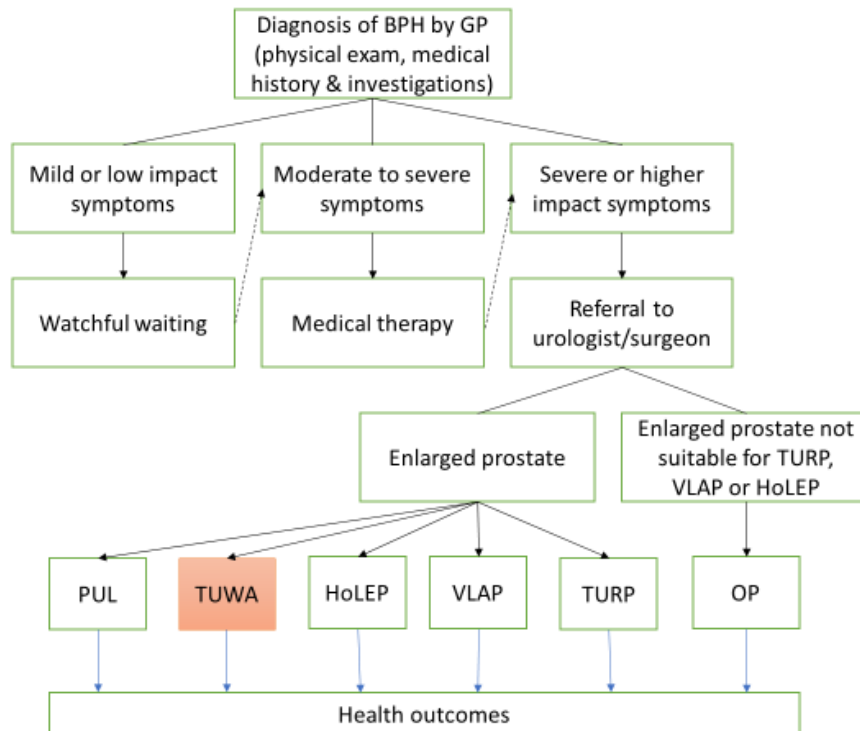


Figure 1: Clinical management algorithm provided in the ADAR

Abbreviations: BPH = benign prostatic hyperplasia; GP = general practitioner; HoLEP = holmium laser enucleation of the prostate; OP = open prostatectomy; PUL = prostatic urethral lift; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation; VLAP = visual laser ablation of the prostate.

Note: the orange box characterizes the changes that the Applicants proposed.

Source: Figure 2, p18 of the ADAR.

The commentary noted that the algorithm included in the Canadian Urological Association Guideline and the European Association of Urology Guideline may be a more appropriate algorithm for this application. These guidelines are endorsed by the USANZ. The commentary provided the Canadian Urological Association algorithm as an alternative (Figure 2).

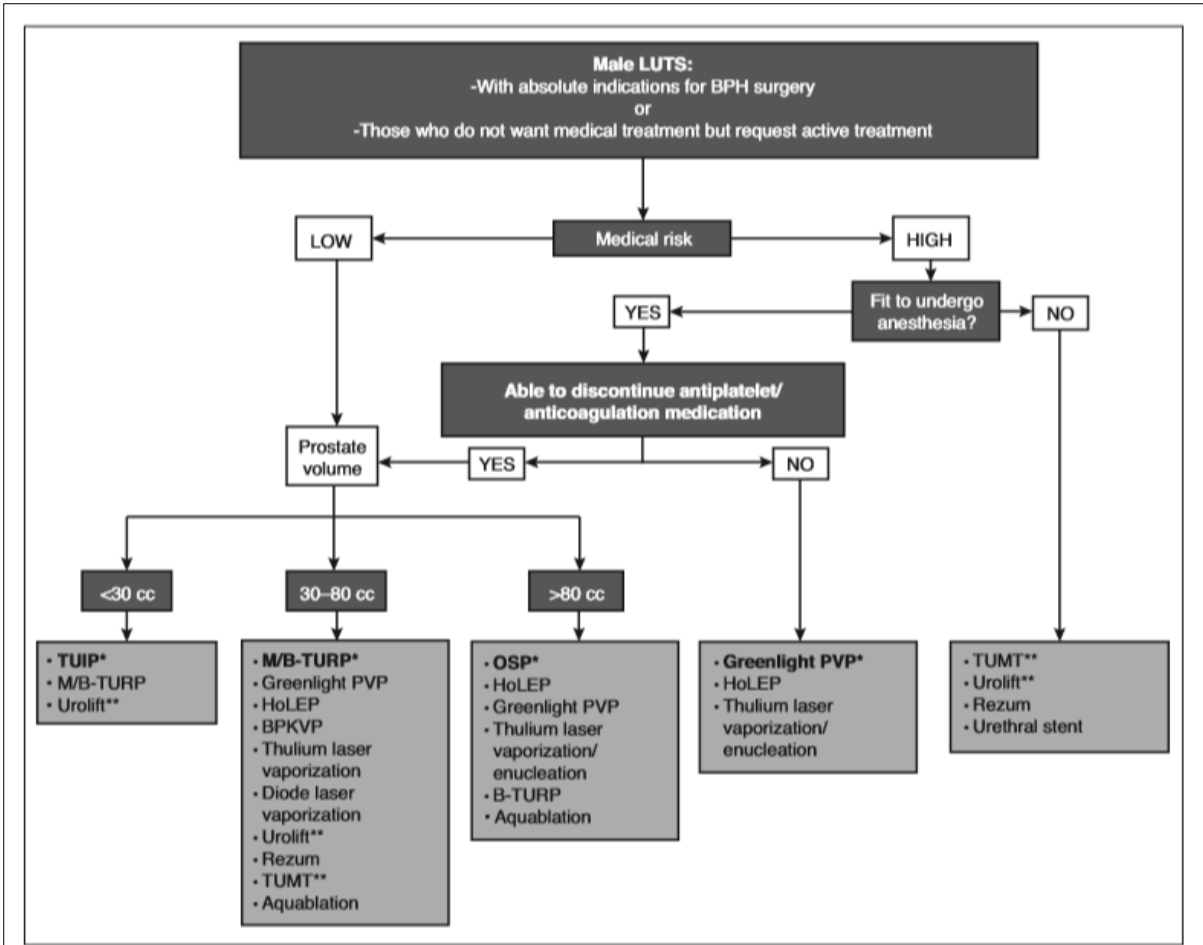


Fig. 3. Treatment algorithm of bothersome lower urinary tract symptoms (LUTS) refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient’s ability to have anesthesia, cardiovascular risk, and prostate volume. *Current standard/first choice. The alternative treatments are presented in alphabetical order. **Must exclude the presence of a middle lobe. BPH: benign prostatic hyperplasia; B-TURP: bipolar transurethral resection of the prostate; HoLEP: holmium laser enucleation of the prostate; M/TURP: monopolar transurethral resection of the prostate; PVP: photoselective vaporization of the prostate; TUIP: transurethral incision of the prostate; TUMT: transurethral microwave therapy.

Figure 2 Alternate clinical algorithm from the Canadian Urological Association

Source: Extract taken from Canadian Urological Association guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH): 2018 update¹; presented as Figure 5, p30 of the commentary.

9. Comparator

The ADAR presented two main procedures as comparators to TUWA: TURP and PUL.

TURP

TURP is considered the gold standard treatment for BPH and is the most frequently used BPH procedure reimbursed on the MBS. TURP consists in the dissection of prostatic tissues through the urethra. It requires several days of hospital stay and general anaesthesia.

¹ Nickel, J. C., Aaron, L., Barkin, J., Elterman, D., Nachabé, M., & Zorn, K. C. (2018). Canadian Urological Association guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH): 2018 update. *Canadian Urological Association Journal*, 12(10). <https://doi.org/10.5489/cuaj.5616>

The relevant MBS item for reimbursement of TURP is item 37203 item (fee \$1,058.80)

PUL

The PUL procedure involves the transurethral insertion of small, permanent UroLift implants, positioned in the prostate to retract the lateral lobes creating anterolateral channels which go from the neck of the bladder to the outside of the prostate. This compression of the prostate reopens the urethra and relieves LUTS. The ADAR nominated PUL as a comparator as it represents a minimally invasive procedure that is similar in level of invasiveness to TUWA and with an increasing utilisation on the MBS.

The relevant MBS item for reimbursement of PUL is item 36811 (\$328.55).

The commentary noted that the ADAR listed other treatment options for LUTS, including those presented in clinical management pathway provided by the applicant, including: TUNA; HoLEP; VLAP and TUMT.

The commentary noted that the ADAR proposed TURP and PUL as main comparators as they were either the most used technique in Australia (TURP) or as they were minimally invasive (PUL). However, the commentary considered that the ADAR did not provide an adequate justification for why only PUL and TURP are the comparators in the ADAR (for example there is no justification for why VLAP and HoLEP were not considered).

Notwithstanding this, the commentary considered that the chosen comparators, TURP and PUL, may be appropriate.

The pre-MSAC response reiterated that TURP and PUL are the appropriate comparators and that VLAP, HoLEP, TUNA and TUMT are less relevant comparators as:

- PUL is a minimally invasive procedure, performed as day surgery and has a similar level of invasiveness, duration and complexity to that of TUWA
- Alternative minimally invasive procedures listed on the MBS (e.g. VLAP, HoLEP) require overnight hospitalisation and have a relatively small market share (TUMT: 0.9%; TUNA: 1.8%; HoLEP: 5.9%; VLAP: 15.6%) relative to TURP (67.5%)
- TURP is considered the gold standard for BPH with the highest utilisation amongst surgical procedures for BPH on the MBS (67.5% in 2018) and the applicant claimed TUWA procedures will substitute from TURP procedures should TUWA be listed on the MBS.

10. Comparative safety

No head-to-head studies of TUWA versus the comparators, PUL or TURP, were identified. Three RCTs were included in the ADAR:

- REZUM-II² study (TUWA versus sham),
- L.I.F.T.³ study (PUL versus sham) and
- BPH6⁴ study (TURP versus PUL).

The REZUM-II and L.I.F.T. studies were double blind and sham-controlled until 3 months after which patients were able to crossover to the treatment arm. The BPH6 study compared

² Minimally Invasive Prostatic Vapor Ablation - Multicenter, Controlled Study for the Treatment of BPH (Rezūm II) - NCT01912339

³ Luminal Improvement Following Prostatic Tissue Approximation for the Treatment of LUTS secondary to BPH (L.I.F.T.)

⁴ Comparison of the UroLift System to TURP for Benign Prostatic Hyperplasia (BPH-6) - NCT01533038

TURP with PUL with 3-month follow-up data. Therefore, indirect comparisons to 3 months was constructed for TUWA versus PUL (via Sham) and TUWA versus TURP, via a two-step indirect comparison as per the visual presentation of the network provided in Figure 3. The key features of the three studies is shown in Table 3.

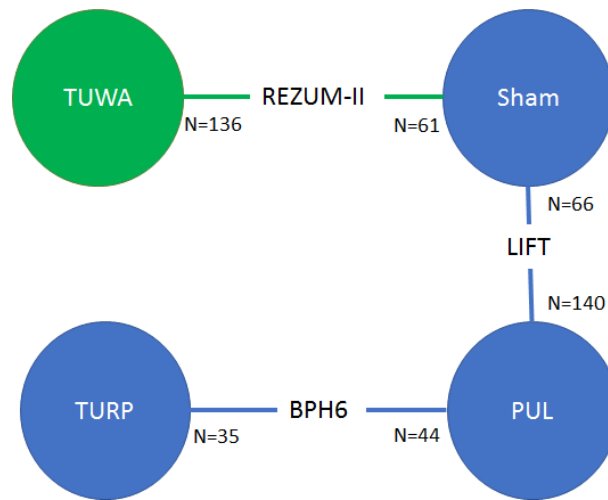


Figure 3 Network of studies for the indirect comparisons

Abbreviations: PUL = prostatic urethral lift; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation.
Source: Figure 3, p19 of the ADAR.

Table 3 Key features of the included evidence

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
Rezum II TUWA v Sham (McVary et al., 2016b) (McVary et al., 2016a, Roehrborn et al., 2017b, McVary and Roehrborn, 2018, McVary et al., 2019)	197 136 TUWA v 61 sham	MC, R, DB until 3 months (patients and assessors), CO, 4 years	Some concerns	Men aged ≥ 50 years with moderate to severe LUTS secondary to BPH, no prior invasive prostate procedures, prostate volume 30 to 80cm ³ , IPSS ≥ 13 , Q _{max} 5 to 15ml/s for voided volume of at least 125ml. <u>Washout from medical treatment</u> 4 weeks: α -blockers, anticholinergics, daily doses of phosphodiesterase-5 inhibitors 3 months: estrogen, androgen-suppressing drugs, anabolic steroids, type II 5 α -reductase inhibitors 6 months: dual 5 α -reductase inhibitors. Medication for LUTS or ED were prohibited for the duration of the study.	<u>Effectiveness outcomes</u> IPSS, QoL, Q _{max} , BPHII, IIEF-15, MSHQ-EjD, incontinence (OAB-q SF and ICS male IS-SF), VAS, PSA <u>Safety outcomes</u> De novo sexual dysfunction, ejaculatory function, acute and late adverse events
L.I.F.T PUL v Sham (Cantwell et al., 2014, McVary et al., 2014, Roehrborn et al., 2017a, Roehrborn et al., 2013, Roehrborn et al., 2015a, Roehrborn et al., 2015b, Rukstalis et al., 2016)	206 140 PUL v 66 sham	MC, R, DB until 3 months (patients and assessors), CO, 5 years	Some concerns	Men aged ≥ 50 years with no prior surgical treatment for BPH, AUASI ≥ 13 , Q _{max} ≤ 12 ml/s for 125ml voided volume, prostate volume 30 to 80cm ³ . <u>Washout from medical treatment</u> 3 days: anticoagulants 2 weeks: α -blocker 3 months: 5 α -reductase inhibitor	<u>Effectiveness outcomes</u> AUASI, QoL, BPHII, IIEF, MSHQ-EjD, MSHQ-Bother, Q _{max} , PVR, IPSS, HRQL, SHIM <u>Safety outcomes</u> Adverse events, de novo sustained ED and anejaculation
BPH6 PUL v TURP (Gratzke et al., 2017, Sonksen et al., 2015)	91 45 PUL v 35 TURP	MC, R, OL, 2 years	High	Men aged ≥ 50 years, IPSS > 12 ; Q _{max} ≤ 15 ml/s for 125ml voided volume, PVR < 350 ml, prostate volume ≤ 60 cm ³ on ultrasound, sexually active within 6 months of the procedure, SHIM > 6 , positive response to MSHQ-EjD (excluding "could not ejaculate"), incontinence severity index score ≤ 4 .	<u>Effectiveness outcomes</u> IPSS, QoR VAS, SHIM, MSHQ-EjD, ISI score <u>Safety outcomes</u> Adverse events (severity measured on the Clavien-Dindo classification system)

Abbreviations: AUASI = American Urological Association Symptom Index; BPH = benign prostatic hyperplasia; BPHII = benign prostatic hyperplasia Impact Index; CO = cross over; DB = double blind; ED = erectile dysfunction; HRQL: Health Related Quality of Life; ICS male IS-SF = International Continence Society Male Incontinence Scale Questionnaire-Short Form; IIEF-EF = International Index of Erectile Function erectile function domain; IPSS = International Prostate Symptom Score; ISI = incontinence severity score; L.I.F.T. = Luminal Improvement Following Prostatic Tissue approximation for the treatment of LUTS secondary to BPH; LUTS = lower urinary tract symptoms; MC = multi-centre; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction; OAB-q SF = Overactive Bladder Questionnaire-Short Form; OL = open label (unblinded); PSA = prostate specific antigen; PUL = prostatic urethral lift; PVR = post-void residual volume; Qmax = peak urinary flow; QoL = quality of life; QoR-VAS = quality of recovery visual analogue scale; R = randomised; SHIM = Sexual Health Inventory for Men; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation; VAS = visual analogue scale.

Source: Table 13, p38 of the commentary.

TUWA versus PUL

For the indirect comparison between TUWA and PUL, comparative data was available at 3 months for the following safety outcomes: procedure related adverse events (AEs), serious procedure related adverse events, serious adverse events, dysuria, haematuria, pelvic pain/discomfort, urinary urgency and urinary retention.

The ADAR acknowledged that the indirect safety assessment between TUWA and PUL was compromised due to differences in the conduct and reporting of AEs between the studies, and discrepancies in event rates in the common reference arm. However, based on the safety outcomes evaluated, the ADAR found no statistically significant differences in terms of the relative risk of an event between TUWA and PUL, supporting the ADAR claim of non-inferiority between TUWA and PUL with respect to safety.

The commentary considered the claim of non-inferior safety of TUWA compared with PUL to be appropriate.

TUWA versus TURP

The ADAR found the indirect comparison of TUWA and TURP was not feasible due to disparities in the time of event reporting between studies (3 versus 12 months), the use of the Clavien-Dindo grading system in the BPH6 study, as well as differences in the invasiveness of the TURP procedure compared with TUWA. Therefore, it was not appropriate to statistically compare rates of specific adverse events for TUWA and TURP.

The ADAR claimed direct evidence from the BPH6 study demonstrated a greater rate of treatment related AEs in the TURP arm relative to PUL, including bleeding, erectile dysfunction and retrograde ejaculation. Erectile dysfunction and retrograde ejaculation events were not reported in the TUWA and PUL arms of REZUM-II and LIFT studies at 3 months. From this information, the ADAR inferred that TUWA is associated with a different safety profile relative to TURP, consistent with the minimally invasive nature of the procedure. On this basis, the ADAR inferred that TUWA is at least non-inferior to TURP with respect to safety.

The commentary agreed that formal indirect comparison of the safety outcomes was not appropriate but noted that both non-serious and serious procedure related AEs (summarised in Table 4) occurred at a higher rate following TURP compared to TUWA: non-serious AEs were reported in 74% TURP patients versus 38% TUWA patients; serious AEs were reported in 14% TURP patients versus 1.5% TUWA patients. The commentary considered a finding of superior safety for TUWA compared to TURP may be more appropriate. Therefore, the applicant's claim of non-inferior safety for TUWA compared to TURP appeared to be a conservative approach.

The pre-MSAC response acknowledged that it may be reasonable to expect a more favourable safety profile for TUWA compared to TURP due to the minimally invasive nature of the TUWA procedure. However, the applicant claimed that the comparative evidence is not compelling enough to be able to conclusively claim superiority in favour of TUWA with respect to safety. The applicant reiterated their claim that TUWA has non-inferior, albeit different, safety relative to TURP. The applicant considered this claim appropriate and conservative in the context of formal statistical indirect comparisons being infeasible.

Table 4 Adverse events for TUWA versus TURP (up to 12 months follow-up)

Event	TUWA				TURP	
	0-3 months		3-12 months		0-12 months	
	N (events)	N (patients) (%)	N (events)	N (patients) (%)	N (events)	N (patients) (%)
All non-serious AEs	164	59 (43.4)	50	29 (21.3%)	NR	NR
All procedure related AEs	138	52 (38.2)	10	8 (5.9%)	Grade 1: 79 Grade 2: 5	Grade 1: 26 (74.0%) Grade 2: 4 (11.0%)
Dysuria	23	23 (16.9)	1	1 (0.7%)	NR	NR
Haematuria, gross	16	16 (11.8)	0	0 (0.0%)	NR	NR
Haemospermia	10	10 (7.4)	0	0 (0.0%)	NR	NR
Urinary frequency	8	8 (5.9)	0	0 (0.0%)	NR	NR
Urinary urgency	8	8 (5.9)	0	0 (0.0%)	NR	NR
Decrease in ejaculatory volume	4	4 (2.9)	3	2 (1.5%)	NR	NR
Urinary retention	5	5 (3.7)	0	0 (0.0%)	0	0 (0.0%)
UTI, suspected	6	5 (3.7)	0	0 (0.0%)	NR	NR
Anejaculation	4	4 (2.9)	0	0 (0.0%)	NR	NR
Epididymitis	4	4 (2.9)	0	0 (0.0%)	2	2 (6.0%)
UTI, culture proven	4	4 (2.9)	0	0 (0.0%)	3	2 (6.0%)
Pain/discomfort of the pelvis	4	4 (2.9)	0	0 (0.0%)	39	21 (60.0%)
Bleeding (Grade 1)	NR	NR	NR	NR	20	20 (57.0%)
Urinary incontinence	NR	NR	NR	NR	6	6 (17.0%)
Erectile dysfunction	NR	NR	NR	NR	3	3 (9.0%)
Retrograde ejaculation	NR	NR	NR	NR	7	7 (20.0%)
Other	NR	NR	NR	NR	4	3 (9.0%)
All serious AEs	8	7 (5.1)	11	9 (6.6%)	NR	NR
All procedure related serious AEs	3	2 (1.5)	0	0 (0.0%)	Grade 3a: 0 Grade 3b: 5	Grade 3a: 0 (0.0%) Grade 3b: 5 (14.0%)
Bleeding (Grade 3b)	NR	NR	NR	NR	2	2 (6.0%)
Stricture (meatal, urethral, bladder neck) (Grade 3b)	NR	NR	NR	NR	1	1 (3.0%)

Note: For the purpose of this summary, Grade 1 and 2 adverse events according to the Clavian-Dindo Classification were considered non-serious adverse events and Grade 3 were considered serious adverse events.

Abbreviations: AE = adverse event; NR = not reported; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation; UTI = urinary tract infection.

Source: Table 17, p44 of the commentary.

11. Comparative effectiveness

TUWA versus PUL

For the key patient-relevant outcome, International Prostate Symptom Score (IPSS) which assesses severity and frequency of urinary symptoms secondary to BPH, the ADAR found no statistically significant difference in the indirect treatment effect between TUWA and PUL (indirect mean difference: -1.7, 95%CI: -4.8, 1.4). Based on an established minimally important clinical difference (MCID) of three points for IPSS, the upper bound of the 95%CI of 1.4 was within the margin of non-inferiority. The ADAR stated this supported the claim of

non-inferior effectiveness of TUWA relative to PUL with respect to improvements in urological symptoms.

The ADAR also found no statistically significant differences between TUWA and PUL in terms of key secondary outcomes including post-void residual volume (PVR), IPSS-quality of life (IPSS-QoL), BPH- Impact Index (BPH-II), Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD); whilst improvements in peak urinary flow (Qmax) statistically favoured TUWA. The ADAR claimed this supported the non-inferiority of TUWA relative to PUL with respect to improvements in objective measures of urinary function, improvements in BPH-specific QoL indicators and preservation of ejaculatory function. The ADAR acknowledged that the 95% CIs slightly fell outside the margin of non-inferiority for IPSS-QoL (0.5 points) and BPH-II (1 point), despite point estimates being close to zero. The ADAR claimed the wide 95% CIs should be interpreted within the context of the indirect nature of the comparison.

The ADAR claimed a naive comparison of retreatment rates demonstrated that the proportion of subjects who received medical and surgical retreatment for BPH within 4 years of their index procedure was lower in the TUWA arm of REZUM-II (**redacted%** and **redacted%**, respectively) compared with the PUL arm of LIFT (9.3% and 13.6%, respectively). Furthermore, a *post-hoc* life-table analysis of retreatment rates by Tallman (in press) found that the proportion free of retreatment through 4 years was significantly higher for TUWA treated subjects relative to PUL (**redacted%** vs. **redacted%**; log-rank $p = \text{redacted}$). The ADAR claimed this indicated a potentially greater durability of effect for TUWA relative to PUL over the long-term.

The benefits and harms of TUWA, relative to PUL, and as measured by the critical patient-relevant outcomes are summarised in Table 5.

Table 5 Balance of clinical benefits and harms of TUWA, relative to PUL, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Indirect treatment difference (95%CI)	TUWA versus sham (95%CI)	PUL versus sham (95%CI)	Comments
IPSS – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊕⊖	-1.7 (-4.805, 1.405)	-6.90 (-9.05, -4.75)	-5.20 (-7.44, -2.96)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring TUWA. Upper 95%CI within established NIM of 3, supporting non-inferiority in IPSS between TUWA and PUL.
Qmax – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	3.4 (1.165, 5.635)	5.70 (4.10, 7.30)	2.30 (0.74, 3.86)	Results are statistically significant in favour of TUWA relative to PUL.
PVR – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	-30.3 (-62.050, 1.450)	-17.80 (-40.43, 4.83)	12.50 (-9.77, 34.77)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring TUWA, however disparity in treatment effects in common sham arms biases results in favour of TUWA.
IPSS-QoL – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	0 (-0.658, 0.658)	-1.20 (-1.66, -0.74)	-1.20 (-1.67, -0.73)	No statistically significant difference evident (95%CI of the ITE crosses 0). Upper 95%CI marginally falls outside of the NIM of +0.5 previously applied in literature, largely due to the indirect nature of comparison.
BPH-II – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	-0.1 (-1.458, 1.258)	-1.90 (-2.86, -0.94)	-1.8 (-2.76, -0.84)	No statistically significant difference evident (95%CI of the ITE crosses 0), numerically favouring TUWA. Upper 95%CI marginally falls outside of the NIM of +1 previously applied in literature, largely due to the indirect nature of comparison.
MSHQ-EjD EF – 3 months	K=2, N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	-0.16 (-1.632, 1.312)	0.34 (-0.84, 1.52)	0.50 (-0.38, 1.38)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring PUL. The lower bound of the 95%CI was within the NIM of -2 previously applied in literature, supporting non-inferiority.
Free from retreatment through 4 years	K=2; N=275; naive comparison	⊕⊖⊖⊖	Difference: redacted %; log-rank p = redacted	redacted %	redacted %	The proportion of patients free from retreatment through 4 years was significantly higher with TUWA relative to PUL.
All related AEs	K=2; N=403 – One-step ITC of RCTs	⊕⊕⊖⊖	1.462 (0.611, 3.499)	3.89 (1.77, 8.56)	2.66 (1.83, 3.87)	No statistically significant difference evident (95%CI of the ITE crosses 1).

Abbreviation: BPH-II = benign prostatic hyperplasia Impact Index; CI = confidence interval; EF = ejaculatory functioning; IPSS = International Prostate Symptom Score; IPSS-QoL = International Prostate Symptom Score-Quality of Life; ITC = indirect treatment comparison; ITE = indirect treatment effect; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NIM = non-inferiority margin; PUL = prostatic urethral lift; PVR = post-void residual volume; Qmax = Peak urinary flow rate; RCT = randomised controlled trial; TUWA = transurethral water vapour ablation.

^a GRADE Working Group grades of evidence (Guyatt 2013); See evidence profile (Appendix C) for reasons for quality of evidence grading
 ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 2, p20 of the ADAR.

The commentary noted the long-term data comparing TUWA and PUL is subject to greater uncertainty and a higher risk of bias due to the use of a single-arm study design for these results. However, the commentary considered the comparison between TUWA and PUL, using short- and long-term data, supported the finding of non-inferior effectiveness.

The pre-ESC response claimed that five-year results from the REZUM-II trial, published since the lodgement of the ADAR, support the sustained efficacy of TUWA, with a mean reduction from baseline of 10.4 points in IPSS and an improvement of 4.3 mL/sec in maximum urinary flow rate (McVary 2020). The applicant highlighted that the surgical retreatment rate of 4.4% in the TUWA arm of the REZUM-II remained consistent between years 4 and 5 post-procedure (McVary 2020). The applicant also referred to a recently published systematic review by Miller (2019; n=200) which estimated the annual rate of surgical reintervention after PUL to be 6.0% per year (95% CI: 3.0% to 8.9%), with higher annual reinterventions rates observed in studies with longer follow up (4.3% per year with ≤ 1 year mean follow-up versus 10.7% per year with 1-3 years follow up, p=0.04).

TUWA versus TURP

The ADAR found no statistically significant difference in the indirect treatment effect between TUWA and TURP (mean difference: -1.6, 95%CI: -6.8, 3.6) for the key patient-relevant outcome evaluating urological symptoms, IPSS.

The ADAR also found no statistically significant differences between TUWA and TURP in terms of key secondary outcomes including PVR, IPSS-QoL and BPH-II and claimed this supported the non-inferiority of TUWA relative to TURP. However, improvements in Qmax statistically favoured TURP. The ADAR noted the results for the ejaculatory function score on the MSHQ-EjD statistically favoured TUWA relative to TURP and suggested this demonstrated that TUWA preserved ejaculatory function.

The ADAR noted that retreatment rates beyond 24 months were not available from the BPH6 study, which limited a comparative assessment of durability over the longer term. However, the ADAR claimed a slightly greater proportion of subjects had undergone surgical retreatment in the TURP arm of BPH6 relative to the TUWA arm of REZUM-II at 24 months (5.7% versus **redacted**%) which supported the durability of effect of TUWA relative to TURP.

The benefits and harms of TUWA, relative to TURP, and as measured by the critical patient-relevant outcomes are summarised in Table 6.

Table 6 Balance of clinical benefits and harms of TUWA, relative to TURP, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Indirect treatment difference (95%CI)	TUWA versus PUL, via sham (95%CI)	TURP versus PUL (95%CI)	Comments
IPSS – 3 months	K=3 (N=494) ITC of RCTs	⊕⊙⊙⊙	-1.6 (-6.783, 3.583)	-1.7 (-4.8, 1.4)	-0.1 (-4.2, 4.1)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring TUWA. Upper 95%CI falls outside of the established NIM of +3, however, wide CIs largely results from multi-step indirect comparison.
Qmax – 3 months	K=3 (N=494) ITC of RCTs	⊕⊕⊙⊙	-5.8 (-10.469, -1.131)	3.4 (1.165, 5.635)	9.2 (5.1, 13.3)	Results are statistically significant in favour of TURP relative to TUWA
PVR – 3 months	K=3 (N=494) ITC of RCTs	⊕⊕⊙⊙	10.3 (-34.779, 55.379)	-30.3 (-62.050, 1.450)	-40.6 (-72.6, -8.6)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring TURP.
IPSS-QoL – 3 months	K=3 (N=494) ITC of RCTs	⊕⊙⊙⊙	-0.3 (-1.375, 0.775)	0 (-0.658, 0.658)	0.3 (-0.6, 1.1)	No statistically significant difference evident (95%CI of the ITE crosses 0), numerically favouring TUWA. Upper 95%CI marginally falls outside of the NIM of +0.5 previously applied in literature, largely due to the multi-step indirect nature of comparison
BPH-II – 3 months	K=3 (N=494) ITC of RCTs	⊕⊕⊙⊙	-1.5 (-3.637, 0.637)	-0.1 (-1.458, 1.258)	1.4 (-0.3, 3.0)	No statistically significant difference evident (95%CI of the ITE crosses 0) numerically favouring TUWA. Upper 95%CI within nominated NIM of 1, supporting non-inferiority between TUWA and PUL.
MSHQ-EjD EF – 3 months	K=3 (N=494) ITC of RCTs	⊕⊕⊙⊙	3.54 (1.057, 6.023)	-0.16 (-1.632, 1.312)	-3.7 (-5.7, -1.7)	Results are statistically significant in favour of TUWA relative to TURP.

Abbreviations: BPH-II = benign prostatic hyperplasia Impact Index; CI = confidence interval; EF = ejaculatory functioning; IPSS = International Prostate Symptom Score; IPSS-QoL = International Prostate Symptom Score-Quality of Life; ITC, indirect treatment comparison; ITE = indirect treatment effect; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NIM = non-inferiority margin; PUL = prostatic urethral lift; PVR = post-void residual volume; Qmax = Peak urinary flow rate; RCT = randomised controlled trial; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation.

^a GRADE Working Group grades of evidence (Guyatt 2013); See evidence profile (Appendix C) for reasons for quality of evidence grading.
⊕⊕⊕⊕ High quality: We are very confident that the true effect lies close to that of the estimate of effect. **⊕⊕⊕⊙ Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **⊕⊕⊙⊙ Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. **⊕⊙⊙⊙ Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 3, p22 of ADAR.

The commentary did not consider a finding of non-inferior effectiveness between TUWA and TURP to be appropriate. The commentary noted that TURP appears to be associated with improved IPSS over 24 months (results from a naïve comparison) and QMax (results from the indirect and naïve comparisons). Conversely, TURP is associated with worse ejaculatory function scores over 24 months.

Clinical claim

The ADAR claimed that:

- relative to PUL, TUWA is non-inferior with respect to effectiveness and safety.
- relative to TURP, TUWA is non-inferior with respect to efficacy and safety.

12. Economic evaluation

Based on a clinical claim of non-inferior safety and effectiveness of TUWA versus PUL and TURP, the ADAR presented a cost comparison to illustrate the relative cost of conducting TUWA compared to PUL and TURP in treating BPH.

The commentary considered this approach to be acceptable if MSAC accepts the non-inferiority claim. The commentary did not consider the finding that TUWA has non-inferior safety and effectiveness compared to TURP to be appropriate.

The pre-MSAC response maintained that TUWA has non-inferior safety and effectiveness compared to TURP and therefore claimed the cost comparison analysis provided is the most appropriate approach to the economic evaluation.

Table 7 Summary of the economic evaluation

Perspective	Healthcare system
Comparator	PUL (primary) and TURP (secondary)
Type of economic evaluation	Cost comparison
Sources of evidence	<u>Outcomes</u> : REZUM-II, LIFT, BPH6 studies <u>Costs</u> : MBS, PHDB, PL and Whitty (2013) ^a
Software packages used	Microsoft Excel Office 365 MSO

Abbreviations: MBS = Medicare Benefits Scheme; PL = Protheses List; PUL = prostatic urethral lift; TURP = transurethral resection of the prostate; Source: Table 4, p24 of the ADAR.

The commentary noted that PUL and TUWA were assumed to be same day procedures, whereas TURP included overnight hospital stay in the ADAR cost model. The commentary stated this assumption is not valid where catheterisation is used for TUWA procedures, as catheterised patients will be admitted for the period in which the catheter is in place. For example, in the REZUM-II trial, catheterization immediately after the procedure was at the discretion of the physician with 90.4% (122 of 135) of patients being catheterized for a mean 3.4 days. The study reported 68% (83 of 122) of the catheterizations. The applicability of catheterisation to the patient population and implications for the costing model were not described.

The pre-ESC response acknowledged a proportion of TUWA patients will require a catheter and an overnight hospitalisation but claimed catheterisation does not necessitate an overnight hospitalisation. The Brisbane Urology Clinic⁵ notes TUWA is performed as day surgery at their clinic, with patients receiving a catheter post procedure and subsequently recovering at home. The applicant maintained the median TUWA (and PUL) procedure is expected to be a same day procedure, irrespective of catheter use.

The disaggregated results of the cost comparison are provided in Table 8. The ADAR stated TUWA procedures are estimated to cost **\$redacted**, compared to \$5,189 for PUL procedures and \$5,373 for TURP procedures. As such, TUWA is claimed to provide cost savings of

⁵ <https://brisbaneurologyclinic.com.au/procedures-we-perform/rezum-water-vapour-therapy/>

\$redacted per procedure compared with PUL and cost savings of **\$redacted** per procedure compared to TURP.

Table 8 Cost comparison: TUWA versus PUL and TURP

Row	Cost category	TUWA	PUL	TURP	Source / calculation
A	Medical service costs	\$1,023	\$550	\$1,300	Table 72 of the ADAR
B	Consumables cost	\$redacted	\$0	\$412	Table 74 of the ADAR
C	Capital costs	\$redacted	\$0	\$0	Table 75 of the ADAR
D	Hospital stay	\$1,293	\$1,293	\$3,662	Table 77 of the ADAR
E	Prostheses	\$0	\$3,346	\$0	Table 78 of the ADAR
F	Total	\$redacted	\$5,189	\$5,373	A+B+C+D+E
G	Incremental cost of TUWA		\$redacted	\$redacted	Calculated

Source: Table 5, p24 of the ADAR.

The major cost difference was associated with average length of hospital stay for TURP and number of devices per PUL procedure. The commentary noted it is reasonable to expect that minimally invasive procedures would reduce hospital costs.

Sensitivity analyses

The ADAR sensitivity analyses indicated that the primary uncertainties in the cost comparison analysis related to hospitalisation costs across all procedures, capital costs associated with TUWA and device use associated with PUL.

The commentary noted the sensitivity analyses showed cost rankings are relatively robust to changes in key assumptions. A reduction in TURP length of stay to **redacted** results in TURP being less costly than TUWA.

The commentary presented additional sensitivity analyses for the number and cost of loops used in TURP and the use of MBS item 37207 (\$880.30). The commentary noted that these had no impact on the cost ranking of procedures but changed cost differences to varying degrees. If only **redacted** Urolift devices were used per PUL procedure, then PUL would be less costly than TUWA. These estimates differ considerably to base values for TURP length of stay and Urolift devices per procedure included in the cost comparison model.

Table 9 presents the sensitivity analyses conducted by the ADAR and commentary around key drivers of the cost comparison.

Table 9 Sensitivity analysis

	Incremental cost of TUWA	
	TUWA versus PUL	TUWA versus TURP
Base case	\$redacted	\$redacted
TURP hospitalisation costs		
ALOS for TURP = 1 day (Base case: 2 days)	\$redacted	\$redacted
ALOS for TURP = 3 days (Base case: 2 days)	\$redacted	\$redacted
TUWA capital costs		
Procedures per device per year = 10 (Base case: 50)	\$redacted	\$redacted
Portable generator life span = 5 years (Base case: 10 years)	\$redacted	\$redacted
PUL prostheses costs		
Urolift devices per procedure = 3 (Base case: 4.7)	\$redacted	\$redacted
Urolift devices per procedure = 4 (Base case: 4.7)	\$redacted	\$redacted
Urolift devices per procedure = 5 (Base case: 4.7)	\$redacted	\$redacted
MBS item 37207 \$880.30. (Base case: TUNA MBS \$842.10)	\$redacted	\$redacted
No. of loops/fibres used per TURP patient = 1 (Base case: 1.13)	\$redacted	\$redacted
Cost per loop used per TURP patient = \$402 (Base case: \$365 per loop)	\$redacted	\$redacted
MBS fee for TUWA equivalent to fee for VLAP (\$1058).	\$redacted	\$redacted

Abbreviations: ALOS = average lengths of stay; MBS = Medicare Benefits Scheme; PUL = prostatic urethral lift; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate; TUWA = transurethral water vapour ablation.

Source: Table 66, p88 of the commentary.

The commentary noted the key drivers of the economic model include average length of hospital stay for TURP and Urolift devices per procedure (Table 10).

Table 10: Key drivers of the economic model

Description	Method/Value	Impact
ALOS for TURP	Average length of stay is varied between 1 and 3 days for TURP.	High. Reductions in the average length of stay favours the comparator. TUWA is more costly than TURP at an average stay of redacted day for TURP. Changes in this variable changed intervention cost ranking.
Urolift devices per procedure	An average of 4.7 Urolift devices per procedure was assumed in the base case (from the BPH6 trial). It was increased to 5 and reduced to 3 in the sensitivity analysis provided with the ADAR	High. The Urolift device was estimated to cost \$712, which is a large component of total PUL cost. Increases or decreases in devices per procedure have large cost impacts. A reduction to redacted devices per procedure changed procedure cost ranking, with PUL less expensive than TUWA. Based on trial results, only a small proportion of PUL patients would receive 3 devices per procedure
Cost per loop used per TURP patient	The cost per loop of \$365 was taken the Whitty (2014) study. The study is 8 years old, so the cost is increased by 10% to account for inflation.	Moderate. The increase to \$402 per loop has a moderate impact on cost, given the relative cost per loop is significant. It did not change intervention cost ranking.

Abbreviations: ALOS = average length of stay; PUL = prostatic urethral lift; TURP = transurethral resection of the prostate, TUWA = transurethral water vapour ablation.

Source: Table 67, p88 of the commentary.

13. Financial/budgetary impacts

The ADAR used a market share approach to estimate the financial implications of listing TUWA for BPH on the MBS. The ADAR considered this appropriate, stating the BPH market is a mature MBS market with several treatment options currently available and TUWA is expected to wholly substitute from existing services (i.e. no increase to the BPH market). The financial implications to the MBS resulting from the proposed listing of TUWA are summarised in Table 11.

Table 11 Total costs to the MBS associated with TUWA

Row	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
Intervention (TUWA)		-	-	-	-	-
A	Number of services	redacted	redacted	redacted	redacted	redacted
B	Total cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
C	-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
D	-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Substituted services		-	-	-	-	-
E	Number of services	redacted	redacted	redacted	redacted	redacted
F	Total cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
G	-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
H	-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net financial impact						
I	Total cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
J	-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
K	-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Table 6, p24 of the ADAR.

The ADAR estimated the net financial cost to the MBS by substituting the proposed cost of TUWA (Fee, \$842.10, 75% rebate \$631.60) for TURP (Fee, \$1,058.80, 75% rebate \$794.10) and PUL (Fee, \$328.55, 75% rebate \$246.45). Based on **redacted** TUWA services

substituting for **redacted** TURP and **redacted** PUL services in Year 1, the net cost to the MBS was estimated to be **\$redacted** in this year. It increased to **\$redacted** in Year 5.

The commentary noted that the increased cost to the MBS reflects the higher MBS fee for TUWA compared to PUL.

The commentary also noted that the ADAR estimated **redacted** TUWA procedures in Year 1 increasing to **redacted** by Year 5 by applying uptake rates of **redacted%**, **redacted%**, **redacted%**, **redacted%** and **redacted%** based on current use of MBS item 37201 and assumptions about TURP/PUL substitution (Table 12). However, the commentary found it was not clear how these estimates were derived, which reflect more than **redacted%** increase in TUWA procedures over 5 years. No details were provided about the clinical capacity to perform this volume of procedures, what training would be needed (and associated costs) and BPH characteristics of the Australian patient population to support substitution assumptions (prostate size, IPSS score, suitability for TURP verse minimally invasive procedures). As such, there is considerable uncertainty about uptake estimates and presented sensitivity analyses.

Table 12 Use and cost estimates for TUWA

Row	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Source / calculation
A	BPH treatment market	redacted	redacted	redacted	redacted	redacted	Figure 25 of the ADAR
B	Uptake of TUWA, %	redacted%	redacted%	redacted%	redacted%	redacted%	Assumption
C	Est. TUWA utilisation	redacted	redacted	redacted	redacted	redacted	A*B
D	MBS fee	\$842.10	\$842.10	\$842.10	\$842.10	\$842.10	Proposed
E	Total cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	C*D
F	-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	C*\$631.60
G	-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	E-F

Source: Table 87, p161 of the ADAR.

In regards to the substitution assumptions used in the ADAR, the applicant clarified that the applied assumptions regarding substitution are based on current trends in BPH treatment use. The applicant maintained the applied substitution rates are reasonable, and alternative substitution rates are not expected to significantly impact the expected financial impact of TUWA.

The ADAR included sensitivity analyses for the key uncertainties in the budget impact analysis: TUWA uptake rates and the distribution of substitution between existing services (Table 13).

An increased uptake from **redacted%** Y1 to **redacted%** Y3 had a greater impact than the substitution scenario of TURP **redacted%** and PUL **redacted%**. The commentary included sensitivity analyses on higher growth rate in BPH services and differing MBS item cost for TUWA (MBS Item37207, \$880.30). Changes in these assumptions had limited impact on net MBS benefits.

Table 13 Total costs to the MBS associated with listing TUWA for BPH

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	-	-	-	-	-
TUWA services	redacted	redacted	redacted	redacted	redacted
Net cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Increased uptake (10% Y1 to 20% Y3)					
TUWA services	redacted	redacted	redacted	redacted	redacted
Net cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Substitution based on current market shares: Open prostatectomy 0.6% TUNA 1.8% TURP 67.5% Greenlight 15.6% TUMT 0.9% HoLEP 5.9% PUL 7.7%					
TUWA services	redacted	redacted	redacted	redacted	redacted
Net cost of services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
-MBS costs (75% rebate)	\$redacted	\$redacted	-\$redacted	\$redacted	\$redacted
-Co-payments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Higher growth rate (3%)					
-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
MBS Item for 37207 (\$880.30)					
-MBS costs (75% rebate)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Table 74, p95 of the commentary.

The commentary noted that the estimates did not include state and territory government costs in the budget impact analysis as most services would be provided in private hospitals.

Table 14 Net cost to the Protheses List of listing the Rezūm disposable delivery device

Row	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Source / calculation
A	TUWA procedures	redacted	redacted	redacted	redacted	redacted	Table 83 of the ADAR
B	Cost per Rezūm disposable delivery device	\$1,950	\$1,950	\$1,950	\$1,950	\$1,950	Applicant
C	Total cost to the PL	\$1,205,191	\$1,406,623	\$1,615,371	\$1,831,435	\$1,868,013	A*B
D	Substituted of PUL procedures	redacted	redacted	redacted	redacted	redacted	Table 85 of the ADAR
E	Urolift systems per PUL procedure	4.7	4.7	4.7	4.7	4.7	BPH6 study ^a
F	Total substitution of Urolift systems	redacted	redacted	redacted	redacted	redacted	D*E
G	Cost per Urolift system	\$712	\$712	\$712	\$712	\$712	PL billing code: TX055
H	Substituted TURP procedures	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	F*G
I	Net cost to the PL	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	C-H

Abbreviations: BPH = Benign prostatic hyperplasia; MBS = Medical Benefits Scheme; PL = protheses list; PUL = prostatic urethral lift; TUWA = Transurethral water vapour ablation.

^a As applied in the cost comparison.

Source: Table 87, p164 of the ADAR.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Implementation of MBS Review Taskforce recommendation	ESC noted the MBS taskforce review recommended MBS item 37207 (for VLAP) be repurposed as a new item for ‘ablative procedures of the prostate for BPH’ including by laser, electrocautery, high energy microwave or RF energy. If this recommendation proceeds, TUWA could be captured by this item (albeit at a higher MBS fee than proposed in this application).
Item descriptor	Whether there is a need for additional retreatment operation item number (within 10 days). Whether the item descriptor should include the specification for treatment of benign prostatic hyperplasia in patients with moderate to severe lower urinary tract symptoms.
Comparator	VLAP and HoLEP may also have been appropriate additional comparators.
Evidence for non-inferiority	Only indirect treatment comparisons are available; there are no phase 3 head-to-head data. Overall, ESC considered TUWA is likely non-inferior to PUL in terms of effectiveness and safety in both short and longer term. TUWA is likely inferior to TURP with respect to longer term effectiveness (although non-inferior in the short term) and has a different, and possibly superior, safety profile to TURP.
Cost of consumables	The out-of-pocket costs for patients for consumables could be up to \$redacted .
Prostheses List	The applicant should confirm if it has received any advice from the Prostheses List Advisory Committee on the suitability of the Rezūm device for inclusion on the Prostheses List or if it has a submission to the PLAC in-train.
Economic evaluation	The cost comparison may not be appropriate given the difference in effectiveness. Although TUWA appears less expensive than TURP it is not clear if the price differential appropriate captures the difference in effectiveness. The absence of a cost comparison with VLAP may be problematic as it is possible that TUWA may be dominated by VLAP.
Financials	The claimed save to the MBS may be overestimated.

ESC discussion

ESC noted that this application was requesting Medicare Benefits Schedule (MBS) listing of transurethral water ablation (TUWA), a minimally invasive procedure for the treatment of benign prostatic hyperplasia (BPH).

ESC noted that this procedure is currently being claimed under MBS item number 37201 for transurethral needle ablation (TUNA). ESC noted that TUNA involves direct radio-frequency (RF) ablation of the prostate whereas TUWA uses RF to generate steam (water vapour) to ablate the prostate. ESC recalled that the MBS Review Taskforce had recommended MBS item 37207 for visual laser ablation of prostate (VLAP) be repurposed for ablative procedures of the prostate for BPH including by laser, electrocautery, high energy microwave or RF, but noted that this had yet to be implemented. ESC noted further advice from the Department that the general ablative item will now only consolidate electrocautery and microwave ablative procedures into one item. VLAP and TUNA/TUWA will be retained as separate MBS services.

ESC noted that unlike the item descriptor for TUNA (MBS item 37201), the proposed MBS item for TUWA does not specify that the procedure is only for men who are not fit for transurethral resection of the prostate (TURP). ESC queried whether the proposed item descriptor should specify the treatment of BPH in patients with moderate to severe lower urinary tract symptoms (LUTS). ESC also queried whether an additional item number for a retreatment operation within 10 days is required.

ESC noted that MSAC had considered whether to include patient eligibility criteria in the MBS item for VLAP (level of symptoms, prostate size, use of anticoagulants) during its review of the fee for that procedure in March 2019 [MSAC 1518]. On that occasion, MSAC advised against including patient eligibility criteria in the item description.

ESC noted this application had progressed as an Applicant Developed Assessment Report (ADAR) via an expedited pathway (bypassing the PICO⁶ Advisory Sub-Committee [PASC]) using the PICO Confirmation from MSAC Application 1518 for endoscopic non-contact (side-firing) VLAP for benign prostatic hyperplasia. As such, the appropriate comparators for TUWA had not been considered by PASC.

ESC noted that the comparators presented for TUWA by the applicant were TURP and prostatic urethral lift (PUL). ESC considered that TURP is the gold standard for BPH treatment and is an appropriate comparator.

ESC noted that other comparative procedures shown in the clinical management algorithms, such as VLAP and holmium laser enucleation of the prostate (HoLEP), were also not included as comparators in the ADAR and may be appropriate comparators. ESC noted that TUNA is no longer recommended in international guidelines.

ESC noted that the clinical evidence is based on indirect treatment comparisons from three (3) randomised clinical trials (RCT): the REZUM-II study (TUWA vs. sham control), L.I.F.T study (PUL vs. sham control) and BPH6 study (PUL vs. TURP). Using the three RCT, the ADAR constructed indirect comparisons to 3 months for TUWA versus PUL (via sham) and TUWA versus TURP (via a two-step indirect comparison). ESC noted the indirect comparisons makes any conclusions regarding the comparative safety and effectiveness of TUWA uncertain. ESC also acknowledged the risk of bias in the L.I.F.T and REZUM-II studies due to the crossover treatment study design, resulting in un-blinding at 3 months and making long-term assessments less certain. ESC further noted the sources of bias for the BPH6 study included the lack of blinding and the use of a composite outcome.

ESC agreed with the commentary that the REZUM-II and L.I.F.T trials can be used for indirect comparison for TUWA vs. PUL as the sham control arms are similar, but the comparison is strongest up to 3 months, when the crossover occurred. ESC noted that quantitative statistical indirect treatment comparisons could not be performed for TUWA vs. TURP due to difference in grading classification used and timing of safety assessment (3 months vs 12 months) in the three RCTs.

ESC noted the differing conclusions regarding comparative for TUWA vs. TURP between the ADAR (TUWA has non-inferior safety), the commentary (TUWA has superior safety) and the pre-ESC response (TUWA has a different safety profile). ESC considered overall a conclusion of different, but likely superior safety for TUWA versus TURP may be reasonable.

⁶ Population, Intervention, Comparator and Outcome

ESC agreed with the ADAR and commentary that TUWA has non-inferior safety compared with PUL.

In terms of effectiveness, ESC considered that International Prostate Symptom Scores (IPSS) reported by the trials data were a key clinical outcome and noted that, at 3 months post-procedure, there were no statistically significant differences among the three procedures, supporting a clinical of non-inferior effectiveness in the short term (3 months). However, ESC noted that, at 24 months, TURP showed a greater improvement in IPSS from baseline than TUWA. ESC noted the differences in secondary outcomes: Qmax (mL/s) favoured TURP, but the ejaculatory function score (MSHQ-EJD) favoured TUWA. ESC agreed with the commentary's conclusion that the ADAR's claim that TUWA had non-inferior effectiveness compared to TURP was not appropriate in the long term. ESC also agreed with the ADAR and the commentary that TUWA has non-inferior effectiveness in the long term compared with PUL.

ESC noted that minimally invasive prostate procedures such as TUWA are not done without general anaesthesia in Australia. In addition, ESC noted that while a post-procedure urethral catheter is used in most TUWA patients, it does not require routine overnight hospital admission. However, ESC noted a suprapubic catheter may be required in some patients instead of a urethral catheter. ESC suggested the applicant comment on the need for, and costs associated with, a suprapubic catheter after TUWA in its response to MSAC. ESC considered this to be a significant adverse event that could require hospitalisation and which would subsequently affect the economic evaluation. Following the ESC meeting, the applicant clarified that suprapubic catheter insertions are not performed routinely with the TUWA procedure in Australia, unless in very rare circumstances. The applicant claimed indwelling urethral catheter is the standard approach to catheterisation in TUWA procedures in Australia.

ESC noted the submission presented a simple cost-comparison for the three procedures, but considered this may not be appropriate given that non-inferiority has not been established between all procedures. In addition, the cost-comparison did not include any reintervention costs or costs for adverse events or complications. Nonetheless, at the applicant's requested MBS fee of \$842.10, TUWA appears slightly less expensive than either PUL or TURP (see Table 8). If the MBS fee for TUWA were the same as the current fee for VLAP, TUWA remains modestly cost-saving (see Table 9). However, the absence of a comparison with VLAP means ESC could not advise MSAC on the comparative overall cost of VLAP versus TUWA. This is potentially problematic since MSAC has previously advised VLAP and TURP to be non-inferior in terms of effectiveness and safety. If VLAP is less expensive overall than TURP, it is possible that VLAP will also be less expensive than TUWA and that VLAP will dominate TUWA.

ESC noted that the applicant used a market share approach to support its claim that TUWA will be cost-saving to the MBS and the Prostheses List. The claimed save relies on cost-offsets if TUWA is substituted for PUL (cost-offsets of between \$redacted in year 1 and \$redacted in year 5, and is based on an assumption that redacted UroLifts® will be used per PUL procedure. However, ESC considered that the number of UroLift® devices used and the number of substitutions could be overestimated, thus also overestimating the overall cost savings (\$redacted in year 1 to \$redacted in year 5).

ESC also noted the financial impacts would need to be re-calculated if the Department proceeds with a generic listing for ablative procedures of the prostate for BPH.

ESC noted the potential for significant out-of-pocket costs for patients (up to \$redacted) associated with the use of the Rezūm device in TUWA. ESC noted the applicant indicated it wished to have Rezūm added to the PL, but ESC queried whether the Rezūm device qualifies as a prosthesis. ESC requested the applicant advise MSAC whether it has sought advice from the PLAC on the suitability of the Rezūm device for inclusion on the PL, or whether the applicant has an in-train application with the PLAC.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

TUWA is a minimally invasive procedure that can be conducted in 20min under local anaesthesia and no overnight hospital stay. TURP is the most frequent treatment option taking approximately 1 hour under general anaesthesia at an average length of stay of three days (median two days). MSAC considered TUWA has different but likely superior safety compared to TURP and short-term non-inferior efficacy. The long-term benefits of TUWA, including a sustained reduction of IPSS, are confirmed in 5-year results for the active treatment arm of the multicenter, randomized, controlled trial published in the Journal of Urology April 2020 (McVary KT, Roehrborn CG). The Applicant accepts the proposed holistic review of all treatments for BPH management including short and long-term outcomes. The Applicant agrees with MSAC's consideration that some patients may prefer TUWA as a treatment option over other treatment options as it appears to relieve symptoms of BPH in the short-term, the patient-reported outcomes are acceptable, and it is a quick and minimally invasive procedure. The Applicant considers the preservation of sexual function is an additional benefit of TUWA that may influence patient preference between treatment options. The Applicant looks forward to working with the DoH to ensure patient access to TUWA on the MBS.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)