Assessment report: MT413 Rezum

Document cover sheet

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Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. Please refer to NICE's Policy on managing interests for board members and employees.

None

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Rider on responsibility for report

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

Instructions for EAC:

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

The Assessment Report is an important component of the information available to the Medical Technologies Advisory Committee (MTAC) when developing its provisional and, following consultation, final recommendations on the technology.

The template should be completed with reference to the NICE 'Medical Technologies Evaluation Programme methods guide'. The headings and prompt questions in the template provide a consistent structure for the assessment of the company's submission but the assessment, format and presentation may be adapted by the EAC to maximise the clarity of the report.

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Contents

ABBREVIATIONS

Term	Definition
BPH	Benign prostatic hypertrophy
BPHII	Benign prostatic hyperplasia impact index
CI	Confidence interval
DHSC	Department of Health & Social Care
DSA	Deterministic sensitivity analysis
ED	Erectile dysfunction
EAC	External Assessment Centre
HES	Hospital episodes statistics
HIFU	High-intensity focused ultrasound
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICS	International continence score
ICER	Incremental cost-effectiveness ratio
IFU	Instructions for use
IPSS	International Prostate Symptom Score
IQR	Interquartile range
KoL	Key opinion leader
LoS	Length of stay
LUTs	Lower urinary tract symptoms
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NIHR	National Institute for Health Research
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient related outcome measure
QALY	Quality-adjusted life-year
QoL	Quality of life
QUORUM	Quality of Reporting of Meta-analyses
PSA	Probabilistic sensitivity analysis
RCT	Randomised Controlled Trial
SD	Standard deviation
TEAP	Transurethral ethanol ablation of the prostate
TUNT	Transurethral microwave thermotherapy
TUNA	Transurethral needle ablation
TUMT	Transurethral microwave therapy

TURis	Transurethral resection in saline
TURP	Transurethral resection of the prostate
TUVP	Transurethral vaporisation of the prostate
VAS	Visual Analogue Scale
Vs	Versus

Executive Summary

Rezum is a minimally invasive procedure that uses steam ablation in the treatment of men with symptomatic benign prostatic hyperplasia (BPH). Four studies, reported in 10 publications, were identified as relevant to the decision problem by both the company and EAC. The principal evidence was derived from the Rezum II trial (n = 197), which reported a comparison of Rezum with sham with outcomes at 3 months (McVary et al., 2016b), and single armed longitudinal data reported at 12 months (McVary et al., 2016b, McVary et al., 2016a), 24 months (Roehrborn et al., 2017c), 36 months (McVary and Roehrborn, 2018) and 48 months (McVary et al., 2019). Additionally, a prospective case series (n = 65) was identified reporting data at 12 months (Mynderse et al., 2015, Dixon et al., 2015) and 24 months (Dixon et al., 2016b), as well as two retrospective observational studies reporting data at 12 months (Darson et al., 2017) (n = 131) and 6 months (Mollengarden et al., 2018) (n = 127).

There was unequivocal evidence reported from the RCT that Rezum was associated with significant improvements in urinary flow (Qmax) and HRQoL compared with sham, with an IPSS reduction of 50% observed in the intervention arm compared with 20% in the sham arm. The observed improvement of around 10 IPSS points (minimally important difference 3 points) persisted throughout follow up to 4 years; an effect that was also consistently observed in the observational studies. Rezum was not associated with any peri-procedural adverse events, although there were 8 serious adverse events in 7 subjects reported at 0 to 3 months (5.1%). Rezum did not result in worsening of sexual function compared with sham, but there was limited evidence of deterioration compared with baseline over later time points. After 4 years, 45 patients had withdrawn from the Rezum II study (34%), of whom 6 had required reoperations (2 with repeat Rezum) and 7 were censored for using BPH medication.

Overall, the evidence base was supportive of Rezum being a safe and clinically effective treatment for BPH. There was an important gap in the evidence base in a lack of direct evidence comparing Rezum with other interventions. An indirect comparison with UroLift reported that Rezum was at least as effective in improving symptoms and urological outcomes, and required less reoperations. However, there was an absence of any evidence comparing Rezum with TURP, GreenLight laser, or HoLEP.

One cost-effectiveness study reported that Rezum dominated UroLift, but the EAC considered this study to be of poor methodological quality and lacked generalisability to the NHS.

The company reported a *de novo* cost-consequence analysis that incorporated a cohort Markov decision model with a time perspective of 4 years. It compared Rezum with TURP, UroLift, GreenLight laser and HoLEP. The main inputs informing the model were device cost, theatre time, hospital length of stay, non-serious and serious adverse events (AEs, including permanent incontinence), and the need for reoperation. One scenario analysis included the effect of erectile dysfunction (ED) in sexually active men.

The EAC appraised the model and validated it through replication in the programming language R. The model was clearly structured, transparently reported, and captured most of the important aspects of NHS health resource usage associated with the management of BPH. The main limitation of the model was that it assumed the technologies were equally effective, when this was unlikely to be the case. The model had key uncertainties in some of its inputs, as there was a lack of empirical data to evidence them. This applied particularly to costs relating to procedural duration, hospital LoS, and patient discharge pathways.

The EAC fixed some errors in the model concerning deterministic formulae and probabilistic sensitivity analysis (PSA). Additionally, the EAC adjusted some of the model's parameters to more accurately reflect published empirical data and expert opinion, and used these data as the base case. Rezum was found to be cost-saving by > £497 compared with UroLift, TURP, and HoLEP. Rezum remained cost-saving when all parameters were subjected to one-way deterministic sensitivity analysis (DSA). Furthermore, threshold analysis undertaken by the EAC did not identify any plausible values for these variables that made Rezum cost-incurring compared with these technologies. Scenario analysis, which investigated the effect of ED in a subgroup of sexually active men, did not materially affect the direction or magnitude of results. PSA indicated there was a ≥ 97.5% chance Rezum was cost-saving compared with UroLift, TURP, and HoLEP.

However, Rezum was found to be slightly cost-incurring (£62 per patient over 4 years) compared with GreenLight laser. When PSA was applied, only 27.6% of simulations reported that Rezum was cost-saving (mean extra cost of Rezum was £64, 95% credible interval -£137 to £278). The EAC therefore considered that, when considered over the 4 years perspective of the model, Rezum was approximately cost-neutral compared with GreenLight laser. This assumes that GreenLight, like Rezum, is used as a day case in nearly all patients. If it is not, then Rezum would be expected to be cost-saving.

In conclusion, the evidence demonstrates that Rezum is clinically effective and, as a minimally invasive procedure, it has benefits over other interventions that are likely to be valued by some men. In most scenarios,

Rezum is likely to be significantly cost-saving, although this needs to be considered in the context of a lack of evidence comparing the clinical efficacy and durability of Rezum with more invasive surgical options.

1 Decision problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	Men requiring prostatic surgery to relieve lower urinary tract symptoms due to prostatic hyperplasia with a prostatic volume of greater than 30cm^3 (equivalent to 30g)	None	None
Intervention	Rezum	None	None
Comparator(s)	Surgical invasive interventions: • Monopolar or bipolar transurethral resection of the prostate (TURP); • Holmium laser enucleation of the prostate (HoLEP) • GreenLight laser • Open prostatectomy Minimally invasive interventions such as: • UroLift	Open prostatectomy removed as a comparator	NICE CG97 states "Only offer open prostatectomy as an alternative to TURP, TUVP or HoLEP (see 1.5.2) to men with prostates estimated to be larger than 80 g". Using HES data, the company identified only 27 cases of open prostatectomy performed in the NHS of England in 2018/2019 (Section 7 of submission). The EAC accepts this and considers the removal of open prostatectomy is justified.
Outcomes	Patient outcomes • Relief of symptoms associated with BPH (IPSS) • Maximum flow rates (Qmax) • •Residual urine volumes • Benign prostatic hyperplasia impact index (BPHII) • International Prostate Symptom Score Quality of Life (IPSS-QOL) • Quality of life • Preservation of sexual function and urinary continence (ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function-Erectile Function; EF, erectile function domain; MSHQEjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction (EjD); ICS score, International Continence Society score)	None	None

Decision problem	Scope	Proposed variation in company submission	EAC comment
	• Reduction in prostate volume • The need for and/or duration of catheterisation • Medication use • Time to normal daily activities <u>System outcomes</u>: • Length of hospital stay • Rates of surgical re-treatment for BPH • Healthcare associated infections • Staff time to train to perform the procedure <u>Adverse events</u>: • Device-related adverse events. • Rate of dysuria (pain) • Rate of persistent LUTS (poor stream, frequency) • Rate of urinary retention • Rate of requirement of subsequent surgical re-intervention		
Cost analysis	Comparator(s): • Surgical invasive interventions • Minimally invasive interventions Costs will be considered from an NHS and personal social services perspective. Hospital setting should be considered. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Open prostatectomy not included in the economic model	Not including open prostatectomy is reasonable as it has been excluded as a comparator in the Scope.

Decision problem	Scope	Proposed variation in company submission	EAC comment
Subgroups	Men for whom surgical invasive procedures such as TURP or HoLEP is unsuitable because of the risks of blood loss or anaesthesia Men with a prostate size greater than 80 cm3 (equivalent 80g). Men aged <50 years	None	None
Special considerations, including issues related to equality	The risk of having an enlarged prostate increase with age. Certain groups of men are more prone to prostate enlargement because of being overweight or underlying conditions such as diabetes. Age and disability are protected characteristics under the equality act 2010	None	None

2 Overview of the technology

Rezum, (Boston Scientific, formerly NxThera Inc.) is a Class IIb medical device (Medical Device Directive 93/42/EEC) intended for use to relieve lower urinary tract symptoms (LUTS), obstructions and reduce prostate tissue associated with benign prostate hyperplasia (BPH). It is indicated for use in men with a prostate volume ≥ 30cm^3. This includes treatment of prostate with hyperplasia of the central zone and/or a median lobe (Boston Scientific, 2019).

The technology uses the heat from radiofrequency-generated water vapour to ablate excess prostate tissue with the aim of relieving symptoms. The technology consists of a portable generator and a single-use disposable delivery device. The delivery device is introduced into the body through the urethra and is guided to the prostate using a telescopic lens, which can be placed within the delivery device. Radiofrequency energy is produced by the generator and applied to an induction coil in the delivery device. This heats up a controlled amount of water outside of the body to generate vapour or steam. The steam is then delivered to the prostate, where it ablates obstructive prostate tissue. The procedure is expected to last up to 20 minutes and can be done as day-case surgery. Rezum is indicated for treating prostates with a median lobe or elevated central zone tissue, and with volumes greater than 30 cm^3. There is currently no specified upper limit for eligible prostate size when used in Europe (EAC External correspondence log, 2019).

There are two versions of the device. The C1 device (August 2015) featured a manually powered needle driver. This has been superseded and is no longer

commercially available. The C2 device, introduced in November 2016, features a generator powered needle. The company confirmed that the mechanism of action, steam generation, was unchanged, and therefore so was the efficacy and safety of the technology. The EAC agrees that this explanation implies clinical equivalence between device versions. The proof of concept study (Dixon *et al.*, 2015) and the Rezum II trial (McVary et al., 2016c) used the C2 version (EAC External correspondence log, 2019).

At the EAC's request, the company provided information environmental impact of the technology and any sustainability considerations (EAC External correspondence log, 2019).

3 Clinical context

The company reported the NICE patient pathways algorithm for men with LUTS (NICE, 2019) in Section 3 of the clinical evidence submission. A box to indicate the likely place of therapy with Rezum was placed between drug reviews (7) and surgery (8). The EAC considered that this was the appropriate place in therapy for Rezum, and this has been confirmed by NICE clinical experts (EAC External correspondence log, 2019).

The NICE clinical pathways are based on the NICE clinical guideline *Lower urinary tract symptoms in men* (CG97) (NICE, 2015a). NICE recommend a stepwise approach to the management of men with LUTS caused by BPH, with conservative management being recommended first-line, and drug treatment (anticholinergics, 5-alpha reductase inhibitors, alpha blockers) being recommended if conservative management is unsuccessful or inappropriate. Drug treatment should be regularly reviewed as part of an active surveillance or active intervention plan.

Surgical treatment is recommended if voiding or storage symptoms are severe, or if drug treatment and conservative management options have been unsuccessful or are not appropriate. NICE CG97 recommends the following surgical interventions as first-line (NICE, 2015a):

- Transurethral resection of the prostate (TURP)
- Monopolar transurethral vaporisation of the prostate (TUVP)
- Holmium laser enucleation of the prostate (HoLEP)

Additionally, transurethral incision of the prostate (TUIP) is recommended for men with prostates < 30 g, and open prostatectomy is an option form men with prostates > 80 g. The following minimally invasive treatments are not recommended: transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), high-intensity focused ultrasound (HIFU), transurethral ethanol ablation of the prostate (TEAP) and laser coagulation.

CG97 was last published and updated in 2015. Since then, one minimally invasive technology, one laser technology, and one surgically invasive technology to treat BPH have become available to the NHS (not including Rezum), and have been positively assessed in the Medical Technologies Evaluation Programme (MTEP):

- Transurethral resection in saline (TURis, Olympus Medical) is a bipolar electrosurgery system designed for use when surgical intervention is indicated for prostatic enlargement. Its main benefits over monopolar TURP include a reduced risk of transurethral resection syndrome and reduced healthcare resource use. TURis has received a positive recommendation from NICE (NICE, 2015c).

- UroLift (Teleflex) uses adjustable, permanent implants to pull excess prostatic tissue away so that it does not narrow or block the urethra. Unlike the other comparator technologies, it does not reduce tissue bulk through excision, ablation, or necrosis. Urololift received a positive recommendation from MTEP, who stated “The clinical case for adopting the UroLift system for treating lower urinary tract symptoms of benign prostatic hyperplasia is supported by the evidence. The UroLift system relieves lower urinary tract symptoms while avoiding the risk to sexual function associated with transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP). Using the system reduces the length of a person's stay in hospital. It can also be used in a day‑surgery unit” (NICE, 2015d).

- GreenLight 180-W treatment (Boston Scientific) operates through photoselective vaporisation of prostatic tissue. It was given a positive recommendation by MTEP, who stated “The case for adopting GreenLight XPS for treating benign prostatic hyperplasia is supported in non-high-risk patients. GreenLight XPS is at least as effective in these patients as transurethral resection of the prostate (TURP), but can more often be done as a day-case procedure, following appropriate service redesign” (NICE, 2016).

In some aspects, the EAC considered the closest comparator to Rezum was likely to be UroLift, as this is also a minimally invasive technology that may be considered in the same position of the patient pathway as Rezum, which was confirmed by NICE clinical experts (EAC External correspondence log, 2019). However, UroLift is mechanistically different from the other comparators in that it is tissue-sparing, and potentially reversible. The other comparators are ablative and fall on a “spectrum of radicality”, from Rezum at one end, to GreenLight laser, TURP, and HoLEP at the other end. The more invasive surgical options, such as TURP and HoLEP may offer more permanent

improvements, but with the tradeoff of potentially more procedurally related morbidity (Woo, 2017). The NICE clinical experts agreed that GreenLight laser could be placed in the pathway somewhere between the minimally and surgically invasive modalities (EAC External correspondence log, 2019).

Special considerations, including issues related to equality

No specific equality issues were identified by the EAC for this technology.

4 Clinical evidence selection

4.1 Evidence search strategy and study selection

A description of the search process and methods used by the company to identify relevant published and unpublished clinical data is in Section 10, Appendix A of the clinical evidence submission (Part 1). An error by the company in duplicate reporting of additional Cochrane searches was noted by the EAC, however this had no impact on the search results. The primary search strategy was deemed acceptable by the EAC, although its search terms and syntax had to be adapted to suit the functionality of our different database platform (OvidSP). The adapted company searches were re-run by the EAC to ensure that no relevant studies were missed.

The inclusion criteria applied by the company to their primary literature sift were well described and appropriate to the scope of the decision problem. Review articles and conference abstracts were excluded, which the EAC agreed was appropriate, in favour of selecting higher quality, published and peer reviewed studies, which report primary data. However, the company then presented seven conference abstracts in section 4, Table 2 of their clinical evidence submission, contravening these stated exclusion criteria. At a teleconference between NICE, the EAC and the company on 03/09/2019, it was clarified that these seven abstracts were specifically selected because they reported additional information not otherwise contained in the published studies, in a relevant UK setting (see EAC correspondence log, Newcastle EAC, 2019). Four of the abstracts identified by the company reported on the same study. The EAC therefore undertook further validation of the company's selection of conference abstracts, as described in Appendix A. Abstracts containing relevant data in a UK setting are listed in Table A4, Appendix A and cited, where appropriate, in the assessment report.

4.2 Included and excluded studies

The company identified included nine published and peer-reviewed "studies" in their literature search. Five of these publications related to the Rezum II trial (Roehrborn et al., 2017c, McVary et al., 2019, McVary and Roehrborn, 2018, McVary et al., 2016c, McVary et al., 2016a). Two studies were on the "proof of

concept study, reporting data at 1 and 2 years (Dixon *et al.*, 2016b, Dixon *et al.*, 2015). The remaining two citations related to two retrospective observational studies (Mollengarden et al., 2018, Darson et al., 2017). Hence, although nine publications were identified, these pertained to four unique studies only.

The EAC identified and included all the company's publications following its literature search and sifting process. The EAC also included a publication which the company had excluded (EAC External correspondence log, 2019), relating to the "proof of concept" study, which reported outcomes relevant to the scope (Mynderse *et al.*, 2015). No other relevant studies were included following screening. Thus in total, the EAC included ten publications reporting on four individual studies (separate cohorts of patients). The details of these are listed in Table 4.1.

Table 4.1. *Studies included by the EAC.*

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Rezum II trial (McVary et al., 2016a, McVary et al., 2016c, McVary and Roehrborn, 2018, McVary et al., 2019, Roehrborn et al., 2017a) Multicentre US	RCT comparing Rezum with sham with primary endpoint at 3 months (ITT analysis), when blinding was removed. Following washout at 6 months, sham patients were offered treatment with Rezum. Rezum patients followed up as a prospective case series at 1, 2, 3, and 4 years (PP analysis). Intervention: ● Comparator: ●	Patients with symptomatic BPH (moderate to severe LUTS). Inclusion criteria (NCT01912339): Male subjects > 50 years of age who have symptomatic BPH. IPSS score ≥ 13. Qmax): ≥ 5 ml/sec to ≤ 15 ml/sec with minimum voided volume of ≥ 125 ml. PVR ≤ 250 ml. Prostate volume > 30 and ≤ 80 g. 15 Urological sites. 197 patients randomized in a 2:1 ratio (136 sham, 61 sham). Total of 188 patients from intervention and crossed over from sham. At 4 years, total of 90 patients were analysed. ●	PROM and QoL outcomes: IPSS IPSS-QoL (question 8) BPHII ICS score IIEF-EF MSHQ function MHSQ bother Clinical outcomes: Qmax PVR Reduction in prostate volume Healthcare resource use: Number catheterised Requirement for retreatment Adverse events: Device and procedure related adverse events Persistence of LUTs Dysuria Post-operative UTIs. ●	The Rezum II trial consisted of three analyses: RCT comparing Rezum with sham (n=188) (McVary et al., 2016c). Cross-over trial derived from participating sham patients (n=53) (Roehrborn *et al.*, 2017a). Prospective case series with follow up at 1 year (McVary et al., 2016c), 2 years (Roehrborn *et al.*, 2017a), 3 years (McVary and Roehrborn, 2018), and 4 years (McVary *et al.*, 2019). Additionally there were analyses conducted separately on sexual function (McVary *et al.*, 2016a).

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Proof of concept study (Mynderse et al., 2015, Dixon et al., 2016, Dixon et al., 2015) Dominican Republic, Czech republic, Sweden.	Prospective case series reporting on men treated with Rezum. Multicentre. Follow up at baseline, 1 month, 3 months, 6 months, 12 months, and 24 months. Intervention: ●	Men with moderate to severe LUTS secondary to BPH. Inclusion criteria: Age: 45 years IPSS: 15; Qmax: 15 ml/sec PVR: <300 ml; Prostate volume: 20 to 120 ml. Baseline (n = 65) 2 year follow up (n = 43, IPSS outcome). ●	PROM and QoL outcomes IPSS IPSS-QoL BPHII IIEF-EF MSHQ function MSHQ bother Clinical outcomes Qmax PVR Reduction in prostate volume Adverse events: Device and procedure related adverse events Persistence of LUTs Dysuria Post-operative UTIs. ●	The study by Dixon *et al.* (2015) was a proof of concept study. The study was single-armed, thus outcomes are reported longitudinally (relative to baseline). Patients were subject to a washout period for BPH related drugs before enrolment.
(Darson *et al.*, 2017) Retrospective case series US	Retrospective analysis of men receiving Rezum. 2 centres Patients recruited consecutively with data collected at baseline, 1 month, 3 to 6 months, and 12 months. ●	Patients with moderate to severe LUTS secondary to BPH receiving treatment with Rezum. Baseline (n = 131) 12 months (n = 87, IPSS outcome) ●	PROM and QoL outcomes IPSS IPSS-QoL Clinical outcomes Qmax PVR Voided volume	The study by Darson *et al.* (2017) reported longitudinal data (relative to baseline). Subgroup analysis was performed based on symptom severity (moderate LUTS and severe LUTS)

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
(Mollengarden et al., 2018) Retrospective case series US	Retrospective analysis of men receiving Rezum. Single centre Data collected at baseline, 15 to 45 days, 46 to 90 days, and 91 to 180 days. ●	Patients undergoing treatment with Rezum procedure. LUTS severity: mild (10.4%), moderate (44.8%), severe (44.8%). Baseline (n = 129) 91 to 180 days (n = 89) ●	IPSS Qmax PVR	The first 25 patients were part of the Rezum II study population. The remainder of the patients were selected for treatment based on the provider's clinical judgment. The authors compared the cohorts and found no significant differences so analysed the data of the combined cohort.

Abbreviations: BPH, benign prostatic hyperplasia; BPHII, benign prostatic hyperplasia impact index; ICS, international continence score; IPSS, International Prostate Symptom Score; ITT, intention to treat; LUTS, lower urinary tract symptoms; MSHQEjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; PROM, patient orientated outcome measure; PVR, post void residual volume; Qmax, peak urinary flow rate; QoL, quality of life; PP, per protocol; TURP, transurethral resection of prostate; UTI, urinary tract infection.

5 Clinical evidence review

5.1 Overview of methodologies of all included studies

The included studies consisted of one RCT (Rezum II trial) (McVary *et al.*, 2016a) which reported comparative outcomes with sham at 3 months. Patients in the intervention arm were then followed up as a prospective case series for 2 years (Roehrborn *et al.*, 2017c), 3 years (McVary and Roehrborn, 2018), and 4 years (McVary *et al.*, 2019). Consenting patients in the control arm participated in a cross over trial (Roehrborn *et al.*, 2017c). The other studies included were non-comparative. One included study, cited as a "proof of concept" study, was a prospective case series reporting outcomes at 1 year (Mynderse *et al.*, 2015, Dixon *et al.*, 2015), and 2 years (Dixon *et al.*, 2016b). Two of the studies were retrospective observational studies reporting follow up at 1 year (Mollengarden et al., 2018, Darson et al., 2017). All the studies were fully published in peer-reviewed journals. In total, 497 patients were enrolled into the included studies (436 receiving Rezum as index treatment, 61 initially receiving sham, of whom 53 of whom crossed over to Rezum).

5.2 Critical appraisal of studies and review of company's critical appraisal

The company critically appraised the Rezum II trial using the Cochrane Collaboration's tool for assessing the risk of bias in randomised trials (Higgins *et al.*, 2011) in Section 7 of the submission, as part of the evidence synthesis (see Section 7). This was appropriate. The company reported the Rezum II trial was at low risk of bias in all domains except for detection bias, where it was unclear if assessment of results was performed blind to treatment. The company did not critically appraise the observational studies.

5.2.1 Rezum II trial

The EAC has independently critically appraised the Rezum II trial (see Appendix B). This study can be considered in two parts, as a comparative RCT reporting data up to 3 months, and a single-armed observational study reporting data up to 4 years. This was clearly illustrated in each of the published studies using CONSORT methodology (e.g. see Figure 1 of McVary *et al.*, 2019). The EAC considered the RCT was generally of high-quality. There was no evidence of patient selection bias, with both arms being statistically equivalent at baseline. Performance bias was minimised by blinding the patients, although it was unclear how effective masking could have been, and it was not possible to blind the treating physician. During this patient-blinded phase, the risk of detection bias was relatively low, as most outcomes were assessed through the use of self-administered questionnaires. Nearly all patients completed the comparative phase of the study, and

intention to treat (ITT) analysis was used, so attrition bias was not present at this stage. However, there was a risk of reporting bias, because most the secondary outcomes were not defined in the study protocol (NCT01912339).

The prospective case series, derived from the patients receiving the intervention, was subject to considerably more potential for bias. As patients were unmasked, there was a potential for detection bias, especially since most outcomes were subjective (Higgins and Green, 2015). Analysis of the single-armed data was performed *per protocol* (PP) and attrition rates were significant, with 34% of patients not providing outcome data at 4 years (McVary *et al.*, 2019). There was also a potential for reporting bias, and there does not appear to have been any attempt to account for multiple comparisons when significance levels were reported. Finally, it should be considered that the cross-over analysis did not report on a true cross-over study, as there was no randomisation in the order of interventions received (Mills *et al.*, 2009).

5.2.2 Observational studies

Single-armed observational studies offer only weak inference of causality, and require either explicit comparisons with uncontrolled data sources (e.g. historical data) or implicit extrapolation for their interpretation (e.g. before and after effect) (AHRQ, 2013). Nevertheless, they can be useful in determining the effect of surgical procedures, in particular where the longitudinal effects are immediate, large and sustained.

The prospective study by Dixon *et al.* (2015) (n = 65) did not report how patients were enrolled, which risks inappropriate patient selection. Study outcomes were pre-defined in a trial protocol (NCT02943070), with most being derived from self-reported questionnaires. Follow up was carried out up to two years. At 1 year follow up, 89% (58/65) of men reported data, and at 2 years, the figure was 66% (43/65), indicating there was the potential for attrition bias. The EAC considered this study was well designed and clearly reported.

The other 2 observational studies used retrospective analysis. Whilst retrospective studies can incorporate efficient and inexpensive study designs, an intrinsic weakness is that they can only analyse data that was routinely collected in the past, which may have been collected at indefinite times, and thus tend to be limited in their reporting of outcomes. The study by Darson *et al.* (2017) was relatively large, enrolling 131 patients who received treatment with Rezum. It was not clear if enrolment was consecutive. Reporting of outcomes was limited, but included measurement of IPSS. Follow at 1 year was clearly reported. The study by Mollengarden *et al.* (2017) had a similar sample size (n = 129), although 25 of these patients were also part of the

Rezum II trial cohort. Only a limited number of outcomes were reported up to a maximum follow up of 180 days. Because of this, the EAC considered this study was the least informative of those included.

5.3 Results from the evidence base

The company reported results by study in Section 4 (Table 4), and in a narrative format in Section 8. Additional synthesised data was reported in Section 7. The results reported were not clearly structured, and in some cases sections were difficult to read in context. The EAC has therefore independently reported the results directly from the primary studies.

Results have been reported by outcome to reflect those listed in the scope of the decision problem, but divided into additional subcategories (Patient orientated outcomes measures [PROMs], clinical outcomes, healthcare resource use). Outcomes related to adverse events are reported in Section 6. Tables and figures reported in the company's submission are not duplicated; rather graphs are reported to compare results for compatible outcomes reported in multiple studies.

5.3.1 Patient orientated outcome measures

IPSS score

The International Prostate Symptom Score (IPSS) is a validated questionnaire used to assess symptoms of BPH. It includes 7 dimensions scored from 1 to 5 (incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia) (IPSS score, 2019). Higher scores represent worse symptoms, so a decrease in IPSS is indicative of symptom improvement.

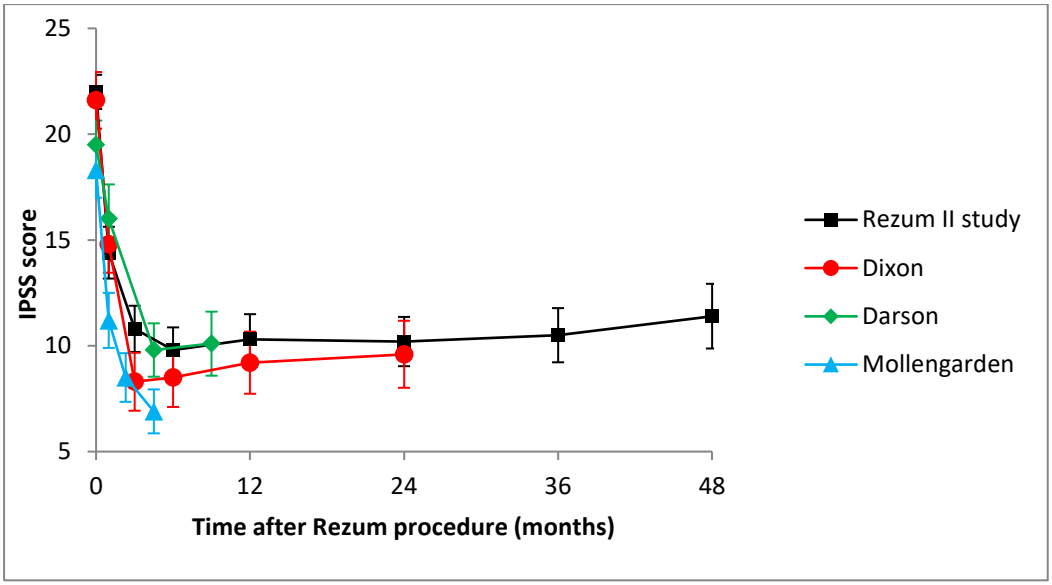
IPSS was reported in all the included studies, with the Rezum II study reporting comparative data with sham at 3 months (primary efficacy outcome) (McVary et al., 2016c). Patients in the Rezum arm had a mean (± SD) IPSS score of 22.0 ± 4.8 at baseline and 10.8 ± 6.5 3 months post-procedure, with a mean difference of -11.2 (95% CI -12.5 to -9.9). For patients receiving sham, the mean IPSS score was 21.9 ± 4.7 at baseline and 17.5 ± 7.6 at 3 months post-procedure, with a mean difference of -4.3 (95% CI -6.1 to -2.5). There appeared to be a statistically significant sham effect (p value not stated), but the difference in the change of IPSS in Rezum compared with sham was also statistically significant (p <0.0001). This 3 month comparative improvement was also reported in patients participating in the cross over study (n = 50 with paired data), where a mean change of -3.9 (95% CI -5.8 to -2.0) was observed in the sham phase, compared with -10.0 (95% CI -12.1 to -8.0) after Rezum (p = 0.0004).

Longitudinal data from the Rezum II trial indicated that improvements in IPSS relative to baseline were persistent. At 1 year, the mean (± SD) IPSS was 10.3 ± 6.7 (n = 121), at 2 years was 10.2 ± 6.2 (n = 109), at 3 years was 10.5 ± 6.1 (n = 99), and 4 years was 11.4 ± 7.4 (n = 90) (McVary *et al.*, 2019). All these values were significantly less than base line ($p < 0.0001$).

In the prospective study by Dixon *et al.* (2015), the baseline IPSS was 21.6 ± 5.5 (n = 64). This improved to 14.8 ± 8.4 after 1 month (n = 66) and 8.3 ± 5.8 after 3 months (n = 62). Longer term, the improvements persisted with IPSS values of 8.5 ± 7.0 (n = 62), 9.2 ± 6.5 (n = 58) and 9.6 ± 6.5 9 (n = 43) after 6 months, 1 year and 2 years respectively (all $p < 0.001$) (Dixon *et al.*, 2016b, Dixon *et al.*, 2015). The retrospective study by Darson *et al.* (2017) reported a baseline IPSS of 19.9 ± 6.7. This reduced to 9.8 ± 6.9 (n = 115) after 3 to 6 months, and 10.1 ± 7.2 (n = 87) after 12 months (both $p < 0.0001$). Mollengarden *et al.* (2018) reported a baseline mean IPSS of 18.3 ± 7.5 (n = 129). After about 1 month, this reduced to 11.2 ± 6.4, with further reductions to 8.5 ± 5.9 and 6.9 ± 5.0 at later time points (around 3 and 6 months, $p <0.001$).

The longitudinal reduction in IPSS are illustrated in Figure 5.1. It can be seen that from a baseline of severe symptoms (IPSS 20 to 35), Rezum was associated with a reduction in symptoms to borderline moderate (IPSS 8 to 19) or mild symptoms (IPSS ≤ 7). A 3 point reduction in IPSS is considered to be the minimally important clinical difference (Barry *et al.*, 1995). This effect persisted for at least 4 years. Reductions in IPSS of -14.9 points at 3 months ($p < 0.001$, n = 181) have also been observed in a UK setting (Johnston *et al.*, 2019).

Figure 5.1. *Reduction in IPSS following treatment with Rezum (error bars indicate 95% CI).*



IPSS-QoL

The IPSS-QoL score is question 8 of the IPPS, which states "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" (IPSS score, 2019). Scores range from 0 (delighted) to 6 (terrible), thus a lower score indicates patient benefit. This outcome was reported in 3 studies.

In the Rezum II trial, the baseline mean IPSS-QoL score 4.4 ± 1.1 (SD). There was a mean reduction of -2.1 (95% CI -2.4 to -1.8) in the Rezum arm at 3 months, compared with -0.9 (95% CI -1.3 to -0.5) in the sham arm. The larger reduction in the Rezum was statistically significant (p <0.0001) (McVary et al., 2016c). The cross-over study reported a reduction of -0.8 (95% CI -1.2 to -0.2) following sham, compared with -2.0 (95% CI -2.5 to -1.5) following Rezum (p = 0.024). This improvement in QoL persisted for at least 4 years, when there was a -2.0 ± 1.7 reduction from baseline (p < 0.001).

The prospective study by Dixon *et al.* (2015) reported persistent reductions in IPSS-QoL above 2.5 points from 3 months onwards. At 2 years, a reduction of -2.6 ± 1.7 (n = 43) was reported (p < 0.001) (Dixon *et al.*, 2016b). Analysing retrospective data, Darson *et al.* (2017) reported a reduction of -1.9 ± 1.8 at around 12 months (p < 0.0001).

BPHII score

The Benign Prostatic Hyperplasia Impact Index (BPHII) is a validated self-administered questionnaire used to assess the impact on quality of life caused by urinary symptoms in men with BPH (Angalakuditi et al., 2010). Lower scores indicate less patient symptoms.

BPHII was collected throughout the Rezum II trial (McVary et al., 2016c). After 3 months, BPHII reduced from a baseline of 6.3 ± 2.8 to 2.9 ± 2.9, a reduction of -3.4 (95% CI -4.0 to -2.8). The corresponding figures for the sham intervention were a baseline of 6.2 ± 2.9, reducing to 4.7 ± 3.5, equating to a reduction of -1.5 (95% CI -2.3 to -0.7). The greater reduction observed with Rezum was significant ($p = 0.0003$). Furthermore, long term data indicated that this change was persistent, with a reduction of -3.5 ± 3.4 ($p < 0.0001$) observed at 4 years (n = 90) (McVary *et al.*, 2019).

The prospective observational study by Dixon *et al.* (2015) reported a baseline BPHII score of 6.8 ± 2.9 (n = 62). This reduced to 2.2 ± 2.4 at 3 months, 2.0 ± 2.3 at 1 year, and 2.3 ± 2.5 at 2 years; which was an overall reduction of -4.8 ± 3.5 at the latter time point ($p < 0.001$).

ICS score

The International Continence Score (ICS) was reported in the Rezum II trial (McVary et al., 2016c). Direct comparative or cross-over data with sham at 3 months was not reported, but longitudinal data was (Rezum arm only). At baseline, the ICS male score was 4.5 ± 2.9 (SD, n = 135). At 1 year this decreased to 3.0 ± 2.8 (n = 120, p < 0.0001), to 3.0 ± 2.6 (n = 109, p < 0.0001) at 2 years, 3.1 ± 2.8 (n = 99, p < 0.0001) at 3 years, and 3.2 ± 2.8 (n = 89, p = 0.0024) at 4 years (McVary *et al.*, 2019). Thus, there was a persistent reduction in ICS of about 1 unit.

OAB scores

Overactive bladder scores (OABs) were not included in the Scope but were reported in the Rezum II trial and are reported here for completeness. Mean OAB symptom scores improved by 14.6 ± 18.0 in the Rezum arm compared with a worsening of -8.0 ± 17.9 in the sham group after 3 months (p =0.022). OAB HRQoL improved in both groups, but more so in patients receiving Rezum (17.5 ± 18.8) than those receiving sham (8.3 ± 15.37, p = 0.001). Similar results were reported in the cross-over study (Roehrborn *et al.*, 2017c). Improvements in OAB symptom score and HRQoL compared with were observed at all time-points up to 4 years (McVary *et al.*, 2019).

IIEF-EF score

The International index of erectile function (IIEF), erectile function domain, was reported in the Rezum II trial (McVary et al., 2016c, McVary et al., 2016a). Lower scores represent worse sexual function of satisfaction. There was a change of -0.3 ± 5.6 (SD) in patients treated with Rezum compared with those treated with sham at 3 months. This difference was not significant (p = 0.795), nor was there a significant difference in patients who crossed over to Rezum from sham. Longitudinal data reported no significance difference in IIEF-EF compared with baseline except after 4 years, where there was a decrease -2.5 ± 2.5 (p = 0.0333, n = 58), indicating deteriorating sexual function.

MSHQ-EjD

Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) was assessed in the Rezum II trial (McVary et al., 2016c, McVary et al., 2016a). This was reported as longitudinal function and bother scores. The baseline MSHQ function score was 9.3 ± 1.7 (n = 91). This remained stable up to 2 years. However, there were significant declines to 8.4 ± 4.5 (n = 64, p = 0.046) and 8.2 ± 4.6 (n = 56, p = 0.038) reported at 3 and 4 years respectively. Conversely, there were improvements observed in the MHSQ

bother score in the 3 years. The baseline score was 2.2 ± 1.7 (n = 91), which decreased to 1.5 ± 1.5 (n = 79, p -0.0017) at 1 year, 1.7 ± 1.7 (n = 70, p = 0.0018) at 2 years, and 2.0 ± 1.7 (n =64, p = 0.153) at 3 years. At 4 years, there was no significant difference from baseline (2.0 ± 1.7 [n = 56, p = 0.6495) (McVary *et al.*, 2019). Thus whilst ejaculatory function remained static and then trended towards decline throughout the study, there was a perception of improvement in the earlier years of the study.

5.3.2 Clinical outcomes

Maximum flow rate (Qmax)

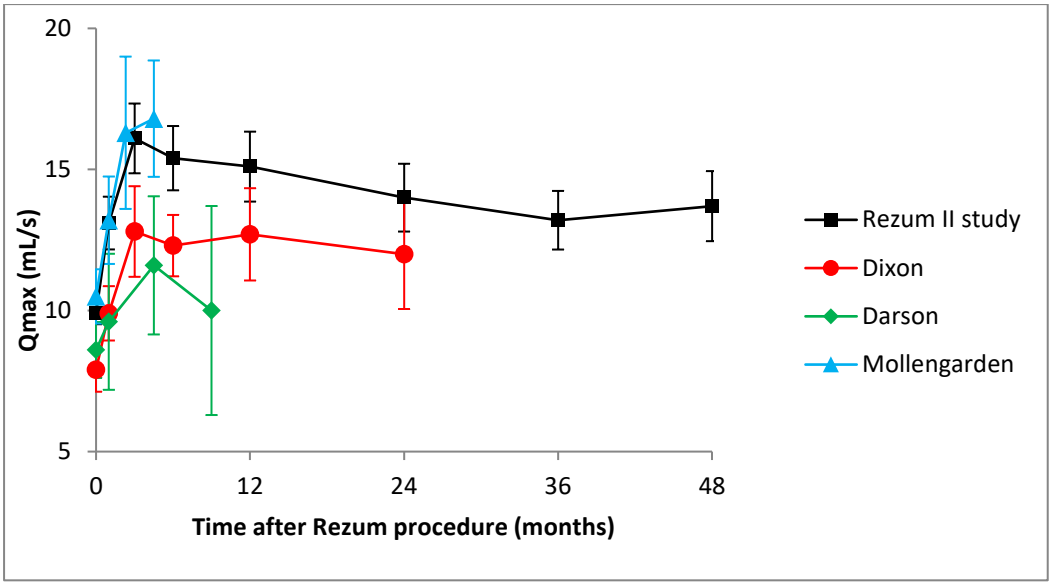
The maximum flow rate (Qmax) is a uroflowmetry measure, with lower values indicating possible bladder outlet obstruction. This is an objective measurement, although Qmax is subject to high levels of intra-individual variability. All the included studies reported this outcome.

The Rezum II trial reported a baseline Qmax of 9.9 ± 2.3 mL/s which improved to 16.1 ± 7.3 mL/s following Rezum treatment. For the sham arm, the baseline was 10.4 ± 2.1 mL/s, which slightly increased to 10.8 ± 4.0 at 3 months. This was an increase of Qmax of 6.2 ± 7.1 mL/s for Rezum, compared with an increase of 0.5 ± 4.2 mL/s for sham (p < 0.0001) (McVary et al., 2016c). The minimally important difference of Qmax is considered by clinical experts to be 2 mL/s (NICE, 2015b), so the improvements observed in the Rezum arm (but not the sham arm) were clinically significant. There was an improvement of 6.2 ± 6.8 mL/s in sham patients who crossed over to Rezum (n = 49, p < 0.0001). This improvement was persistent up to 4 years. At this time point, there was a 4.2 ± 5.7 mL/s increase compared with baseline (n = 81, P < 0.0001).

In the prospective case series by Dixon *et al.*(2015), the baseline Qmax score was 7.9 ± 3.2 mL/s. There was a significant improvement of about 4.5 mL/s at follow up periods of 3 months, 6 months, 1 year and 2 years (all p <0.001). Darson *et al.*(2017) reported an improvement in Qmax from a baseline of 8.7 ± 4.7 mL/s to 11.6 ± 7.7 mL/s after 3 to 6 months (p = 0.04) in their retrospective analysis. However, at 12 months, there was no significant difference from baseline (change of 1.5 ± 5.9 mL/s, p = 0.4). Mollengarden *et al.* (2018) reported improvements in Qmax of 3.2 ± 5.0 mL/s, 6.0 ± 8.8 mL/s, and 5.9 ± 7.3 mL/s at around 1 month, 3 months, and 6 months respectively (all p < 0.001).

A summary of the longitudinal Qmax data reported in the included studies is reportedly graphically in Figure 5.2.

Figure 5.2. *Improvements in Qmax following treatment with Rezum (error bars indicate 95% CI).*



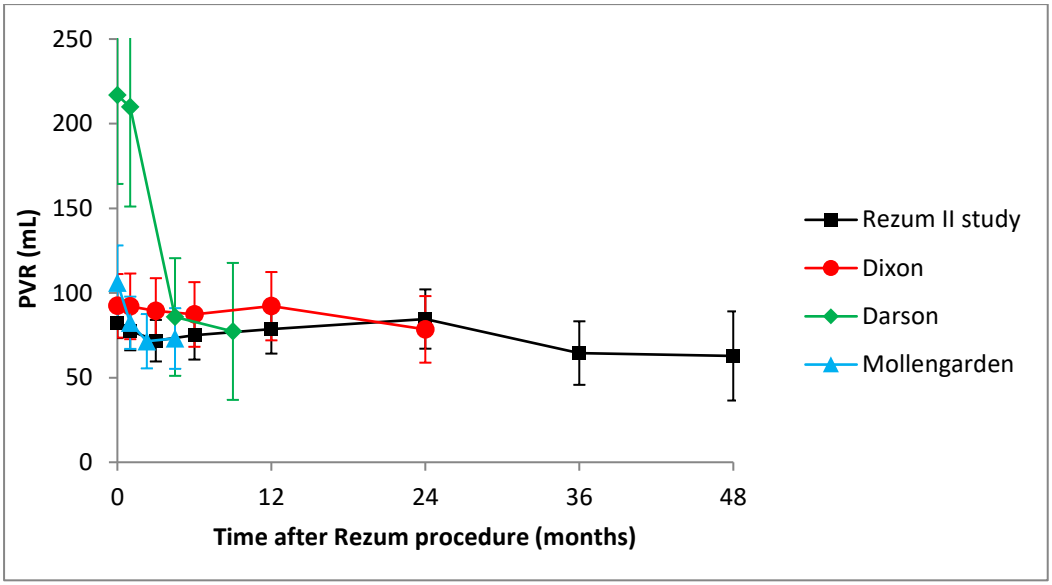
Post-void residual urine volume (PVR)

Post-void residual urine volume (PVR) a measurement of urine retention, is usually estimated with ultrasound. Whilst PVR is an objective measurement, it is subject to a high degree of intra- and inter-patient variability, and does not accurately reflect LUTS severity, prognosis, or need for surgical management (Mochtar et al., 2006). Post-void residual urine volume was measured in all the included studies. In the Rezum II trial, there was a non-significant mean decrease of -10.6 ± 68.3 (SD) mL in the Rezum arm, compared with 7.2 ± 77.4 mL in the sham arm (p = 0.108). Longitudinal data did not report significant improvements up to 4 years with the exception of 3 years, which may have been a chance finding (McVary *et al.*, 2019).

The prospective case series by Dixon *et al.* (2015) reported significant improvements in PVR compared with baseline at 1 month (-25 ± 92.3 mL), 3 months (-29.9 ± 78.0 mL), and 1 year (-27.6 ± 82.9 mL). The changes at 6 months and 2 years were not statistically significant. The retrospective study by Mollengarden *et al.* (2018) reported moderate decreases in PVR of -19.3 ± 104.7 mL (p = 0.046), -32.0 ± 111.5 mL (p = 0.003), and -34.8 ± 119.7 mL (p = 0.005) at around 1 month, 3 months, and 6 months respectively compared with baseline. In contrast to the other studies, Darson *et al.* (2017) reported a very large and sustained reduction in PVR compared with baseline (-158.- ± 221.8 mL at around 3 months and -159.0 ± 254.7 mL at around 12 months, p < 0.0001). The baseline PVR was particularly high in this study 216.8 ± 286.6 mL (n = 115).

A summary of the longitudinal PVR data reported in the included studies is reportedly graphically in Figure 5.3.

Figure 5.3. *Changes in PVR following treatment with Rezum (error bars indicate 95% CI).*



Reduction in prostate volume

The Rezum II trial did not report how much prostate volumes were reduced by treatment with Rezum. However, this outcome was reported in a publication associated with the prospective case series (Mynderse *et al.*, 2015). This study reported the mean volume of ablative lesions 1 week after Rezum therapy was 8.2 cm^3 (range 0.5 to 24.0 cm^3). At 6 months, whole prostate volume was reduced by a mean of 28.9% (from 61.2 cm^3 to 43.5 cm^3). The transition zone volume was reduced by 38.0% (from 36.3 cm^3 to 22.5 cm^3) compared with baseline.

Need for and/or duration of catheterisation

The Rezum II trial allowed post-procedural catheterisation at the discretion of the treating physician (McVary et al., 2016c). In the Rezum arm, 90.4% (122/135) of patients were catheterised for a mean 3.4 ± 3.2 (SD) days. Of these, 68% (83/122) were discretionary and 32% (39/122) were due to an unsuccessful voiding trial before discharge. In the control arm, 19.7% of men were catheterised for a mean of 0.9 ± 0.8 days. The retrospective study by Mollengarden *et al.* (2018) reported that a traditional urethral catheter was placed in 65.1% of patients and was kept in for an average of 4.4 ± 4.3 days (range 1 to 26 days). A spanner prosthetic stent was used in the remainder of patients.

Medication use

Medication use was not an outcome in any of the included studies. In the Rezum II trial, one of the inclusion criteria was a washout period for the following drugs: antihistamines (1 week); alpha-blockers, anticholinergics or daily dose phosphodiesterase type 5 inhibitors (4 weeks); oestrogen, androgen suppressing drugs, anabolic steroid or type II 5a-reductase inhibitors (3 months); dual 5a-reductase inhibitors (6 months). In this study, 7 patients (approximately 5%) dropped out over the course of 4 years because they recommenced BPH medication. Concurrent medication for BPH was also an exclusion criterion for the study by Dixon *et al.* (2015). The study by Darson *et al.* (2017) stated that Rezum was offered as an alternative to medication for symptomatic relief.

One retrospective study reported that 89.5% of patients who were on an alpha blocker or 5-alpha reductase inhibitor (85/95) before the procedure were off all prostate related medication at their latest follow up (Mollengarden et al., 2018).

Time to normal activities

In the Rezum group, the median time for resumption of usual activities after discharge (typically after removal of the catheter) was 4 days (range (0 to 90 days). For patients receiving sham, this period was 1 day (range 0 to 15 days) (McVary et al., 2016c).

5.3.3 Healthcare resource use

Length of hospital stay

This outcome was not reported in any of the included studies

Rates of surgical retreatment for BPH

One patient (0.7%) was reported as requiring surgical retreatment (TURP or laser) at 12 months in the seminal publication of the Rezum II trial (McVary et al., 2016c). At 2 years, 3 patients required TURP or laser retreatment (2.7%). Another patient was excluded at this point because they had a repeat treatment of Rezum (Roehrborn *et al.*, 2017c). No additional retreatment with TURP or laser was required after 3 years, although an additional patient was censored for requiring repeat Rezum treatment (McVary and Roehrborn, 2018). The authors reported that at 4 years, the surgical re-intervention rate was 4.4% (6/135) (McVary *et al.*, 2019). The six re-interventions consisted of 1 open prostatectomy, 3 plasma-button transurethral vaporisations of the prostate, and 2 patients retreated with the Rezum procedure.

The retrospective study by Darson *et al.* (2017) reported that 3 patients underwent TURP 7 to 12 months after the procedure due to obstructing residual tissue or insufficient improvement. Additionally, one patient had a second Rezum procedure 12 months later (overall rate estimated at 2.3% in first year). The study by Mollengarden *et al.* (2018) reported that 3 patients (2.3%) underwent an additional BPH surgery for persistent LUTS. This consisted of repeated Rezum procedure (n = 2) and a photovaporisation procedure (n = 1).

Health-care associated infections

This outcome was not reported by any of the included studies.

Staff time to train to perform the procedure

This outcome was not reported by any of the included studies.

5.3.4 Subgroups

Three subgroups were identified in the Scope. The first of these was “Men for whom surgical invasive procedures such as TURP or HoLEP is unsuitable because of the risks of blood loss or anaesthesia”. No evidence was identified on the included studies on this subgroup, and indeed most men with significant comorbidities would be excluded from studies of Rezum. The EAC accepts that as Rezum does not require usually general anaesthesia and would be expected to be associated with less serious blood loss events than surgically invasive treatments (see Section 6), it would be an appropriate option for this subgroup.

The second subgroup was “Men with a prostate size greater than 80 cm^3 (equivalent 80g)”. Men with a prostate gland volume of > 80 cm^3 was an exclusion criterion in the Rezum II trial (McVary et al., 2016c). Men enrolled into the prospective case series (Dixon *et al.*, 2015) had prostate volumes between 20 and 120 mL, with a mean volume of 48.8 ± 20.7 mL (SD), but no analyses on prostate gland size was undertaken. This cohort appears to be similar to those recruited in the Darson *et al.* study (2017), where the mean prostate size was 45.1 ± 23.4 mL. Mean prostate volume was slightly larger in the study by Mollengarden *et al.* (2018) at 52.6 ± 17.0 mL. This study performed correlation analysis on the pre-treatment prostate size against changes in IPSS and Qmax. No correlation was identified between gland size and either symptom or flow rate improvement post-treatment.

The effect of the size of prostate gland on clinical outcomes was the subject of an abstract by a UK group (Sarkar *et al.*, 2019), which performed subgroup analysis by stratifying patients into groups with < 80 mL (n = 128) and > 80 mL (n = 33) prostate volumes. After 3 months, there were no significant differences reported in IPSS or QoL scores, with the authors commenting that Rezum was a suitable technique for men with larger prostates; however, it was noted that further research to determine a “sensible upper limit” would be useful.

The third subgroup was “men aged < 50 years”. Patients recruited into the Rezum II trial had a mean age of about 63 years, whilst those in the observational studies were slightly older. No study investigated the relationship between age and outcomes. However, it is noted that patient preference for minimally invasive interventions may be related to age (for instance, to minimise the risk of post-procedural sexual dysfunction).

5.3.5 Summary

The results of the included studies, ordered by outcomes reported in the Scope, are reported in Table 5.1. The comparative results from the Rezum II

trial (McVary et al., 2016c) show unequivocally that Rezum therapy is associated with statistically significant improvements in PROMs relating to urological health, compared with sham. This is supported by evidence that Rezum improves Qmax (but the evidence for improving PVR is less conclusive). Furthermore, these improvements are gained without significantly affecting sexual function, at least in the short-term.

Longitudinal data from observational studies (Mollengarden et al., 2018, Dixon et al., 2016b, Darson et al., 2017), including the prospective case series derived from the Rezum trial (McVary *et al.*, 2019), were supportive of urological benefits enduring for at least 4 years. Over this period, 4.4% of patients required reoperation in the Rezum II trial (McVary *et al.*, 2019), although there was some uncertainty in these results due to substantial patient attrition.

There were gaps in the evidence regarding the use of healthcare resources, which were in general not reported in the published studies. Additionally, because the studies were relatively small, the precision of data on adverse events was limited. Limited subgroup analysis did not find differences in treatment safety and efficacy in men with larger prostates, although further research is required identify treatment thresholds for this parameter.

Table 5.1. *Summary of results from included studies.*

	Outcome taken from the decision problem	Evidence from the Rezum II trial RCT component: 3 month comparison with sham.	Evidence from comparative observational studies (including Rezum II case series): comparison with baseline.	EAC comment on validity of evidence*
PROM/QoL (urology)	IPSS**	Primary outcome (McVary et al., 2016c) Rezum: -11.2 (95% CI -12.5 to -9.9) Sham: -4.3 (95% CI -6.1 to -2.5) Significantly favours Rezum (p < 0.0001) Cross over data (Roehrborn et al., 2017c) Rezum: -10.0 (95% CI -12.1 to -8.0) Sham: -3.9 (95% CI -5.8 to -2.0) Significantly favours Rezum (p = 0.0004)	4 years, change of -10.1 ± 7.6 (McVary et al., 2019). 2 years, change of -12.1 ± 7.9 (Dixon et al., 2016b) 12 months, change of -9.4 ± 8.7 (Darson et al., 2017) 91 to 180 days, change of -11.6 ± 7.0 (Mollengarden et al., 2018)	**Strong evidence** that Rezum improves IPSS scores at 3 months compared with sham treatment. **Strong evidence** that Rezum improves IPSS scores relative to baseline up to 4 years. Overall, there is unequivocal evidence that Rezum causes clinically significant improvements in urological symptoms in the short-term. This improvement is highly likely to be persistent (up to 4 years) and generalisable.
	IPSS-QoL**	RCT data (McVary et al., 2016c) Rezum: -2.1 (95% CI -2.4 to -1.8) Sham: -0.9 (95% CI -1.3 to -0.5) Significantly favours Rezum (p < 0.0001) Cross over data (Roehrborn et al., 2017c) Rezum: -2.0 (95% CI -2.5 to -1.5) Sham: -0.8 (95% CI -1.2 to -0.3) Significantly favours Rezum (p = 0.0024)	4 years, change of -2.0 ± 1.7 (McVary et al., 2019). 2 years, change of -2.0 ± 1.8 (Dixon et al., 2016b) 12 months, change of -1.9 ± 1.8 (Darson et al., 2017)	**Strong evidence** that Rezum improves IPSS-QoL scores at 3 months compared with sham treatment. **Strong evidence** that Rezum improves IPSS scores relative to baseline up to 4 years. Rezum is associated with an approximate 2 point improvement in QoL, which is clinically important. This improvement persists for at least 4 years.
	BPHII**	RCT data (McVary et al., 2016c) Rezum: -3.4 (95% CI -4.0 to -2.4) Sham: -0.9 (95% CI -2.3 to -0.7) Significantly favours Rezum (p < 0.0003) Cross over data (Roehrborn et al., 2017c) Rezum: -2.9 (95% CI -3.9 to -2.0)	4 years, change of -3.5 ± 3.4. (McVary et al., 2019). 2 years, change of -4.8 ± 3.5 (Dixon et al., 2016b)	**Strong evidence** that Rezum improves BPHII scores at 3 months compared with sham treatment. **Strong evidence** that Rezum improves BPHII scores relative to baseline up to 4 years.

	Outcome taken from the decision problem	Evidence from the Rezum II trial RCT component: 3 month comparison with sham.	Evidence from comparative observational studies (including Rezum II case series): comparison with baseline.	EAC comment on validity of evidence*
		Sham: -1.3 (95% CI -3.1 to -0.5) Significantly favours Rezum (p = 0.00241)		Rezum is associated with important improvements in urinary symptoms, as measured by BPHII.
	ICS score**	Not reported	4 years, change of -0.9 ± 2.8. Significant change from baseline (p = 0.0024) (McVary et al., 2019).	**Strong evidence** that Rezum is associated with significant improvement in ICS up to 4 years
PROM/QoL (sexual)	IIEF-EF**	Cross over data (Roehrborn et al., 2017c) Rezum: -0.9 (95% CI -0.9 to -2.7) Sham: -0.1 (95% CI -2.7 to 2.5) No significant difference from sham (p = 0.5972)	4 years, change of -2.5 ± 8.7 Non-significant from baseline (p =0.0333) (McVary et al., 2019).	**Moderate evidence** that Rezum does not worsen sexual function compared with sham. After 4 years, there is a non-significant trend towards worsening sexual function, but this may reflect the effects of age.
	MSHQ-EjD function†	Cross over data (Roehrborn et al., 2017c) Rezum: -0.4 (95% CI -1.6 to 0.8) Sham: -0.6 (95% CI -0.3 to 1.4) No significant difference from sham (p = 0.2825)	4 years, change of -1.8 ± 4.4 Significant from baseline (p =0.0038) (McVary et al., 2019).	**Moderate evidence** that Rezum does not worsen ejaculatory dysfunction compared with sham. After 4 years, there is some evidence of worsening ejaculatory function (but this is non-comparative).
	MSHQ-EjD bother**	Cross over data (Roehrborn et al., 2017c) Rezum: -0.1 (95% CI -0.6 to 0.8) Sham: -0.3 (95% CI -0.6 to 0.5) No significant difference from sham (p = 0.6778)	4 years, change of -0.1 ± 1.8 Non-significant from baseline (p =0.6495) (McVary et al., 2019).	**Moderate evidence** that Rezum does not worsen ejaculatory bother compared with sham. After 4 years, there is some evidence of worsening ejaculatory bother (but this is non-comparative).
Clinical manage	Qmax†	RCT data (McVary et al., 2016c) Rezum: 6.2 (95% CI 5.0 to 7.0) Sham: 0.5 (95% CI -0.6 to 1.5) Significantly favours Rezum (p < 0.0001)	4 years, change of 4.2 ± 5.7 (McVary et al., 2019). 2 years, change of 3.7 ± 6.5 (Dixon et al., 2016b)	**Strong evidence** that Rezum improves urinary flow at 3 months compared with sham treatment. **Strong evidence** that Rezum improves urinary flow relative to baseline up to 4 years.

	Outcome taken from the decision problem	Evidence from the Rezum II trial RCT component: 3 month comparison with sham.	Evidence from comparative observational studies (including Rezum II case series): comparison with baseline.	EAC comment on validity of evidence*
		Cross over data (Roehrborn et al., 2017c) Rezum reduction: 6.3 (95% CI 4.3 to 8.3) Sham reduction: 0.2 (95% CI -0.9 to 1.3) Significantly favours Rezum ($p < 0.0001$)	12 months, change of 1.5 ± 5.9 (Darson et al., 2017) 91 to 180 days, change of 5.9 ± 7.3 (Mollengarden et al., 2018)	
	PVR**	RCT data (McVary et al., 2016c) Rezum: -10.6 (95% CI -22.3 to 1.1) Sham: 7.2 (95% CI -12.6 to 27.0) No significant difference ($p = 0.108$)	4 years, change of -9.2 ± 72.2 (McVary et al., 2019). 2 years, change of -15.6 ± 93.1 (Dixon et al., 2016b) 12 months, change of -159.0 ± 254.7 (Darson et al., 2017) 91 to 180 days, change of -34.8 ± 119.7 (Mollengarden et al., 2018)	**Weak evidence** that Rezum improves voiding compared with sham. **No consistent evidence** that Rezum improves voiding over the longer term (up to 4 years). Overall, the evidence for Rezum improving urine voiding is weak. Individual data is highly variable.
	Reduction in prostate volume**	Not reported.	After 6 months, there is a 28.9% (17.7 cm^3) reduction in whole prostate volume compared with 1-week post-procedure (Mynderse et al., 2015).	**Moderate evidence** that Rezum shrinks prostate volume. Note: statistical analysis not reported. There may have been a degree of swelling at baseline (1 week post-procedure.
	Need for and/or duration of catheterisation	90.4% (122/135) of patients were catheterised for a mean 3.4 ± 3.2 days in the Rezum arm (McVary et al., 2016c).	Not reported.	**Limited evidence** for catheterisation. This was not an outcome but procedural method; the degree of catheterisation will depend on clinical practice.
	Medication use**	Not reported.	89.5% of patients stopped BPH medication (Mollengarden et al., 2018)	**Weak evidence** Rezum allows for cessation of BPH medication.
	Time to daily activities**	RCT data (McVary et al., 2016c) Rezum: median 4 days (range 0 to 90 days)	Not reported.	**Moderate evidence** that normal activity can be resumed after about 4 days (upon removal of catheter). However, this outcome will

	Outcome taken from the decision problem	Evidence from the Rezum II trial RCT component: 3 month comparison with sham.	Evidence from comparative observational studies (including Rezum II case series): comparison with baseline.	EAC comment on validity of evidence*
		Sham: median 1 day (range 0 to 15 days)		depend on clinical practice following discharge.
Healthcare resource use	Length of hospital stay**	Not reported.	Not reported.	**No evidence.**
	Rates of surgical re-treatment for BPH**		4.4% after 4 years (McVary et al., 2019). 2.3% after 1 year (Mollengarden et al., 2018, Darson et al., 2017)	**Weak evidence** that the re-treatment rate is about 1% per year. Evidence based on low patient numbers and may not be generalisable.
	Healthcare associated infections**	Not reported.	Not reported.	**No evidence.**
	Staff time to train to perform the procedure	Not reported.	Not reported.	**No evidence.**

Abbreviations: BPHII, benign prostatic hyperplasia impact index; ICS, international continence score; IIE-EF, International Index of Erectile Function (erectile function domain); IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; MSHQEjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR, not reported; PVR, post void residual volume; Qmax, peak urinary flow; QoL, quality of life, TURP, transurethral resection of prostate; UTI, urinary tract infection.

* EAC's opinion on the strength of evidence. Strong evidence means direct consistent evidence of significant effect size from RCT and observational studies. Moderate evidence means evidence of some effect from RCT or observational studies, but there is some inconsistency. Weak evidence indicates there is a trend towards an effect, but this may not be statistically significant or there is inconsistent reporting of results.
** Reduction indicates patient benefit.
† Increase indicates patient benefit.

6 Adverse events

The company summarised adverse events (AEs) relating to the Rezum procedure from their literature searches in section 6 of their evidence submission. The EAC cross-checked these against the original papers, added missing details and tabulated under same categories as the adverse event outcomes listed in the decision problem, with the exception of *rate of requirement of subsequent surgical re-intervention*, as this was already included as a system outcome (see section 5.3.3). Where reported, details of study withdrawals or numbers lost to follow up are also presented (Table 6.1).

The company also searched the FDA Manufacturer and User Facility Device Experience (MAUDE) database for the Rezum brand name for reports dated from 01/06/2010 to 30/06/2019. 45 records were found with event dates ranging from 01/03/2018 to 29/05/2019, with the exception of one earlier report, of an event dated 19/12/2016. The company summarised these reports in their submission, in the context of known potential adverse events, including painful urination (dysuria), blood in the urine (haematuria), blood in the semen (haematospermia), decrease in ejaculatory volume, suspected urinary tract infection (UTI), and urinary frequency, retention or urgency. The company concluded that the risk/benefit profile for Rezum is within the expected range compared to comparator BPH treatments. However, they did not provide any comparative evidence to substantiate this assertion.

The EAC repeated the search of the MAUDE database on 24/09/2019 and found a total of 78 records, 21 of which were reports of events dated within the period covered by the company in their submission, but reported to the FDA after the date of their search (30/06/2019). A further 12 reports were of new events which occurred in the period 04/06/2019 to 29/08/2019.

Six of the 78 records were reports of device malfunctions between May and August 2019, five of which related to plastic material being out of place and / or obstructing the device, although without clinical consequences to the patient. Such events in the UK would be potentially reportable to the MHRA, under the Yellow Card Scheme. The other 72 records were categorised as injuries, with no deaths reported. The EAC reviewed each of the narrative reports and concurs with the company assessment that most were known potential adverse events as listed in the device instructions for use (IFU), although of varying duration and severity. There was one report of a heart attack which occurred six days after a Rezum procedure, for which the patient received a cardiac stent and surgery for a suprapubic catheter due to a blood clot in the bladder. They spent time in the intensive care unit (ICU) over a period of 3 weeks and had further surgery at 21 days post-Rezum. No further information was available.

However, it is important to note that the FDA states that their medical device report data alone “cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.” The fact that there is no denominator figure of total procedures undertaken means these MAUDE reports cannot be set in context of all patients treated with Rezum in the USA.

The EAC agrees with the company in their submission that there are no Rezum adverse event reports in the MHRA database.

The NICE Expert Advisors did not raise any safety concerns; although one emphasised the lack of any RCT evidence comparing Rezum with either TURP or another accepted minimally invasive device such as UroLift, to demonstrate both safety and efficacy of the technology.

NICE Interventional Procedures Guidance IPG625 (NICE, 2018b) recommended the Rezum procedure under “standard arrangements” for clinical governance, consent and audit, signalling that the technology was considered safe, based on evidence available at that time (including the pivotal RCT). The types of procedural complications noted in IPG625 and its evidence overview IP1555 (NICE, 2018a) are comparable with those in the FDA MAUDE database and published literature to date. The case of heart attack recorded in MAUDE has not been attributed to the procedure; therefore the EAC concludes that no new safety concerns are raised in this evaluation.

Table 6.1. *Adverse events reported in included studies.*

	Rezum II RCT (McVary et. al)†	**Prospective case series (Dixon et. al)‡**	**Darson et al., 2017**	**Mollengarden et al., 2018**
Withdrawals (or lost to FU)	45 subjects excluded from analysis @ 4 years FU, none attributed to procedure or device-related AEs: • 15 lost to follow-up • 12 withdrew consent (2 with a cancer diagnosis) • 7 censored for use of BPH medications • 4 censored for use of testosterone at follow-up • 1 missed clinic visit • 6 underwent a secondary treatment for LUTS (1 open prostatectomy, 3 plasma-button TURP, and 2 retreated with Rezum)	58/65 (89.2%) remained at 1 year. 7 subjects did not complete the study; • 3 lost to follow-up • 2 relocated • 2 poor health including 1 with previously undiagnosed prostate cancer (radical prostatectomy). 43/65 (66.2%) remained at 2 years In the 12- to 24-month period, 15 subjects exited from the study: • 4 lost to follow-up • 2 missed the 24-month follow-up visit • 2 died	Not reported	2/129 (1.6%) lost to FU

	Rezum II RCT (McVary et. al)†	Prospective case series (Dixon et. al)‡	Darson et al., 2017	Mollengarden et al., 2018
		• 2 had other treatment (1 open prostatectomy, 1 TURP • 5 had a second phase of treatment with convective RF water vapour thermal therapy		
Device-related adverse events (or serious procedure-related adverse events)	No perioperative device or procedure-related AEs 8 serious AEs in 7 subjects reported at 0-3 months (5.1%), of which 3 serious AEs in 2 subjects were adjudicated as procedure-related (1.5%), comprising: - 1 *de novo* extended urinary retention [1] - 1 nausea and vomiting due to alprazolam In the crossover group at 3-12 months (n=53), 8 serious AEs reported in 6 subjects (11.3%), of which 3 serious AEs in 2 subjects were	No perioperative serious device or procedure-related AEs 3 serious AEs adjudicated as procedure-related in 1 subject reported at 0-1 months (1.5%) (subsequently underwent TURP) No serious AEs adjudicated as procedure-related from 1 month onwards Non-serious AEs adjudicated as related to the procedure (summarised in this table) included urinary retention,	No perioperative device or procedure-related AEs	Not reported

	Rezum II RCT (McVary et. al)†	Prospective case series (Dixon et. al)‡	Darson et al., 2017	Mollengarden et al., 2018
	adjudicated as procedure-related (3.8%), comprising: - 1 subject with bladder contracture and bladder calculi 6 months after Rezum - 1 urosepsis after FU cytoscopy	dysuria, urinary urgency, suspected UTI, haematuria, poor stream, other painful/discomfort, nocturia, urinary frequency, urethral secretion (without haematuria or stones), fever, terminal dribbling, scrotal pain/discomfort and urge urinary incontinence.[3] No late occurring device or procedure-related AEs were reported in the 12- to 24-month follow-up.		
Rate of dysuria (pain)	23/136 (16.9%) at 0-3 months 1/136 (0.7%) at 3-12 months	14/65 (21.5%)[3]	Not reported	Not reported
Rate of persistent LUTS (poor stream, frequency)	Urinary frequency: 9/136 (5.9%) at 0-3 months Urinary urgency: 9/136 (5.9%) at 0-3 months	1 patient had persistent LUTS (poor stream, frequency, and urinary retention) adjudicated as 3 separate serious	Non-persistent ≤3.8% of 131 patients comprising: urinary frequency, urgency, frequency and urgency, haematuria and nocturia.	Post-void dribbling: 5/129 (3.9%) (Clavien-Dindo Grade I). Persistence of this event not reported; however, 3/129

	Rezum II RCT (McVary et. al)†	Prospective case series (Dixon et. al)‡	Darson et al., 2017	Mollengarden et al., 2018
	None reported at 3-12 months	device/procedure related events (Clavien-Dindo Grade IIIb). The median lobe had not been treated and a TURP procedure was undertaken at 42 days Non-serious AEs adjudicated as related to the procedure[3]: - Poor stream: 9/65 (13.8%) - Urinary frequency: 4/65 (6.2%) - Urinary urgency: 13/65 (20.0%) - Nocturia: 5/65 (7.7%) - Terminal dribbling: 2/65 (3.1%)	Mild-moderate severity and most resolved within a short time, with or without routine treatment.	(2.3%) of patients underwent additional intervention for persistent LUTS (2 repeat Rezum and one photovaporisation of the prostate).
Rate of urinary retention	De novo, extended: 1/136 (0.7%)[1] Acute: 5/136 (3.7%) at 0-3 months None reported at 3-12 months	22/65 (33.8%) urinary retention (duration of inadequate voiding >24 h)[3]	14/131 (10.7%) in the post-operative period, resolved within a short time, with or without treatment	18/129 (14.0%) (of which 2/18 Clavien-Dindo Grade III, 16/18 Clavien-Dindo Grade I)

	Rezum II RCT (McVary et. al)†	Prospective case series (Dixon et. al)‡	Darson et al., 2017	Mollengarden et al., 2018
Other complications included in economic model				
Urinary tract infection (UTI)	Culture proven UTI: 4/136 (2.9%) Suspected UTI: 5/136 (3.7%) Epididymitis: 4/136 (2.9%)	Suspected UTI: 13/65 (20.0%) (resolved with antibiotics within a few days to 4 weeks)[3] Fever: 3/65 (4.6%)[3] Urethral secretion – without haematuria or stones: 3/65 (4.6%)[3]	Not reported	UTI: 22/129 (17.1%) (Clavien-Dindo Grade II) Epididymo-orchitis: 2/129 (1.6%) after 4 to 12 months FU (Clavien-Dindo Grade II)
Bleeding or blood transfusion	Gross haematuria: 16/136 (11.8%) Haematospermia: 10/136 (7.4%)	Haematuria: 9/65 (14%)[3]	Absolute rate of haematuria not reported, but ≤3.8% of 131 patients had non-serious AEs comprising: urinary frequency, urgency, frequency and urgency, haematuria and nocturia	Not reported
Bladder neck contracture or stricture	1/53 (1.9%) in crossover group, 6 months after Rezum[2]	Not reported	Not reported	Bladder neck contracture: 1/129 (0.8%) within 4 to 12

	Rezum II RCT (McVary et. al)†	Prospective case series (Dixon et. al)‡	Darson et al., 2017	Mollengarden et al., 2018
				months FU (Clavien-Dindo Grade III) Urethral stricture: 5/129 (3.9%) within 4 to 12 months FU (Clavien-Dindo Grade III)
Incontinence	Not reported	Urge incontinence 1/65 (1.5%)[3]	Not reported	5/129 (3.9%) after 4 to 12 months FU (Clavien-Dindo Grade I)

† Data from (McVary et al., 2016a) and prospective case series at 2 years (Roehrborn et al., 2017c), 3 years (McVary and Roehrborn, 2018), and 4 years (McVary et al., 2019)
‡ Data at 1 year FU from (Dixon et al., 2015), and 2 years FU (Dixon et al., 2016)
1. Adjudicated as a procedure-related adverse event (McVary et al., 2016a), ITT analysis (n=136) at 3 months FU
2. Adjudicated as a procedure-related adverse event (McVary et al., 2016a) in the crossover group (n=53) at 6 months post-Rezum
3. Adjudicated as a procedure-related non-serious adverse event (Dixon et al., 2016) up to 24 months FU

7 Evidence synthesis and meta-analysis

There was no direct evidence identified in the literature comparing Rezum with any comparator technology listed in the scope. Because of this, the company reported data on an indirect comparison of Rezum compared with another minimally invasive technology, UroLift, the subject of MTG26 (NICE, 2015d). This was possible because UroLift was compared with sham in the LIFT study (Roehrborn *et al.*, 2017b). The LIFT study had a very similar design and implementation to the Rezum II trial (Woo, 2017), and several authors contributed to both studies. Like the Rezum II trial, the LIFT study was an RCT which randomized patients to receive UroLift (n = 140) or sham (n = 66) with follow up at 3 months. The primary efficacy outcome was change to the IPSS score. After 3 months, patients in the UroLift arm were unblinded and were followed up at regular intervals up to 5 years.

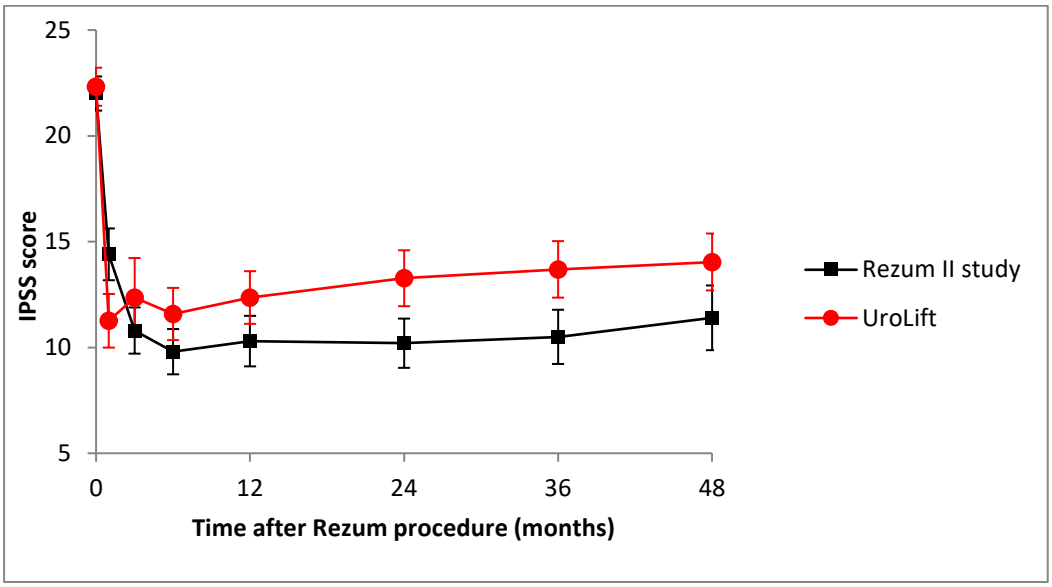
The EAC has reviewed the data the company used for the comparison, which was also reported in a conference abstract (Hernandez *et al.*, 2019). It is unlikely this study abstract has been peer-reviewed, and formal critical appraisal of it by the EAC was not appropriate because a systematic review and meta-analysis was not presented, rather one study of each intervention was indirectly compared. The EAC did not identify any important flaws in the methodology reported. The studies enrolled patients with similar baseline characteristics (Table 1 and Table 2 of Section 7 of the submission). The main difference was that the Rezum II trial did not exclude patients with median lobe obstruction, which accounted for 31.1% of patients (median lobe or elevated bladder neck from central zone hyperplasia) (McVary et al., 2016c). The sham response was similar in each study, with the exception of PVR, which did not demonstrate a positive sham response in patients receiving UroLift.

Five outcomes were compared at 3 months. These were IPSS, IPSS-QoL, BPHII, Qmax, and PVR. The results are reported in Figure 2 of Section 7 of the submission. The results for each intervention at 3 months were similar with no statistical differences detected. The exception to this was the peak urinary flow rate, which was significantly higher in patients receiving Rezum (3.4 mL/s [95% CI 1.2 to 5.6 mL/s]). A change of 2 mL/s may be regarded as a minimally important clinical difference (NICE, 2015b).

The company reported a graph of freedom from retreatment for Rezum and UroLift in Figure 3 (Section 7 of submission) that showed the rate of retreatment was significantly higher for UroLift than for Rezum (p = 0.04, log rank test). At 4 years, the rate of retreatment for Rezum was 4.4% (McVary *et al.*, 2019). This compared with a rate of retreatment of 13.6% for UroLift after 5 years (Roehrborn *et al.*, 2017b). The EAC has graphed the IPSS scores for each intervention compared with baseline for 4 years post-procedure in

Figure 7.1. It can be seen that whilst both technologies are associated with rapid and enduring falls in IPSS (i.e. improvements in LUTS), Rezum appears to result in a greater improvement in this outcome over time.

Figure 7.1. *Longitudinal IPSS scores associated with Rezum and UroLift (error bars indicate 95% CI).*



These data give confidence that Rezum is at least as effective as UroLift in terms of patient outcomes, and is associated with a significantly reduced need for surgical retreatment. Like Rezum, UroLift is regarded as a minimally invasive treatment for BPH and is positioned on the same part of the clinical pathway (EAC External correspondence log, 2019). NICE experts have also indicated that GreenLight laser is positioned "next" on the pathway. However, the primary evidence to support this technology was an RCT comparing GreenLight with TURP, the GOLIATH trial (Bachmann *et al.*, 2014). As no comparison with sham has been undertaken for GreenLight, it is not possible to indirectly compare these interventions.

8 Interpretation of clinical evidence

The safety and efficacy of Rezum is supported by 1 RCT (McVary et al., 2016c), which also provided data for a cross-over study (Roehrborn *et al.*, 2017c) and a prospective case series reporting data up to 4 years (McVary *et al.*, 2019); 1 prospective case series reporting data at 2 years (Dixon *et al.*, 2016b), and 2 retrospective observational studies (Mollengarden et al., 2018, Darson et al., 2017). Data reported from these studies provide unequivocal evidence that Rezum improves objective urological measurements (Qmax) and urinary symptoms experienced by the patient for at least 4 years.

Concurrent to the urological symptom improvement, no significant decline in sexual function was observed in the early years following treatment, an important consideration when deciding which treatment modality to use.

The patient population these studies enrolled is reported in Table 8.1. This population is consistent with patients who have symptomatic BPH with symptoms refractory to medical management. These patients also appear to be representative of those in the NHS of England and Wales, with no important issues concerning generalisability identified. Additionally, the benefits of Rezum have been reported in an NHS setting (Johnston *et al.*, 2019).

There were two important gaps in the evidence. Most notably, there was no direct evidence identified comparing Rezum with any of its comparators. There was unpublished indirect evidence that showed Rezum was at least as effective as UroLift, and treatment is likely to be more durable, requiring fewer retreatments, at least in the medium (4 years). However, comparative evidence of any type with TURP, HoLEP, and GreenLight, was lacking. Secondly, there was a lack of data on outcomes related to healthcare resource use, which instead had to be informed by expert opinion or unpublished abstracts. This meant that some of the claimed benefits made by the company (Section 2 of the submission) could not be directly substantiated by published clinical evidence. In turn, this meant there was some uncertainty in the economic analysis (see Section 9).

Table 8.1. *Baseline characteristics of included studies.*

Characteristic	Rezum II RCT and case series (McVary 2016b)		Prospective case series (Dixon 2015)	Retrospective case series (Darson, 2017)	Retrospective case series (Mollengarden, 2017)
	Rezum arm (n = 135)	Sham (n = 61)	Rezum (n = 65)	Rezum (n = 131)*	Rezum (n = 129)
Age (years)	63.0 (7.1)	62.9 (7.0)	66.7 (7.7)	70.9 (9.4)	67.4 (8.0)
BMI (Kg/m^2)	28.7 (4.4)	28.1 (5.0)	26.1 (3.4)	NR	NR
Prostate volume (cm^3)	45.8 (13.0)	44.5 (13.3)	48.8 (20.7)	45.1 (23.4)	52.6 (17.0)
PSA (ng/ml)	2.1 (1.5)	2.0 (1.6)	3.9 (4.2)	3.5 (5.6)	2.45 (1.91)
IPSS	22.0 (4.8)	21.9 (4.7)	21.6 (5.5)	19.5 (6.6)	18.3 (7.5)
IPSS-QoL	4.4 (1.1)	4.6 (2.3)	4.3 (1.1)	NR	NR
Qmax (ml/sec)	9.9 (2.3)	10.4 (2.1)	7.9 (3.2)	8.6 (4.9)	10.5 (4.3)
PVR (ml)	82.0 (51.5)	85.5 (51.6)	92.4 (77.3)	217 (287)	106 (127)
ICS	4.4 (2.8)	4.4 (1.1)	NR	NR	NR
MSHQEjD	7.8 (4.1)	9,0 (3.8)	NR	NR	NR
OAB bother	39.6 (18.0)	39.9 (18.3)	NR	NR	NR
OAB HRQoL	64.5 (20.0)	66.7 (16.9)	NR	NR	NR

Abbreviations: BMI, body mass index; BPHII, benign prostatic hyperplasia impact index; ICS, international continence score; IPSS, International Prostate Symptom Score; MSHQEjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR, not reported; OA, overactive bladder questionnaire; PVR, post void residual volume; Qmax, peak urinary flow rate; QoL, quality of life.

Number in parentheses is standard deviation, where reported.

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8.1 Integration into NHS

Currently, there are no published, peer-reviewed studies reporting data on the use of Rezum in the NHS. However, several studies have been published in abstract form. A summary of these is reported in Table A4, Appendix A. These lend support that Rezum can be integrated into the NHS of England and Wales and the technology can provide the benefits seen in the international clinical evidence literature.

The company described system changes that would be required to adopt Rezum in Section 3 of the submission. The company has positioned Rezum as being between pharmacotherapy (typically following medical treatment failure) and more invasive surgery such as TURP, HoLEP, which usually requires in-patient care. As a minimally-invasive treatment, Rezum is normally performed as a day-case, requiring no overnight stay. In this respect it most closely resembles UroLift, which has already been adopted into the NHS (NICE, 2015d). Both these treatments could be undertaken interchangeably in the same setting (EAC External correspondence log, 2019). The picture is less clear for GreenLight, which can be performed as a day case in some patients, but is considered to be more invasive than UroLift of Rezum.

The company stated “there are no additional tests or investigations that will be required with the use of Rezum. It requires the same level and understanding of clinical presentation required of TURP or alternative therapies”. The EAC agrees with that Rezum will not require additional diagnostic or management strategies. In addition, the Rezum procedure allows for treatment of patients with median lobe or elevated central zone hyperplasia, who are currently contraindicated to treatment with UroLift.

The company listed the training requirements for Rezum in Section 3 of the submission. This comprises of a two-day training course of foundational training and simulator training. This is offered free of charge by the company but will result in an opportunity cost to the NHS.

8.2 Ongoing studies

The company identified two ongoing studies. One study was identified from internal sources, this was the anticipated 5-year follow up of the Rezum II trial, due for publication in 2020. The other study was identified by the EAC and is reported briefly below (NCT03605745).

The EAC searched the following databases for ongoing studies as part of the additional literature search: Clinicaltrials.gov, World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) and ISRCTN registry. From these searches, the EAC identified protocols for three completed studies: the RCT (n=197, NCT01912339, 2016), and two single arm studies which have no results/publication shared (Rezum I pilot n=50, NCT02943070, 2018), (Rezum FIM, n=15, NCT02940392, 2018). Two additional ongoing studies were also identified (one of which was identified by the company NCT03605745). These are reported in Table 8.2.

Table 8.2. *Ongoing studies identified by the EAC.*

Study title, reference	**Status, estimated completion**	**Population (n)**	**Primary outcome measure(s)**	**Secondary outcome measure(s)**
Minimally Invasive Prostatic Vapor Ablation - Multicenter, Single Arm Study for the Treatment of BPH in Large Prostates (Rezūm XL) (NCT03605745)	Recruiting Primary completion: Sept 2020 Study completion: March 2023	Single arm, prospective non-randomised (n=88) in patients with large prostates (prostate volume >80 cm^3 to ≤150 cm^3)	IPSS improvement [6 months]; Post-procedure device related serious complications [6 months]	Device-related catheterization rate [6 months]; Absolute IPSS improvement [6 months]; percentage IPSS responders [1, 2, 3 years]
A Pilot Study to Assess Efficacy and Safety of Methoxyflurane for Pain Control During Convective Thermal Therapy Using Rezūm System in Benign Prostatic Hyperplasia (BPH) (NCT04029012)	Not yet recruiting Study start date: Sept 2019 Study completion: Dec 2019	Single-arm (n=10)	Pain intensity [immediately after final injection of Rezum]	None

9 Economic evidence

9.1 Published economic evidence

9.1.1 Search strategy and selection

The company used the same search strategies for clinical and economic evidence, as reported in Part 1 and Part 2 of their submission. The EAC validation of company searches also identified relevant economic studies, including the same published study included by the company, plus one conference abstract and one published review article, both of which were excluded by the EAC on the basis of study type. The EAC was therefore satisfied that all the relevant economic studies had been identified and the company's economic search strategy had been adequate for this purpose.

9.1.2 Published economic evidence review

The company reported on two economic studies that were relevant to the decision problem. One study was a fully published, peer-reviewed economic analysis (Ulchaker and Martinson, 2018). This was the only economic study identified by the EAC through its literature search. The other study reported by the company was a pending conference abstract that was flagged as commercial in confidence. It has been accepted for the EU ISPOR conference in Copenhagen (2nd to 6th November 2019).

The study by Ulchaker and Martinson (2018) reported a cost-effectiveness analysis framework using a cohort Markov decision analytic model. This study adopted a 2 year time horizon from an American third party payer persepective, and compared six treatment options in men with symptomatic BPH. These were pharmacotherapy (generic and propietary); minimally invasive treatments defined as Rezum, UroLift, and Prostiva (a radiofrquency thermal device); and surgically invasive treatments consisting of TURP or GreenLight laser. Treatment with HoLEP was not considered. The study was costed in US dollars and used IPSS units as the effectiveness measure. The company described the study in Table 1 of the economic submission, but did not formally critical appraise it. The EAC has done so in Appendix C using the Drummond checklist (Drummond *et al.*, 2005). Overall the EAC considered the study was of poor methodological quality. This was because there was a lack of information given on the informing clinical studies, and lack of transparency on the adjustments required to calculate IPSS values, baseline values and the values adopted on reinterventions, and adverse events. This rendered the results of the model highly uncertain. Additionally the model had a limited time horizon of 2 years and reported aggregated treatment costs that were very different to the NHS of England and Wales.

The abstract, by Shore *et al.* (2019) (listed in company submission) was entitled “Cost-Effectiveness of Convective Water Vapor Energy Therapy Compared to Prostatic Urethral Lift for Treatment of Benign Prostatic Hyperplasia”, and was provided by the company. It was a cost-utility analysis that compared Rezum with UroLift in patients with symptomatic BPH over a 4-year time horizon. The perspective appears to have been from that of a US third party payer. As it was an abstract, no formal critical appraisal was possible. The study was funded by Boston Scientific, the manufacturer of Rezum.

9.1.3 Results from the economic evidence

The company reported the results of the published economic study (Ulchaker and Martinson, 2018) in Table 1 and Table 2 of the submission. The EAC has cross-referenced these results with the source data and found them to be accurate. The principal results of the study are reported in Table 9.1.

Table 9.1. *Principal results of the economic study by Ulchaker and Martinson (2019).*

Treatment	Procedural costs*	Total costs**	IPSS***	ICER (cost/IPSS unit)
Rezum (Base comparator)	$2489	$2582	10.2	N/A
Pharmacotherapy†	N/A	$1736	18.9	$97
UroLift	$6230	$6386	11.4	-$3058 DOMINATED
GreenLight	$4661	$5099	7.4	$900
TURP	$4821	$5181	6.4	$686

Abbreviations: ICER, incremental cost-effectiveness ratio; IPSS, international prostate symptom score; TURP, transurethral resection of prostate;.

* Includes diagnostic work up, post-procedure assessment, and 1 year check-up.
** Mean costs at 2 years (including management of adverse events)
*** Mean IPSS score at 2 years follow up. Pre-procedural score assumed to be 22.
† Assuming generic drugs. Initiation cost (6 months) $519, thereafter $394 per cycle.

Rezum therapy dominated treatment with UroLift, having an initial procedural cost which was estimated to be $3500 less expensive, and being slightly more efficacious. Probabilistic sensitivity analysis (PSA) indicated that there was a 100% chance that Rezum was both less costly and more effective than UroLift. The more invasive procedures (TURP and GreenLight) were both more effective than Rezum, but also considerably more costly. It is not possible to report if they are cost-effective options compared with Rezum without a relevant willingness-to-pay threshold for a point of IPSS, or minimally important difference (3 points).

The abstract reported that Rezum was associated with a gain in quality-adjusted life-years (QALYs) of 3.548 compared with 3.489 (difference 0.059) for UroLift over 4 years. As Rezum was also significantly less expensive ($2269 vs. $7109), it dominated UroLift. Rezum was less expensive than UroLift 100% of the time and associated with higher QALYs more than 95% of the time, using PSA.

The results from these studies are supportive of Rezum being less expensive, more effective, and cost-effective, compared with UroLift. Rezum is less expensive than the invasive surgical procedures of TURP and GreenLight, but was also found to be less effective in terms of reducing symptoms (Ulchaker and Martinson, 2018).

9.2 Company de novo cost analysis

9.2.1 Development of economic model

The company developed a decision analytic model that incorporated elements of a previous health technology assessment (HTA) (Lourenco *et al.*, 2008) funded by the National Institute for Health Research (NIHR), that was partly used to inform NICE CG97 (NICE, 2015a), as well as the included economic study (Ulchaker and Martinson, 2018). The model structure, key assumptions, clinical inputs, adverse events, and procedure costs were developed and drafted, and presented to key opinion leaders (KoLs, five UK clinical experts in the field, named in Section 3 of the economic submission) in June 2019. Following discussion on this presentation, changes to the model and inputs were decided by consensus. The EAC has been provided with a copy of the presentation as well as changes made to the model as a result of this discussion.

The EAC considered the model development process was appropriate and transparent. Whilst formal expert elicitation techniques (Peel *et al.*, 2018) may have added to the robustness of the model, these approaches are difficult to undertake within the timeframe of MTEP assessment. Furthermore, the company used published data for clinical and costing inputs wherever possible, including data previously used in NICE HTAs.

9.2.2 Economic model structure

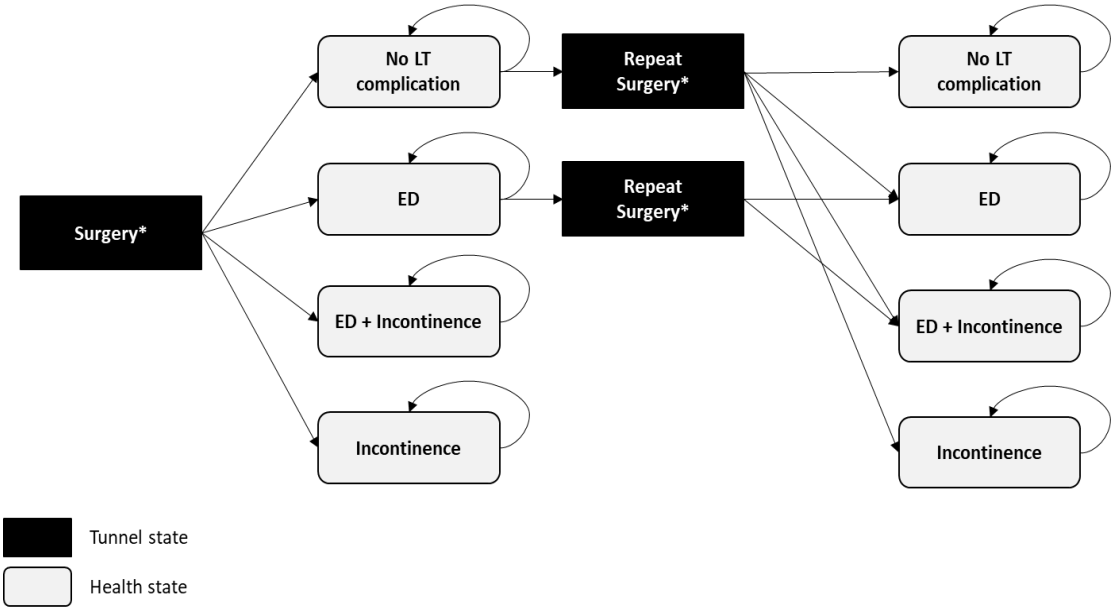
The company reported a *de novo* economic model that compared Rezum to four comparators: UroLift (considered as minimally invasive treatment); GreenLight laser therapy; HoLEP; and TURP (all considered as surgically invasive). The latter therapy was modelled as a hybrid between conventional mono-polar TURP and bipolar TURP (as there were differences in consumable costs, length of stay and complication rates). UroLift (NICE, 2015d), GreenLight (NICE, 2016) and bipolar TURP (transurethral resection in

saline [TURis]) (NICE, 2015c) have been the subjects of previous MTEP guidance.

The model incorporated a cohort Markov structure, with a time horizon of 4 years and a cycle length of 3 months. It was programmed using Microsoft Excel, and was clearly and transparently structured, with each technology assigned its own sheet containing relevant parameters including transition probabilities, procedure and AE costs, and results (undiscounted and discounted total costs). There were also sheets providing the same information for each parameter, by procedure, to facilitate comparisons between technologies. Summarised results and sensitivity analyses were presented on separate sheets, with tornado diagrams used to present univariate deterministic sensitivity analysis (DSA) and incremental cost difference curves for PSA. The model also had inbuilt functionality to model sexually active men with no prior history of erectile dysfunction (ED).

The structure of the model is illustrated in Figure 9.1, taken from the company's submission, and is described in Section 3 of the economic submission. For each comparator, the simulated cohort undergoes an initial surgical procedure modelled as one-cycle tunnel state, where they are subject to costs associated with the procedure as well as short term adverse AEs, consisting of AUR ([acute urinary retention] non-serious and serious), UTI (non-serious and serious), bleeding (non-serious and serious) bladder contracture/stricture (serious), and transurethral resection (TUR) syndrome (serious). There are two permanent AEs that inform the long-term heath states of the model. These are ED and urinary incontinence; additionally there is a health state for concomitant ED and incontinence. Erectile dysfunction only informs costs in the specific ED scenario analysis (programmed as a "switchable" option). Following treatment, patients may require surgical retreatment for recurrence of LUTs. Patients with ED can have retreatment for LUTs, but this has no effect on their ED status. Patients with urinary incontinence are assumed to be contraindicated for further surgery.

Figure 9.1. *Structure of the de novo economic model.*



Abbreviations: LT, long-term; ED, erectile dysfunction
*Surgical tunnel states include risk of short-term complications with surgery

The company listed the assumptions informing the model structure in Table 2 of the economic submission. The EAC has replicated this table, and responded with its opinion on whether the assumptions were justified in Table 9.3. In the main, the EAC considered that the assumptions were justified; therefore no change was required to the structure base case of the model. Inevitably, some of the assumptions were associated with uncertainty (due to limited empirical data and use of expert opinion). Further assumptions were reported in Table 3 and 4 of the economic submission. These were all appropriate for the MTEP programme.

One fundamental assumption of the company's submission was that the technologies had equivalent efficacy in alleviating LUTS. The company stated in the Model Overview section (page 16) that "Part 1 of this submission demonstrates that Rezum is associated with similar clinical outcomes with respect to alleviating symptoms of LUTS as all surgical and minimally invasive comparators". However, other than the indirect comparison with UroLift (Section 7 of the submission), no comparisons of efficacy with other technologies were undertaken, because no comparative studies were identified. This is important, because there is an implicit relationship between deterioration of LUTS (treatment efficacy and permanency) and the need for retreatment that may not have been adequately captured by the model.

A review of the clinical efficacy of the comparator technologies is beyond the scope of this Assessment Report. However, Figure 9.2 illustrates longitudinal data taken from trials used to inform the economic submission. These trials have enrolled patients with similar baseline characteristics, that is, the patient characteristics were homogenous (see Table 9.2). The data suggests the technologies may not be equivalent in reducing LUTS, as measured using IPSS, a contention that was confirmed by NICE clinical experts (EAC External correspondence log, 2019). Conversely, other technologies may not preserve sexual function to the extent that Rezum does, although this is captured by the model. These issues are discussed in Section 10.

Figure 9.2. *Longitudinal IPSS values following the procedure. Data taken from Rezum II trial (McVary et al., 2016c), LIFT trial (UroLift) (Roehrborn et al., 2017b), and GOLIATH trial (TURP and GreenLight laser) (Thomas et al., 2016).*

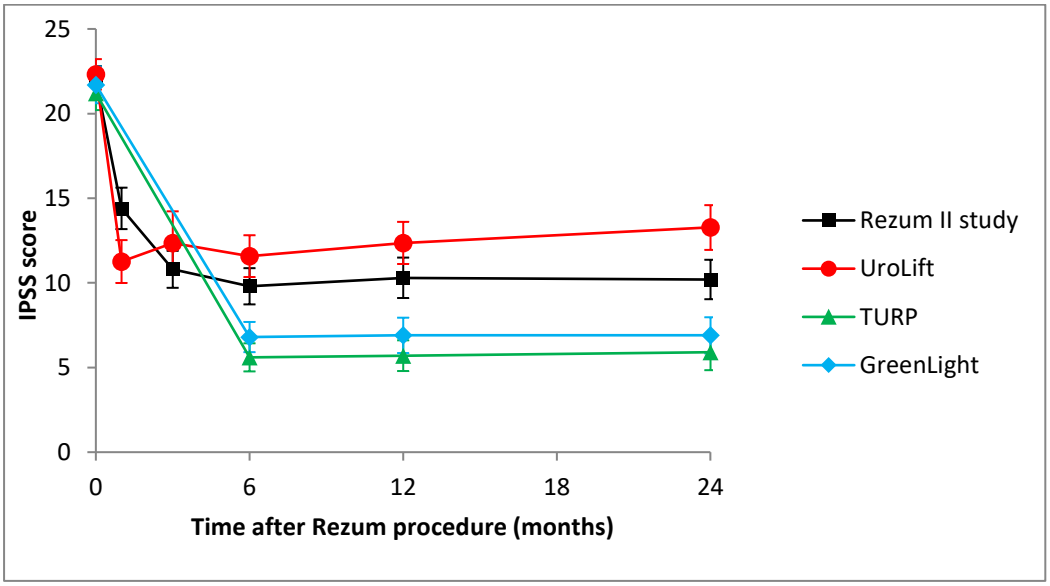


Table 9.2. *Baseline patient characteristics of studies used to inform economic submission.*

	Rezum (n = 135) Rezum II trial (McVary et al., 2016c)	**UroLift (n = 140) LIFT trial (Roehrborn et al., 2013)**	**GreenLight (n = 136) GOLIATH trial (Bachmann et al., 2014)**	**TURP (n = 133) GOLIATH trial (Bachmann et al., 2014)**	**TURP (n = 35) BPH6 trial (Sonksen et al., 2015)**
Age (years)	63.0 (7.1)	67.0 (8.6)	65.9 (6.8)	65.4 (6.6)	65 (6.4)
BMI (Kg/m^2)	28.7 (4.4)	28.3 (4.2)	27.3 (3.9)	27.5 (3.8)	NR
Prostate volume (cm^3)	45.8 (13.0)	44.5 (12.4)	48.6 (19.2)	46.2 (19.1)	41 (13)
PSA (ng/ml)	2.1 (1.5)	2.4 (2.0)	2.7 (2.1)	2.6 (2.1)	2.6 (2.1)
IPSS	22.0 (4.8)	22.5 (5.4)	21.2 (5.9)	21.7 (6.4)	23 (5.9)
IPSS-QoL	4.4 (1.1)	4.6 (1.1)	NR	NR	NR
Qmax (ml/sec)	9.9 (2.3)	8.9 (2.2)	9.5 (3.0)	9.9 (3.5)	9.5 (3.2)
PVR (ml)	82.0 (51.5)	85.6 (69.2)	110.1 (88.5)	109.8 (103.9)	102 (87)
ICS	4.4 (2.8)	NR	NR	NR	NR
MSHQEjD	7.8 (4.1)	8.7 (3.2)	NR	NR	9 (2.3)
OAB bother	39.6 (18.0)	NR	NR	NR	NR
OAB HRQoL	64.5 (20.0)	NR	NR	NR	NR

Abbreviations: BMI, body mass index; BPHII, benign prostatic hyperplasia impact index; ICS, international continence score; IPSS, International Prostate Symptom Score; MSHQEjD, Male Sexual Health Questionnaire for Ejaculatory Dysfunction; NR, not reported; OA, overactive bladder questionnaire; PVR, post void residual volume; Qmax, peak urinary flow rate; QoL, quality of life.

Number in parentheses is standard deviation, where reported.

Table 9.3. *Principal structural assumptions in the de novo model.*

Assumption	Company justification	Company source	EAC opinion
All short-term complications with surgery are assumed to be independent and non-mutually exclusive.	This assumption is consistent with data reported in clinical trials.	Trial and HTA evidence (Roehrborn et al., 2013, McVary et al., 2016c, Lourenco et al., 2008, Bachmann et al., 2014)	This assumption is consistent with clinical evidence and is logically consistent.
Only short-term complications commonly reported to be associated with BPH surgery that required medical interventions were considered in the model. This assumption meant that some severe events reported in the pivotal trials for Rezum and UroLift were not captured in the model. The Rezum pivotal trial reported two severe device- related adverse events that were not captured in the model: 1 case of nausea, requiring hospital admission and 1 case of urosepsis. Similarly, the LIFT study reported two severe adverse events related to the procedure that were not captured in the model: 1 case of clot retention and 1 subject who required removal of a bladder stone at 12 months.	The inclusion of these events was discussed with clinicians consulted during model development who provided feedback that such events are not common to BPH surgery and were likely to be one-off events. Furthermore, the impact of including these in the model was expected to be very low as the rates would have been <1% for each adverse event type.	Trial evidence (Roehrborn et al., 2013, Roehrborn et al., 2017c, McVary et al., 2016c)	This is not a conservative assumption as it favours Rezum and UroLift (potentially introduces bias). However, the EAC recognises that introducing the AEs into the model is problematic because: • The data for each AE consists of one person. • It is unclear if the AEs are causally linked to the intervention. • Scenario analysis (unreported) showed the inclusion of rare adverse events made little difference to the results. • Similar rare AEs may have occurred in other comparator technologies that have not been reported. For instance, typically systematic reviews and meta-analyses do not report very rare AEs. A full description of AEs associated with Rezum, including device related AEs, is discussed in Section 6.
While most short-term complications occur within 90 days of surgery, some short-term complications are reported up to 6 months post-surgery. Data on adverse events was therefore extracted	This assumption was applied to replicate the Markov structure applied in prior BPH models (Lourenco et al., 2008) and account for the fact that most	Not applicable	The EAC accepts that given the structure of the model, where the procedural intervention is a one-cycle tunnel state, this is a reasonable simplification.

Assumption	Company justification	Company source	EAC opinion
from clinical trials up to 6 months post-surgery and where complications occurred between 3-6 months post-surgery, they are assumed to occur by 3 months for accounting purposes.	short-term complications are resolved within 90 days of surgery.		
Adverse events were categorised by two levels of severity namely non-severe and severe, where non-severe adverse events were assumed to be treated in primary care. Non-severe events were defined as non-acute, non-severe or ≤ grade 2 and included urinary retention, urinary tract infection and bleeding.	Complications were stratified by severity as non-severe events are expected to incur substantially lower costs. This assumption is consistent with the resource use assumptions applied in the GreenLight MTEP model (NICE MTG 29) and was validated with clinical experts consulted during model development.	NICE MTG29 (NICE, 2016). Clinical experts	The premise of classifying AEs as non-serious and serious is justifiable. In the Rezum II trial (McVary et al., 2016c), AEs were categorised as non-severe or severe, although the system used was not specified. In the GOLIATH trial (Bachmann et al., 2014), the Clavien-Dindo grade (Dindo et al., 2004) was used to inform AE severity for GreenLight and TURP. UroLift AE severity was not graded in LIFT trial (Roehrborn et al., 2013). The company's approach to estimating AE rates and severity was acceptable, although there are inevitably some uncertainties. For instance, the company informed the EAC during its fact check that short-term bleeding events reported in the Rezum trial did not require medical intervention. However, the EAC has confirmed that costs associated with AEs were not a principal driver of the economic model (see Section 9.3.2), so has not updated this data.
Adverse events with TURP and HoLEP were sourced from Lourenco et al. (2008), however this meta-analysis did not report adverse events by severity. The following assumptions were therefore applied to calculate the rates of severe and non-severe events for Mono-TURP, Bi-TURP and HoLEP:	Lourenco et al. (2008) reported results from a meta-analysis previously used to inform NICE guidance. 1. Clinical experts consulted during model development. They provided feedback that the majority (estimated ~90%) of	HTA and trial evidence (Lourenco et al., 2008, Bachmann et al., 2014) and Clinical Expert Opinion.	A hybrid method of estimating AEs for TURP and HoLEP, using meta-analysis and RCT data, was appropriate, but introduced some uncertainty into the model. Note: costs associated with AEs were not a principal driver of the economic model (see Section 9.3.2).

Assumption	Company justification	Company source	EAC opinion
1. 90% of UTI events were assumed to be non-severe. 2. The distribution of severe and non-severe urinary retention events was sourced from the TURP arm of GOLIATH RCT (Backmann et al. 2014). 3. All bleeding, bladder neck contracture / stricture / bladder stones and transurethral resection syndrome (TUR) events reported in Lourenco et al. (2008) were assumed to be severe.	urinary tract infections after surgery were non-severe and could be treated at home / primary care with medication. 2. The GreenLight RCT reported the rates of urinary retention for TURP by grade. 3. Clinical experts provided feedback that bleeding events occurring with TURP are expected to be grade 3+ and that all stricture / TURs events are treated in secondary care.		
All incontinence events were assumed to be moderate / severe and permanent.	This replicates the assumption applied in Lourenco et al. (2008). The same assumption was applied and accepted in the Neotract MTEP submission for UroLift (NICE, 2015d).	HTA (Lourenco et al., 2008) NICE MTG26 (NICE, 2015d)	The risk of permanent incontinence was a feature of the meta-analysis and economic model of the HTA (Lourenco et al., 2008), and this assumption was accepted for NICE MTG26 (NICE, 2015d). Based on precedent, the EAC accepts this assumption.
Patients that have incontinence after the initial procedure remain in the same health state and cannot have repeat surgery for LUTS.	This replicates the assumption applied in Lourenco et al. (2008), justified because permanent incontinence is contraindicated for further surgical treatments	HTA (Lourenco et al., 2008)	Permanent incontinence being a contraindication for further surgery for LUTS was a feature of the meta-analysis and economic model of the HTA (Lourenco et al., 2008). Based on this precedent, the EAC accepts this assumption.
The risk of incontinence for Rezum and UroLift is zero.	For Rezum and UroLift no cases of permanent incontinence post-procedure have been reported in clinical trials. This replicates the assumption that was applied and accepted	Trial data (Roehrborn et al., 2013, Roehrborn et al., 2017c, McVary et al., 2016a)	The EAC accepts that cases of serious, permanent urinary incontinence are likely to be low for Rezum. However, due to the small sample size, it may not be assumed to be zero. Urinary incontinence was reported in 1.5% (Dixon et al., 2015) and 3.9% of patient (Mollengarden et al., 2018) in observational studies, but these were low grade (see Section 6)

Assumption	Company justification	Company source	EAC opinion
	in the Neotract MTEP submission for UroLift (NICE, 2015d)		and not likely to generate the costs used in the model As Rezum uses thermal energy to destroy tissue, there is a plausible mechanism for urinary incontinence, which could be severe (EAC External correspondence log, 2019). The EAC has therefore changed the incontinence rate for Rezum and UroLift to 1%, based on HES data for UroLift. This is regarded as a conservative assumption.
All revision surgeries after TURP and UroLift are repeated with TURP. If symptoms reoccur after a UroLift procedure, it is expected that a TURP procedure would be performed alongside an operation to remove the original LIFT implants.	This assumption replicates the assumption applied in the UroLift MTEP submission for UroLift and is consistent with clinical opinion.	NICE MTG29 (NICE, 2016). Clinical experts	Data from the LIFT trial (Roehrborn et al., 2017b) reports 12 patients underwent TURP or laser treatment (not specified) and 7 patients had repeat UroLift over a 5 year follow up. Base case therefore updated to reflect empirical evidence 63% received TURP (12/19) and 37% receive repeat UroLift (7/19).
50% of revision surgeries after Rezum or GreenLight are repeated with TURP. Where symptoms return after an initial Rezum or GreenLight procedure, patients may opt to have the same index surgery or have a TURP.	A 50% split between TURP and the index surgery was assumed because clinical opinion suggests that this decision is likely to vary by hospital	Assumption informed by clinical opinion.	In the Rezum II trial (4 year follow up) (McVary et al., 2019), 3 patients received TURP or laser treatment (not specified) and 2 patients received repeat Rezum. Breakdown of retreatment modalities not reported in GOLIATH trial (GreenLight laser) (Thomas et al., 2016). The EAC has changed the retreatment of Rezum to 40% Rezum and 60% TURP to reflect trial data.
No revision surgeries occur with HoLEP	HoLEP is an ablative procedure therefore a repeat procedure is not appropriate as all tissue has already been removed	Clinical Expert Opinion	This is consistent with the HTA model (Lourenco et al., 2008): “HoLEP was treated as a TURP substitute but without the possibility that it could be repeated as it was believed that it removes so much tissue that there can be no subsequent treatment”.

Assumption	Company justification	Company source	EAC opinion
			Clinical experts were unanimous that there was the potential for surgical retreatment on rare occasions (e.g. when not all of the prostate is enucleated) (EAC External correspondence log, 2019). However, as this could not be quantified, but was definitely considered to be rare, the HTA assumption was allowed to stand.
Mortality is excluded from the model.	Prior economic models (NICE, 2016, NICE, 2015d, Lourenco et al., 2008) did not include mortality due to limited evidence suggesting treatments for BPH influences overall survival. Hence, due to the short time horizon of the model, mortality was excluded from the model.	Not applicable	The EAC agrees mortality is not relevant to the model.
The risk of developing incontinence or ED with repeat surgery is assumed to be the same as the initial procedure.	There is no data reporting these outcomes in repeat surgery or suggest that these rates differ.	Not applicable	The EAC accepts there is no data to inform this transition probability. There is also a lack of data to support the continued efficacy of repeat procedures.

Abbreviations: ED, erectile dysfunction; HES, hospital episodes statistics; HoLEP, holmium laser enucleation of prostate; TURP, transverse resection of prostate.

9.2.3 Validation of the economic model

The EAC validated the company's Excel model by replicating it using the programming language R (R Core Team, 2019). The EAC identified formulae errors in the transition probability matrices during the validation process. These related to incorrect application of the proportions of patients retreated with TURP affecting the UroLift, HoLEP and GreenLight arms. The EAC confirmed this model error with the company. These errors had a minimal impact on the base case and sensitivity analysis due to bulk of costs coming from device and short-term complications. All differences were less than £10, with the maximum difference identified in DSA in the scenario when changing the reoperation proportion with TURP in the Rezum arm to 0% which resulted in UroLift being £547.70 cost saving instead of £538.87 (i.e. £8.86 difference). The model was quickly updated by the company. Due to the small impact on results, the company was not asked to update the narrative or tables of their report. Note that in the Assessment Report, reference to the company's results refer to the printable economic submission document (uncorrected data) rather than the corrected Excel model (version 3).

The EAC used two approaches to replicating the model. Firstly, a patient level micro-simulation approach was used (York Health Economics Consortium, 2016). Because this model type incorporates first-order uncertainty, there will always be variation in the results each time the model is run. Secondly, the EAC developed a cohort Markov simulation, equivalent to the *de novo* model reported by the company. This should give exactly the same results as the company's model other than minor variation due to rounding differences or technical issues such as application of half-cycle correction.

The results of the two approaches, compared with the company *de novo* model, are presented in Table E1, Appendix E. The results are very similar, demonstrating the underlying validity of the model. The EAC was thus satisfied the model functioned as reported for the calculation of the base case.

The EAC analysed the Excel code for the DSA undertaken by the company. Although the changes of +/- 20% used in the one-way DSA appeared simple, it was complicated by the fact the company did not directly apply the 20% change to the point estimate of the all events, but rather they applied the change to the relative risk estimated in the HTA (Lourenco et al., 2008). This affected some values concerning bipolar TURP and HoLEP only. The EAC could not exactly replicate this (see Table E2). However, the EAC were satisfied that the discrepancies had no material impact on the results.

The EAC also identified a systematic error in the PSA concerning the LoS of all the interventions. Additionally, there was a specific error concerning GreenLight where data from the GOLIATH trial (Bachmann et al., 2014) was erroneously used instead of data from an observational study (Ajib et al., 2018). This is explained in more

detail in Appendix E. This error significantly skewed the results for this intervention. The EAC fixed these errors and consequently updated the results of the PSA.

9.2.4 Economic model parameters

The company reported its estimates for four key economic parameters used in the model in Table 3 of the economic submission. The EAC has accepted most of these estimates, with some reservations (see Table D1, Appendix D).

Surgical retreatment

Surgical retreatment rates and follow-up periods determine the transition probabilities for repeat surgery. The values have been taken from empirical evidence where possible. For Rezum and UroLift, the data used was reported directly in the sham-controlled trials (Roehrborn et al., 2017b, McVary et al., 2019), which was considered valid by the EAC. The EAC also used data from these trials to inform the treatment modality used for repeat surgeries. The reasons for retreatment were not reported in most these studies, but it is likely that in many cases it would be because the patient remained symptomatic after treatment, or LUTS returned. This was not captured by the model. For Rezum, 4/6 retreatments were undertaken because failure to treat an identified median lobe or elevated central zone in the initial treatment (McVary et al., 2019).

For TURP and GreenLight, retreatment rates were informed by historical data (Madersbacher et al., 2005) used in the HTA (Lourenco et al., 2008). These data are now over 20 years old and may not reflect improving techniques, such as the transition to bipolar TURP. However, reported rates of retreatment in the more recent GOLIATH study (Thomas et al., 2016) are not supportive of improvements in this parameter.

The mode of retreatment was largely informed by expert opinion, although the EAC has replaced these estimates with empirical evidence where available. Multiple retreatments were not allowed by the model. This was appropriate, since there was no data to support more than one retreatment, and it is likely to be a rare occurrence which would not impact materially on results.

Duration of surgical operations

The duration of surgical operations was a key driver in the model, as surgical costs, obtained through the Information Services Division (ISD) of Scotland (ISD Scotland, 2018), are expensive (see Section 9.2.5). The company retained estimates of procedure duration from MTG26 (NICE, 2015d) for TURP and UroLift, whilst GreenLight (Bachmann et al., 2014) and HoLEP (Li et al., 2014) were informed more directly from empirical evidence. The operational duration of Rezum was informed by empirical data reported in an abstract reporting on 181 Rezum procedures (Johnston

et al., 2019). This value, 17.5 minutes, was at the lower end of the estimates from KoLs (17 to 25 minutes).

There is considerable uncertainty in these estimates, which are likely to be variable depending on setting, expertise, and on a patient by patient basis. More fundamentally, operation times may not accurately reflect the true resource use of the procedure. NICE clinical experts have confirmed that the time in the actual theatre is just one part of the overall procedure, with pre-procedural preparation and post-procedural recovery being important aspects of the process (EAC External correspondence log, 2019). For instance, differences in the cost of anaesthesia, and the implications for staffing levels, were not factored in the model. However, this was likely to be a conservative assumption that did not bias the minimally invasive procedures of Rezum and UroLift. The Rezum II trial reported most patients received oral sedation only (69%), with the remainder receiving a prostate block (21%) or conscious sedation (10%) (McVary et al., 2016c). UroLift procedures were conducted almost exclusively with local anaesthesia (Roehrborn et al., 2013). In contrast, TURP and GreenLight required general anaesthesia or nerve blocks in the GOLIATH trial (Bachmann et al., 2014).

Another issue that should be considered is the extent that shorter operation durations free theatre resources for other uses. In practice it is likely that the shorter surgical operational times associated with Rezum will lead to the availability of more theatre slots (EAC External correspondence log, 2019), but this will not be directly proportional to theatre time, and thus the model is limited in this aspect. This could potentially lead to bias in favour of Rezum.

Uncertainty in theatre time has been addressed using threshold DSA in Section 9.3.3.

Length of hospital stay

The company used LoS data estimated in MTG26 for UroLift (NICE, 2015d) for TURP, UroLift, and Rezum. The estimate for GreenLight was taken directly from an observational study (Ajib et al., 2018) whilst HoLEP was derived from the HTA (Lourenco et al., 2008). These assumed that Rezum and UroLift are currently performed in the NHS as a day case procedure. NICE clinical experts were unanimous that this is the case (EAC External correspondence log, 2019). The company estimated LoS for both the minimally invasive procedures as 0.5 days, or 12 hours.

The unit cost of a full day case was assumed to be £370. This is the cost of an excess bed day and extracted from NHS reference costs for excess bed days (NHS Improvement, 2018), see Section 9.2.5. This is not an ideal surrogate cost for comparison of different treatment modalities. Ideally, HRG codes would be used to account for hospital costs which are specific for each intervention. However, this was

not possible in this case, because bipolar and monopolar TURP, and GreenLight laser and HoLEP, could not be disaggregated. Additionally, there is currently no equivalent code for Rezum.

Excess bed days are used to account for the heterogeneous case mix of patients within a healthcare resource group (HRG), as even within an HRG the complexity of patient clinical needs vary. In some cases, patients could be discharged sooner with more consistent clinical practice and organisation within the hospital. Furthermore, medically fit patients cannot be discharged due to delays in setting up support packages. Excess bed days are not a useful measure of cost for inpatient stay if patient has treatment, as they only cover bed, food, accommodation, utilities, and management costs.

The value of 0.5 excess bed days is likely to have overestimated the true value of the package of care as it is an averaged measure of inpatient care, whereas patients receiving Rezum or UroLift are likely to be placed in recovery rooms with less intensive clinical needs. The EAC thus considered the LoS costs to be conservative and therefore unlikely to bias estimates in favour of Rezum. Conversely, it was unclear if the more invasive procedure of GreenLight could be routinely offered as a day case or whether a bed would need to be booked; this could add considerably to the real-life costs of this procedure. The EAC noted that the mean estimates for hospital stay for GreenLight in the GOLIATH trial (66 hours, European setting) (Bachmann et al., 2014) were very different to that reported by the observational study of Ajib *et al.* (2019) used in the model, which was 0.7 days (17 hours, Canadian setting). However, the EAC accepted the latter estimate as it was consistent with GreenLight being used in a day case setting, which was the basis of the recommendation in MTG29 (NICE, 2016).

Rezum patients are typically discharged with a catheter *in situ*, and require an out-patient appointment to have this removed (EAC External correspondence log, 2019). This cost was not captured by the model. However, post-discharge costs for other modalities were also not accounted for. These costs are not easily quantified. The EAC regards this as a limitation of the model that adds some uncertainty to the results.

Adverse events

The company reported the probabilities of AEs occurring in the model in Table 5 of the economic submission.

Two types of AE were included in the model. Firstly, there were short-term AEs associated with the procedure associated with a one off cost which included acute urinary retention, bladder neck contracture/structure, bleeding/blood transfusion, transurethral resection and urinary tract infection. Secondly, there were long term AEs (ED and urinary incontinence) associated with on-going costs. In both cases,

AEs were not mutually exclusive, meaning it was possible for a hypothetical patient to have multiple AEs. Additionally, short-term events were classified as non-severe, requiring treatment in primary care, or severe, requiring secondary care management. Thus the following events were included:

- Short-term non-severe: urinary retention; urinary tract infection (UTI); bleeding.
- Short term severe: urinary retention; bladder neck contracture; bleeding/transfusion; TUR syndrome; UTI.
- Long-term: urinary incontinence; ED.

The EAC was satisfied these covered the AEs associated with the BPH interventions. The company reported the estimates for the incidence of AEs in Table 5 of the economic submission, together with a rationale and reference to the source of evidence. The EAC has cross-referenced the data with the sources and confirmed that it is accurate.

The incidence data for AEs was taken from a variety of sources. For Rezum the data was taken exclusively from the Rezum II trial (McVary et al., 2016c), UroLift data was reported from the LIFT trial (Roehrborn et al., 2013), and for GreenLight data was reported from the GOLIATH trial (Bachmann et al., 2014). Data for TURP and HoLEP was extracted from a meta-analyses reported in the HTA (Lourenco et al., 2008). It is unclear if data reported from these disparate sources was truly comparable, with issues such as completeness of AE reporting and definitions of AEs and severity causing uncertainty. This was particularly true for data reported from the meta-analysis which itself was comprised of several older studies of unknown quality. Nevertheless, the EAC accepted these data on the basis they had been used to inform the HTA and previous MTGs.

The EAC made two changes to the base case in respect to AE incidence. Firstly, the EAC changed the value for a minor, short-term bleeding incident from 0% to 13.8% based on the reporting of gross haematuria and haematospermia reported in the Rezum II trial (McVary et al., 2016c). This was a conservative estimate likely to overestimate bleeding incidents, but these are associated with relatively low costs (GP consultation). The minor bleeding rate for UroLift was changed to 4% reflecting data from the LIFT trial (Roehrborn et al., 2013). Secondly, clinical experts indicated that urinary incontinence could occur with Rezum and UroLift (EAC External correspondence log, 2019), but it was possible the RCTs were underpowered to detect this. Therefore, as a conservative measure, the EAC adjusted these values from 0% to 1%, which reflected HES analysis undertaken by the EAC for UroLift (1% patients having persistent incontinence 1 year post-procedure). The EAC also made minor changes to the rates of ED after reviewing the empirical evidence for these.

9.2.5 Resource identification, measurement and valuation

The assumptions concerning equipment costs were reported in a Table (page 33) in the economic submission. The EAC has responded to these assumptions in Table 9.5. In summary, the EAC considered the assumptions were generally fair and all were conservative with respect to Rezum.

The cost of the technologies themselves was an important driver of the model. The company reported a breakdown of the bundled costs of the devices used in the model in tabular format in the economic submission. The EAC has appraised these values in Table D2, Appendix D. In general, the EAC accepted the values used by the company with some minor adjustments to the way TURP costs were calculated (aggregated cost of bipolar and monopolar TURP).

The company used a micro-costing approach to the costs of AEs, with urinary incontinence and ED having annual costs, and all other AEs having one-off costs. For annual costs of urinary incontinence, the company used an estimate previously accepted in MTG26 (NICE, 2015d), inflated to 2019 costs using the CPI. The EAC considered this appropriate. Data informing the resource use associated with ED was sourced from a UK-based HTA (Ramsay et al., 2012) and used appropriate unit costs. The EAC considered this was appropriate and the cost was conservative, as it was quite low (2 GP visits per year and generic drug prescriptions). Costs for non-serious short-term AEs were based on the cost of a GP visit and associated interventions (diagnostics and drugs). Whilst the EAC was not always able to exactly replicate these costs, differences were not sufficient to materially change the *de novo* model results.

The EAC has assessed the costs of serious short-term AEs (acute urinary retention, bladder neck/contracture, bleeding, TUR syndrome, and grade 3+ UTI) and reported these in Table D3, Appendix D. .

Table 9.5. *Cost assumptions (applied to all comparators).*

Assumption	Justification	Source	EAC comment
Procedure costs include equipment, theatre time and hospital length of stay	This approach includes all costs incurred from an NHS perspective	Not applicable	This assumes that pre-and immediate post-operative management is equivalent (i.e theatre preparations and recovery rooms). This may not be true, and may in particular depend on use of anaesthesia and the associated staffing costs (EAC External correspondence log, 2019). For instance, in the Rezum II trial (McVary et al., 2016c) 68.9% of patients received oral sedation only, 20.9% had a prostate block and 10.2% received conscious intravenous sedation. In the LIFT trial, 99% of patients received local anaesthesia (Roehrborn et al., 2017b). In contrast, in the GOLIATH trial (TURP or GreenLight) around 60% of patients received general anaesthesia, with the remainder receiving a spinal block (Bachmann et al., 2014). This is a conservative assumption that does not favour Rezum or UroLift.
All procedures are associated with the same levels of operating staff. The cost of theatre time is based on the average unit cost per minute in an operating theatre in Scotland, for a urology procedure	This unit costs includes theatre overheads as well as staff time and is expected to reflect an average cost of theatre time for urology procedures in the NHS	ISD Scotland, 2018	The information services division of NHS Scotland reports average theatre costs per hour by speciality (ISD Scotland, 2018). This is inclusive of staff, utility, and infrastructure costs. There is no equivalent data for the NHS of England and Wales. This may be a conservative assumption if staffing levels are lower for Rezum and UroLift, as indicated by NICE clinical experts (EAC External correspondence log, 2019).
The number of pre- and post-operative tests and healthcare visits does not differ between any of the surgical interventions and are assumed to be similar to the costs applied in the UroLift MTEP model (MTG 26)	Clinical feedback suggests the pre-and post-operative pathway is similar for all surgical options This assumption replicates the assumptions applied and accepted in the UroLift MTEP	NICE MTG26 (NICE, 2015d) Clinical experts	This is a reasonable assumption that was accepted in MTG26 (NICE, 2015d). As these costs are applied equally to all the interventions, they report information on the absolute costs associated with the technologies, but do not inform relative incremental costs. However, note this does not necessarily cover costs associated with discharge which include catheterisation, and subsequent removal of catheters. These are likely to be

Assumption	Justification	Source	EAC comment
			different for each technology but were not included in the model.
The equipment costs for each comparator include consumables, capital and servicing costs where applicable and all equipment costs applied in model exclude VAT	This approach is aligned with NICE guidelines for economic evaluation	NICE 2013	This is consistent with NICE HTA guidance (Section 5.5.10) (NICE, 2013).
The length of stay with Rezum is assumed to be the same as UroLift. An assumption of 0.5 days was applied in the base-case, sourced from the manufacturer's submission to the MTEP assessment MTG 26. This is expected to be a conservative assumption as the EAC revised this assumption to consider shorter lengths of stay of 0.25 and 0.125 based on clinical opinion in scenario analysis	There is no data on the length of stay for Rezum therefore in our analysis we assumed the length of stay with Rezum was the same as UroLift as the pre-and post-preparation and monitoring are similar, both technologies are associated with a very low risk of complications and the procedure time with Rezum is expected to be lower or similar to UroLift	NICE MTG26 (NICE, 2015d) Clinical experts	This is a reasonable assumption. The unit cost of length of stay is based on bed stay; this is could overestimate the costs of day cases treated with UroLift and Rezum (i.e. conservative assumption). Length of stay is investigated as threshold analysis (Section 9.3.3).

9.2.6 Sensitivity analysis

The company reported extensive sensitivity analysis in the economic submission. This consisted of:

- Scenario analysis. One scenario was modelled, the effect would be of introducing ED as an AE in a presumptive population who are sexually active. However, it was noted that this analysis was not reflected in the Scope. Furthermore, there were no scenario analyses on the subgroups that were included in the Scope (men for whom surgical invasive procedures such as TURP or HoLEP is unsuitable because of the risks of blood loss or anaesthesia; men with a prostate size greater than 80 cm3 [equivalent 80g]; and men aged <50 years)

- Deterministic sensitivity analysis (DSA), one-way. The effect of changing a single parameter by 20% either way on the model. These were reported as Tornado plots which made it possible to visualise the key drivers of the model.

- Probabilistic sensitivity analysis (PSA). One thousand simulations were performed by applying random draws to parameter distributions. Most model parameters were subject to PSA; these are reported in Table 11 of the economic submission. The proportion of simulations reporting cost savings were used to calculate the probability each technology was cost-saving compared with Rezum.

Following the fixing of errors in the company's coding (see Section 9.2.3 and Appendix E), the EAC was largely satisfied with the sensitivity analysis the company performed, but had some reservations. One of these was that the DSA was restricted to 20% variation, which might not cover the feasible range of variability in some parameters, particularly ones that were poorly evidenced. For these parameters, a broader range of values should be considered (for instance, the use of 95% CI). However, the key drivers of the model were concerned with hospital resource, specifically hospital length of stay and procedure time, and the unit costs associated with these, for which no distributional data were available. Because of this, the EAC undertook threshold sensitivity analysis to establish at what point, if any, these parameters made Rezum or the comparator cost neutral (see Section 9.3.3).

9.3 Results from the economic modelling

The EAC made some adjustments for to the base case of the model, and results reported by the EAC have incorporated these adjustments. A summary of these changes are reported in Table 9.6. Results reported in this Assessment Report are based on these model inputs.

Table 9.6. *EAC adjustments to parameters informing the base case analysis.*

Issue	Change	Justification
CPI data used to inform inflationary changes	Updated to use most recent data published by ONS	Using ONS data from 18/09/2019 (ONS, 2019).
Formulae errors in company model	The formulae have been corrected.	To repair model so it reports the results the company intended.*
All revision surgeries with UroLift use TURP	Change to 12/19 (63.2%) use TURP, 7/19 (36.8%) use repeat UroLift	Reflects actual data from LIFT trial (Roehrborn et al., 2013). Note, 12/19 received TURP or laser, but we do not know what the laser was and this option may not be universally available, so default to gold standard treatment.
50% of revision surgeries for Rezum use TURP, 50% use Rezum	60% use TURP, 40% use Rezum	In the Rezum II trial (McVary et al., 2019) there were 6 reoperations. One was an open prostectomy (not modelled), 2 were repeat Rezum, and 3 were TURP. Proportions based on this.
Reoperation rate for GreenLight is 5.8% over 5 years.	Change to 6.9% over 5 years.	GOLIATH study reported reoperation rate was 18% higher for GreenLight (Thomas et al., 2016) (Note, this is 2 year data, with events heavily skewed towards the first year, so absolute data could not be used).
Proportion mono polar/bipolar TURP is 50:50	Change to 25% mono TURP and 75% bi TURP	Clinical expert advises mono-TURP now not as commonly used and being phased out (EAC External correspondence log, 2019).
Probability bleeding (short term) is 0% for Rezum	Change to 13.8% (n=189)**	Including cases of gross haematuria (n=16) and haematospermia (n=10) (McVary et al., 2016c). Consistent with observational data (Dixon et al., 2015)
Probability bleeding (short term) is 0% for UroLift	Change to 4.0% **	LIFT study data for haematuria (Roehrborn et al., 2013)
Probability of post-procedural urinary incontinence for Rezum and Urolift is 0%	Change to 1%	Based on clinical feedback (EAC External correspondence

Issue	Change	Justification
		log, 2019) and HES data for UroLift.
Probability of erectile dysfunction after TURP is 10% ***.	Change to 8%	Subtracting sham effect (2%) (Miner et al., 2006).
Probability of erectile dysfunction after GreenLight or HoLEP is 2% (average between TUMT [1%] and TUNA [3%]) ***.	Change to 1%	Based on review data (Miner et al., 2006) and assumption laser treatment more closely resembles TUMT than TUNA.
Cost of GreenLight device £550	Change to £540	Cost in NHS Supply Chain (NHS Supply Chain, 2019)
Cost of bed day £370	Change to £365	Weighted average of elective and non-elective bed days
Abbreviations: CPI, consumer price index; HoLEP, holmium laser enucleation of the prostate; TUMT, transurethral microwave therapy; TUNA, transurthethral needle ablation of prostate; TURP, transurethral resection of the urethra. * One of the formulae has been changed again following EAC's changes to base case. ** The company informed the EAC during its fact check that bleeding events associated with Rezum were not severe enough to warrant medical intervention. However, as these AEs had little impact on the results, and there is similar uncertainty with respect to other AEs and technologies, the EAC has not re-reported the data. *** Only relevant for ED scenario analysis.		

9.3.1 Base case results

A comparison of the company's and the EAC's base case results is reported in Table 9.7. The company reported that Rezum was cost-saving over 4 years compared with the other technologies. For TURP, UroLift, and HoLEP this cost-saving was substantial, ranging from £497 (UroLift) to £569 (TURP), to £651 (HoLEP). Compared with GreenLight, the cost-saving was small, at £25. Considering the 4 year perspective of the model, the EAC would consider this to be cost-neutral.

Using the EAC's parameter estimates, the base case cost of Rezum, UroLift, and GreenLight were slightly increased (£88, £54, and £1 respectively), whilst the cost of TURP and HoLEP were slightly decreased (£80 and £19 respectively) compared with the company submission. Rezum was still cost-saving compared with TURP, UroLift, and HoLEP, but was slightly cost-incurring compared with GreenLight (by £49). Again, the EAC would consider Rezum to be approximately cost-neutral compared with GreenLight over the course of 4 years, whilst cost-saving compare with the other technologies.

A breakdown of the costs associated with each technology is illustrated in Figure 9.3. As can be seen, most of the costs attributable to Rezum and UroLift are due to associated device costs (bespoke consumables); whereas TURP and HoLEP have higher surgical and hospital costs. GreenLight is somewhere in between these, perhaps reflecting its position between a minimally invasive and surgically invasive procedure in the patient pathway (EAC External correspondence log, 2019). Costs

associated with treating AEs, including incontinence, accounted for only a small proportion of total costs.

Table 9.7. *Comparison of company's and EAC's base case results.*

Individual costs	Mean discounted cost per patient (£), after 4 years (Company base case)					Mean discounted cost per patient (£), after 4 years (EAC base case)				
	Rezum	**TURP**	**UroLIFT**	**GL**	**HoLEP**	**Rezum**	**TURP**	**UroLIFT**	**GL**	**HoLEP**
Device Cost	1,348.00	165.20	1559.45	550.0	448.83	1,348.00	187.74	1537.67	540.00	448.71
Theatre Costs	233.98	882.42	401.10	663.15	1,072.14	233.98	882.42	401.10	663.15	1,072.14
Cost of Hospital Stay	185.16	992.45	185.16	259.22	733.23	182.50	914.33	182.50	255.50	722.70
Cost of pre and post tests	490.40	490.40	490.40	490.40	490.40	490.40	490.40	490.40	490.40	490.40
Cost of treating short-term adverse events	21.60	260.76	1.70	240.96	137.29	26.88	271.23	3.23	240.96	137.29
Cost of treating incontinence	0.00	207.15	0.00	95.54	252.75	84.02	174.54	84.02	92.42	244.49
Repeat surgery & short-term complications	96.09	112.25	266.57	100.44	0.00	97.05	110.44	257.67	118.28	0.00
Cost of treating repeat incontinence*	1.73	3.68	4.42	2.69	0.00	2.32	3.10	6.02	2.83	0.00
Total Costs	**2,376.95**	**3,114.32**	**2,908.79**	**2,402.41**	**3,134.65**	**2465.15**	**3034.20**	**2962.61**	**2403.55**	**3115.74**
Net diff vs Rezum	**0**	**-737.37**	**-531.84**	**-25.45**	**-757.70**	**0**	**-569.07**	**-497.48**	**+61.58**	**-650.60**

Abbreviations: GL, GreenLight; HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the urethra.
* Incontinence caused by repeat surgery. Green indicates Rezum is cost-saving; Red indicates Rezum is cost-expending.

As most of the costs were incurred during the procedure or in immediate after-care, the large majority of costs were incurred in year 1. This is illustrated in Figure 9.4.

Figure 9.3. *Breakdown of costs of the technologies. Costs of testing removed (assumed equivalent across all technologies).*

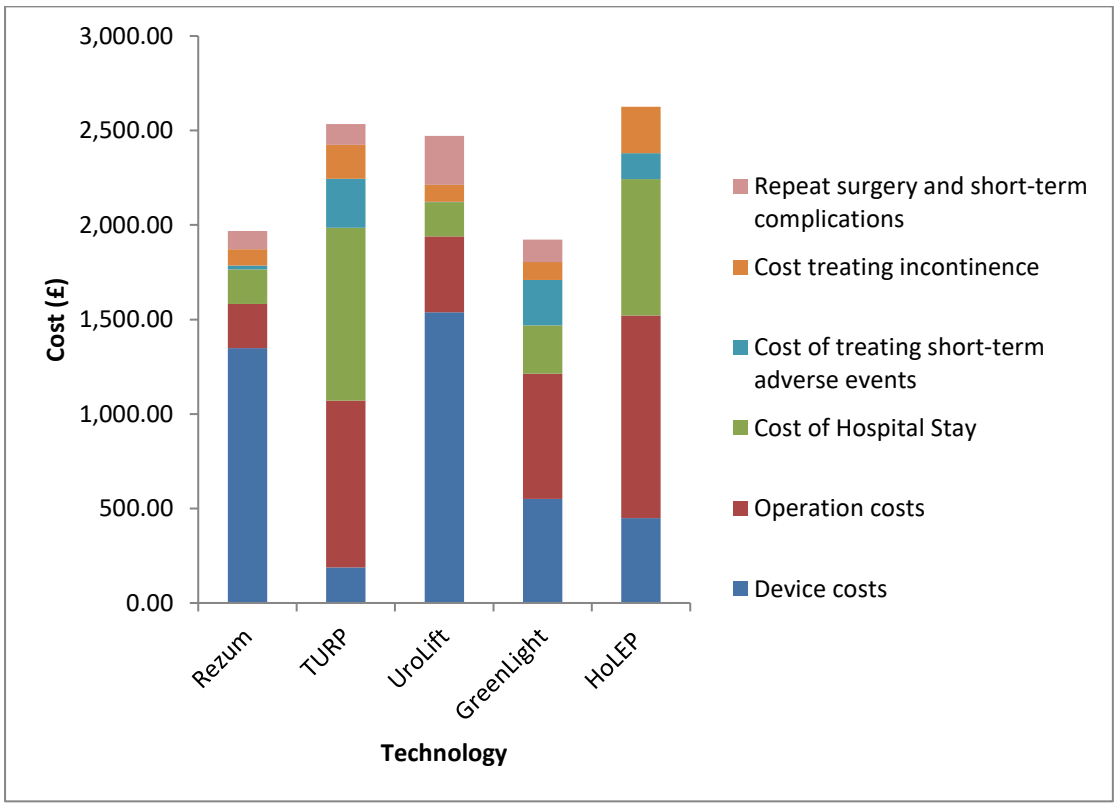
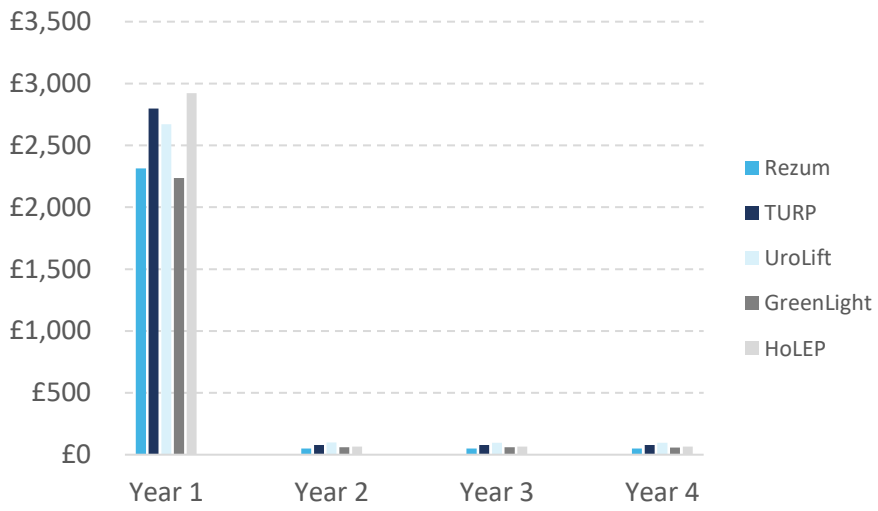


Figure 9.4. *Total costs by year accrued.*



9.3.2 Sensitivity analysis results

Scenario analysis

The company reported scenario analysis in a subgroup of sexually active men without a history of ED. This was not based directly on empirical evidence from this group; rather it switched the model to include AEs associated with new onset or significantly worsening ED, which is reduced by minimally invasive treatments such as Rezum and UroLift compared with more invasive surgical intervention. It is unclear how many men this scenario would apply to, as sexual dysfunction is often experienced concomitantly with LUTS. In the Rezum II trial, about one third of men (33.6%) were classified as having normal sexual function at baseline (McVary et al., 2016b).

The EAC updated results of this analysis are reported in Table 9.8. The additional costs associated with ED slightly increased the cost of the other technologies compared with Rezum, but did not change the direction of results in any case (including GreenLight). The largest increase in costs was associated with the use of TURP, at £59 over 4 years. It should be considered that real cost savings over the whole BPH population might be appreciably less than this, as about two thirds of men will experience limited or no benefit (unless Rezum ws specifically targeted at this population).

Table 9.8. *Breakdown of costs in scenario including erectile dysfunction (EAC data).*

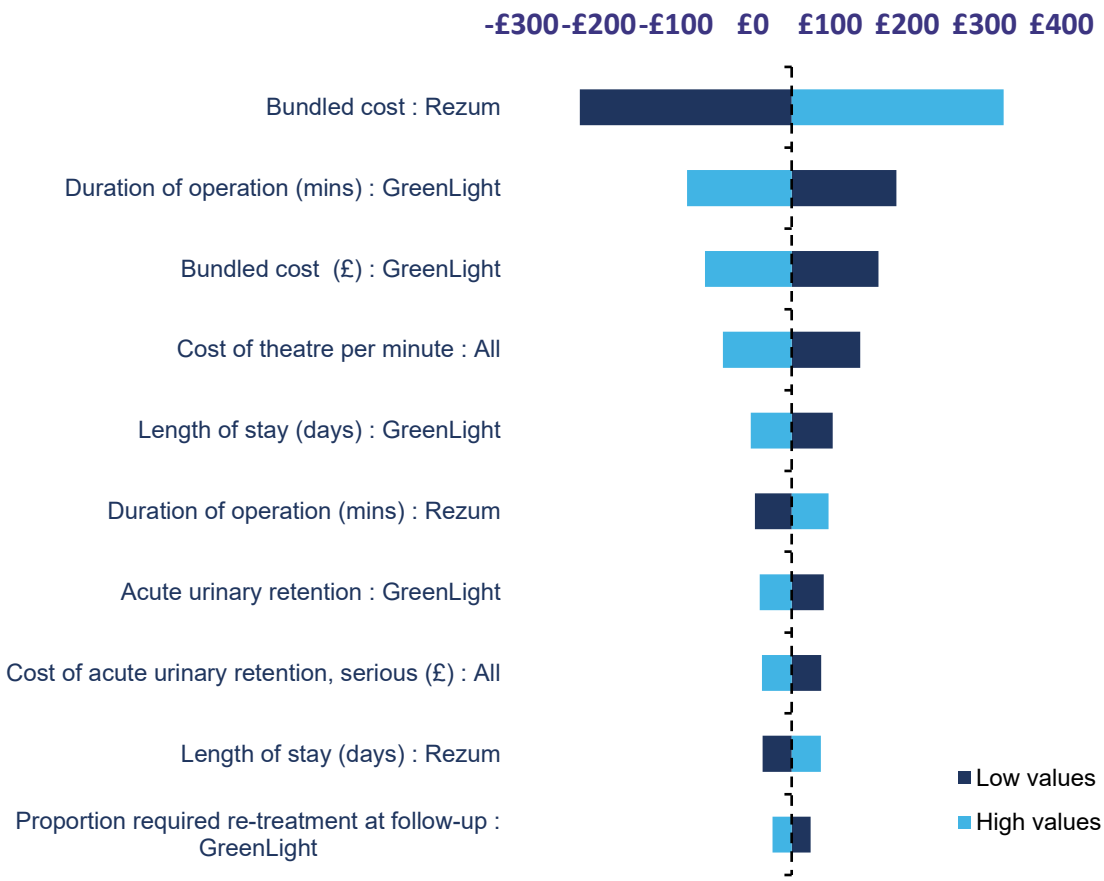
Cost breakdown	**Mean discounted cost per patient (£), after 4 years (EAC basecase)**				
	Rezum	**TURP**	**UroLIFT**	**GL**	**HoLEP**
Device Cost	1,348.00	187.74	1537.67	550.00	448.71
Theatre Costs	233.98	882.42	401.10	663.15	1,072.14
Cost of Hospital Stay	182.50	914.33	182.50	255.50	722.70
Cost of pre and post tests	490.40	490.40	490.40	490.40	490.40
Cost of treating short-term adverse events	26.88	271.23	3.23	240.96	137.29
Cost of treating incontinence	84.02	174.54	84.02	92.42	244.49
Cost of treating erectile dysfunction*	0.00	57.39	0.00	7.15	7.32
Repeat surgery & short-term complications	95.29	110.44	257.64	118.52	0.00
Cost of treating incontinence (repeat surgery)	2.16	3.10	6.02	2.83	0.00
Cost of treating erectile dysfunction (repeat)*	0.49	2.00	1.58	0.85	0.00
Total Costs	**2463.71**	**3093.60**	**2964.19**	**2411.54**	**3123.06**
Net diff vs Rezum	**N/A**	**-627.88**	**-498.47**	**+54.18**	**-657.34**
Difference from EAC base case	*+0.49*	*+£59.40*	*+1.58*	*+7.99*	*+7.32*

Abbreviations: GL, GreenLight; HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the urethra.
* Additional costs.
Green indicates Rezum is cost-saving; Red indicates Rezum is cost-expending.

One-way deterministic sensitivity analysis

The company reported Tornado diagram for Rezum vs. each of the technologies in the economic submission (pages 65 to 69). The EAC recalculated results appear similar, with Tornado diagrams all being well to the left of break-even threshold (£0). The exception to this is the comparison with GreenLight, illustrated in Figure 9.5.

Figure 9.5. *Tornado diagram illustrating DSA on Rezum vs. GreenLight.*



As can be seen, the model is particularly sensitive to changes in device costs and costs associated with the procedure (theatre time and hospital LoS). Therefore the EAC subjected these to threshold analysis (Section 9.3.3).

Probabilistic sensitivity analysis

The company reported the results of the PSA in the economic submission ion pages 70 to 73. For TURP, UroLift, and HoLEP there was >99% probability that Rezum was cost-saving. For GreenLight, the probability Rezum was cost-saving was 62.1%.

The EAC fixed errors in the company's PSA (see Section 9.2.3) and reran the company's PSA with the updated data inputs. There was ≥ 97.5% that Rezum was cost-saving for all the technologies except GreenLight. For GreenLight, only a 27.6% of the simulations reported Rezum was cost-saving (see Figure 9.6). The PSA data is reported in Table 9.9.

Figure 9.6. *Probabilistic sensitivity analysis of Rezum vs. GreenLight.*

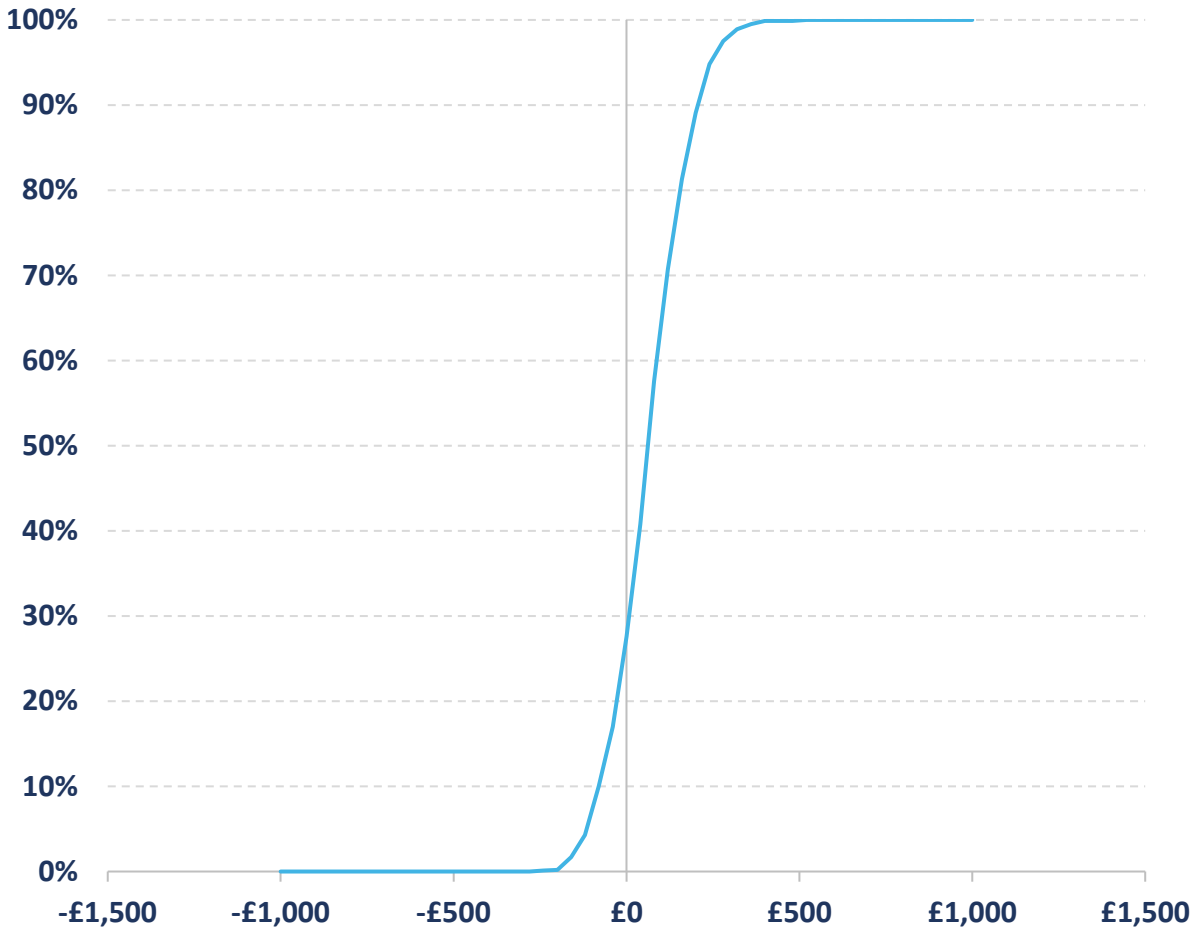


Table 9.9. *Summary of deterministic and probabilistic data.*

Technology	Mean discounted cost per patient (£), after 4 years (EAC base case)		Probabilistic 95% credible intervals	Number of simulations where Rezum is cost-saving
	Deterministic value	Probabilistic value		
TURP	-569	-825	-2274 to -31	97.9%
UroLift	-497	-511	-1022 to -1	97.5%
GreenLight	+62	+64	-137 to +278	27.6%
HoLEP	-651	-788	-2012 to -39	97.7%

Abbreviations: HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate.

Key: Green means Rezum is cost-saving; red mean Rezum is cost-incurring.

9.3.3 Additional results

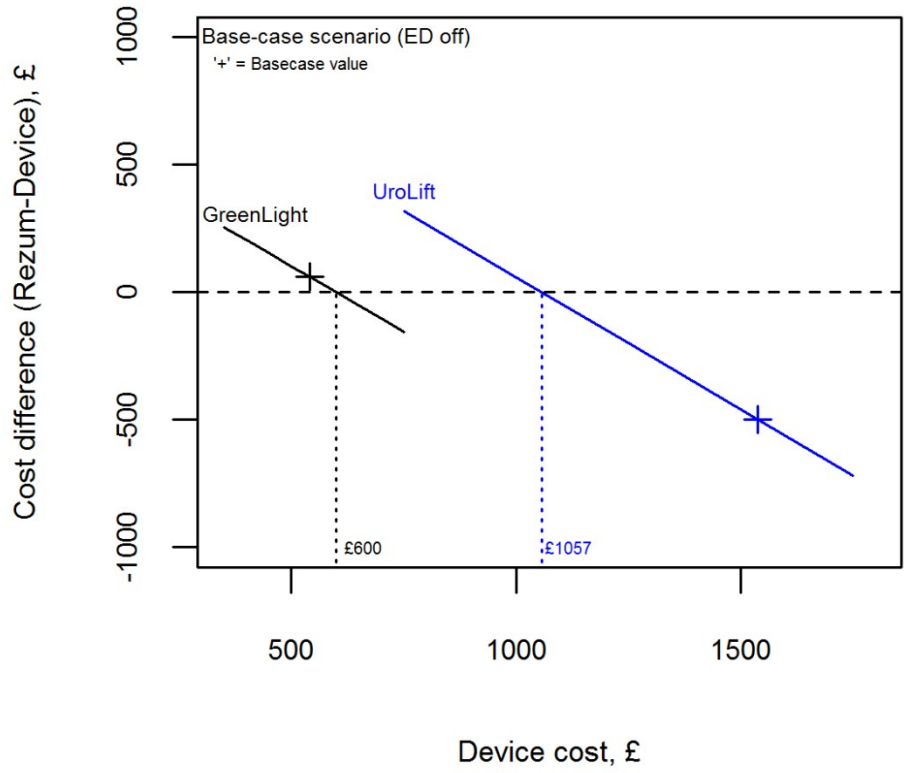
The EAC conducted additional threshold and two-way deterministic analyses, focusing on GreenLight, as it was found to be less costly than Rezum using deterministic analysis, and UroLift, which also had a high device cost, and was the most comparable device, being the only other truly minimally invasive procedure. Threshold comparison with the other modalities did not yield meaningful results.

Device cost

For deterministic threshold analysis of device costs, the EAC assumed the cost of Rezum was a fixed cost (£1348.00 per device), but varied the costs of the other devices (see Figure 9.7).

In the EAC base case scenario, Rezum was £61.58 *cost incurring* per procedure compared with GreenLight. This meant that Rezum could only be considered to be cost-saving when the GreenLight device cost exceeded a threshold of £600. Rezum was cost-saving compared with UroLift by a margin of £497.48 per procedure, meaning the cost of the UroLift device would need to drop below £1057 in order to become cost-saving. The EAC considered this price was not plausible. TURP and HoLEP were always cost-incurring, even if their respective device costs were set to zero.

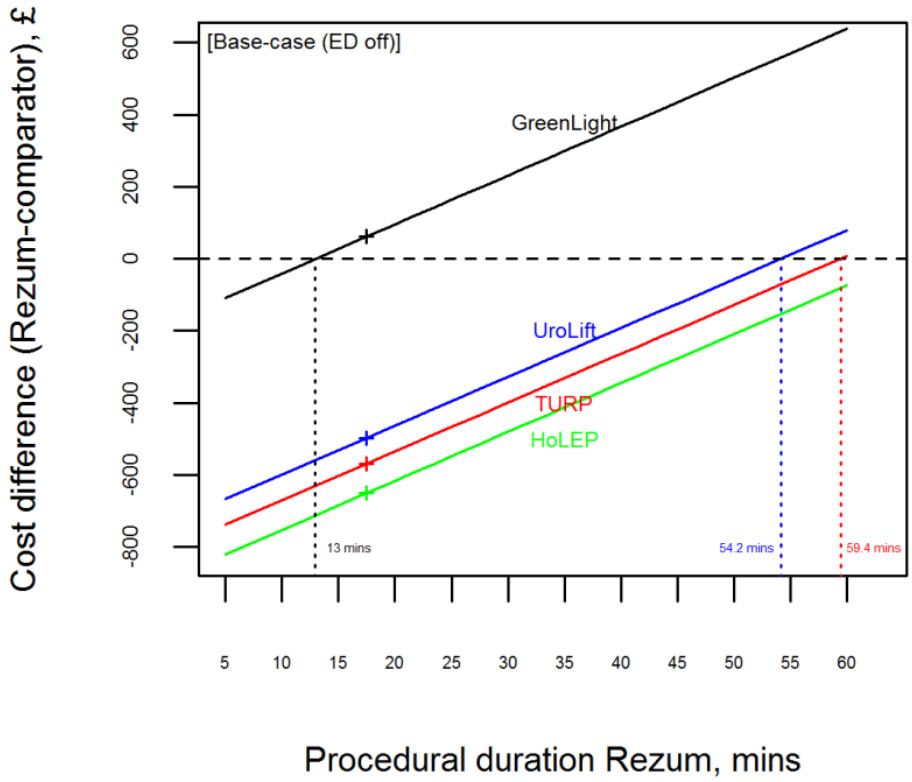
Figure 9.7. *Threshold analysis of device costs. Note + symbol denotes the device cost used in the model.*



Operation times

A time of 17.5 minutes surgery time was used in the base case of the model, based on evidence from a conference abstract (Sarkar et al., 2019). Deterministic analysis showed the model was sensitive to this value. Threhold analysis is reported in Figure 9.8. If the surgery duration is reduced to 13 minutes, Rezum becomes cost-saving compared with GreenLight. This is duration is less than any estimates made by the KoLs. If the surgery time for Rezum is increased to 54.2 minutes, then UroLift becomes cost-saving compared with Rezum. This is an implausibly high value. Larger increases are required to make TURP or HoLEP cost-saving.

Figure 9.8. *Threshold analysis of surgery time. Note + symbol denotes the device cost used in the model.*



The results of two-way DSA, comparing the effect of varying operating times on Rezum and UroLift, are reported in Table 9.10 and 9.11. It can be seen Rezum becomes cost-saving if GreenLight operation times exceed 60 minutes. Rezum is cost-saving compared with UroLift at if they are assumed to take the same time.

Table 9.10. *Two-way sensitivity analysis on operation times: Rezum vs. GreenLight.*

		Rezum (mins)				
		15	30	45	60	75
GreenLight (mins)	15	£501.34	£704.93	£908.52	£1,112.11	£1,315.70
	30	£295.98	£499.57	£703.16	£906.76	£1,110.35
	45	£90.63	£294.22	£497.81	£701.40	£904.99
	60	-£114.73	£88.86	£292.45	£496.04	£699.63
	75	-£320.08	-£116.49	£87.10	£290.69	£494.28

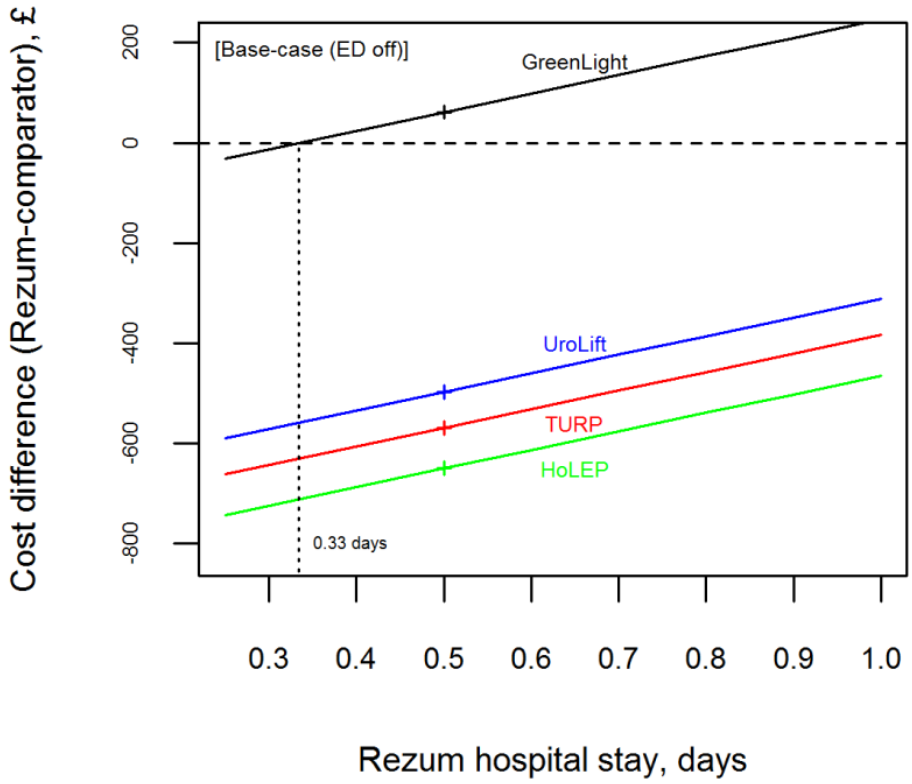
Table 9.11. Two-way sensitivity analysis on operation times: Rezum vs. UroLift.

		Rezum (mins)				
		15	30	45	60	75
UroLift (mins)	15	-£323.81	-£120.22	£83.37	£286.96	£490.55
	30	-£531.41	-£327.82	-£124.23	£79.36	£282.95
	45	-£739.01	-£535.42	-£331.83	-£128.24	£75.35
	60	-£946.61	-£743.02	-£539.43	-£335.84	-£132.25
	75	-£1,154.21	-£950.62	-£747.03	-£543.44	-£339.85

Hospital length of stay

Figure 9.9 reports threshold analysis of changing the LoS of hospital stay for Rezum. If LoS could be reduced on average to 0.33 days, this would make Rezum cost saving. Rezum would only be cost-incurring compared with the other technologies if the procedure required at least one overnight stay. According to NICE clinical experts, this is not plausible (EAC External correspondence log, 2019).

Figure 9.9. *Threshold analysis of length of hospital stay. Note + symbol denotes the device cost used in the model.*



The EAC explored this further with two-way sensitivity analysis. If GreenLight required an overnight stay, then it becomes cost-incurring (Table 9.12). This is a plausible possibility (EAC External correspondence log, 2019). On the other hand, there was no plausible combination of LoS data that made UroLift cost saving (Table 9.13).

Table 9.12. *Two-way sensitivity analysis on hospital LoS: Rezum vs. GreenLight.*

		Rezum (days)				
		0.25	0.5	0.75	1.00	1.25
GreenLight (days)	0.25	£137.14	£229.77	£322.40	£415.04	£507.67
	0.50	£43.70	£136.33	£228.97	£321.60	£414.23
	0.75	-£49.74	£42.90	£135.53	£228.16	£320.80
	1.00	-£143.17	-£50.54	£42.09	£134.73	£227.36
	1.25	-£236.61	-£143.98	-£51.34	£41.29	£133.92

Table 9.13. *Two-way sensitivity analysis on hospital LoS: Rezum vs. UroLift.*

		Rezum (days)				
		0.25	0.5	0.75	1.00	1.25
UroLift (days)	0.25	-£495.66	-£403.02	-£310.39	-£217.76	-£125.12
	0.50	-£590.11	-£497.48	-£404.85	-£312.21	-£219.58
	0.75	-£684.57	-£591.94	-£499.30	-£406.67	-£314.04
	1.00	-£779.03	-£686.40	-£593.76	-£501.13	-£408.49
	1.25	-£873.49	-£780.85	-£688.22	-£595.59	-£502.95

9.4 EAC interpretation of economic evidence

The EAC has appraised the *de novo* model reported by the company that compared the costs associated with Rezum and four comparators (TURP, UroLift, GreenLight, and HoLEP) over a 4 year time perspective. The EAC considered the model was well constructed, transparent, and captured the important aspects of NHS health resource usage that informed the true costs of these treatments. The main limitation of the model was that it did not take into account the efficacy of each technology in relieving LUTS. Other limitations concerned whether costs associated with operation times and hospital stay, and post-discharge care (not accounted for) were reflective of true NHS costs.

The EAC independently reconstructed the model in R programming language using patient-level micro-simulation and Markov cohort methodologies, and validated its functionality. The EAC appraised the models inputs, and adjusted some of these using empirical evidence from the literature and additional expert opinion in an attempt to improve the accuracy of the model. Additionally, errors in the PSA were identified and fixed.

The EAC's revised model found that Rezum was associated with significant cost-savings when compared with TURP, UroLift or HoLEP of ≥ -£500. However, Rezum was slightly cost-incurring compared with GreenLight (+£62), although this might be considered approximately cost-neutral over the 4 year time horizon. A scenario analysis on a subgroup of sexually active men did not alter the direction, nor had much impact on the magnitude, of the results. One-way DSA indicated that the cost-saving potential of Rezum was most sensitive to changes in device costs, as well as costs associated with operation duration and hospital stay; but, other than for GreenLight, changes to these did not alter the direction of results. The EAC confirmed this using threshold analysis, and found Rezum remained cost-saving compared with TURP, UroLift and HoLEP for all plausible input parameters. PSA reported Rezum was cost-saving compared with TURP, UroLift and HoLEP in nearly all simulations. However, Rezum was only cost-saving compared with GreenLight in 27.6% of simulations (+£64, 95% credible interval -£137 to +£278).

The results of the *de novo* model were partly supported by one published cost-effectiveness study, which reported that Rezum dominated UroLift (Ulchaker and Martinson, 2018). However, this study was regarded to be of relatively poor methodological quality and the costs of the interventions were high and not transparent.

In conclusion, the EAC is satisfied that Rezum offers the potential for cost-savings compared with UroLift, TURP, and HoLEP. The comparison with UroLift, where Rezum was cost-saving by £497 is important as both these minimally invasive treatments are used in similar settings at similar points in the patient pathway. The cost-saving potential of Rezum compared with GreenLight is less clear cut, and may partly depend on the procedural costs, surgicall efficiency and recovery times and settings associated with both modalities. In particular, GreenLight would need to be used in a day case setting to be cost-saving (Ray et al., 2016).

Considering the totality of evidence reported in the economic submission, the EAC believes the case for adoption of Rezum is supported.

10 Conclusions

10.1 Conclusions on the clinical evidence

The principal clinical evidence to support the use of Rezum comes from the Rezum II trial. This was an RCT (n = 197) that compared Rezum with sham at 3 months, and followed patients receiving the intervention for up to 4 years (n = 120). Other evidence consisted of a prospective case series (2 years follow up, n = 65), 2 retrospective observational studies (n =131 and n = 129). The methodological quality of the RCT and observational studies were considered to be good and the data reported generalisable to the NHS.

The RCT reported the procedure was completed with a 100% success rate, although 2 patients (1.5%) experienced serious procedural AEs. Compared with sham, there was strong evidence that Rezum improved urinary flow (Qmax), but not voiding (PVR). There was strong evidence that Rezum improved symptoms of LUTS (IPSS and BPHII) and HRQoL (IPSS-QoL), whilst retaining sexual function. Longitudinal data from the Rezum II trial and the observational studies reported Rezum improved Qmax compared with baseline, and this effect persisted for up to 4 years. There was strong evidence that Rezum improved LUTS over this time period, with a non-significant trend indicating deteriorating sexual function.

Overall, the evidence base was strongly supportive of Rezum being a safe and effective treatment for LUTS in men with BPH. However, there was a lack of direct evidence that compared Rezum with the comparator technologies. The company reported an indirect comparison with UroLift, which was also the subject of a sham-controlled trial, which showed that Rezum was at least as effective, but required less reoperations. However, there was an absence of any comparative evidence of Rezum with TURP, GreenLight laser, or HoLEP. NICE clinical experts were unanimous that these more invasive treatments were likely to be associated with improved clinical benefits, but direct evidence was required to confirm this.

In conclusion, Rezum is an effective treatment for LUTS in men with BPH, and is a valid treatment option for the NHS. Rezum has specific advantages and disadvantages compared to other surgical options. Specific indications for Rezum may include its use in men with BPH of the median lobe; men who are earlier in disease progression and who want to retain sexual function; and men in whom a more invasive surgical treatment is not wanted, or is contraindicated.

10.2 Conclusions on the economic evidence

One cost-effectiveness study set in the US was identified. The study, which used IPSS points as the effectiveness measure, reported Rezum dominated UroLift and was significantly cost-saving, though not as effective, compared with TURP and GreenLight laser.

The company reported a *de novo* cost consequence analysis incorporating a Markov cohort simulation with a time perspective of 4 years. The main inputs informing the model included device cost, theatre time, hospital LoS, non-serious and serious AEs, and need for reoperation. The EAC replicated and appraised the model. The model was clearly structured, transparently reported, and captured most of the important aspects of NHS health resource usage for Rezum, UroLift, GreenLight laser, TURP and HoLEP. The main limitation of the model was that it assumed the technologies were equally effective when this unlikely to be the case (it may be an “apples and pears” comparison). Additionally, key inputs on procedural duration and post-procedural recovery and settings were subject to uncertainties. There was additional uncertainty whether efficiency gains associated with Rezum (in decreased surgical time) would be realised in the NHS.

The EAC adjusted some of the model’s parameters to more accurately reflect published empirical data and expert opinion, and used these data as the base case. Rezum was found to be cost-saving by approximately ≥ £500 compared with UroLift, TURP, and HoLEP. One-way DSA showed the model was most sensitive to variations in the resource use and costs associated with theatre duration and hospital LoS. The EAC tested these parameters with threshold analysis, but did not identify any plausible values for these variables that made Rezum cost saving compared with TURP, UroLift, or HoLEP. Scenario analysis, which investigated the effect of ED in a subgroup of sexually active men, did not materially affect the direction or magnitude of results.

Rezum was found to be slightly cost-incurring (£62) compared with GreenLight; with only 27.6% of PSA simulations reporting Rezum was cost-saving.

In summary, the model showed Rezum was likely to have significant cost-saving potential compared with the minimally invasive UroLift, based mainly on it having less expensive device (consumable) costs; and invasive surgical techniques such as TURP and HoLEP, based on lower theatre and recovery costs. It is likely to be approximately cost-neutral compared with GreenLight laser, although this is subject to considerable uncertainties including the setting GreenLight is used in and whether it can be performed as a day case in most subjects. There is certainly scope for Rezum to be cost-saving compared with GreenLight if system efficiencies can be achieved, in particular

if Rezum could be used in an outpatient setting (EAC External correspondence log, 2019).

Thus the EAC concludes that cost should not be a barrier for implementation of Rezum. As each treatment modality has its own advantages and disadvantages, the choice of treatment for BPH should be based on clinical need and indication.

11 Summary of the combined clinical and economic sections

There is strong evidence from an RCT that Rezum is associated with significant improvements in urological outcomes and HRQoL compared with sham. There is evidence from observational studies that these improvements persist for at least 4 years, and that deterioration in erectile function is likely to be modest over this period. Indirect evidence reports Rezum is at least as effective as UroLift and requires less reoperations up to 4 years. However, currently there is a lack of direct evidence comparing Rezum with other more invasive technologies to treat BPH.

The company reported a *de novo* Markov cohort simulation that reported Rezum was cost-saving compared with all the comparators in scope. The EAC adjusted some of the inputs and found that Rezum remained cost saving (by ≥ £500) for all the technologies except for GreenLight, where Rezum incurred a deterministic cost of £62 over 4 years (approximately cost neutral). Using PSA, there was 27.6% chance that Rezum was cost-saving compared with GreenLight (additional mean cost £64, 95% credible interval -£137 to +£278). However, this assumes GreenLight can be used as effectively in the same day case setting as Rezum is.

The EAC has therefore concluded that Rezum is a clinically effective option for treatment of BPH and is cost-saving in most scenarios. It should be offered as a treatment option in appropriately indicated men.

12 Implications for research

There is good evidence from an RCT that Rezum is effective in the management of BPH compared with sham, and by extension, drug treatment (Gupta et al., 2017). However, there is a lack of direct comparative evidence on the efficacy and safety of Rezum compared with other interventions. An indirect comparison has shown that Rezum is at least as effective as UroLift, but currently data is lacking comparing Rezum with more invasive surgical modalities. Direct comparisons are necessary to answer the question of whether the advantages relating to minimally invasive procedures (including reduced AEs, reduced effect on sexual function, and reduced LoS and resource use) outweigh possible limitations of the technology (possible reduced effectiveness and permanence). A direct comparison with bipolar TURP (considered by some as gold standard treatment) as a minimum would be welcomed. This might also allow for the possibility of network meta-analyses to make indirect comparisons with GreenLight laser.

As an intervention with an immediate and large before and after effect, it would also be useful to undertake a prospective observational study to assess the longitudinal effects of Rezum in an NHS setting. This would have the advantage of being less expensive and quicker to set up than an RCT. Such research, possibly in the form of a BPH registry, should include regular collection of HRQoL data (IPSS as a minimum) and requirement for reoperation (including data on which repeat intervention is used). Ideally, the registry would have long-term follow up extending beyond 5 years so the true benefits and costs of Rezum treatment could be established.

Treatment of BPH is an active field, and in recent years several new technologies have become available whilst others have been superseded. Each technology has its own specific advantages and disadvantages which are suited for particular clinical indications. This, along with the concept of shared decision making where patients help decide the management option that suits their preferences, makes this a complex clinical area. NICE CG97 was published in May 2010 and last updated in 2015 (NICE, 2015a). Since then, TURis (NICE, 2015c), UroLift (NICE, 2015d), and GreenLight laser (NICE, 2016) and now Rezum have all been the subject of MTGs (single technology assessments). An update of this clinical guidance, incorporating a multiple technology systematic review of the latest literature, would consolidate these MTGs and provide appropriate clinical direction on their use.

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ULCHAKER, J. C. & MARTINSON, M. S. 2018. Cost-effectiveness analysis of six therapies for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *ClinicoEconomics and Outcomes Research,* 10**,** 29-43.
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14 Appendices

Appendix A - Literature searches and evidence selection

Appendix B – Critical appraisal of clinical evidence

Appendix C – Critical appraisal of economic evidence

Appendix D – Cost inputs to the economic model

Appendix E – Technical validation of the company's *de novo* model

Appendix A – Literature searches and evidence selection

Critique of the company's search methods

The Peer Review of Electronic Search Strategies (PRESS) Checklist was used to inform the EAC critique of the company's search strategies (McGowan et al., 2010).

A primary literature search was conducted by the company in March 2019. These searches found 726 records from Medline, Embase and Pubmed databases, using the STN platform. Additional searches were undertaken by the company in July 2019, including trials registries, to inform the evidence synthesis and meta-analysis for indirect treatment comparison of Rezum versus Urolift, as reported in Section 7 of the clinical submission. Lastly, the company hand searched various international urology society websites and a selection of topic-specific terms in Google and Google Scholar, to identify conference abstracts.

This EAC validation of the adapted company literature search strategies identified 534 records for screening from database searching (after duplicates were removed). The EAC identified 106 studies requiring full paper retrieval from the initial screening. From these, ten publications were identified as being in scope of the decision problem and formed the clinical evidence base for EAC appraisal. The EAC literature search and sifting are summarised in a PRISMA diagram (Moher et al., 2009) in Figure A1.

The EAC had identified and excluded 56 potentially eligible conference abstracts during the full paper review (listed in Table A3). As the company had tabulated seven conference abstracts in section 4 of their clinical evidence submission, they were also asked for and provided a long list of all 22 conference abstracts which were known to them, but had been excluded as either irrelevant, or matched with published outputs (to avoid double counting). These are listed in the EAC correspondence log. The EAC cross checked the company exclusions against the conference abstracts in Table A3, to ensure that no relevant UK data were missed. Nineteen of the 22 abstracts excluded by the company were also identified and excluded by the EAC from the primary literature search (at either initial screening, or full paper review). Additional searches were undertaken for the remaining three excluded conference abstracts using Google Scholar and the Healthcare Databases Advanced Search (HDAS) platform. Two were found and confirmed as excluded appropriately, the third was an abstract presented at two different conferences and already accounted for as excluded by the EAC in Table A3.

Search sources

Additional information resources used by the EAC for the validation of company searches are shown in Table A1. These included economic databases, such that all relevant clinical and economic evidence could be identified and selected in a single sift. Trials registries were also searched, in order to inform section 8.2 of this assessment report, i.e. ongoing studies.

Table A1: *Databases and information resources*

Database / information resource	**Interface / URL**
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)	OvidSP
Embase <1996 to 2019 Week 33>	OvidSP
Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
University of York Centre for Reviews and Dissemination (CRD) database including Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Clinicaltrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform	http://apps.who.int/trialsearch/
ISRCTN registry	http://www.isrctn.com/

Results of the EAC searches were downloaded and imported into EndNote reference management software. The records were de-duplicated using several algorithms. The database searches retrieved 784 records, with 534 records remaining for assessment after deduplication (Table A2). Ten unique records were identified from trials registries.

Table A2: *EAC validation of company searches: database results*

Database / information resource	**Records identified**
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)	54
Embase <1996 to 2019 Week 33>	161
Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)	318
University of York Centre for Reviews and Dissemination (CRD) database including Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and NHS Economic Evaluation Database (NHS EED)	0
PubMed	251
Clinicaltrials.gov	10
WHO International Clinical Trials Registry Platform (ICTRP)	5

Database / information resource	Records identified
ISRCTN registry	0
TOTAL from literature databases	**784**
TOTAL from trial registries	**15**
TOTAL after deduplication (within-set and against results retrieved by the validation of adapted company searches)	**544 (534 titles and 10 records from trials registries)**

EAC validation of the company's primary search

The primary EAC search strategy is presented below. Full search strategies for other databases are available on request.

A.1: Source: Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 04, 2019>

Interface / URL: OvidSP
Database coverage dates: 1946 to Aug 16 2019. Updated daily.
Search date: 16/08/19
Search strategy:
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1 (rezum or rez?m or rezumTM or nxthera or (nx and thera)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (100)
2 Lower Urinary Tract Symptoms/ or Prostatic Hyperplasia/ (22828)
3 (LUTS adj5 urinary tract).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3262)
4 (lower urinary adj5 symptom*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8942)
5 (BPE or BPH or BPO).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (13105)
6 benign prostat*.mp. (18821)

7 (prostat* adj5 enlarg*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2158)
8 (prostat* adj5 hyperplas*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (26883)
9 (prostat* adj5 hyper plas*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4)
10 (prostat* adj5 obstruc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2472)
11 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (38463)
12 1 and 11 (44)
13 (RF adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3240)
14 (RF adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
15 (RFA adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4840)
16 (RFA adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
17 (radiofreq* adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading

word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (19182)
18 (Radiofreq* adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2)
19 (radio freq* adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1055)
20 (Radio freq* adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1)
21 (water vapour adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23)
22 (water vapour adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
23 (water vapor adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (128)
24 (water vapor adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
25 (water induced adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept

word, rare disease supplementary concept word, unique identifier, synonyms] (16)
26 (water induced adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
27 (waterinduced adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
28 (waterinduced adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
29 (steam adj5 (thermal or thermotherap* or ablat* or convective)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (135)
30 (steam adj5 thermo therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
31 (convective adj5 (wave or energy)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98)
32 hyperthermia.mp. (34337)
33 Hyperthermia, Induced/ (16027)
34 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (54951)
35 11 and 34 (551)
36 12 or 35 (566)
37 36 (566)
38 limit 37 to (english language and yr="2013 -Current") (54)

Figure A1. *PRISMA flow diagram of EAC's validation of primary clinical literature searches.*

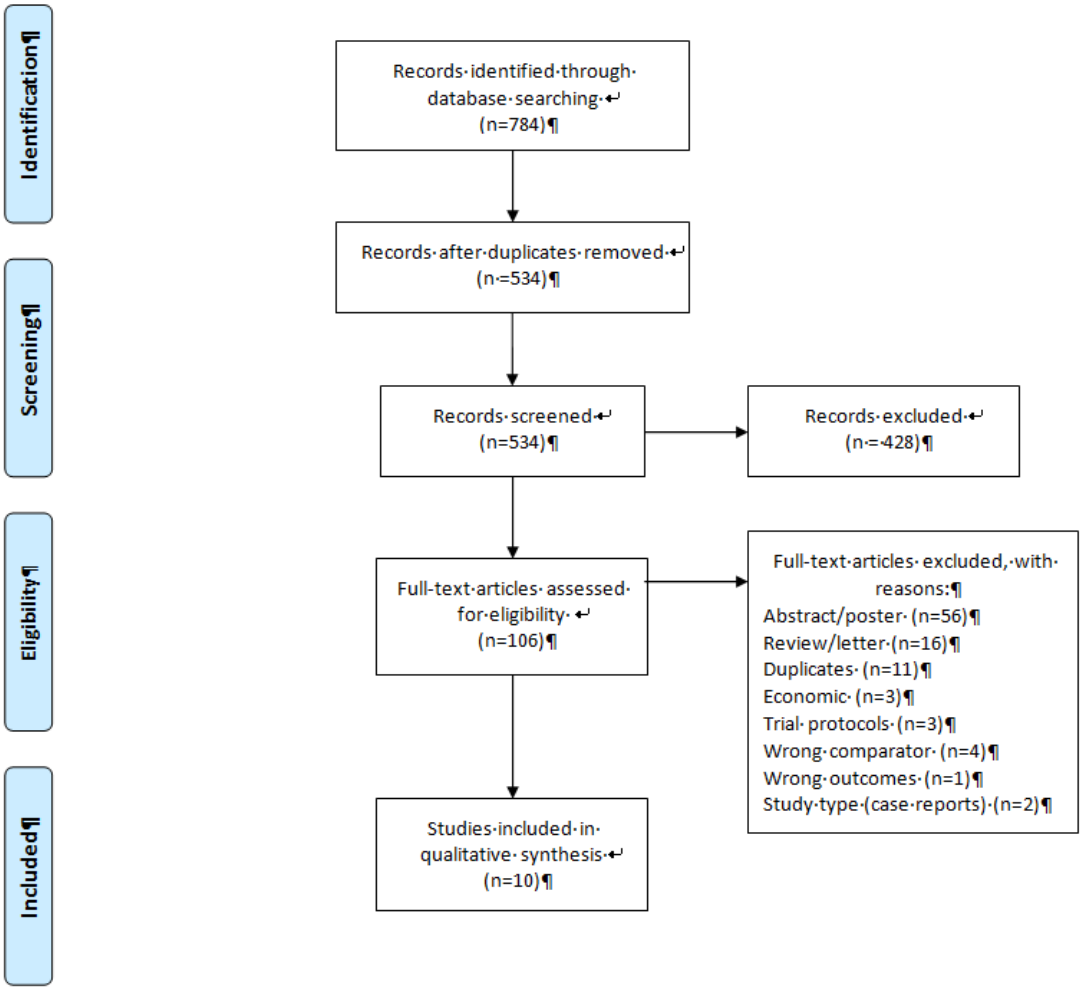

Table A3: *56 conference abstracts identified from the EAC validation of the primary literature search*

Albala DM, McVary K, Roehrborn C. Convective water vapor thermal therapy: 3-year durable outcomes of a randomized controlled study for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. Canadian urological association journal. 2018;12(9):S197-.
Albala DM, McVary KT, Roehrborn CG, Ulchaker JC. Transurethral convective radiofrequency water vapor thermal therapy for symptomatic benign prostatic hyperplasia: twoyear outcomes of a randomized, controlled, and prospective crossover study. Canadian urological association journal. 2017;11(9):S326-S7.
Avant R, Yang D, Hebert K, Gopalakrishna A, Helo S, Andrews J, et al. Rezum Prostate Ablation for Large Gland (>=80 grams) Prostates. Journal Of Sexual Medicine. 2019;16(4 Supplement 1):S117-S8.
Bliucukis R, Skov-Jeppesen SM, Lund L. A prospective study of Rezum (Water Vapor Thermal Therapy) for lower urinary tract symptoms associated with benign prostatic hyperplasia. Scandinavian Journal of Urology. 2019;53(Supplement 221):3.
Butcher MJ, Dixon C, Wagrell L, Tornblom M, Pacik D, Cedano E, et al. Preserving sexual function with the Rezum system: Using steam therapy to treat LUTS/BPH. Journal Of Sexual Medicine. 2015;12(Supplement 2):161.

Dixon C CC, Rodriguez R, Larson T. Development of Convective Water Vapor Energy for Treating Localized Prostate Cancer: First-In-Man Early Clinical Experiences. Journal of Endourology. 2016;30(S2).
Dixon C, Cabanas C, Rijo E, Huidobro C, Larson T. Development of convective water vapor therapy (steam) for focal therapy of prostate cancer. In vivo treatment and immediate radical prostatectomy. Journal of Endourology. 2014;28(SUPPL. 1):A32-A3.
Dixon C, Cedano ER, Pacik D, Vit V, Varga G, Wagrell L, et al. Convective water vapor energy (WAVE) ablation: Twoyear results following treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Journal of Urology. 2016;195(4 SUPPL. 1):e457.
Dixon C, Cedeno ER, Pacik D, Varga G, Vit V, Mynderse L. Transurethral water vapor therapy for BPH; 1-year clinical results of the first-in-man and Rezum I clinical trials using the Rezum system. Journal of Urology. 2014;191(4 SUPPL. 1):e762.
Dixon C, Rijo Cedano E, Pacik D, Vit V, Varga G, Mynderse L, et al. Transurethral water vapor therapy for BPH; Initial clinical results of the first in man trial and RezumTM i pilot study. European urology, supplements. 2013;12(1):e631.
Dixon C, Rijo-Cedano E, Pacik D, Vit V, Varga G, Mynderse L, et al. Transurethral high energy water vapor therapy for BPH; Initial clinical results of the first-in-man and Rezum 1 clinical trials using the Rezum system. Journal of Endourology. 2013;27(SUPPL. 1):A340-A1.
Dixon CM CC, Huidobro C, Larson TR. Development of Convective Water Vapor Energy Therapy for Treating Localized Prostate Cancer: First-In-Man Early Clinical Experiences. Journal of Endourology. 2015;29(S1).
Garcia C, Woo H. The impact on medicare billing practices with the introduction of Rezum technology. BJU international. 2019;123(Supplement 2):36-7.
Gupta N, Holland B, Delfino K, Dynda D, Beahrs JR, Wagrell L, et al. Convective radiofrequency water vapor energy prostate ablation (Rezum) effectively treats urinary retention. Journal of Urology. 2017;197(4 Supplement 1):e337.
Gupta N, Holland B, Dynda D, Kohler T, McVary K. Comparison of convective radiofrequency water vapor energy ablation of prostate (Rezum) to MTOPS trial cohort. Journal of Urology. 2017;197(4 Supplement 1):e511.
Gupta N, Kohler T, McVary K. Convective radiofrequency water vapor energy ablation (Rezum®) effectively treats lower urinary tract symptoms due to benign prostatic enlargement regardless of obesity while preserving erectile and ejaculatory function. Journal of Urology. 2017;197(4):e609-.
Gupta N, Kohler T, McVary K. Convective radiofrequency water vapor energy ablation effectively treats lower urinary tract symptoms due to benign prostatic enlargement regardless of obesity while preserving erectile and ejaculatory function: results of a multicenter, randomized, controlled trial. European urology, supplements. 2017;16(3):e521-e2.
Gupta N, Kohler TS, McVary KT. Convective water vapor energy ablation effectively treats lower urinary tract symptoms due to benign prostatic enlargement while preserving erectile and ejaculatory function: results of a multicenter, randomized, controlled trial. Journal Of Sexual Medicine. 2017;14(2):e33-.
Gupta N, Rogers T, Mahon J, McVary K. Is Sexual Function Better Preserved After Water Vapor Thermal Therapy Or Medical Therapy For Lower Urinary Tract Symptoms Due To Benign Prostatic Hyperplasia? Journal Of Sexual Medicine. 2019;16(4):S122-.
Haider R, Galiano M, Ingels A, Barret E, Rozet F, Sanchez-Salas R, et al. Precocious evaluation of first French experience of benign prostatic hyperplasia management by water vapor thermal therapy with Rezum system. European urology, supplements. 2018;17(4):e2110-e2.
Helo S, Tadros N, Gupta N, Holland B, Dynda D, Kohler TS, et al. Comparison of lower urinary tract symptoms and sexual function response to convective radiofrequency thermal therapy of prostate (Rezum) to mtops study cohort. Journal Of Sexual Medicine. 2018;15(2 Supplement 1):S58.
Helo S, Tadros N, Gupta N, Holland B, Dynda D, McVary K. COMPARISON OF CONVECTIVE RADIOFREQUENCY THERMAL THERAPY OF PROSTATE (REZUM) TO MTOPS STUDY COHORT SEXUAL FUNCTION RESPONSE AT 3 YEARS. Journal of Urology. 2018;199(4 Supplement 1):e833.

Helo S, Tadros N, Gupta N, Kohler TS, McVary KT. Convective radiofrequency thermal therapy (Rezum) effectively treats lower urinary tract symptoms due to benign prostatic hyperplasia regardless of obesity while preserving erectile and ejaculatory function. Journal Of Sexual Medicine. 2018;15(2 Supplement 1):S18.
Hillelsohn J, Tokar S, Valenzuela R. A Novel Prostatic Block for Minimally Invasive Treatment for BPH. Journal Of Sexual Medicine. 2019;16(4 Supplement 1):S124.
Johnston M, Gehring T, Montgomery J, Rajkumar G, Emara A, Nedas T, et al. Rezum water vapour thermal therapy for benign prostatic hyperplasia: Early results from the United Kingdom. Journal of Clinical Urology. 2018;11(Supplement 1):70.
Johnston M, Shah T, Emara A, Gehring T, Farmer T, Nedas T, et al. MP01-03 REZUM WATER VAPOUR ABLATION THERAPY FOR BENIGN PROSTATIC HYPERPLASIA: INITIAL RESULTS FROM THE UNITED KINGDOM. The Journal of urology. 2019;201(Supplement 4):e1-e2.
Johnston M, Shah T, Emara A, Gehring T, Farmer T, Nedas TG, et al. Rezum steam ablation therapy for benign prostatic hyperplasia: Initial results from the United Kingdom. European urology, supplements. 2019;18(1):e1489-e90.
Joseph Mahon* M, IL; Nikhil Gupta, New Brunswick, NJ;, Tyson Rogers M, MN; Bradley Holland, Springfiled, IL;, Kevin McVary M, IL. 3-YEAR OUTCOMES OF SEXUAL FUNCTION AFTER WATER
Li J, Sidebottom R. Does a learning curve exist for treating lower urinary tract symptoms with Rezum? Canadian urological association journal. 2018;12(9 Supplement 4):S244.
Li J, Sidebottom R. Effects of Rezum on lower urinary tract symptoms, with a focus on urgency: A single-center, prospective analysis. Canadian urological association journal. 2018;12(9 Supplement 4):S243-S4.
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Table A4. *Summary of selected relevant conference abstracts in a UK setting.*

Abstract identification*	**Source of identification****	**Title**	**Brief description**	**Used in Assessment Report?**
BAUS P8-2 Ahmed et al. (2018), UK	Company submission	Unknown	Observational study of 79 men undergoing treatment with Rezum. Outcomes	Not used

Abstract identification*	Source of identification**	Title	Brief description	Used in Assessment Report?
			included urodynamics, IPSS, and PSA.	
PD19-04 AUA 2019 Elterman et al (2019)	Company submission	Unknown	Indirect comparison of Rezum vs. UroLift	Not used
MP45-12 Journal of Urology (Hernandez et al., 2019)	Company submission. Identified in EAC literature search.	Convective water vapor energy therapy (WAVE) versus prostatic urethral LIFT (PUL) for the treatment of symptomatic benign prostatic hyperplasia (BPH): an indirect comparison anchored on sham control.	Indirect comparison of Rezum vs. UroLift	This was the basis of the company's indirect comparison (Section 7 of submission). Cited in page 47 of Assessment Report.
37th World Congress of Endourology (WCE) Sarkar et al. (2019). Also 3 other publications. (Johnston *et al.*, 2019)	Company submission. Identified in EAC literature search. Identified by a NICE expert advisor.	Rezum steam ablation therapy for benign prostatic hyperplasia: Initial results from the United Kingdom	Prospective case series (n = 181) with 12 months follow up set in the UK. Outcomes: • IPSS • IPSS QoL • Qmax • PVR • Operation time Reported in multiple sources with different first authors.	Supports generalisability of Rezum procedure to the UK (page 49). Supports procedural duration (page 119).
WCE 2019 (ID 702068) Sarkar *et al.* (2019)	Identified by a NICE expert advisor.	Could Rezum water vapour ablation therapy for benign prostate enlargement be an option for patients with urinary retention? The first UK centre experience.	Case series of 25 patients. 3 months follow up. Outcomes: • IPSS • IPSS QoL • Qmax • PVR • Proportion TWOC	Not used (unclear if these patients have been double counted).

Abstract identification*	Source of identification**	Title	Brief description	Used in Assessment Report?
WCE 2019 (ID 702144) Sarkar *et al.* (2019)	Identified by a NICE expert advisor.	*Is Rezum™ Water Vapour ablation therapy a suitable option for men with larger prostate glands?*	Subgroup analysis comparing men with prostates <80 mL (n = 128) with >80 mL (n = 28).	Subgroup analysis of prostate size (page 33).

Abbreviations: BAUS, British Association of Urological Surgeons; IPSS, international prostate symptom score; PSA, prostate specific antigen; PVR, post-void residual volume; Qmax, peak flow rate; QoL, quality of life; TWOC, trial without catheter.

* Italicised text from company submission. It has not been possible to retrieve all of these abstracts.

** Several abstracts were reported in multiple conferences or formats.

Appendix B – Critical appraisal of clinical evidence

Table B1. *Critical appraisal of Rezum II trial.*

Bias domain	**Source of bias**	**Support for Judgement**	**Review authors' judgement (assess as low, unclear, or high risk of bias)**
Selection bias	Random sequence generation	Subjects stratified by baseline severity (IPSS). Randomisation performed with an electronic program using permuted blocks of random sizes, stratified by investigational site, in a 2:1 ratio allocation.	Low risk of bias
	Allocation concealment	Not described. No significant differences detected in baseline characteristics supports successful implementation of randomisation and allocation.	Unclear risk of bias.
Performance bias	Blinding of participants and personnel*	Participants were blinded to the intervention by being "draped to prevent them from visualising the treating physician and the device". Treating clinicians could not be blinded. 56% of patients receiving sham guessed their allocation.	Low risk of bias.
Detection bias	Blinding of outcome assessment*	Most patient outcomes were self-administered questionnaires, including the primary outcome (IPSS). These were subjective outcomes. Patients were made aware of allocation after 3 months; after this pint they were not blinded. Participants in the cross over study were therefore not blinded. Unclear if investigators measuring clinical outcomes (e.g. Q_{max}) were blinded, or if analysts were blinded.	Low risk of bias (<3 months, comparative study) High or unclear risk of bias (>3 months, cross over and case series studies).
Attrition bias	Incomplete outcome data*	For comparative study (3 months), attrition rate was very low and analysis was ITT. For cross over and prospective case series, attrition rate was higher, and PP analysis was performed.	Low risk of bias (<3 months, comparative study) High risk of bias (long-term case series studies).

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
		At 4 years, 90/136 (66%) of randomised patients reported data. Reasons for dropping out were described where possible, but 15 were lost to follow up after 4 years.	
Reporting bias	Selective reporting	Primary efficacy outcome defined and power calculations undertaken. Primary safety outcome defined in protocol (NCT01912339) not explicitly reported, but appears to have been met. Secondary outcomes not reported in protocol. Statistical adjustment for multiple comparisons appear not to have been performed.	High risk of bias
Other bias	Anything else, ideally pre-specified.	Study supported by NxThera.	Unclear risk of bias.
*Assessments should be made for each main outcome or class of outcomes.			

Appendix C – Critical appraisal of economic evidence

Table C1. *Critical appraisal of Ulchaker and Martinson, 2018.*

Study question	Response (Yes/No/Not clear/NA)	EAC comments
1. Was the research question stated?	Yes	Objective clearly stated in abstract.
2. Was the economic importance of the research question stated?	Yes	Background information on the condition and economic impact clearly explained.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The study was set in the US healthcare system from the perspective of the health care payer.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The study included a range of treatments for BPH which included pharmacotherapy, minimally invasive treatments (Rezum, UroLift, and Prostiva), and surgically invasive treatments. HoLEP was not considered.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	This was a cost-effectiveness study, using IPSS points as the measure of effectiveness.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	No	Full citations were reported. However, it was not clear how the reported data was used or adjusted.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	As there is a lack of comparative evidence , several studies were used to inform effectiveness estimates.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	No meta-analyses were performed.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	IPSS score, a measure of BPH symptom severity. However, it was not transparent how adjusted values were derived from the source literature.
12. Were the methods used to value health states and other benefits stated?	No	Effectiveness studies were referenced. Relative improvements were used as patient IPSS differed at baseline, but it was not clear how this was done.
13. Were the details of the subjects from whom	No	Only minimal information on baseline IPSS scores reported.

Study question	Response (Yes/No/Not clear/NA)	EAC comments
valuations were obtained given?		
14. Were productivity changes (if included) reported separately?	NA	
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	No	Aggregated costs were reported.
17. Were the methods for the estimation of quantities and unit costs described?	No	Costs were derived from “2016 Medicare national average fee schedules”. These are detailed in Table 2, but details of unit use and costs not reported.
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Model structure was illustrated and described narratively.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The model structure was justified narratively. Alte
22. Was the time horizon of cost and benefits stated?	Yes	2 years time horizon, 6 month cycles. Unclear if half-cycle correction was used.
23. Was the discount rate stated?	Yes	3% discount rate applied.
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	Unclear if discounting was applied to IPSS as well as costs.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	PSA was applied. No deterministic analysis performed.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Not clear	Methodology was stated, but not values: “Uncertainty was evaluated using a probabilistic sensitivity analysis in which IPSSs used normal distributions and rates per cycle used beta-binomial distributions”.

Study question	Response (Yes/No/Not clear/NA)	EAC comments
30. Were relevant alternatives compared?	Yes	
31. Was an incremental analysis reported?	Yes	ICERs (Table 3), CE planes, and CEAC were reported but could have been more clearly presented.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Only aggregate data reported.
33. Was the answer to the study question given?	Yes	Clear conclusion reported.
34. Did conclusions follow from the data reported?	Yes	The results reported the conclusion.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Important limitations of the studies were discussed concerning heterogeneity of patient population, uncertainty in patient pathways, and small study sample sizes.
36. Were generalisability issues addressed?	No	It is unclear how generalisable this study is to other settings.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ (59). Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination		

Appendix D – Cost inputs to the economic model

Table D1. *Clinical parameters used in the de novo model.*

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
Proportion requiring re-treatment at follow-up, Follow-up time point. Determines the transition probability for repeat surgery	Rezum	0.044, 4 years (McVary et al., 2019)	Retreatment after 4 years follow-up in pivotal study	This is value correctly reflects the 4 year results of the Rezym II trial (prospective case series). Note that an additional 7 patients (5.1%) were censored because they required treatment with BPH medication. This patient pathway was not modelled.
	Monopolar TURP	0.058, 5 years HTA (Lourenco et al., 2008)	Reported cumulative incidences of a secondary TURP after primary TURP at 1, 5 and 8 years of 2.9%, 5.8% and 7.4% respectively	This data was from a 2005 observational study which analysed data between 1992 and 1995 (Madersbacher et al., 2005). The EAC accepts this as it was used in the original HTA, however, the robustness of these data today is questionable. The GOLIATH study (Thomas et al., 2016) reported rate of reoperation of 7.6% for TURP at 2 years; however, most cases occurred within the first year so this data cannot be reliably extrapolated.
	Bipolar TURP	0.058, 5 years HTA (Lourenco et al., 2008)	Assumed to be the same as Mono-TURP. This assumption is consistent with the assumption applied in the Lourenco et al. (2008) model	There is no data on the reoperation rate of bipolar TURP.
	UroLift	0.136, 5 years (Roehrborn et al., 2017b)	The LIFT study reported a cumulative revision rate of 10.7% at 3 years and 13.6% at 5 years	These data are correct. Note: 15 patients (10.7%) were censored for recommencing BPH medication.

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
	GreenLight	0.058, 5 years HTA (Lourenco et al., 2008)	Assumed to be the same as Mono-TURP justified because Lourenco et al. (2008) assumed TUVP had the same retreatment rate as TURP. Furthermore, the GOLIATH RCT also found no difference in retreatment between TURP and GreenLight XPS at 2 years	There was no statistically significant difference between the treatment arms in the GOLIATH trial, but results did indicate a possible higher retreatment values for GreenLight (9.0% for GreenLight vs. 7.6% for TURP, relative increase of 18%). The EAC has consequently revised the reoperation rate for GreenLight up by 18% to reflect this.
	HoLEP	0, 5 years Assumption	No retreatment with HoLEP permitted justified because retreatment after HoLEP is expected to be very rare. Elmansy et al. (2011), 5-year data for reoperation with HoLEP (0.7% at 62 months) however their definition of retreatment included stricture which is captured as a short term event in the model.	NICE clinical experts advised that reoperation may be required with HoLEP, due to incomplete abalation of prostate tissue. However, as the company states, this is likely to be very rare and will not therefore significantly impact on the model.
Proportion retreated with TURP Determines the weighted average cost and risk of incontinence and ED associated with repeat surgery	Rezum	0.5 Assumption	The choice to retreat with Rezum or TURP is expected to vary by hospital / patient	This assumption is reasonable and agrees with limited empirical evidence from the Rezum II trial, where 3 patients had repeat TURP/laser, and 2 had repeat Rezum (McVary et al., 2019).
	Monopolar TURP	1.00 Assumption	All TURP is expected to be retreated with TURP	
	Bipolar TURP	1.00 Assumption	All TURP is expected to be retreated with TURP	
	UroLift	1.00 MTG26 (NICE, 2015d) Assumption	Most patients are expected to be retreated with TURP if LIFT implants need to be removed or symptoms return	The LIFT trial (Roehrborn et al., 2017b) reported 63.2% TURP/Laser (12/19) and 36.8% repeat UroLift (7/19). As the type of laser was not specified, and laser technologies may not be

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
				available to all providers, the EAC has assumed 63.2% received gold standard TURP in the model, with the remainder receiving repeat UroLift.
	GreenLight	0.5 Assumption	The choice to retreat with GreenLight or TURP is expected to vary by hospital / patient	The GOLIATH trial did not report on the retreatment modalities (Thomas et al., 2016). This is a reasonable assumption considering the lack of data.
	HoLEP	0.0 Assumption	It would not be appropriate to perform a TURP after a HoLEP procedure.	The EAC agrees with this assumption.
Duration of operation (mins) Used to calculate the cost of operation	Rezum	17.5 (Johnston et al., 2019)	Conference abstract reporting outcomes in Rezum procedures in NHS hospitals, selected as the only published sourced obtained from a UK hospital. This procedure time was compared to procedure times estimated by 3 other NHS providers using Rezum, collected by the manufacture. Estimates ranged between 17 and 25 minutes and were provided by Basingstoke and North Hampshire Hospital (Author of abstract), Imperial College Healthcare NHS Trust, South Warwickshire NHS Foundation Trust and Wye Valley NHS Trust.	The duration of operation is a key driver of the de novo model. Estimates of operation duration are intrinsically uncertain and dependent on many factors such as the clinical setting and experience of the treating team. Additionally, operation times may not reflect the true procedural costs. The EAC has accepted these estimates in the base case, as they have been used to inform previous MTG publications. However, threshold analysis has been undertaken where the model is sensitive to operation times.
	Monopolar TURP	66.0 (NICE, 2015d)	The UroLift submission, modified by the EAC team	

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
			applied a procedure time of 66 minutes. The original UroLift submission applied a procedure time of 60 minutes.	
	Bipolar TURP	66.0 (NICE, 2015d)	As above	
	UroLift	30.0 (NICE, 2015d)	Assumption applied by the manufacturer informed by clinical opinion. Please note, that this was amended to 60 minutes by the External Assessment Group (EAG) to apply the rate reported in a clinical trial. 30 minutes was applied in the base-case of our model as this was more consistent with the feedback reported by clinical experts consulted during model development.	
	GreenLight	49.6 (Bachmann et al., 2014)	Procedure time reported in GOLIATH	
	HoLEP	80.2 (Li et al., 2014)	Pooled analysis found a 14.19 minute increase in procedure times relative to TURP. This was applied to the procedure time for Mono-TURP to calculate procedure time with HoLEP	
Length of stay (days)	Rezum	0.5 (NICE, 2015d) Assumption	Replicates the length of stay applied in base-case Neotract submission. Length of stay	Length of stay is an important contributor to costs in the model. However, there is considerable

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
Used to calculate cost of hospital stay			data for Rezum has not been published nor was it collected by hospitals consulted during model development. The length of stay was expected to be similar to other minimally invasive procedures as the preparation and recovery times are expected to be similar and the procedure time with Rezum is similar or shorter. Assuming a length of stay of 0.5 days for all minimally invasive procedures is expected to be conservative and may be considerably shorter. The EAC considered scenario analyses where this was varied to 0.25 days and 0.125 days (3 hours as a day-case procedure) for a UroLift procedure.	uncertainty regarding costs associated with length of stay and their true implications to the NHS. The EAC has accepted these estimates in the base case, as they have been used to inform previous MTG publications. However, threshold analysis has been undertaken where the model is sensitive to hospital dwell time.
	Monopolar TURP	3.03 (NICE, 2015d) Assumption	Length of stay applied in original UroLift submission, obtained from NHS reference cost data	
	Bipolar TURP	2.33 (NICE, 2015d) (Lourenco et al., 2008)	Calculated as summation of length of stay with TURP and the WMD obtained from the meta-analysis (Lourenco et al. 2008)	

Parameter/outcomes	Technology	Value and source	Rationale	EAC comment
	UroLift	0.5 (NICE, 2015d) Assumption	Length of stay applied in base-case Neotract submission	
	GreenLight	0.7 (Ajib et al., 2018)	Analysis of 5 year prospectively gathered data base on GreenLight XPS-180 procedures	
	HoLEP	1.98 (Lourenco et al., 2008)	Calculated as summation of operating time with TURP and the WMD obtained from the meta-analysis (Lourenco et al. 2008). Hospital Episodes Statistics (HES) data 2018/2019	
Abbreviations: HoLEP, holmium laser enucleation of prostate; TURP, transverse resection of prostate; WMD, weighted mean difference.				

Table D2. *Bundled costs of Rezum and its comparators.*

Procedure	Assumption	Justification	Source	EAC comment
Rezum, bundled cost	The equipment costs for Rezum, include: • A consumable cost of £1,348 per patient • No generator and annual servicing costs is applied because this is provided free of charge	Assumptions provided by manufacturer, based on list price	Manufacturer	The company has not provided a breakdown of costs for Rezum; the cost reported is for consumables required for one procedure. The company provides the generator and maintenance costs, as well as training (which will incur a 2 day opportunity cost per clinician). Staffing costs are included in theatre costs.

Procedure	Assumption	Justification	Source	EAC comment
				NHS Supply chain has a published cost of £1617.20, including VAT and delivery (NHS Supply Chain, 2019). Cost minus VAT is £1336.96. The EAC therefore accepts the value by the company.
TURP (monopolar and bipolar), bundled costs	The cost of a TURP is calculated as a weighted cost between Mono- and Bi-TURP, using the consumable costs reported in the GreenLight 2016 submission, updating prices to 2018/19 The distribution of Mono and Bi-TURP is assumed to be 50:50. This assumption is varied in scenario analysis to consider Mono and Bi-TURP separately	This approach replicates the assumption applied and accepted in the GreenLight MTEP submission (MTG 29). This assumption was also tested with clinical experts during model development. Furthermore, scenario analyses compared Rezum to TURP where 100% and 0% of procedures are done with Mono-TURP respectively	MTG29 Assessment Report (NICE, 2016)	The EAC has checked this assumption and found it to be valid. However, feedback from the EAC's clinical experts (EAC External correspondence log, 2019) indicated that bipolar TURP is now used more frequently than monoplar TURP, and that monopolar TURP is replaced by bipolat TURP when the technology is re-acquisitioned. Therefore, the EAC has assumed that 75% of cases of TURP use bipolar technology in the base case.
	The cost of TURP includes: Mono-TURP includes: • 1 Mono-Loop per surgery, unit cost £52.60, plus 4 bags of glycine fluid, unit cost of £5.34, plus 0.5 roller ball pieces per surgery, unit cost £50 Bi-TURP includes: • 1 Bi-Loop per surgery, unit cost £189.34 Mono or Bi-TURP, includes:	This approach replicates the equipment costs assumptions applied in the GreenLight MTEP submission (MTG 29), updated in consultation with clinical experts No capital investment is required as TURP is a mature technology	MTG29 Assessment Report (NICE, 2016)	The aggregated consumable cost in MTG29 for TURP was £190.50. The aggregated costs in the de novo model (adjusted for inflation using CPI) was £165.20. Assuming 75% of TURP are bipolar, the figure used in the EAC's base case was £187.79.

Procedure	Assumption	Justification	Source	EAC comment
	• 1 Ellik evacuator per patient, unit cost £21.04 • No capital or servicing costs			
UroLift, bundled costs	The cost of UroLift assumes: • 4.4 implants per patient at a unit cost of £354.42 (unit cost of £330 as reported in the 2016 submission, inflated to 2018/19 prices). No capital or servicing costs was applied	This approach replicates the cost assumptions applied in the UroLift MTEP submission (MTG26) (NICE, 2015d), updated by the External Assessment Centre (EAC) after consultation with clinicians	NICE MTG26, assessment report (NICE, 2015d) Clinical experts	The cost of UroLift was £1325 in the MTG26 model, which has been inflated by the company in the *de novo* model to £1559.45. The EAC were unable to identify device costs of UroLift on NHS supply chain and this granularity was not reported in the Innovation Technology Payment (ITP) of NHS England. It is possible the cost of UroLfift has been fixed since MTG26; if this was the case application of CPI would be inappropriate. However, in the absence of direct costing data and because of other precedents, the EAC has accepted the validity of the company's approach.
GreenLight, bundled cost	The cost of GreenLight XPS includes: • 1 GreenLight XPS Fiber at unit cost provided by the manufacturer • No capital or service costs are applied	This approach is aligned with the cost assumptions applied in the GreenLight submission (MTG 29), updated with current price lists provided by the manufacturer	MTG29 Assessment Report (NICE, 2016)	The cost of GreenLight was £550 in the MTG29 model. This reflects the current list price and has not been inflated using the CPI. THE NHS supply chain lists a cost of £600 for a laser fibre HPS fibre (NHS Supply Chain, 2019). Minus VAT, this is £540. The EAC noted that the de novo model was highly sensitive to the cost of GreenLight (see Section 9.3.2).
HoLEP, bundled cost	HoLEP is calculated as a weighted cost between single and reusable Fibers,	Replicates the cost assumptions applied in	MTG29 (NICE, 2016).	The EAC has checked that this was the approach used in MTG29.

Procedure	Assumption	Justification	Source	EAC comment
	using the consumable costs reported in the GreenLight 2016 submission (MTG 29), updated to reflect 2018/19 prices: Assumed a 50% split between use of single and reusable HoLEP Fiber • Single use requires: 1 single use fiber per patient at unit cost of £189.34 ; 1 suction tubing at unit cost of £21.04 p.p., • Recurrent use: 1 reusable fiber for every 25 procedures at unit cost of £736.34; 1 fibre stripper and cleaver p.p at unit cost of £52.60 • Both procedures require 1 morcellator cutting blade per procedure (p.p) at unit cost of £210.38; suction tubing at unit cost of £21.04; 0.17 omni-jugs at unit cost of £7.36; and 1 Ellik Evacuator at unit cost of £21.04 The capital cost per patient is calculated assuming: • Unit cost of HoLEM device: £92042.12 as the average cost across 4 models of HoLEP • Unit cost of HoLEM Morcellator: £31,557.30 as the average cost across 4 models of HoLEP • Assumes 250 patients are treated in an average hospital with HoLEP equipment • The lifespan of capital equipment is assumed to be 10 years. Amortisation rate: 3.5%, aligned with discounting assumption	the GreenLight MTEP submission revised by the EAC (MTG29), updated with current price lists provided by Boston scientific.	Manufacturer, average price negotiations; updated assumptions applied by the EAC in the MTG29 assessment of GreenLight.	The EAC considered it may be inappropriate to include capita costs for HoLEP if this is regarded as an established technology (as with TURP) with hospitals already equipped the technology. Additionally, the amortisation rate should be 10% per annum, to reflect the 10 year expected life span of the technology. A technology cost per procedure of £448.83 was used in the *de novo* model.

Procedure	Assumption	Justification	Source	EAC comment
Abbreviations: CPI, consumer price index; HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the urethra; VAT, value added tax.				

Table D3. *Costs of severe AEs used in the de novo model.*

Cost parameter	Company calculation and cost	Justification and cost used	Source	EAC comment
Annual cost per patient with incontinence	The cost of permanent incontinence was sourced from the UroLift MTEP submission (MTG 26), applying the unit costs reported in the submission, inflating using the health component of CPI and applying percentages for proportion of patients expected to require each treatment, informed by clinical opinion. The following resource use, per 12-month period considering the proportion of patients requiring each treatment: Technology: £0 Staff: £0 Hospital costs: £0 Other Items: 3 catheters per day (£1590.09, by 20%), 1 indwelling (£58.25, 20%), 5mg Oxybutynin twice daily (£35.72 by 50%), combination of other anticholinergics (£267.54 by 50%), 1 pad per day (£138.62 by 20%), 1 overnight bag per night (£40.77 by 20%), 1 bag support (£349.47 by 20%), leg sleeve and Stalock bard per week (£543.62 by , Sheath appliances, 1 district nurse visit per week, 1 specialist nurse visit every 6 weeks Total: The total cost per patient per year of: £2,152.88, was inflated using the CPI to be £2,356.97 in 2018/19	Replicates a similar approach applied and accepted in the NICE MTEP process **£2,356.97**	MTG26 (NICE, 2015d), updated using CPI	The EAC has not checked the micro-costed data. However, as this cost has been used in a previous MTG, the EAC considers this was a valid approach.
Annual cost per patient	The annual cost of treating ED was calculated applying the following resource use assumptions:	Resource use assumptions are sourced from Ramsey et al. 2012, an economic	(Ramsay et al., 2012)	The EAC considered this approach to costing was appropriate and the cost established was conservative, as the

Cost parameter	Company calculation and cost	Justification and cost used	Source	EAC comment
with erectile dysfunction	Technology: £0 Staff: Patients with ED attend 2 GP visits per year (2 x £37.40) Hospital costs: £0 Other Items: 82.2% are prescribed generic sildenafil 100mg once weekly, at an annual cost of £10.40. This cost reflects the lowest cost, generic drug reported in BNF 2019 • 15.4% are prescribed Alprostadil: 20 µg once weekly, at an average cost of £556.14 . This cost reflects the average of 3 variation reported in BNF, 2019 • 20% are prescribed a vacuum pump at an average cost of £148, replaced once per year.This cost is the average device cost reported in an NHS PresQIPP report, inflated to 2018/19 prices. Total: £198.76	evaluation of radiotherapy for prostate cancer, updated with consideration of the guidelines (NHS PrescQIPP 2015) This study did not report statistics for use of vacuum pumps therefore an assumption was applied Penile prosthesis implantation was not considered as the uptake for Penile prosthesis to treat ED after open proctectomy was reported to be 0.3% and this rate is likely to be even lower post TURP. Therefore, including penile prosthesis implantation was expected to have minimal impact on the model results **£198.76**	NHS PrescQIPP, 2015 BNF 019	resource use reported (2 GP appointments and use of generic drugs) did not appear exaggerated.
Cost of acute urinary retention	The cost of AUR was sourced from Annemans et al. (2005), which assumes Alfuzosin as a first line treatment. This cost includes hospitalisation, medication, primary care and secondary care visits and risk of proctectomy if treatment fails Technology: £0 Staff: £0 Hospital costs: £0	Replicates the assumptions applied in the UroLift MTG26 submission **£3061.79**	Annemans et al. (2005), cited in MTG26	The cost of management of acute urinary retention was substantial at £3061.79. The base cost of this AE was taken from a UK economic study published in 2005 (Annemans et al., 2005). This cost (£2029), which was the estimated cost of treatment of acute urinary incontinence using Afuzosin, may have been superseded by changes to specific drug

Cost parameter	Company calculation and cost	Justification and cost used	Source	EAC comment
	Other Items: The cost reported in Annemans et al. (2005) includes hospitalisation, medication, primary care and secondary care visits and risk of proctectomy if treatment fails The total cost of £2029 was inflated from 2002 to 2019, using CPI			costs and patient pathways not accurately reflected by CPI inflation. However, as the cost had only limited impact on the overall results (due to its relative rarity), it was left unchanged.
Cost of bladder neck contracture / stricture	The cost of bladder neck contracture / stricture was sourced from the reference cost for bladder procedure in NHS hospitals Technology: £0 Staff: £0 Hospital costs: £330.00 Other Items: £0	Applies the same reference cost as UroLift MTG26 MTEP submission **£330.00**	NHS reference costs 2017/2018 LB15E (Minor Bladder Procedures, 19 years and over)	The cost of bladder neck contracture or stricture was based on NHS Reference costs 2017/18 (LB15E Minor bladder procedures, 19 years and over). This was £330, consistent with the submission.
Cost of acute bleeding event (Grade 3 / blood transfusion)	The cost of treating acute bleeding or blood transfusion was calculated applying the following assumptions: Technology: £0 Staff: £0 Hospital costs: 2.7 units of standard red cells at a unit cost of £121.85, inflated using CPI Other items: £0	Applies the same reference cost as UroLift MTG26 MTEP submission **£357.95**	NHS reference costs 2017/2018 LB15E (Minor Bladder Procedures, 19 years and over)	The company estimated the cost of severe bleeding on the basis of 2.7 units of standard red cells. The EAC calculated this cost was £329 rather than £358; however this difference had minimal impact on results.
Cost of TUR syndrome	The cost of treating TURs includes time in high dependency unit (2 days) plus time in a ward (2 days) Technology: £0 Staff: £0 Hospital costs: 2 days in high dependency ward (£693.00) and 2 days in normal ward £358.00 Other items: £0	Replicates the assumptions applied in the UroLift MTG26 submission updated with 2017/18 reference costs **£2,102.00**	NHS reference costs 2017/2018	The company estimated the cost of TUR syndrome as £2102, citing 2 days in high dependency ward (£693.00) and 2 days in normal ward (£358.00). The EAC were unable to confirm these costs but they appear to be reasonable.

Cost parameter	Company calculation and cost	Justification and cost used	Source	EAC comment
Cost of severe UTI (Grade 3+ / severe)	The cost of treating acute (grade 3+) UTI was sourced from NHS reference cost for UTI treatment in hospital Technology: £0 Staff: £0 Hospital costs: £781.00 Other items: £0	Replicates the assumptions applied in the UroLift MTG26 submission updated with 2017/18 reference costs **£781.00**	NHS reference costs 2017/2018 LA04S	The cost of severe UTI (grade 3+) was based on NHS Reference costs 2017/18 (LA04S Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-1). The cost of £781 was verified by the EAC.

Appendix E – Technical validation of the company's de novo model.

Table E1 *EAC replication and validation of the company de novo economic model*.

	Technology	Company results £	Updated company results* £ (difference)	EAC patient-level simulation** £ (difference)	EAC cohort simulation £ (difference)
ED functionality **OFF** (Base case)	Rezum	2376.95	Same	2383.06 (+0.26%)	2378.01 (+0.04%)
	TURP (mono and bipolar)	3114.32	Same	3122.58 (+0.27%)	3114.84 (+0.02%)
	UroLift	2908.79	2913.21 (+0.17%)	2933.17 (+0.69%)	2915.99 (+0.10%)
	GreenLight	2402.41	Same	2410.41 (+0.33%)	2403.33 (+0.04%)
	HoLEP	3134.65	Same	3139.65 (+0.16%)	3137.09 (+0.08%)
ED functionality **ON** (Scenario)	Rezum	2377.56	Same	2383.14 (+0.23%)	2378.67 (+0.05%)
	TURP (mono and bipolar)	3188.54	Same	3200.87 (+0.39%)	3189.45 (+0.03%)
	UroLift	2910.36	2916.33 (+0.21%)	2935.06 (+0.64%)	2919.32 (+0.10%)
	GreenLight	2417.78	Same	2428.52 (+0.44%)	2418.87 (+0.05%)
	HoLEP	3149.30	Same	3150.77 (+0.05%)	3151.88 (+0.08%)

Abbreviations: HoLEP, holmium laser enucleation of the prostate; TURP, transurethral resection of the prostate.
* Results from *de novo* model after the errors were corrected.
** 100,000 simulations

Table E2. *Differences in company and EAC DSA estimates in some parameters.*

	Company			EAC		
	DSA	**DSA lower**	**DSA upper**	**DSA**	**DSA lower**	**DSA upper**
Non-acute urinary retention : Bi-TURP	0.019731	0.012628	0.028412	0.019731	0.015785	0.023677
Non-acute urinary retention : HoLEP	0.008192	0.005243	0.011797	0.008192	0.006554	0.009831
Non-serious urinary tract infection : HoLEP	0.05292	0.033869	0.076205	0.05292	0.042336	0.063504
Acute urinary retention : Bi-TURP	0.065769	0.042092	0.094708	0.065769	0.052615	0.078923
Acute urinary retention : HoLEP	0.027308	0.017477	0.039323	0.027308	0.021846	0.032769
Bladder neck contracture / stricture : Bi-TURP	0.0966	0.061824	0.139104	0.0966	0.007728	0.11592
Bladder neck contracture / stricture : HoLEP	0.0588	0.037632	0.084672	0.0588	0.04704	0.07056
Bleeding / Blood transfusion : Bi-TURP	0.0824	0.052736	0.096	0.0824	0.06592	0.09888
Bleeding / Blood transfusion : HoLEP	0.0216	0.013824	0.031104	0.0216	0.01728	0.02592
Transurethral resection syndrome : Bi-TURP	0.0054	0.003456	0.007776	0.0054	0.00432	0.00648
Transurethral resection syndrome : HoLEP	0.0093	0.005952	0.013392	0.0093	0.00744	0.01116
Urinary tract infection : Bi-TURP	0.006	0.00384	0.00864	0.006	0.0048	0.0072
Urinary tract infection : HoLEP	0.00588	0.003763	0.008467	0.00588	0.004704	0.007056
Incontinence : Bi-TURP	0.0177	0.011328	0.025488	0.0177	0.01416	0.02124
Incontinence : HoLEP	0.0291	0.018624	0.041904	0.0291	0.02328	0.037539

EAC fixes to company's PSA

The EAC identified errors which affected the company PSA analysis for length of stay which affected Rezum, Mono-TURP, Bi-TURP, UroLift, and HoLEP arms. This caused each simulation to sample number from between the upper DSA limit and upper PSA limit (instead of sampling between the lower and upper PSA limits). To correct this the EAC made the following changes in the "Sensitivity" worksheet in V3 of the company model:

- Cell O151 "=EXP(NORM.INV(RAND(),LN(N151),(LN(T151)-LN(**S**151))/(2*1.96)))"

- Cell O153 "=EXP(NORM.INV(RAND(),LN(N153),(LN(T153)-LN(**S**153))/(2*1.96)))"

- Cell O155 "=EXP(NORM.INV(RAND(),LN(N155),(LN(T155)-LN(**S**155))/(2*1.96)))"

- Cell O157 "=EXP(NORM.INV(RAND(),LN(N157),(LN(T157)-LN(**S**157))/(2*1.96)))"

- Cell O161 "=EXP(NORM.INV(RAND(),LN(N161),(LN(T161)-LN(**S**161))/(2*1.96)))"

A separate error was detected for PSA analysis for length of stay in the GreenLight arm. The PSA was sampling from a mean of 0.7 days with a standard error of 5.489 taken from n=133 referencing to Ajib 2018. The EAC can confirm that the mean of 0.7 hospital days did come from this source, however this hospital stay was derived from 370 patients with a 95% confidence interval between 0.5-0.8 (i.e. standard error of 0.076) days. The standard error applied in the company model originated from the GOLIATH study which stated a mean hospital stay of 65.5 hours with a standard deviation of 63.3 (which gives standard error of 5.468 when accounting for n=134). The EAC made the following changes in the "Sensitivity" worksheet in V3 of the company model to ensure data from the Ajib 2018 source was applied correctly:

- S159 changed to 0.5

- T159 changed to 0.8

- O159 changed to "=EXP(NORM.INV(RAND(),LN(N159),(LN(T159)-LN(S159))/(2*1.96)))"

- Values in U159 and V159 deleted.