National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT564 GreenLight XPS for treating benign prostatic hyperplasia

Consultation comments table

Guidance update MTAC2 date: 16th September 2022

There were 9 consultation comments from 1 consultee:

- 1 company representative

The comments are reproduced in full, arranged in the following groups:

- Recommendations (comments 1 and 2)
- Clinical parameters: Length of stay (comments 3 to 8)
- General comment (9)

#	Consultee ID	Role	Section	Comments	NICE response FINAL
Recommendations					
1	1	Company representative	1.2	The EAC confirmed GreenLight XPS's potential cost savings when compared with standard treatments such as TURP and HoLEP when they stated, "The results of two economic evaluations (short-term decision tree or long-term Markov model) consistently report the potential for cost savings associated with GreenLight when compared with TURP and HoLEP." We feel this is not currently reflected in the recommendations and is an	Thank you for your comment. NICE editorial changes have removed cost saving statements from the recommendations and moved this information to the rationale section under "Why the committee made these recommendations". Rationale currently states "The cost modelling suggests GreenLight XPS is likely to be cost saving

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				important factor to state at the beginning of the guidance. We suggest that for both clarity and consistency with previous guidance (MTG29), it would be more accurate to use the following statement: “Cost modelling estimates that GreenLight XPS is cost saving compared with standard treatments such as transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP). More comparative data should continue to be collected on cost saving outcomes when using GreenLight XPS in people that may be considered as high-risk, including those with larger prostates and a higher risk of bleeding.”	compared with TURP and HoLEP. By how much depends on day case proportions, length of stay and procedure length. A minor change was made for clarity to state that “although there is enough evidence to recommend GreenLight XPS for people with BPH, including those in high-risk groups, further data is still needed to be more certain about cost savings in those with larger prostates and a higher risk of bleeding”
2	1	Company representative	Question: Are the recommendations sound and a suitable basis for guidance to the NHS?	Yes, as long as the cost-saving potential of GreenLight XPS is explicitly stated in the recommendations.	Thank you for your comment. Please see comment 1 regarding the suggested wording of recommendations cost saving.
Clinical Parameters					
3	1	Company representative	3.13	We remain concerned that the economic results reported in the draft guidance only refer to the EAC’s revised base case analysis for the Markov model, applying a length of stay of 1.6 days for GreenLight. We contend that it is factually incorrect to use a 1.6-day length of stay sourced from HES data because this combines GreenLight and HoLEP lengths of stay. This is particularly relevant because the MTG49 model utilised a length of stay for GreenLight of 0.7 days, sourced from Ajib et al 2018.	Thank you for your comment. The committee considered your comment carefully and agreed that 0.7 days of the length of stay (Los) from Ajib et al. (2018) was not robust because of the limitations of the study (a non-comparative single-centre study). The EAG applied 1.6 days for the length of stay, which was based on NHS activity (from 11,420 admissions) but we acknowledge the company’s comment that this data did not differentiate GreenLight from HoLEP procedure.

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				The reduction in cost savings suggested by the EAC's model for GreenLight, compared to the original model reviewed by NICE and published under MTG49, are mainly driven by the EAC change in length of stay from 0.7 days to 1.6 days. The impact of this change is potentially highly significant and is therefore a very important piece of data to get correct. In addition, this change is not supported by the opinions of 5 clinical experts who, in Table 23 of the EAC report, validated that an estimated length of stay of 0.7 days for GreenLight in the general population is reasonable. We suggest that the evidence of a 0.7-day length of stay for GreenLight, as demonstrated by Ajib et al (2018) and utilised in MTG49, should be utilised in this model as it is inaccurate to rely on HES data which incorporates the length of stay of a main comparator. Should NICE/EAC not be prepared to make this adjustment we contend that the use of the HES 1.6-day length of stay data should be stated clearly in the guidance as well as stating that this is not reflective of current clinical practice.	Seven Clinical experts considered 1.6 days for GreenLight and HoLEP and 2.3 days for TURP to be reasonable. One explicitly stated that length of stay was shorter for GreenLight than HoLEP, and one explicitly stated that length of stay was shorter for bipolar than monopolar TURP (EAG Correspondence Log, 2022). The EAG did additional analyses to consider the possible size of cost savings with GreenLight XPS by applying different values to length of stay. These values were derived from the British Association of Urological Surgeons Bladder Outflow Obstruction Audit data (2019) (See details in Appendix 2). The committee decided to add section 3.15 in the guidance to summarise the additional analyses and results. **Additional scenario analyses varying length of stay explore the size of cost saving using GreenLight compared with TURP and HoLEP** There was no comparative data on the length of stay. The company estimated a length of stay of 0.7 days for GreenLight based on a single arm, single centre study in Canada (Ajib et al. 2018). The EAG applied a 1.6-day length of stay derived from NHS activity data (hospital episode data). Both data sources had limitations (see details in table 22 of the assessment report update, Newcastle EAG 2022). After the public consultation, the EAG did additional analyses to consider the possible size of cost savings with GreenLight XPS by applying different values for length of stay. One scenario was informed clinical expert opinion which reported GreenLight XPS length of stay to be 1 day, with LoS for HoLEP and TURP kept at 1.6days and 2.3 days respectively. Two

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					additional scenarios were informed by the British Association of Urological Surgeons Bladder Outflow Obstruction Audit data (2019), which reported mean length of stay was 1.15days and 1.13days for GreenLight XPS, 1.69 and 1.48 days for HoLEP, 2.57days and 2.20days for mTURP and 1.99 days and 1.63days for bTURP in people with and without a catheter pre operatively respectively. The results of these analyses showed GreenLight XPS remained cost saving by between £236 and £489 against TURP and by between £357 and £452 against HoLEP." The committee was also aware that variations in the length of stay across Trusts are dependent upon the day case setup. It decided to add section 4.9 to state the impact of service set-up on length of stay. '**Service set up is important when optimising day case proportions and length of stay** Clinical experts explained that NHS urology centres varied in how services were set up. For example, some hospitals have extended opening hours to support day case surgery for GreenLight XPS but other centres require hospital admission. The committee understood that how services were set up could explain the large variations in length of stay and proportion of day cases across the centres. It agreed that willingness to set up day case services would be important to optimise the potential savings with GreenLight XPS."
4	1	Company representative	Question: Are the summaries of clinical and	No, we believe that the summaries of resource savings regarding length of stay for GreenLight are not	Thank you for your comment. NICE editorial changes have removed cost saving statements from the recommendations and moved this information to the

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			resource savings reasonable interpretations of the evidence?	reasonable interpretations of the evidence and are factually incorrect. We remain concerned that the economic results reported in the draft guidance only refer to the EAC's revised base case analysis for the Markov model, applying a length of stay of 1.6 days for GreenLight. We contend that it is factually incorrect to use a 1.6-day length of stay sourced from HES data because this combines GreenLight and HoLEP lengths of stay. This is particularly relevant because the MTG49 model utilised a length of stay for GreenLight of 0.7 days, sourced from Ajib et al 2018. The reduction in cost savings suggested by the EAC's model for GreenLight compared to the original model reviewed by NICE and published under MTG49 are mainly driven by the EAC change in length of stay from 0.7 days to 1.6 days. The impact of this change is potentially highly significant and is therefore a very important piece of data to get correct. In addition, this change is not supported by the opinions of 5 clinical experts who, in Table 23 of the EAC report, validated that an estimated length of stay of 0.7 days for GreenLight in the general population is reasonable. We suggest that the evidence of a 0.7-day length of stay for GreenLight, as demonstrated by Ajib et al (2018) and utilised in MTG49, should be utilised in this model as it is inaccurate to rely on HES data which incorporates the length of stay of a main comparator. Should NICE/EAC not be prepared to make this adjustment we contend that the use of the HES 1.6-day length of stay data should be stated clearly in the	rationale section under "Why the committee made these recommendations". Rationale states "The cost modelling suggests GreenLight XPS is likely to be cost saving compared with TURP and HoLEP. By how much depends on day case proportions, length of stay and procedure length. While the EAGs base case results are reported, additional scenario analyses were considered to address the potential size of the cost savings (see the response to comment 3) and as is discussed in section 4.13 of the guidance, the committee concluded that "GreenLight XPS is likely to be cost saving but by how much is uncertain, particularly for high risk groups"

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				guidance as well as stating that this is not reflective of current clinical practice.	
5	1	Company representative	3.13	We contend that the length of stay reported here for GreenLight (1.6 days) is not an accurate representation of clinical practice, for the reasons outlined in the additional comment on subsection 3.13. It is confusing to report a scenario where the length of stay is shorter for TURP or HoLEP than for GreenLight, as this is not clinically likely. This is noted on page 15 of the draft guidance; "The clinical experts agreed that the scenarios of length of stay or proportion of day cases that would make GreenLight XPS cost-incurring are unlikely in clinical practice." We believe that in the interest of greater clarity, it would be beneficial to add the following statement to the end of section 3.13; "The EAC concluded that this was clinically unlikely, this view was also supported by the clinical experts."	Thank you for your comment. The scenarios referred to in the comment, where the length of stay was shorter for TURP or HoLEP, were the threshold analyses. The clinical experts confirmed that this was clinically unlikely across the NHS and the committee were satisfied with a proposed amendment to clarify this. The wording in section 3.13 has been amended to clarify "The clinical experts agreed that the scenarios of length of stay or proportion of day cases that would make GreenLight XPS cost-incurring are clinically unlikely across the NHS."
6	1	Company representative	3.10	The scenario reporting a day-case rate of 43.6% with TURP was deemed by the EAC and clinical experts as "clinically unlikely" (see p112 of the EAC assessment report update). This is also noted on page 15 of the draft guidance; "The clinical experts agreed that the scenarios of length of stay or proportion of day cases that would make GreenLight XPS cost-incurring are unlikely in clinical practice." We believe that in the interest of greater clarity, it would be beneficial to add the following statement to the end of section 3.10; "The EAC concluded that this was clinically unlikely, this view was also supported by the clinical experts."	Thank you for your comment. The committee heard clinical experts agreed that the day-case rate of 43.6% was clinically unlikely across the NHS for TURP. A minor change was made to section 3.10 for clarity to state: "The EAC's threshold analysis suggested that when maintaining 68% of GreenLight XPS done as a day-case procedure, using GreenLight XPS would be cost-incurring if the proportion of day-case procedures for TURP or HoLEP increased above 43.6% and 56% respectively. The EAG and clinical experts agreed that these thresholds were clinically unlikely across the NHS"

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7	1	Company representative	4.14	The last sentence in this section refers to “length of stay”. We believe this is a typographical error and should be “length of procedure”.	Thank you for your comment and for highlighting this typographical error. Section 4.15 has been corrected to state “length of procedure”
8	1	Company representative	**Question:** Has all of the relevant evidence been taken into account?	No, it is not clear to what extent the unpublished review submitted “academic in confidence” to NICE in November 2021 has been taken into account as the EAC questioned the quality of this publication. This review has subsequently been updated and was published in a peer reviewed PUBMED indexed journal. Please find below the reference. Burtt G, Springate C, Martin A, Woodward E, Zantek P, Al Jaafari F, Muir G, Misrai V. The Efficacy and Safety of Laser and Electrosurgical Transurethral Procedures for the Treatment of BPO in High-Risk Patients: A Systematic Review. Research and Reports in Urology. 2022;14:247.	Thank you for your comment. The committee considered your comment carefully, and was aware that this systematic review was accepted for publication on 01 June 2022 and published on 17 June 2022, which was after the NICE Draft Guidance was released on 15 June 2022. The EAG reviewed the unpublished systematic review at the time of assessment (see details in Appendix B4 of the assessment report update). After the consultation, the EAG also critiqued the published systematic review (Full details of the EAG critique of the published systematic review can be found in Appendix 1.). The committee was advised that the main methodological concerns stated in section 9.4 of the EAG ARU report in the subsection “Clinical parameters and variables” remain the same. The committee decided to amend the wording of section 3.11 for clarity and add section 3.12 to summarise the EAG’s consideration of the published systematic review. **‘The company presented a new Markov model, which included a high-risk population scenario** 3.11 The company submitted a new cost model during the guidance update. It applied a Markov model structure which allowed for retreatment and had a 4-year time horizon. The model included everyone who needed treatment for BPH and had a high-risk group scenario, which was informed by the results of an unpublished systematic review. The

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					EAG considered the unpublished systematic review to be low quality and the results of the review were not robust because of methodological concerns (see details of the EAG's critique in the economic model parameters of section 9.4 of the Assessment Report Update. Newcastle External Assessment Group, 2022). 3.12 During the consultation, the systematic review was published (Burtt et al, 2022). The EAG reviewed and critiqued the published review. It considered that the publication provided no new evidence and the key methodological concerns remained (section 3.11). The EAG concluded the published review was not sufficiently robust to inform a cost model for the high-risk population.'
General comments					
9	1	Company representative	**Question**: Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	Response 'None that we are aware of.'	Thank you for your comment.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."

Appendix 1

EAG critique of Burtt et al. 2022 systematic review (27/07/2022)

During the GID-MT564 GreenLight XPS Assessment Report Update (ARU), in November 2021 the Company submitted an unpublished systematic review (Burtt *et al.* 2021). This was critiqued by the EAG and included within the ARU (April 2022), but both the review and the EAG's critique were fully redacted in the version of the documents that went out to public consultation due to the academic-in-confidence (AiC) status of the review. The EAG advised NICE that the review could be submitted to a pre-print server to enable the information to be available in the public domain for transparency. During the public consultation period for NICE Guidance Update GID-MT564, which commenced on the 15 June 2022, the Company highlighted that an updated version of the systematic review was published (Burtt *et al.* 2022). The EAG updated their critique of the systematic review based on the PRISMA guidelines for reporting systematic reviews (PRISMA 2020 Checklist, Table 3). The EAG note that the journal received the manuscript on 19 February 2022, that the literature searches were carried out on 28 March 2022, accepted for publication on 1 June 2022 and published on 17 June 2022.

Due to the volume of primary evidence included within the systematic review, the EAG have focused their critique on the evidence relevant to GreenLight XPS 180 W; the EAG have not considered the robustness, accuracy, or completeness of evidence highlighted by the authors as relevant to GreenLight 120 W or other power, GreenLEP, TURP, or HoLEP.

Literature search

The EAG note that Burtt *et al.* (2022) repeated the literature search and included additional search terms on 28 March 2022, when compared to Burtt *et al.* (2021) (where the searches were conducted on 07 December 2020). The methods section of the Burtt *et al.* (2022) states that the searches were conducted in Medline, Pubmed and Embase databases on 28 March 2022, supplemented by grey literature searches; however, the EAG notes that the search strategies provided in the

Supplementary Information were for Medline and Embase (Table S1), and Cochrane library (Table S2), there was no strategy provided for Pubmed. Therefore, it is unclear which databases were searched.

Study Eligibility

The EAG note that the published systematic review included additional clarification regarding the inclusion and exclusion criteria applied (Supplementary Table S4). The population of interest within the systematic review was defined as patients considered high-risk for standard TURP, Table 1, which the EAG compared with the NICE Final Scope, 2021.

Table 1: Definition of high-risk patients included in the systematic review.

High-risk definition applied in Burtt *et al.* 2022	EAG comment
Increased bleeding risk (including anticoagulant and antiplatelet use)	Patients at risk of bleeding sequelae defined in NICE Final Scope as: including people on anticoagulation therapy, with a history of bleeding disorders, those with a history of atrial fibrillation, an implanted prosthetic heart valve, implanted coronary stents, patients on aspirin therapy for prior coronary events, patients with prior deep vein thrombosis [DVT] or a high risk of DVT, stroke survivors, haemophiliacs, and patients who do not wish to have blood transfusions. Duration of medication use not defined in systematic review.
Larger prostate volume (>80 ml)	Different threshold stated in NICE Final Scope to define large prostates (>100 ml).
A history of urinary retention or presence of an in-dwelling catheter	Patients with urinary retention is a subgroup of interest defined within NICE Final Scope.
Older age (>80 years)	Not included within NICE Final Scope.
Significant comorbidity	Not explicitly defined within the eligibility criteria of the systematic review. The EAG note that papers included for this patient group within the systematic review include patients with ASA III and VI, or >3; frailty scores between 2 and 5; “various high-risk factors”; obesity; coronary artery disease; immunocompromised; neurological disease; critically ill; high cardiovascular or pulmonary risk; or elderly with comorbidity. Not included within NICE Final Scope

Studies were included if data was reported for a population who were all deemed high-risk. An example, provided in the systematic review, states: *“many studies included men with a mean prostate size >80 mL, but were only included in the review if data were reported for a subgroup who all had a prostate size of >80 mL, or where the lower value of the 95% confidence interval was above this threshold”.* The

authors also state that for consistency the analysis of specific risk factors was based on the primary risk category the study reported on and was included for. It is unclear to the EAG how this was conducted in practice as many of the studies include patients with multiple risk factors. For example, Thomas *et al.* (2019) reported on outcomes in 106 patients with urinary retention (subgrouped by post-operative voiding and non-voiding), with mean (SD) prostate volume of 155.6 (82.4) and 140.9 (55.4) ml respectively.

Interventions of interest included GreenLight (results reported separately for 180 W, 120 W and power undefined), GreenLEP, Holium laser, Thulium laser, diode laser, enucleation of the prostate, bipolar vaporisation, transurethral resection of the prostate (TURP; monopolar or bipolar). All surgical comparators, including single-arm studies with no comparator arm, and those with sham comparators, were included. Hybrid techniques were excluded from the systematic review, however, it is unclear how conversions to alternative procedures were handled. For example, in the studies by Trujillo *et al.* (2021), Misrai *et al*. (2016), and Valdivieso *et al.* (2018), 4% (8 of 206 patients with prostate larger than 80 ml), 8% (5 of 60 patients with prostate larger than 80 ml), and 8% (7 of 88 of patients with prostate larger than 100 ml) respectively undergoing GreenLight 180 W XPS required conversion to TURP.

Outcomes of interest included functional outcomes (IPSS, Qmax, PVR), need for and duration of catheterisation, length of stay and day-case rates, need for transfusion, re-intervention rates, long-term complications, complications relating to urinary retention. The EAG notes that procedural duration, reasons for re-intervention (for bladder neck contracture, urethral stricture, clot retention, haematuria, recurrent benign prostatic hyperplasia (BPH)) and Clavien grade of complications (grade 3, 4, 5) were also recorded but not explicitly described in the method section.

Randomised, single-arm interventional, retrospective or prospective observational study designs were included in the systematic review, with sample size restriction of 20 or more high-risk patients. The EAG notes that this approach would omit small case series and case reports of rare complications; introducing bias when describing the safety profile of the included interventions.

Results

Burtt *et al.* (2022) included more than 100 additional studies (across all interventions) when compared to the results of Burtt *et al.* (2021). However, the absolute number of papers and patients included in the published systematic review was not reported consistently:

- the abstract at the start of the systematic review reports the inclusion of 276 papers and 32,722 patients;
- the PRISMA flow diagram (Supplementary Figure S1) reported inclusion of 268 papers and 31,862 patients;
- the cross-tabulation of outcomes for each study group by risk factor (Supplementary Table S6), includes a total of 270 papers and 32,484 patients;
    - large prostate: 147 papers, 19,342 patients;
    - urinary retention: 37 papers, 4,287 patients;
    - antithrombotic agents: 53 papers, 5,757 patients;
    - comorbidities: 21 papers, 1,923 patients;
    - age greater than 80 years: 12 papers, 1,175 patients.

  The EAG also noted that two papers appear twice in Supplementary Table S6 (Li *et al.* 2018 and Samir *et al.* 2019).

The EAG notes that eligibility criteria have not been applied consistently. For example:

- Incorrect sample size: 5 studies were reported as having a sample size less than 20 in Supplementary Table S6 of the systematic review (Enikeev *et al.* 2018, (n=12); Jae *et al.* 2012, (n=19); Mitchell *et al*. 2014; (n=19); Monoski *et al.* 2006, (n=6); Seki *et al.* 2007, (n=11)). Due to time constraints the EAG has not retrieved these papers to verify sample size.

- Undefined sample size: Supplementary Table S6 of the systematic review states that the sample size is not reported in 5 studies, therefore it is unclear to the EAG how these were considered against the eligibility criteria (Grosso *et al.* 2020; Laine-Caroff *et al.* 2020; Reimann *et al.* 2018; Terada *et al.* 2018; Verrienti *et al.* 2019). The EAG have confirmed that Verrienti *et al.* (2019) included 126 patients with Charlson Comorbidity Index score of 3 or greater (Table 1). The abstract by Laine-Caroff *et al.* (2020) included 332 patients undergoing BPH surgery, however the abstract did not report how many patients were in the subgroup of patients undergoing GreenLight PVP and those undergoing open simple prostatectomy. The EAG also note that the latter study abstract was later fully published (Laine-Caroff *et al.* 2021) and also included in the systematic review (duplicate results) which confirmed 132 GreenLight PVP and 200 open simple prostatectomy subgroups, however the EAG notes that the prostate volume and number of participants were incorrectly reported in Supplementary Table S6 of the published systematic review. The remaining three studies do not report the sample size of the high-risk subgroup.

- Duplicate studies: conference abstracts were also included within the systematic review, which often lack peer-review, contain limited information and led to duplication of results. For example: abstracts by Grosso *et al.* (2020) and Verrienti *et al.* (2019) both report on results from 187 patients from 2 referral centres within the same study period (March 2017 to January 2019) therefore likely reporting on the same patient group; however results from both are included in the systematic review. Additionally, the results from the abstract by Rieken *et al.* (2014) and Lee *et al*. (2014) are fully reported in Lee *et al*. (2016), yet results from all three were included within the synthesis of the systematic review.

- Inappropriate reason for exclusion: the EAG notes that the study by Mesnard *et al.* (2021), investigating the safety and efficacy of GreenLight XPS 180 W in patients with haemophilia and included within the ARU, was excluded in the systematic review. The reason for exclusion reported by the authors was identified as an 'irrelevant population' in Supplementary Table S5. The EAG

consider this to be inappropriate, as the population of interest would be considered as high-risk based on the systematic review group 1 (increased bleeding risk), or group 5 (significant comorbidity). However, the EAG confirms that this study would have been appropriately excluded due to sample size in line with the eligibility criteria defined by the systematic review, as it included only 13 BPH patients, 5 undergoing TURP, 5 undergoing GreenLight and 3 undergoing simple prostatectomy.

- Definition of risk category not applied consistently: despite the definition of older age (greater than 80 years), the EAG notes that Liu *et al.* 2020 included patients with age being *greater or equal to* 80 years. Similarly for definition of large prostate (greater than 80 ml), the EAG notes that Bachmann *et al.* (2014) included patients with a prostate *greater or equal to* 80 ml.

The total number of studies including GreenLight XPS 180 W as the intervention cannot be easily identified due to poor and inconsistent reporting. For example, Table 1 of the systematic review summarises the total number of patients and studies included in the full systematic review subgrouped by intervention, study methodology, and primary high-risk category. This includes a total of 44 studies using GreenLight XPS 180 W when adding studies together by study methodology (1 RCT, 6 single-arm studies, 6 prospective observational, 31 retrospective observational), but only 42 studies using GreenLight XPS 180 W when adding studies by the main category of high-risk assigned (large prostates, N=17; urinary retention, N=6; anticoagulants or antiplatelets, N=9; comorbidities, N=3; mixed risk-factors, N=7). Furthermore, the PRISMA flow diagram documenting the literature search states that 36 studies using GreenLight XPS 180 W were included, whereas only 35 studies were included within Supplementary Table S6 cross-tabulation of the outcomes for each included study using GreenLight XPS 180 W. The EAG reviewed these 35 studies, Table 2:

- 6 were considered within the original AR (West and Woo 2015; Hueber *et al.* 2013; Hueber *et al.* 2015; Nicholson *et al.* 2015; Altay *et al.* 2015; Bachmann *et al.* 2012);

- 13 were included in the ARU by the EAG (Trujillo *et al.* 2021; Pierce *et al.* 2021; Liu *et al.* 2020; Barco-Castillo *et al.* 2020; Valdivieso *et al.* 2018; Reimann *et al.* 2018; Azizi *et al.* 2017; Meskawi *et al.* 2017; Campobasso *et al.* 2020; Lee *et al.* 2016; Knapp *et al.* 2017; Eken & Soyupak 2018; Goueli *et al.* 2017);

- 4 were incorrectly assigned to GreenLight 180W:

    - Zhang *et al.* (2021) compares outcomes of bipolar plasmakinetic enucleation of the prostate with transurethral resection of the prostate (TURP),

    - Placer *et al.* (2018) reports outcomes in patients receiving holmium laser enucleation of the prostate (HoLEP),

    - Misrai *et al.* (2016) compared GreenLight PVP 120-180W (mixed power) with GreenLEP 120W,

    - Andres *et al.* (2015) used Ceralas HPD 180 W (and only abstract was available in English).

- 3 studies were available as a conference abstract with the full publication included within the original assessment report (Bachmann *et al.* 2014) or within the ARU (Reiken *et al.* 2014; Lee *et al.* 2014);

- 4 studies were available as conference abstracts only with no full paper publication identified, limited reporting of methods and results, and likely lack of peer-review (Goueli *et al.* 2018, which may overlap with Goueli *et al.* 2017, ; Chiu *et al.* 2019; Haudebert *et al.* 2020, which may overlap with Huet *et al.* 2019; Mousa *et al.* 2018;).

- 4 studies were identified by the EAG but treated as single arm studies (comparator not in line with NICE Final Scope, 2021), and did not report rare adverse event and therefore not fully tabulated in the ARU (Huet *et al.* 2019; Sun *et al.* 2018; Moiroud *et al.* 2019; Lanchon *et al.* 2018);

- 1 study was identified and excluded by the EAG that sought to determine whether urodynamic study predicted voiding outcomes in men with BPH and detrusor underactivity undergoing PVP, where results were statistically compared between subgroups of patients based on their voiding status, with outcomes not reported for the cohort as a whole (Thomas *et al.* 2019).

Table 2: Included studies from Burtt *et al.* 2022, with GreenLight XPS 180W listed as the intervention

#	Study (author, year); Country	Burtt *et al.* (2022)	EAG ARU Included	EAG ARU Excluded	EAG Comment
1.	†Bachmann *et al.* (2014); 9 European countries (N=29 centres)	✓		✓	Study design: abstract: Not included or identified in independent searches as abstract only and pre-dates the original GreenLight guidance. The EAG note that this conference abstract reports outcomes from the GOLIATH trial cohort by prostate volume. Full publications relevant to the GOLIATH trial have been considered within the original GreenLight assessment report (Bachmann *et al.* 2014 (full paper); Bachmann *et al.* 2015; Thomas *et al.* 2015).
2.	West and Woo (2015); Australia	✓		✓	Included in the original assessment report for GreenLight guidance.
3.	Hueber *et al.* (2013); Canada, US, Australia, England (N=7 centres)	✓		✓	Included in the original assessment report for GreenLight guidance.
4.	Zhang *et al.* (2021); China	✓		✓	Intervention; study does not use GreenLight XPS 180 W; compares outcomes of bipolar plasmakinetic enucleation of the prostate with transurethral resection of the prostate (TURP).
5.	Trujillo *et al.* (2021); Columbia	✓	✓		Included within the ARU. The EAG note that the mean ages for the included population are not ≥80 years as suggested in Table S6 of the published review. *Potential overlap with Barco-Castillo et al. (2020); although not explicitly confirmed.*

#	Study (author, year); Country	Burtt *et al.* (2022)	EAG ARU Included	EAG ARU Excluded	EAG Comment
6.	†Placer *et al.* (2018); Spain	✓		✓	Intervention; study does not use GreenLight XPS 180 W; holmium laser enucleation of the prostate (HoLEP).
7.	†Rieken *et al.* (2014); Switzerland (N=2 centres)	✓		✓	Study design: abstract, results fully available in Lee *et al.* (2016), which was included in ARU, and within Burtt *et al.* (2022).
8.	Thomas *et al.* (2019); Canada or US (not explicitly reported)	✓		✓	Outcomes: single-arm study reporting no outcomes relevant to the NICE Final Scope.
9.	†Goueli *et al.* (2018); Canada, US (N=2 centres)	✓		✓	Study abstract, not included in EAG ARU. *Possible overlap with Goueli et al. 2017; although not explicitly confirmed.*
10.	Pierce *et al.* (2021) Canada, US (N=2 centres)	✓	✓		Included within the EAG ARU. *Possible overlap with Meskawi et al. (2017) and Goueli et al. (2017); although not explicitly confirmed.*
11.	†Lee *et al.* (2014); Switzerland (N=2)	✓		✓	Study design: abstract, results fully available in Lee *et al.* (2016), which was included in ARU, and within Burtt *et al.* (2022).
12.	Misrai *et al.* (2016); France	✓		✓	Intervention: Greenlight PVP 120-180 W compared with GreenLEP 120 W
13.	Huet *et al.* (2019); France	✓		✓	Outcomes: Treated as single-arm study (comparator out of scope), rare adverse events not reported, not tabulated by EAG. *Possible overlap with Hauderbert et al. (2020); although not explicitly confirmed.*
14.	†Mousa *et al.* (2018); Saudi Arabia	✓		✓	Study design: abstract: available as abstract only
15.	Hueber *et al.* (2015); Canada, US, France, England, (N=6 centres)	✓		✓	Included in the original assessment report for GreenLight guidance.
16.	Nicholson *et al.* (2015); Australia	✓		✓	Included in the original assessment report for GreenLight guidance.
17.	Lanchon *et al.* (2018); France	✓		✓	Outcomes: Treated as single-arm study (comparator out of scope), rare adverse events not reported, not tabulated by EAG
18.	Altay *et al.* (2015); Turkey	✓		✓	Included in the original assessment report for GreenLight guidance.

#	Study (author, year); Country	Burtt *et al.* (2022)	EAG ARU Included	EAG ARU Excluded	EAG Comment
19.	†Andres *et al.* (2015); Spain	✓		✓	Intervention: does not appear to use GreenLight (Ceralas HPD 180 W stated in Methods) Language: only abstract available in English
20.	Sun *et al.* (2018); China	✓		✓	Outcomes: Treated as single-arm study (comparator out of scope), rare adverse events not reported, not tabulated by EAG
21.	Bachmann *et al.* (2012); Europe, US, Australia (N=7 centres)	✓		✓	Date: before 2015 (MTG29 published)
22.	†Chiu *et al.* (2019); Hong Kong	✓		✓	Study design: abstract: available as conference abstract only
23.	Moiroud *et al.* (2019); France	✓		✓	Outcomes: Treated as single-arm study (comparator out of scope), rare adverse events not reported, not tabulated by EAG
24.	†Haudebert *et al.* (2020); France	✓		✓	Study design: abstract: available as conference abstract only. *Possible overlap with Huet et al. (2019); although not explicitly confirmed.*
25.	Liu *et al.* (2020); China	✓	✓		Included within the EAG ARU.
26.	Barco-Castillo *et al.* (2020); Columbia	✓	✓		Included within the EAG ARU. *Potential overlap with Trujillo et al. (2021); although not explicitly confirmed.*
27.	Valdivieso *et al.* (2018); Canada, US, France (N=4 centres)	✓	✓		Included within the EAG ARU.
28.	Reimann *et al.* (2018); Germany	✓	✓		Included within the EAG ARU.
29.	Azizi *et al.* (2017); Canada, USA (N=5 centres)	✓	✓		Included within the EAG ARU.
30.	Meskawi *et al.* (2017); Canada, USA, France (N=8 centres)	✓	✓		Included within the EAG ARU. *Possible overlap with Goueli et al. (2017) and Pierce et al. (2021); although not explicitly confirmed.*
31.	Campobasso *et al.* (2020); Italy	✓	✓		Included within the EAG ARU.
32.	Lee *et al.* (2016); USA, Switzerland (N=8 centres)	✓	✓		Included within the EAG ARU.
33.	Knapp *et al* (2017); Australia	✓	✓		Included within the EAG ARU.

#	Study (author, year); Country	Burtt *et al.* (2022)	EAG ARU Included	EAG ARU Excluded	EAG Comment
34.	Eken and Soyupak (2018); Turkey	✓	✓		Included within the EAG ARU.
35.	Goueli *et al* (2017); Canada or US (not explicitly reported)	✓	✓		Included within the EAG ARU. *Possible overlap with Meskawi et al. (2017) and Pierce et al. (2021); although not explicitly confirmed.*
	TOTAL	**35**	**13**	**22**	
†Conference abstract					

The EAG also notes that Supplementary Table S6 includes Gondran-Tellier *et al.* (2021), which was assigned to GreenLight (power unspecified) or GreenLEP. This study, conducted exclusively in patients with preoperative urinary catheterisation, was included in the EAG ARU (2022) and does report outcomes of patients undergoing PVP using GreenLight XPS 180 W (n=62) separate to those undergoing endoscopic enucleation (using HoLEP or GreenLEP using 80W laser, n=21).It therefore meets eligibility criteria of the systematic review and the subgroup should have been included within the GreenLight XPS 180 W intervention analysis.

The EAG note that the only new RCT data relevant to GreenLight XPS 180 W came from a conference abstract by Bachmann *et al.* (2014) reporting 1-year outcomes from the GOLIATH trial cohort, subgrouped by prostate size. The EAG note the definition of large prostate applied in the abstract (80 ml or greater) differed to the eligibility criteria of the systematic review (greater than 80 ml), and that the subgroup included 20 patients which was the sample size threshold applied in the systematic review. Full peer-reviewed publications relevant to the GOLIATH trial were considered within the original MTG13 (2013), therefore no new randomised primary evidence has been identified from the published systematic review.

Transparency of reporting

The authors of the systematic review have attempted to cross-tabulate which papers have contributed to each outcome within each high-risk subgroup, however, as this is inconsistently reported the EAG was unable to verify results of the systematic review. For example, Supplementary Table S6 indicates that a total of 41 studies

across all interventions reported on the “re-intervention for recurrent BPH” outcome, however the re-intervention rate for recurrent BPH is only reported in 24 studies in Supplementary Table S13. The duration of follow-up is also not reported for these studies, therefore it is unclear to the EAG what these *rates* represent. The EAG notes that re-intervention for recurrent BPH (Supplementary Table S13) is numerically higher for HoLEP (0% to 3.3%, N=5 studies) than GreenLight 120 W (0% to 2%, N=4), GreenLight other power (0%, N=1), and ThuLEP (1.6%, N=1). However, the EAG notes the number of studies reporting on this outcome is small, the number of included studies also varied by intervention, and the duration of follow-up is not explicitly reported. The systematic review stated that in high-risk populations the benefits of treatment persist for at least four years with GreenLight, Thulium laser therapy and TURP, and for at least three years for HoLEP. However, the authors also acknowledged the lack of studies with follow-up beyond 12 months. Therefore, it is unclear how robust the claim regarding longevity of effect is.

In addition to this, authors report missing data for some of the included studies and it is not clear how these were handled. For example, data for International Prostate Symptom Score (IPSS), Qmax, and PVR has been presented in Figure 1 across baseline, 1, 3, 6, 12, and 24 month timepoints (additional detail provided in Supplementary Tables S8-S10 across baseline, 1, 3, 6, 12, 18, 24, 36, 48 and 60 month timepoints). However, it is unclear to the EAG how many studies contributed to each outcome for each timepoint reported.

The systematic review reports that all surgical techniques reviewed provided good symptomatic relief, improvement in urinary flow rate and reduction in post-void residual urine volume. But given the heterogeneity in baseline characteristics, some primary evidence including Qmax, IPSS, PVR within their eligibility criteria (for example Eken and Soyupak 2018), variable follow-up between studies (ranging between 1 month and 12 years) and lack of paired analysis, the EAG would consider the analysis of these functional outcomes as low quality.

The authors report that the mean operative time is greatest in patients with larger glands across all treatments (when compared with other high-risk categories), and in patients taking anticoagulant and antiplatelet drugs that operating times appear “a little longer” with Holium laser. However, the EAG did not identify any tabulation of

results (in the main paper or supplementary material) to confirm this finding. The authors discuss that the weighted mean length of stay was similar between Greenlight 120 W, GreenLight XPS 180 W, HoLEP and Thulium laser (between 1 and 3 days), and significantly higher with TURP. The authors reported that the weighted lowest occurrence of transfusion was with GreenLight XPS 180 W and highest with mono-polar TURP. Whilst the location of each included study was not explicitly reported in Burtt *et al.* (2022), the EAG notes that the included literature cover a range of countries. Seven studies were set in more than one country and included at least one European centre (Bachmann *et al.* 2012; Bachmann *et al.* 2014; Hueber *et al.* 2013; Hueber *et al*. 2015; Lee *et al.* 2016; Meskawi *et al.* 2017; Valdivieso *et al*. 2018). The remaining 28 studies were set as follows:

- 5 in France (Haudebert *et al.* 2020; Huet *et al.* 2019; Lanchon *et al.* 2018; Misrai *et al.* 2016; Moiroud *et al.* 2019);
- 3 in Canada and USA (Azizi *et al.* 2017; Goueli *et al.* 2018; Pierce *et al.* 2021)
- 3 in Australia (Knapp *et al.* 2017; Nicholson *et al.* 2015; West and Woo 2015);
- 3 in China (Liu *et al.* 2020; Sun *et al.* 2018; Zhang *et al.* 2021);
- 2 in Spain (Andres *et al.* 2015; Placer *et al*. 2018);
- 2 in Switzerland (Lee *et al.* 2014; Reiken *et al.* 2014);
- 2 in Columbia (Barco-Castillo *et al*. 2020; Trujillo *et al.* 2021);
- 2 in Turkey (Altay *et al.* 2015; Eken and Soyupak 2018);
- 2 in either USA or Canada (not explicitly reported) (Goueli *et al.* 2018; Thomas *et al.* 2019)
- 1 in Hong Kong (Chiu *et al.* 2019);
- 1 in Italy (Campobasso *et al.* 2020);

- 1 in Germany (Reimann *et al.* 2018);
- 1 in Saudi Arabia (Mousa *et al.* 2018).

The EAG consider this may introduce bias from variation in clinical practice, particularly relating to length of stay following surgical intervention.

Heterogeneity and robustness of conclusions

The authors note that "*the majority of studies included in the review were observational, in which clinicians may have chosen what they consider to be the safest intervention based on the patients' risk profile*". The authors acknowledge in their limitations that: "*Statistical comparisons were not feasible due to the heterogeneity in both the study methodology and baseline characteristics*". Baseline characteristics (Supplementary Table S7) indicate that patients undergoing GreenLight (180 W, 120 W, or undefined power) were numerically older than patients undergoing other interventions; however no statistical comparison was applied (which is appropriate given reasons above). Within the discussion section, the authors highlighted concerns relating to complications from mono-polar TURP that may mean that patients are not offered surgery when in urinary retention. This further highlights the issue regarding confounding when using observational data and grouping studies by intervention may not be appropriate as these may represent different patient groups. The EAG notes that due to the heterogeneity across study population baseline characteristics, misallocation of intervention in some cases, and lack of transparent reporting of which studies contributed to each outcome that the results of this systematic review are of low quality. The EAG would consider that there is significant confounding by indication across the included studies, which limits the robustness of the conclusions drawn in comparison of different techniques for the treatment of BPH.

Conflict of Interests

The EAG note that Burtt *et al.* (2022) transparently reported the funding source (Boston Scientific) and declared conflicts of interest; three authors being employees of Boston Scientific, two receiving funding from Boston Scientific to conduct the research, and three worked as a consultant for Boston Scientific.

Overall Summary

The EAG would consider the systematic review by Burtt *et al.* (2022) as low quality due to the following main reasons:

- inclusion of conference abstracts (lacking peer-review and leading to inclusion of duplicate outcomes in some cases);
- eligibility criteria not being strictly applied in some cases;
- incorrect allocation of intervention in some cases;
- lack of transparency, preventing the EAG from verifying the included studies and results;
- acknowledged heterogeneity in study methodology and baseline characteristics (confounded by indication).

The EAG therefore does not consider that the published systematic review by Burtt *et al.* (2022) provides any additional evidence which would require an adjustment to the ARU. The EAG would continue to consider that the results from this systematic review remain not robust to be used in the modelling of high-risk patients only and that this approach lacks generalisability to all patients receiving GreenLight XPS 180 W within the NHS.

Specifically, relating to the availability of evidence relating to high-risk groups, the EAG would consider that this evidence supports the draft guidance recommendation that GreenLight XPS 180 W is available as an option to treat BPH in *all* patients, including those at high-risk.

Table 3: PRISMA 2020 checklist (27/07/2022)

First reviewer: KK; Second review: RP

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title: "The Efficacy and Safety of Laser and Electrosurgical Transurethral Procedures for the Treatment of BPO in High-Risk Patients: A Systematic Review" Abstract, results: A total of 276 studies of 32,722 patients reported relevant data. Studies were heterogeneous in methodology, population and outcomes reported Introduction: This systematic literature review was conducted to identify relevant observational and comparative studies of GreenLight (120 and 180 W) Materials and methods, Search Strategy and Study Selection: We searched Medline, PubMed and Embase on 28th March 2022, as well as manually searching for relevant grey literature, for randomised and single-arm clinical trials and observational studies of laser vapourisation and enucleation or TURP in high-risk men with BPO (see Supplementary Information, Tables S1–S3)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract follows appropriate format with Objectives, Methods, Results and Conclusions clearly structured. Authors define 'high-risk' differently compared to NICE document. NICE MT564 Final Scope, 2021. The systematic review defines 'high-risk' as patients with prostates greater or equal to 80 ml (however methods section states greater than 80 ml), taking antithrombotic agents, urinary retention, age greater than 80 years, or have significant comorbidity (undefined).
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	States that 'High risk' groups are often poorly defined. Prior evidence synthesis suggests some benefits of laser therapies in high-risk populations over TURP. Authors state that surgeons will make an onsite assessment of safety and will select the intervention that they think will provide the greatest benefit and/or smallest risk to each individual patient, this review aims to provide synthesis of evidence to support this clinical decision-making.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Final paragraph of 'Introduction: "This systematic literature review was conducted to identify relevant observational and comparative studies of GreenLight (120 and 180 W), Holmium and Thulium laser therapies, and other enucleation and vapourisation therapies, versus standard electrosurgical transurethral resection of the prostate (TURP) in high-risk patients and determine any differences in efficacy and safety". "The aim of this review is to provide surgeons and patients with as comprehensive an evidence base as possible upon which to make these decisions."
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Material and methods section defines patients considered as higher risk of complications if they were undergoing mono-polar TURP as those with: 1. Increased bleeding risk, including anticoagulant and antiplatelet drug use; 2. Large prostate size (>80 ml); 3. A history of urinary retention or presence of an in-dwelling catheter; 4. Older age (>80 years);

Section and Topic	Item #	Checklist item	Location where item is reported
			5. Significant comorbidity. (This is not fully described in the methods or Supplementary material, additional characteristics of these studies are reported in results section) Material and methods, search strategy and study selection: "Studies were included in the review only if relevant data were reported for a population who were all at high risk". Supplementary Table S4 provides a table of inclusion and exclusion criteria. It was noted by the EAG that the definition for high-risk differed to the definition included in the NICE Final Scope, 2021. Hybrid or combination therapies listed within exclusion criteria, however it is unclear how conversion to another procedure was handled. All comparators in scope (including sham intervention or single arm with no comparator). Sample size less than 20 were excluded; therefore, the report may miss rare safety events reported only in case reports or small case series. Conference abstracts are not listed as an exclusion criterion; their inclusion may lack appropriate detail and likely lack peer-review.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search Strategy and Study selection states: "We searched Medline, PubMed and Embase on 28th March 2022, as well as manually searching for relevant grey literature, for randomised and single-arm clinical trials and observational studies of laser vaporisation and enucleation or TURP in high-risk men with BPO". This is supported by Supplementary Table S1-S3; however, a search strategy was supplied for Cochrane library not Pubmed, so it is unclear which database was searched.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Tables S1, S2 and S3 states databases searched on 28th March 2022. Report search strategy and terms used. No filters or limits applied at search stage. No websites explicitly reported for grey literature searches. Figure S1 shows a flow diagram of application of search strategy, removal of duplicated, record screening, full-test review, reasons for exclusion and included studies broken down by intervention. The EAG have noted inconsistencies within Figure S1, for example, 36 studies relevant to GreenLight XPS 180 W were included in the PRISMA flow diagram, however only 35 were tabulated in Supplementary Table S6.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2, Search strategy and study selection: "These records were each screened independently by two researchers according to the inclusion criteria in Table S4, and disagreements reconciled by discussion. All studies potentially meeting the inclusion criteria were retrieved and the full text screened for relevance by two senior researchers independently, with disagreements resolved by discussion". No automation tools were described in the selection process. Studies excluded at full text screen and reasons for exclusion were tabulated in Supplementary Table S5.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3, Search Strategy and Study Selection: "Data were extracted from the publications for all outcomes of interest by one researcher and checked by a second, with disagreements resolved by the project leader." No automation tools were described in the data collection process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not,	Page 3, Material and Methods, types of participant and interventions included: Efficacy and safety outcome measures with comparable data in high-risk groups were extracted including IPSS, Qmax, PVR, bleeding complications, re-intervention rates and hospital length of stay. "Data were extracted for all timepoints and where specific definitions of outcomes e.g. bleeding or haematuria were given these were also recorded."

Section and Topic	Item #	Checklist item	Location where item is reported
		the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3, Material and Methods, types of participant and interventions included: "Other details including baseline characteristics and funding were also extracted."
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Assessment of Risk of Bias: "Risk of bias was assessed by two researchers independently using the Cochrane RoB2 tool for RCTs and questionnaires from the Joanna Briggs Institute for cohort and cross-sectional studies". No automation tools were described in the risk of bias assessment process.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Assessment of Risk of Bias: "Due to the expected heterogeneity in study methodology, populations and assessment of outcomes, no formal statistical synthesis or sensitivity analyses of the results, assessment of publication bias or of the certainty of the body of evidence for each outcome was planned, but data were summarised in tables and charts using R software functions". No further detail provided.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	As per Item 12. Eligible studies tabulated against each patient risk category with outcomes reported.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	No additional clarification is provided in methodology of how missing values were dealt with.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Assessment of Risk of Bias: "data were summarised in tables and charts using R software functions".
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not performed.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Authors note significant heterogeneity across the included literature (Supplementary Table S7) but do not report how this was evaluated nor are any methods to explore or address the heterogeneity described.

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	None performed: page 3 Materials and Methods, assessment of risk of bias: "Due to the expected heterogeneity in study methodology, populations and assessment of outcomes, no formal statistical synthesis or sensitivity analyses of the results, assessment of publication bias or of the certainty of the body of evidence for each outcome was planned, but data were summarised in tables and charts using R software functions" "This lack of comparative data, and the heterogeneity of the observational data, means it is not possible to perform a meta-analysis."
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not explicitly stated, although a "risk of bias" grade was provided for each study within Supplementary Table S6 (with: + / - / ? values).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not stated.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Number of included papers is inconsistently reported across the Abstract, Results and Figure S1 PRISMA flow diagram. Records excluded at full-text screen is stated as 917, but the sum of individual reasons adds to 915.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table S5 includes a list of records excluded at full-text review including reasons for exclusion. The EAG did not comprehensively verify all reasons for exclusion, however incidentally noted that the exclusion reason applied to Mesnard *et al.* (2021), which included patients with haemophillia, was "Irrelevant population basis". Given the eligibility criteria these patients could have been categorised as having increased risk of bleeding or significant comorbidity. This study could have been excluded based upon sample size being less than 20 patients.
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary Table S6 includes a cross-tabulation of each included study and outcomes. Characteristics tabulated for each included: study type, interventions, no of high-risk patients, high-risk subgroup, data collection period, total follow-up period. Five studies had sample size reported as "nr", therefore it is unclear how these were dealt with given the inclusion criteria of 20 patients or more. The EAG did not comprehensively verify all reasons for exclusion, however noted that some studies have had the intervention allocated incorrectly. "References of studies included in the results of the review" is incorporated at the end of the Supplementary Material.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Table S6 offers a risk of bias tool, with vales "-", "+", and "?" assigned.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Authors acknowledge inconsistent reporting across included studies; however no additional clarification was provided as to how this was handled. Supplementary Table S7 is a summary of reported characteristics for each outcome, for each intervention and for each high-risk subgroup. Supplementary Table S8-10 is a tabulation of mean and median IPSS, Qmax and PVR over time by intervention (however, the number of studies contributing at each timepoint not reported).

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary Table S11 is a tabulation of length of stay and day-case rates by intervention with the number of studies contributing to length of stay (not specified how many reporting the median or the mean). Range reported (min, max) and not 95% confidence interval. Supplementary Figure S2 illustrates mean and median hospital length of stay by intervention (different colours for each high-risk subgroup). Supplementary Table S12 is a tabulation of bleeding complications by intervention (not by high-risk subgroup). Supplementary Table S13 is a tabulation of re-intervention rates *from* 3-months post-intervention. However, the duration of follow-up is not reported, therefore the EAG is unclear what these "rates" represent. The EAG also notes that the number of studies reporting re-intervention for recurrent BPH in this table does not align with the cross-tabulation of studies by each outcome in Table S6. Supplementary Table S14 is a tabulation of urinary retention outcomes by intervention (not by high-risk subgroup). Supplementary Figure S3 illustrates reintervention by intervention (key not provided). Supplementary Figure S4 illustrates readmission by intervention (key not provided).
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1 reports the number of patients and studies by study methodology and high-risk factor for each intervention (EAG notes number of patients and number of studies has likely been transposed). Each outcome was reported within Results section; mean and ranges presented. No overall assessment of risk of bias reported in Results section (assessment per study included in Supplementary Table S6).
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Strengths and Limitations: "Statistical comparisons were not feasible due to the heterogeneity in both the study methodology and baseline characteristics." Meta-analyses not conducted.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Authors acknowledge heterogeneity across the included literature; Supplementary Table S7 is a tabulated summary of reported baseline characteristics of high-risk subgroups according to the intervention arm. Strengths and Limitations: "statistical comparisons were not feasible due to the heterogeneity in both study methodology and baseline characteristics". Authors note that "there is no universally-agreed definition of 'high-risk', so thresholds for reporting prostate size, in particular, varied across studies'.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Sensitivity analyses not conducted; EAG would consider this appropriate.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not reported.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Mean and median (with range) reported for some outcomes only. Confidence intervals or certainty of the body of evidence not reported.
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discusses context of results with respect to other systematic reviews and meta-analysis (including Liang *et al.* 2020 stating that this was specific to a high-risk population). Discusses RCTs comparing GreenLight or HoLEP with TURP.
	23b	Discuss any limitations of the evidence included in the review.	Limitations acknowledged by the authors include: • generally incomplete and inconsistent reporting of data from observational studies; • no universally agreed definition of "high-risk" so thresholds for reporting prostate size in particular, varied across studies; • heterogeneity in whether urinary retention was historical or patient had indwelling catheter at the time of admission; • heterogeneity in the type and severity of comorbidities; • heterogeneity in anticoagulant and antiplatelet use; • difficulty in assigning a main high-risk factor due to patients having multiple risk factors; • wide range of follow-up reported (between 1 and 60 months); • measures of compilations varied and were generally poorly reported; • timepoints of perioperative and post-operative outcomes were poorly reported; lack of comparative data (acknowledged that RCTs may be unethical).
	23c	Discuss any limitations of the review processes used.	Statistical comparisons were not feasible due to the heterogeneity in both the study methodology and baseline characteristics. No further limitations of the review process acknowledged.
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion: "Future research should aim to report outcomes and complications in a more standardised way so the relative benefits and harms of these and new interventions can be better determined". Authors acknowledge ethical considerations of conducting RCTs in high-risk populations. Authors state that "benefits of treatment persist for at least 4 years with GreenLight, Thulium laser therapy and TURP, and for at least 3 years for HoLEP", however also acknowledge a lack of studies with follow-up beyond 12 months. Authors also state: "Concerns over complications from mTURP mean that many patients are not offered surgery", however also acknowledges that surgeons will assess which intervention will offer greatest benefit with lowest harm on a per-patient basis. This reinforces that confounding by indication is a significant concern in this analysis.
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not reported.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not reported.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not reported.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding: "This research was funded by Boston Scientific" (manufacturer of GreenLight), role of funders not explicitly reported, however 3 authors are employed by Boston Scientific, two authors (employed by another

Section and Topic	Item #	Checklist item	Location where item is reported
			Company) received funding to conduct the research and the remaining three authors have worked as consultants for Boston Scientific.
Competing interests	26	Declare any competing interests of review authors.	As per item 25.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not reported.

Appendix 2

Responding to comments 3 and 4, the EAG did additional scenario analyses to explore the extent of saving with GreenLight XPS when different length of stay values were applied. These values were based on expert opinions and audit data from the British Association of Urological Surgeons Bladder Outflow Obstruction Audit, 2019 on length of stay in practice of GreenLight XPS, TURP and HoLEP.

Scenario	Mean discounted cost per patient (£), after 4 years (results from updated Company model			Cost difference (GreenLight-Comparator)		EAC Comment [Economic model setting changes]
	GreenLight	TURP	HoLEP	TURP	HoLEP	
Basecase (all): - GreenLight (£540) - HoLEP (remove amortalisation from capital costs) - LoS for GreenLight 1.0 days - LoS for HoLEP 1.6 days - LoS for mTURP and bTURP 2.3 days	£2,514.97	£3,003.58	£2,967.14	-£488.61	-£452.18	Reducing length of stay to 1.0 days (in line with clinical feedback during pre-MTAC meeting)
Basecase (all): - GreenLight (£540) - HoLEP (remove amortalisation from capital costs) - LoS for GreenLight 1.15 days - LoS for HoLEP 1.48 days - LoS for mTURP 2.20 days - LoS for bTURP 1.63 days	£2,566.41	£2,803.30	£2,923.34	-£236.88	-£356.93	Using data provided by BAUS audit in patients with **no catheter present pre-operation**. - bTURP: 1.63 days (n=270 patients) - mTURP: 2.20 (n=178 patients) - HoLEP: 1.48 (n=67 patients) - GL: 1.15 (n=47 patients) Limitations noted by audit: different baseline characteristics between procedure groups, non-normal distribution of LoS
Basecase (all): - GreenLight (£540) - HoLEP (remove amortalisation from capital costs) - LoS for GreenLight 1.13 days - LoS for HoLEP 1.69 days - LoS for mTURP 2.57 days - LoS for bTURP 1.99 days	£2,562.11	£2,940.93	£2,999.99	-£378.82	-£437.88	Using data provided by BAUS audit in patients with **catheter present pre-operation**. - bTURP: 1.99 days (n=286 patients) - mTURP: 2.57 (n=141 patients) - HoLEP: 1.69 (n=81 patients) - GL: 1.13 (n=13 patients) Limitations noted by audit: different baseline characteristics between

Scenario	Mean discounted cost per patient (£), after 4 years (results from updated Company model			Cost difference (GreenLight-Comparator)		EAC Comment [Economic model setting changes]
	GreenLight	TURP	HoLEP	TURP	HoLEP	
						procedure groups, non-normal distribution of LoS,