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Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (Protocol)

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[Intervention Protocol]

Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.

BACKGROUND

Description of the condition

The prostate gland is an organ approximately the size of a walnut that is located below the urinary bladder encircling the urethra (Leissner 1979). Benign prostatic hyperplasia (BPH) is a histological diagnosis defined as an increased number of epithelial and stromal cells in the prostate; this may cause prostatic enlargement and subsequently compression of the urethra and obstruction (Roehrborn 2008). BPH may therefore develop with or without lower urinary tract symptoms (LUTS) in men over the age of 40 (Dunphy 2015). BPH receives clinical significance when associated with bothersome LUTS (Roehrborn 2008). Symptom bother typically correlates with the number and severity of symptoms increased, which relates to both quality of life impairment and treatment seeking (Agarwal 2014). Self-administered questionnaires, namely International Prostate Symptom Score (IPSS), include the quality of life domain to evaluate the relative degree of bother across all LUTS (Barry 1995). Chapple 2017 reported that increasing LUTS severity was associated with worsening men's overall distress using patient perception of bladder condition which is a single-item global question (ranging from 1 (causes no problems at all) to 6 (causes severe problems)). In this Cochrane Review, we will consider the term BPH as prostatic enlargement with LUTS through which to define the disease condition and potential need for intervention.

BPH can progress over time and cause serious consequences, such as acute urinary retention, urinary tract infection, and upper urinary tract deterioration. BPH also results in a negative impact

on public health and a reduction in a person's quality of life (Kozminski 2015; Martin 2014). In Europe, 30% of men over 50 years of age, equivalent to 26 million men, are affected by bothersome LUTS, including storage symptoms (such as urinary frequency, urgency, and nocturia) or voiding symptoms (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding), or both. A yearly reported associated number of medical prescriptions is estimated to be around 11.6 million for 74 million people at risk from 2004 to 2008 (Cornu 2010). The prevalence of LUTS, according to an international study involving 7588 men was 18%, 29%, 40%, and 56% in the ages of 40s, 50s, 60s, and 70s, respectively (Homma 1997). In the USA, 8 million men older than 50 years of age also suffer from BPH (Roehrborn 2008a).

Diagnosis

Initial evaluation of LUTS suggestive of BPH includes patient history, physical examination including a digital rectal examination, urinalysis, prostate specific antigen (PSA) blood test, voiding diary, and IPSS (EAU 2017; McVary 2011). A digital rectal examination is performed to assess the prostate for size, and for any lesions suspicious for cancer. The PSA is secreted by the prostate gland and is found to be abnormally elevated in the presence of prostate cancer, BPH, infection or inflammation of the prostate (EAU 2017; McVary 2011). The IPSS is used to assess urinary symptom severity and quality of life. It is also used to document subjective responses to treatment (Barry 1992; EAU 2017; McVary 2011). Measurement of maximum flow rate (Qmax) and postvoid residual (PVR) are also often used in diagnosis and treatment decisions (EAU 2017; McVary 2011). A low Qmax and a large PVR predict an increased risk of symptom progression (Crawford 2006). Other tests include radiologic imaging, urodynamic evaluation, and cystoscopy to further determine appropriate treatment and predict treatment response (Egan 2016; McVary 2011).

Treatment

Treatment decisions are based on symptoms and the degree of bother noted by the patient. Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and medication (alpha-blockers and 5-alpha reductase inhibitors) (EAU 2017; McVary 2011). If patients have been refractory to conservative and medical treatment, or BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones or diverticula, hematuria, or renal insufficiency, surgical options are considered (EAU 2017; McVary 2011). Until the 1970s, the only option available to treat this condition and relieve LUTS was an open or endoscopic surgery with the aim to remove or resect prostatic tissue to open up the blocked urethra (Pariser 2015). Clinical guidelines recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a standard treatment modality in regards to subjective symptom relief and objective improvements in urinary flow (EAU 2017; McVary 2011), but this procedure is also associated with significant morbidity and long-term complications, including hematuria requiring blood transfusion, urethral stricture, recurrent urinary tract infection, and urinary incontinence. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP (Roehrborn 2003). Furthermore, BPH is a disease common in elderly men who have an increased risk of complications for general anesthesia and the surgery itself (Dunphy 2015; Yoo 2012). Nowadays, other minimally invasive surgeries using electrode, laser, transurethral thermal ablation of the prostate (needle ablation, microwave therapy, and radiofrequency ablative techniques), and mechanical stents have been developed as alternatives to TURP (EAU 2017; McVary 2011). While new laser-based procedures have demonstrated a decrease in short-term complications, such as bleeding, they also have similar adverse effects on sexual dysfunction when compared with TURP (NICE 2015).

Description of the intervention

A less invasive surgical intervention known as the prostatic urethral lift (PUL) has recently become available. The US Food and Drug Administration and the National Institute for Clinical and Health Excellence in the UK approved PUL in September 2013 and September 2015, respectively (McNicholas 2016). As the PUL procedure can be performed under local anesthesia with oral or intravenous sedation, and also performed in men with blood clotting disorders or those on anticoagulant therapy, it is more suitable for men at high risk of general anesthesia (Chin 2012; Woo 2012). Typical inclusion criteria of PUL are a prostate volume between 20 mL and 70 mL, IPSS of 12 or greater, a measured Qmax of 15 mL/s or less, and PVR of less than 350 mL (McNicholas 2016). The PUL system consists of two single use components (delivery device and an implant). The delivery device consists of a hand held pistol grip to which a needle-shaped probe is attached. Each PUL implant consists of a super-elastic nitinol capsular tab, a polyethylene terephthalate monofilament, and a stainless steel urethral end piece. The surgeon inserts the probe into the urethra until it reaches the prostatic urethra (the widest part of the prostatic urethra); a fine needle at the end of the probe deploys and secures an implant in a lobe of the prostate (McNicholas 2016). One end of the implant is anchored in the urethra and the other is attached to the firm outer surface of the prostatic capsule, so pulling the prostatic lobe away from the urethra. This is repeated on the other lobe of the prostate. Systematically, four implants for PUL are delivered to both the right and left lateral lobes of the prostate (at the 2 and 10 o'clock position, distally from approximately 1.5 cm distal to the bladder neck). The median lobe of the prostate in which the ejaculatory duct is located is avoided (McNicholas 2016).

Adverse events of the intervention

Mild adverse events, such as transient dysuria and hematuria are commonly reported with PUL (Chin 2012; Woo 2012). Incontinence was less prevalent with the PUL (5%) compared with TURP (11%) and holmium laser enucleation of the prostate (HoLEP; 14%) (NICE 2015). However, reoperation rates were higher with the PUL (8%) than with TURP (6%) and HoLEP (4%) (NICE 2015). In a feasibility study, implant encrustation occurred when PUL implants are placed too close to the bladder and exposed to static urine (Chin 2012; Woo 2012).

How the intervention might work

The fundamental idea of PUL is the separation and distraction of the enlarged prostatic tissue by a series of implants. The PUL system uses adjustable, permanent implants to hold excess prostatic tissue out of the way and thereby open the narrowed urethra without cutting or removing enlarged prostatic tissue (McNicholas 2016). These implants are shaped as a double-ended hook, and aim to increase the opening of the urethra (McNicholas 2016).

Why it is important to do this review

Until now, it is unclear whether PUL actually translates into more clinical benefits and less adverse events in clinical practice. While there are existing systematic reviews that compare PUL to other therapies used to treat BPH (Jones 2016; Perera 2015; Sanchez-Gomez 2015), these reviews merely pooled efficacy measurements, such as IPSS, Qmax, and PVR from randomized controlled trials (RCTs) or non-RCTs, without discussing the harms of the intervention or assessing the quality of evidence. No systematic review so far has used the same rigorous methodology as a Cochrane Review, which includes the application of the GRADE approach and its focus on patient-important outcomes (Guyatt 2008). In today's era, with the availability of numerous minimally invasive procedures to treat BPH, the findings of this Cochrane Review will be highly relevant to policymakers, healthcare providers and patients alike.

OBJECTIVES

To assess the effects of prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel group RCTs and cluster-RCTs. We will exclude cross-over trials, as these study designs are not relevant in this setting. If we only find RCTs that provide low-quality evidence for a given outcome and comparison, we will also include non-RCTs, such as cohort and cross-sectional studies with concurrent comparison groups, as a source of complementary, sequential or replacement evidence for RCTs (Schunemann 2013a). We will not consider including single-armed studies. We will include studies regardless of their publication status or language of publication.

Types of participants

We will define the eligible patient population as men over the age of 40 with a prostate volume of 20 mL or greater (as assessed by digital rectal examination, and/or ultrasound or cross-sectional imaging), with LUTS as determined by an IPSS of eight or over, and a Qmax of less than 15 mL/sec, as measured by non-invasive uroflowmetry, or invasive pressure flow studies, or both (Dunphy 2015; EAU 2017; McNicholas 2016; McVary 2011). The age limitation is based on the observation that the prevalence of BPH increases in middle-aged and older men, and is infrequent in younger men (Barry 1997; Egan 2016; EAU 2017). We will include studies in which only a subset of participants are relevant to this review (i.e. trials with > 75% participants as relevant to the review), if data are available separately for the relevant subset.

We will exclude trials of men with active urinary tract infection, bacterial prostatitis, chronic renal failure, untreated bladder calculi or large diverticula, a diagnosis of prostate cancer, urethral stricture disease, and prior prostate, bladder neck, or urethral surgery. We will also exclude studies of patients with other conditions that affect urinary symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

Types of interventions

We plan to investigate the following comparisons of experimental intervention versus comparator interventions. Concomitant interventions will have to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- Prostatic urethral lift (PUL)

Comparator interventions

- Sham control (or no intervention)
- Transurethral resection of the prostate (TURP) (monopolar or bipolar)

- Laser ablations of the prostate (e.g. photoselective vaporization of the prostate)
- Laser enucleations of the prostate (e.g. HoLEP)
- Other minimally invasive therapies (e.g. transurethral incision of the prostate, transurethral thermal ablation of the prostate (needle ablation, microwave therapy, and radiofrequency ablative techniques), prostate stent, and prostatic arterial embolization)
- Simple prostatectomy (e.g. open, laparoscopic, and robotic-assisted prostatectomy)

Comparisons

- PUL versus sham control (or no intervention)
- PUL versus TURP
- PUL versus laser ablations of the prostate
- PUL versus laser enucleations of the prostate
- PUL versus other minimally invasive therapies
- PUL versus simple prostatectomy

Types of outcome measures

We will not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urologic symptom scores
- Quality of life
- Major adverse events

Secondary outcomes

- Retreatment
- Erectile function
- Ejaculatory function
- Minor adverse events
- Acute urinary retention
- Indwelling urinary catheter
- Hospital stay

Method and timing of outcome measurement

We will consider clinically important difference for the review outcomes to rate overall quality of the evidence in the 'Summary of findings' table (Jaeschke 1989; Johnston 2013).

Urologic symptom scores

- Mean change measured as a validated scale (such as IPSS).
- We will consider improvement of the IPSS score of three points as a minimal clinically important difference (MCID) to assess efficacy and comparative effectiveness (Barry 1995). If possible, we will use different thresholds of MCID based on the severity of IPSS, with a threshold of three for men with mild LUTS, five for moderate LUTS, and eight for severe LUTS (Barry 1995).

Quality of life

- Mean change measured as a validated scale (such as IPSS-quality of life or BPH Impact Index).
- No threshold was established for the IPSS-quality of life. We will use a MCID of one to assess efficacy and comparative effectiveness (Brasure 2016). We will consider improvement of the BPH Impact Index score of 0.5 as a MCID (Barry 1995).

Major adverse events

- For example, postoperative hemorrhage requiring admission or intervention.
- We will use the Clavien-Dindo classification system to assess surgical complications (Dindo 2004), and will categorize grade III, IV and V complications as major. If the study authors of eligible studies did not use the Clavien-Dindo system, we will judge the adverse events by severity using the available information described in the studies.

Retreatment

- Events requiring other surgical treatment modalities (e.g. TURP) after intervention.

Erectile function

- Mean change, measured as erectile function domain of International Index of Erectile Function (IIEF) or total score of IIEF-5 questionnaire (Rosen 1997).
- We will consider the MCID in the erectile function domain score of IIEF of four (Rosen 2011). If possible, we will use different thresholds of MCID based on the severity of ED, with a threshold of two for men with mild erectile dysfunction, five for moderate erectile dysfunction, and seven for men with severe erectile dysfunction (Rosen 2011). We will also consider IIEF-5 of over five points as MCID (Spaliviero 2010).

Ejaculatory function

- Mean change, measured as Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD; Rosen 2007).

Minor adverse events

- For example, postoperative fever or pain requiring medication.
- We will use the Clavien-Dindo classification system to assess surgical complications (Dindo 2004), and will categorize grade I and II complications as minor. If the authors did not use the Clavien-Dindo system, we will grade the adverse events as described above.

Acute urinary retention

- Events requiring catheterization after intervention.

Indwelling urinary catheter

- Measured in days from intervention to urinary catheter removal.

Hospital stay

- Measured in days from admission to discharge.

There is no reported threshold in adverse events, retreatment, ejaculatory function, acute urinary retention, indwelling urinary catheter, and hospital stay. We will consider the clinically important difference for adverse events, retreatment, and acute urinary retention as relative risk reduction of at least 25% (Guyatt 2011a). We will use a MCID of 25% improvement from baseline in MSHQ-EjD for ejaculatory function (Nickel 2015). We will use a MCID of one day to assess efficacy and comparative effectiveness for indwelling urinary catheter and hospital stay.
We will consider outcomes measured up to and including 12 months after randomization as short-term and later than 12 months as long-term for urologic symptom scores, quality of life, major adverse events, erectile function, ejaculatory function, minor adverse events, and acute urinary retention. We assessed retreatment, indwelling urinary catheter and hospital stay as short-term only.

Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table reporting the following outcomes listed according to priority.

1. Urologic symptom scores.
2. Quality of life.
3. Major adverse events.
4. Retreatment.
5. Erectile function.
6. Ejaculatory function.

Search methods for identification of studies

We will perform a comprehensive search with no restrictions on the language of publication or publication status. We plan to rerun searches within three months prior to the anticipated publication of the review.

Electronic searches

We will search the following sources from inception of each database.

- Cochrane Library via Wiley (Appendix 1).
  - Cochrane Database of Systematic Reviews (CDSR).
  - Cochrane Central Register of Controlled Trials (CENTRAL).
  - Database of Abstracts of Reviews of Effects (DARE).
  - Health Technology Assessment Database (HTA).
- MEDLINE via Ovid (from 1946; Appendix 2).
- EMBASE via Ovid (from 1974; Appendix 3).
- LILACS (Latin American and the Caribbean Health Sciences Literature; www.bireme.br/; from 1982).
- Scopus (from 1966).
- Web of Science (from 1900).

We will also search the following.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/).
- Grey literature repository from the current Grey Literature Report (www.greylit.org/).

If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We will also contact study authors of included trials to identify any further studies that we may have missed. We will contact drug/device manufacturers for ongoing or unpublished trials. We will search abstract proceedings of relevant meetings of the American Urological Association, European Association of Urology, and International Continence Society for the last three years (2015 to 2017) for unpublished studies.

Data collection and analysis

Selection of studies

We will use EndNote 2016 reference management software to identify and remove potential duplicate records. Two review authors (JHJ, KAM, BR, or VN) will independently scan the abstract, title, or both, of remaining records retrieved, to determine which studies should be assessed further through Covidence 2017. Two review authors (JHJ, KAM, BR, or VN) will investigate all potentially relevant records as full text, map records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will resolve any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact study authors for clarification. We will document reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We will develop a dedicated data abstraction form that we will pilot test ahead of time.

For studies that fulfil inclusion criteria, two review authors (JHJ, KAM, BR or VN) will independently abstract the following information, which we will provide in the 'Characteristics of included studies' table.

- Study design.
- Study dates (if dates are not available then this will be reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS, medical pretreatment).
- Participant details, baseline demographics (e.g. age, prostate size, IPSS).
- The number of participants by study and by study arm.
- Details of relevant experimental intervention, such as delivery devices (e.g. size of cystoscope and needle to delivery implants) for PUL and comparator intervention (e.g. monopolar versus bipolar energy, type of laser).
- Definitions of relevant outcomes, and method (e.g. type of instrument, such as IPSS) and timing of outcome measurement (e.g. in months) as well as any relevant subgroups (e.g. based on age, prostate volume, severity of LUTS).
- Study funding sources.
- Declarations of interest by primary investigators.

We will extract outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2x2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. We will resolve any disagreements by discussion, or, if required, by consultation with a third review author (PD).

We will provide information, including trial identifier, about potentially relevant ongoing studies in the table 'Characteristics of ongoing studies'.

We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximize yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete data set aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (JHJ, KAM, BR, or VN) will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third review author (PD). We will present a 'Risk of bias' summary figure to illustrate these findings. We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b; Sterne 2016). We will not combine risk of bias from RCTs with that from non-RCTs due to inherently different biases between each study design (Reeves 2011).

Assessment of risk of bias in RCTs

We will assess risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011b). We will assess the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We will judge risk of bias domains as 'low risk', 'high risk' or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

For selection bias (random sequence generation and allocation concealment), we will evaluate risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we will consider all outcomes similarly susceptible to performance bias.
For detection bias (blinding of outcome assessment), we will group outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.
We define the following endpoints as subjective outcomes.

- Urologic symptom scores.
- Quality of life.
- Major adverse events.
- Erectile function.
- Ejaculatory function.
- Minor adverse events.

We define the following endpoints as objective outcomes.

- Retreatment.
- Acute urinary retention.
- Indwelling urinary catheter.
- Hospital stay.

We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis, and will present the judgment for each outcome separately when reporting our findings in the 'Risk of bias' tables.
For reporting bias (selective reporting), we will evaluate risk of bias at a trial level.
We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Assessment of risk of bias in non-RCTs

We will assess risk of bias in non-RCTs with ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions (Sterne 2016). We will assess the following domains.

- Bias due to confounding.
- Bias in selection of participants into the study.
- Bias in classification of interventions.
- Bias due to deviations from intended interventions.
- Bias due to missing data.
- Bias in measurement of outcomes.
- Bias in selection of the reported result.

We will judge risk of bias domains as 'low risk', 'moderate risk', 'serious risk', 'critical risk', or 'no information' and will evaluate individual bias items as described in Sterne 2016.

Measures of treatment effect

We will express dichotomous data as risk ratios with 95% confidence interval (CIs). We will express continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we will express data as standardized MDs with 95% CIs.

Unit of analysis issues

The unit of analysis will be the individual participant. Should we identify cluster-randomized trials, or trials with more than two intervention groups for inclusion in the review, we will handle these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

We will obtain missing data from study authors, if feasible, and will perform intention-to-treat analyses if data are available; we will otherwise perform available case analyses. We will investigate attrition rates, e.g. dropouts, losses to follow-up and withdrawals, and will critically appraise issues of missing data. We will not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate in a meta-analysis but will provide a narrative description of the results of each study.
We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); we will interpret the I^2 statistic as follows (Deeks 2011).

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting.
If we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully.

Data synthesis

We will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method. We will use Review Manager 5 software to perform analyses (Review Manager 2014).
We will analyze the results for RCTs and non-RCTs separately (Reeves 2011).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to carry out subgroup analyses with investigation of interactions.

- Patient age (less than 65 years versus ≥ 65 years).
- Prostate volume (less than or 40 mL versus > 40 mL).
- Severity of LUTS based on IPSS (score less than or equal to 19 (moderately symptomatic) versus greater than 19 (severely symptomatic)).

These subgroup analyses are based on the following observations.

- Age is a well-known risk factor of BPH surgery. Elderly patients have a higher rate of postoperative complications compared with younger patients (Bhojani 2014; Pariser 2015). The age cut-off is based on the World Health Organization (WHO) definition of old age (WHO 2002).
- The outcomes and complications of minimally invasive procedures, such as TURP correlate with prostate volume (Reich 2008). The prostate volume cut-off greater than 40 cc is based on this being the most commonly used threshold to distinguish 'small' from 'large' for the indication of treatment with a 5-alpha reductase inhibitor (EAU 2017).
- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by the baseline scores (Barry 1995).

We plan to perform subgroup analyses limited to the primary outcomes.

Sensitivity analysis

We plan to perform sensitivity analyses limited to the primary outcomes in order to explore the influence of the following factor (when applicable) on effect sizes.

- Restricting the analysis in RCTs by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk'.

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the GRADE approach (Guyatt 2008). For each comparison, two review authors (JHJ, KAM, BR, or VN) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT 2015. We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011b; Schünemann 2011b). If a meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.
For RCTs, we will take into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also to external validity, such as directness of results for downgrading the quality of evidence for a specific outcome (Schünemann 2011c). For non-RCTs, we will take into account three criteria for upgrading the quality of evidence (large magnitude of effects, all plausible confounding that would reduce a demonstrated effect or suggest a spurious effect when results show no effect, and dose-response gradient) (Schünemann 2011c).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Library search strategy

1	MeSH descriptor: [Prostatic Hyperplasia] explode all trees
2	(prostat* near/3 hyperplasia*):ti,ab,kw
3	(prostat* near/3 hypertroph*):ti,ab,kw
4	(prostat* near/3 adenoma*):ti,ab,kw
5	(BPH or BPO or BPE):ti,ab,kw
6	(prostat* near/3 enlarg*):ti,ab,kw
7	MeSH descriptor: [Prostatism] explode all trees
8	prostatism:ti,ab,kw
9	MeSH descriptor: [Urinary Bladder Neck Obstruction] explode all trees
10	("bladder outlet obstruction" or BOO):ti,ab,kw
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	("Prostatic urethral lift" or urolift):ti,ab,kw
13	#11 and #12

Appendix 2. MEDLINE (via Ovid) search strategy

1	exp Prostatic Hyperplasia/
2	(Prostat* adj3 hyperplasia*).tw.
3	(Prostat* adj3 hypertroph*).tw.
4	(Prostat* adj3 adenoma*).tw.
5	(BPH or BPO or BPE).tw.
6	(prostat* adj3 enlarg*).tw.

(*Continued*)

7	exp Prostatism/
8	Prostatism.tw.
9	exp Urinary Bladder Neck Obstruction/
10	(Bladder* adj3 obstruct*).tw.
11	BOO.tw.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	Prostatic urethral lift.tw.
14	UroLift.tw.
15	13 or 14
16	12 and 15
17	(animals not (humans and animals)).sh.
18	16 not 17

Appendix 3. Embase (via Ovid) search strategy

1	'prostate hypertrophy'/exp
2	(Prostat* NEAR/3 hyperplasia*):ab,ti
3	(Prostat* NEAR/3 hypertroph*):ab,ti
4	(Prostat* NEAR/3 adenoma*):ab,ti
5	'bph':ab,ti OR 'bpo':ab,ti OR 'bpe':ab,ti
6	(prostat* NEAR/3 enlarg*):ab,ti
7	'prostatism'/exp
8	'prostatism':ab,ti
9	'bladder obstruction'/exp
10	(bladder* NEAR/3 obstruct*):ab,ti

(*Continued*)

11	'BOO':ab,ti
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	'Prostatic urethral lift':ab,ti
14	'urolift':ab,ti
15	#13 OR #14
16	#12 AND #15
17	('animals'/exp) NOT ('humans'/exp and 'animals'/exp)
18	#16 NOT #17

CONTRIBUTIONS OF AUTHORS

Jae Hung Jung (JHJ): conceived, designed, and wrote the protocol.

Karen Ann McCutcheon (KAM): wrote the protocol, provided clinical advice and critical content.

Balaji Reddy (BR): wrote the protocol, provided clinical advice and critical content.

Michael Borofsky (MB): wrote the protocol, provided clinical advice and critical content.

Vikram Narayan (VN): wrote the protocol, provided clinical advice and critical content.

Myung Ha Kim (MHK): created search strategies.

Philipp Dahm (PD): conceived, designed, and wrote the protocol, reviewed critical content, and gave final approval.

DECLARATIONS OF INTEREST

JHJ: none known.

KAM: none known.

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Internal sources

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External sources

- No sources of support supplied

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.