Evidence-based Practice Center Systematic Review Protocol

Project Title: Newer Medications for Lower Urinary Tract Symptoms associated with Benign Prostatic Hyperplasia

I. Background and Objectives for the Systematic Review

Benign Prostatic Hyperplasia (BPH) is a "histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone."[1] Men are likely to develop BPH as they age. Half of men ages 51 – 60 years old and 80 percent of men over 80 years old have BPH according to autopsy data.[2]

About half of men with BPH develop an enlarged prostate gland, called benign prostatic enlargement (BPE), and among these, about half develop bladder outlet obstruction (BOO).[3] BOO and/or changes in smooth muscle tone and resistance that can accompany BPH often result in lower urinary tract symptoms (LUTS).[1] LUTS are storage disturbances, such as daytime urinary urgency and nocturia, and/or voiding disturbances, such as urinary hesitancy, weak stream, straining, and prolonged voiding.[2] LUTS affect an estimated three percent of men ages 45 – 49 years old and 30 percent of men over 85 years old.[2] Urinary hesitancy, weak stream, and nocturia are the most commonly reported LUTS.[4] BPH/LUTS negatively impact quality of life[2, 3] and cost the United States over $1 billion annually.[3]

Usually, BPH diagnosis is based on clinical presentation of enlarged prostate and/or bothersome LUTS (daytime urinary urgency and nocturia, and/or voiding disturbances, such as urinary hesitancy, weak stream, straining, and prolonged voiding); other causes of LUTS should be ruled out.[3] Consensus recommendations from the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases presented guidance for evaluation of older men with LUTS associated with BPH (LUTS/BPH).[5] They recommend a basic evaluation including medical history, LUTS severity and bother assessment, physical exam with digital rectal examination, and urinalysis be conducted on men presenting with LUTS without known underlying pathology explaining the symptoms. Treatment decisions can be based on symptoms and typically uroflowmetry and postvoid residual urine (PVR) screening are not necessary.[3] However recent evidence suggests that BPH that has progressed to BOO may not be accurately diagnosed with the basic examination. In light of this, and because the presence of BOO may modify treatment, bladder scans for urine volume can assist in medical decision making when large PVR is suspected.[4] If findings from the basic evaluation do not suggest complicated LUTS, which requires a referral to a urologist, then treatment should be based on the degree of bother created by the LUTS.[5]

Trends in medical management of LUTS/BPH have progressed over the last 25 years. In the early 1990s, the Federal Drug Administration (FDA) approval of medications for BPH shifted LUTS/BPH from a condition requiring a surgical intervention to a chronic condition that could be successfully managed medically.[6] The prevalence of prescriptions and the number of medications used for LUTS/BPH have dramatically increased over

time. Prescribing behavior has changed with the approval of new drugs and the availability of new evidence for efficacy, comparative effectiveness, and harms.[6] Table 1 provides a list of drugs commonly used to treat LUTS/BPH.

The first commonly used monotherapies included selective alpha blockers (AB) and 5-alpha reductase inhibitors (5-ARIs) (Table 1). The American Urological Association (AUA) guideline on the management of BPH suggests that alpha blockers alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment options for men with bothersome LUTS/BPH.[7] Efficacy and safety of these medications is supported by several systematic reviews.[8-12] Due to the potential serious adverse effect of floppy iris syndrome, men should be asked about planned cataract surgery and be counseled to delay AB treatment until after such surgery.[7]

Monotherapy with 5-ARI agents finasteride and dutasteride is another option for LUTS/BPH and BPE.[7] Systematic reviews demonstrate that 5-ARIs are safe and effective[13, 14] and may be better than ABs in preventing disease progression (acute urinary retention and/or the need for surgical intervention).[14]

The AUA guideline also lists AB/5-ARI combinations as appropriate and effective treatment options for men with LUTS/BPH and prostate enlargement.[7] The number of prescriptions for combination therapy (AB/5-ARI) increased after publication of the MTOPS trial (2003) showing better outcomes with the combination than with monotherapy.[6] Comparative effectiveness for combined AB/5-ARI therapy is superior to monotherapy with either medication in men with LUTS/BPH and enlarged prostates with either agent are supported by systematic reviews.[10, 13]

Recently, newer drugs and other drug classes have shown promise in treating LUTS/BPH (Table 1). A new AB, silodosin, was approved for the treatment of BPH in 2008.[7] Several anticholinergics drugs approved for overactive bladder (OAB) have the potential to alleviate symptoms of LUTS/BPH due to the similarity of symptoms such as urgency, frequency, and nocturia, which may or may not be causally related.[15] These drugs work directly on the bladder smooth muscle as opposed to ABs and 5-ARIs, which work directly on the prostate. Anticholinergics have been used more frequently for LUTS/BPH since publication of the TIMES trial (2006).[6]

A new class of drugs, beta-3 adrenoceptor agonists, was recently developed to treat OAB. The proposed advantages over anticholinergics include potentially lower rates of adverse effects and potentially smaller risk of urinary retention.[15] Preliminary conclusions suggest that these drugs may effectively treat LUTS/BPH and use of this class of medications for LUTS/BPH is likely to increase in the future.[16]

Tadalafil, a phosphodiesterase (PDE-5) inhibitor (FDA-approved for the treatment of erectile dysfunction [ED] since 2003) was approved by the FDA for the treatment of BPH in 2011. The common pathology and the high rate of comorbidity between LUTS/BPH and ED likely influenced the early use of ED drugs for LUTS/BPH.[17, 18] Additionally, it is unclear whether alpha blockers are associated with ejaculatory dysfunction and other harms to male sexual function.[18] PDE-5s have also been used in combination with ABs to treat LUTS/BPH. Other PDE-5s have been used off-label to treat LUTS/BPH.

Based on the wide variety of medications available to treat LUTS/BPH, tailoring treatment with single medications or medication combinations may be indicated. Some patients are more bothered by specific symptoms that may be preferentially improved by certain medications. Men with LUTS/BPH often have other health concerns common in

older men and may be on other medications. These factors should be considered when selecting an initial course of medical management.

The primary intent of treatment is to reduce LUTS, improve prostate-related quality of life, and prevent or delay disease progression. There are two validated and widely used, nearly identical instruments used to assess LUTS, the American Urological Association Symptom Index (AUA-SI) and the International Prostate Symptom Score (I-PSS).[7]

Intermediate outcomes such as specific urodynamic parameters (i.e., peak flow, detrusor pressure) are often reported in research. These are not patient centered it is unclear whether they are appropriate bases for treatment decisions.

Current AUA guidelines are available and relevant to current practice. However, these guidelines need to be updated to account for more recently approved medications for LUTS/BPH. Our review will comprehensively assess newer medications for LUTS/BPH newly used in the last 10 years. We will synthesize available data regarding efficacy, comparative effectiveness and adverse effects of one new AB (silodosin); all anticholinergics, beta-2 agonists, and PDE-5s; and medication combinations including these agents. The addition of this evidence synthesis to what is understood about the ABs, 5-ARIs, and AB/5-ARI combinations will provide a comprehensive assessment of all medical management options for LUTS/BPH.

Table 1. Common medications used to treat LUTS associated with BPH

Drug class - Mechanism of action	Medication Generic [Brand]
Alpha 1 blockers - inhibit prostate smooth muscle contraction by blocking the alpha-1 receptor, thus relaxing the dynamic component of blockade decreasing resistance to urinary flow; Since the bladder body only has a negligible density of alpha-1 receptors while the bladder neck contains a substantial amount of alpha-1 receptors, alpha-1-blockers reduce bladder outlet resistance without impairing bladder emptying. Alpha-1 blockers ALSO may regulate prostate growth by inducing apoptosis in both the epithelial and stromal smooth muscle cells without affecting the rate of cell proliferation.	Terazosin[a] [Hytrin]
	Alfuzosin[a] [Uroxandral]
	Doxazosin[a] [Cardura]
	Silodosin[a] [Rapaflo]
	Tamsulosin[a] [Flomax]
5 alpha reductase inhibitors - inhibit 5alpha-reductase, an isoenzyme that metabolizes testosterone to dihydrotestosterone (DHT) in the prostate gland, liver, and skin; blocking conversion of testosterone to DHT and reducing serum and tissue DHT.	Finasteride[a] [Proscar]
	Dutasteride[a] [Avodart]
Anticholinergic agent – relaxes bladder smooth muscle by reducing the muscarinic effect of acetylcholine on smooth muscle.	**Oxybutynin**[b] [Oxytrol]
	Fesoterodine[b] [Toviaz]
	Darifenacin[b] [Enablex]
	Tolterodine Tartrate[b] [Detrol LA]
	Tolterodine[b] [Detrol]
	Solifenacin[b] [Vesicare]
	Trospium [Sanctura]
Beta-3 adrenergic agonist - Increases bladder capacity by relaxing the bladdersmooth muscle during the storage phase of the urinary bladder fill-void cycle	**Mirabegron**[b] [Myrbetriq]
Phospodiesterase type 5 inhibitor - selectively inhibits PDE5 and increases cyclic guanosine monophosphate (cGMP). The smooth muscle cells of the prostate, bladder and surrounding vasculature contain PDE5; inhibiting PDE5 and increasing cGMP levels in these tissues causes smooth muscle relaxation.	**Tadalafil**[a, d] [Cialis]
	Sildenafil[c] [Viagra]
	Avanafil[d] [Stendra]
	Vardenafil[d] [Staxyn, Levitra]

[a]= FDA approved to treat BPH; [b]= FDA approved to treat overactive bladder; [c]= FDA approved to treat erectile dysfunction and hypertension; [d]= FDA approved to treat erectile dysfunction.
Bolded medications are the newer medications that are the focus of this review.

II. The Key Questions

Question 1: What is the efficacy and comparative effectiveness of newer medications alone or in combination for LUTS associated with BPH?

Question 2:

What are the harms and comparative harms of newer medications for LUTS associated with BPH?

Question 3: Do the comparative benefits and harms of newer medications for LUTS associated with BPH differ according to demographic or clinical characteristics?

Population(s)

Adult men (age 45 years and over) with LUTS associated with BPH

Demographic and clinical subgroups of adut men (age 45 years and over) with LUTS associated with BPH (i.e. defined by comorbidities [i.e., BMI status, erectile dysfunction], symptom severity, previous treatment).

Interventions

Newer medications:

- Alpha-blockers - silodosin
- Anticholinergics – oxybutynin, fesoterodine, darifenacin, tolterodine tartrate, tolterodine, solifenacin
- Beta-3 adrenoceptor agonists - mirabegron
- PDE-5 inhibitors – tadalafil, sildenafil, avanafil, vardenafil
- Adjunctive/combination treatment with newer medication

Comparators

- Placebo or other FDA approved medication (Table 1)

Outcomes:

Primary Outcomes

1. LUTS-as measured by the I-PSS, AUA-SI scores
2. Prostate-related bother or quality of life (QoL) (i.e. I-PSS QoL question) or BPH/LUTS impact (BII) scores
3. Disease Progression/Treatment Failure (i.e.,measured by prevention/delay of need for surgical intervention, acute urinary retention (AUR), 3-point increase in IPSS score).

Adverse effects of intervention(s) Common and serious medication side effects

Timing

Short term outcomes - treatment duration between 1 and 6 months

Intermediate outcomes - treatment duration of at least 6 months and less than 1 year

Long term outcomes - treatment duration of 1 year or more

Setting

Outpatient settings

III. Analytic Framework

Figure 1. Analytical Framework for Newer Medications for LUTS/BPH

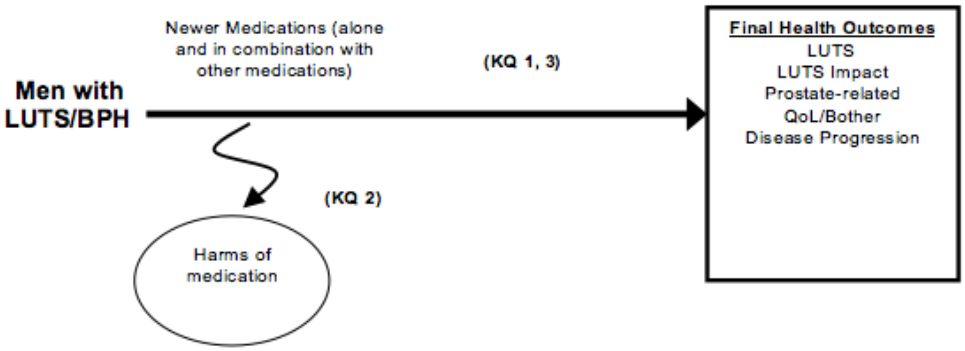

Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how newer medications work in men with LUTS/BPH to improve LUTS, prostate-related quality of life, and prevent or delay BPH progression. Also, adverse events may occur at any point after the treatment is initiated.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 3.

Table 2. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Men with LUTS associated with BPH
Study Objective	To test the efficacy, comparative effectiveness, and harms of newer drugs alone or in combination in treating LUTS/BPH.
Study Design	• Efficacy/comparative effectiveness: RCTs Harms: RCTs and large observational studies (medication for treatment of LUTS/BPH, sample size at least 100; study duration at least 6 months; comparison group)
Outcomes	• Must reports LUTS or adverse effects
Timing	• Efficacy/comparative effectiveness: 4 weeks to 6 months • Sustained efficacy/comparative effectiveness: over 6 months
Publication type	Published in peer reviewed journals. These data may be supplemented grey literature searching if sufficient information to assess eligibility and risk of bias are provided.
Language of Publication	English

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will search Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials for primary health outcomes published and indexed in bibliographic databases. We will attempt to assess long-term or rare harms with nonrandomized controlled trials and large controlled observational studies (n≥100) if RCTs are not available. Our search strategy includes relevant medical subject headings and natural language terms for LUTS/BPH (Appendix A). These concepts were combined with filters to select trials. We will supplement the bibliographic database search with forward and backward citation searching of relevant systematic reviews and other key references. We will update searches while the draft report is under public/peer review.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results will be downloaded to EndNote.. Titles and abstracts will be reviewed by two independent investigators using inclusion criteria (Table 2) to identify studies meeting PICOTS framework. All studies identified as relevant by either investigator will undergo full-text screening. We will track the number of non-English studies that appear eligible based upon English title and abstract to assess the magnitude of studies excluded for language. Two investigators will independently perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. Throughout the screening process, team members will meet regularly to discuss training material and issues as they arise to ensure consistency of inclusion criteria application. Eligible references will be examined to identify the number of unique studies.

We will search for grey literature in ClinicalTrials.gov and to identify completed and ongoing studies. We will search for conference abstracts from the past three years to identify ongoing studies. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature. Information from grey literature will also be used to assess publication and reporting bias and inform future research needs. Additional grey literature will be solicited through a notice posted in the Federal Register and Scientific Information Packets and other information solicited through the AHRQ Effective Health Care website.

C. Data Abstraction and Data Management

Data fields to be extracted will include author, year of publication, sponsorship, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, follow-up duration, participant baseline age, race, and AUA/IPSS scores, and results of primary outcomes and adverse effects. Relevant data will be extracted into web-based extraction forms created in Microsoft Excel. Data will be analyzed in RevMan 5.3 software.[19] Data will be extracted to evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator.

D. Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias of eligible studies will be assessed using instruments specific to RCTs. We will develop an instrument based upon AHRQ guidance.[20] Relevant items will include participant selection, method of randomization, attrition, blinding, allocation concealment, and appropriateness of analytic methods.

One investigator will independently assess risk of bias for eligible studies; a second investigator will review the risk of bias assessment. Investigators will consult to reconcile any discrepancies in overall risk of bias assessments. Overall summary risk of bias assessments for each study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the study results are believable given the study's limitations.

E. Data Synthesis

We will summarize the results in evidence tables and synthesize evidence for each unique comparison with meta-analysis when possible and appropriate. We will explore the possibility of network meta-analysis once we have an understanding of the data available for all potential comparisons. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[21] We will synthesize data using a DerSimonian-Laird random effects model in RevMan.[19] We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes. We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.[21] If the analyses yield substantial heterogeneity (i.e. $I^2 \geq 70\%$), we will we stratify the results to assess treatment effects based on patient or study characteristics and/or explore sensitivity analysis. We will assess efficacy and comparative effectiveness using established thresholds for specific instruments commonly used to measure LUTS/BPH outcomes when they are available. Table 4 provides a list of these instruments, basic psychometric properties, and relevant thresholds for classifying improvement when we were able to identify such in the literature.[22] These thresholds represent the minimal noticeable difference to the patient and may or not equal a minimal important difference. For outcomes measured with instruments that lack established thresholds, we will calculate standard effect sizes and require a small effect size to conclude efficacy or comparative effectiveness.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The overall strength of evidence for primary outcomes of KQ1 within each comparison will be evaluated based on five required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size among studies); (4) precision (degree of certainty around an estimate); and (5) reporting bias.[23] Based on study design and risk of bias, study limitations will be rated as low, medium, or high. Consistency among studies will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single

study) based on the whether intervention effects are similar in direction and magnitude, and statistical significance of all studies. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies. That is, more than one step is needed to reach the conclusion. Precision will be rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions based upon established noticeable differences when available. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these elements, we will assess the overall strength of evidence for each comparison and outcome as:[23]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains.
We will assess strength of evidence for key final health outcomes measured with validated scales.

G. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population (age, race, and country from which the study participants were enrolled), narrow eligibility criteria, and patient and intervention characteristics potentially associated with treatment response different than those described by population studies.[24]

Table 3: Symptom and Quality of Life Scales used to measure or evaluate LUTS associated with BPH

Instrument	Range (points)	Scoring	Thresholds Relevant to Assessing Effectiveness
International Prostate Symptom Score (I-PSS)[a]	0 (asymptomatic) to 35 (very symptomatic)	0 to 7: Mild symptoms 8 to 19: Moderate symptoms 20 to 35: Severe symptoms	-3=slight improvement[b] -5.1=moderate improvement[b] -8.8=marked improvement[b]
BPH Impact Index (BII)	0 to 13	Higher scores represent increased perceived impact of BPH-LUTS on overall health	-0.5=slight improvement[b] -1.1=moderate improvement[b] -2.2=marked improvement[b]
I-PSS Quality of Life Due to Urinary Symptoms	0 to 6	0-2: Delighted to mostly satisfied 3: Mixed 4-6: Mostly dissatisfied to terrible	No thresholds identified

[a] Also known as the American Urological Association symptom score

[b] **Barry, M. J., et al. (1995). "Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients?" Journal of Urology 154(5): 1770–1774.**

V. References

1. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. Journal of Urology. 2011 May;185(5):1793-803. PMID 2011194442.
2. Jarvis TR, Chughtai B, Kaplan SA. Bladder Outlet Obstruction and BPH. Current Bladder Dysfunction Reports. 2014:1-7.
3. Hollingsworth JM, Wilt TJ. Lower urinary tract symptoms in men. BMJ. 2014;349:g4474. PMID 25125424.
4. D'Silva KA, Dahm P, Wong CL. Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. JAMA. 2014 Aug 6;312(5):535-42. PMID 25096693.
5. Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. Journal of Urology. 2013 Jan;189(1 Suppl):S93-S101. PMID 23234640.
6. Filson CP, Hollingsworth JM, Clemens JQ, et al. The efficacy and safety of combined therapy with alpha-blockers and anticholinergics for men with benign prostatic hyperplasia: a meta-analysis. Journal of Urology. 2013 Dec;190(6):2153-60. PMID 23727412.
7. McVary K, Roehrborn C, Avins A. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH) Revised, 2010. American Urological Association Education and Research. Inc; 2010.
8. Yuan J, Liu Y, Yang Z, et al. The efficacy and safety of alpha-1 blockers for benign prostatic hyperplasia: an overview of 15 systematic reviews. Current Medical Research & Opinion. 2013 Mar;29(3):279-87. PMID 23323875.
9. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. Urology. 2005 Oct;66(4):780-8. PMID 16230138.
10. MacDonald R, Wilt TJ, Howe RW. Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. BJU International. 2004 Dec;94(9):1263-70. PMID 15610102.
11. Wilt TJ, MacDonald R, Nelson D. Tamsulosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. Journal of Urology. 2002 Jan;167(1):177-83. PMID 11743300.
12. Wilt TJ, Howe W, MacDonald R. Terazosin for treating symptomatic benign prostatic obstruction: a systematic review of efficacy and adverse effects. BJU International. 2002 Feb;89(3):214-25. PMID 11856101.
13. Hollingsworth JM, Wei JT. Does the combination of an alpha1-adrenergic antagonist with a 5alpha-reductase inhibitor improve urinary symptoms more than either monotherapy? Current Opinion in Urology. 2010 January;20(1):1-6. PMID 2010049481.
14. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clinical Therapeutics. 2007 January;29(1):17-25. PMID 2007135431.
15. Suarez O, Osborn D, Kaufman M, et al. Mirabegron for male lower urinary tract symptoms. Current urology reports. 2013;14(6):580-4.
16. Kaplan SA. Re: beta3-adrenoreceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men. Journal of Urology. 2014 May;191(5):1344-6. PMID 24745510.
17. Carson CC, Rosenberg M, Kissel J, et al. Tadalafil - A therapeutic option in the management of BPH-LUTS. International Journal of Clinical Practice. 2014 January;68(1):94-103. PMID 2013802282.
18. Yan H, Zong H, Cui Y, et al. The Efficacy of PDE5 Inhibitors Alone or in Combination with Alpha-Blockers for the Treatment of Erectile Dysfunction and Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: A Systematic Review and Meta-Analysis. Journal of Sexual Medicine. 2014

June;11(6):1539-45. PMID 2014388517.
19. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen; 2012.
20. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ. 2012.
21. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology. 2011 Nov;64(11):1187-97. PMID 21477993.
22. Barry MJ, Williford WO, Chang Y, et al. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? Journal of Urology. 1995 Nov;154(5):1770-4. PMID 7563343.
23. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. 2013.
24. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412. Accessed on AHRQ Publication No. 11-EHC019-EF.

VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A: Search Strategy

BPH Medline RCTs SRs Harms

1. *Prostatic Hyperplasia/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
7. exp *Lower Urinary Tract Symptoms/
8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Urinary Bladder Neck Obstruction/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. silodosin.mp.
16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
19. oxybutynin.ti,ab.
20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.
32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.

44. viagra.ti,ab.
45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. exp Review Literature as Topic/
61. or/55-60
62. cochrane.ab.
63. embase.ab.
64. (psychlit or psyclit).ab.
65. (psychinfor or psycinfo).ab.
66. or/62-65
67. reference list$.ab.
68. bibliograph$.ab.
69. hand search.ab.
70. relevant journals.ab.
71. manual search$.ab.
72. or/67-71
73. selection criteria.ab.
74. data extraction.ab.
75. 73 or 74
76. review/
77. 75 and 76
78. comment/
79. letter/
80. editorial/
81. animal/
82. human/
83. 81 not (82 and 81)
84. or/78-80,83
85. 61 or 66 or 72 or 77
86. 85 not 84
87. randomized controlled trials as topic/
88. randomized controlled trial/
89. random allocation/

90. double blind method/
91. single blind method/
92. clinical trial/
93. clinical trial, phase i.pt.
94. clinical trial, phase ii.pt.
95. clinical trial, phase iii.pt.
96. clinical trial, phase iv.pt.
97. controlled clinical trial.pt.
98. randomized controlled trial.pt.
99. multicenter study.pt.
100. clinical trial.pt.
101. exp Clinical trials as topic/
102. or/87-101
103. (clinical adj trial$).tw.
104. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
105. placebos/
106. placebo$.tw.
107. randomly allocated.tw.
108. (allocated adj2 random$).tw.
109. 103 or 104 or 105 or 106 or 107 or 108
110. 102 or 109
111. case report.tw.
112. case report.tw.
113. letter/
114. historical article/
115. 111 or 112 or 113 or 114
116. 110 not 115
117. 14 and 53
118. (ae or to or po or co).fs.
119. (safe or safety).ti,ab.
120. side effec*.ti,ab.
121. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
122. exp Product Surveillance, Postmarketing/
123. exp "Drug-Related Side Effects and Adverse Reactions"/
124. exp Adverse Drug Reaction Reporting Systems/
125. exp Clinical Trials, Phase IV as Topic/
126. exp Poisoning/
127. (toxicity or complication* or noxious or tolerability).ti,ab.
128. 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127
129. 117 and (86 or 116 or 128)
130. limit 129 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or

directory or editorial or festschrift or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts)
131. 129 not 130
132. limit 131 to "all child (0 to 18 years)"
133. limit 132 to "all adult (19 plus years)"
134. 131 not 132
135. 134 or 133
136. 135 and ("166".mp. or 128) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
137. 135 and 86

BPH Embase RCTs SRs Harms

1. *Prostate hypertrophy/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
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8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Bladder Neck stenosis/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
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16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
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20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.
32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.
44. viagra.ti,ab.

45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. or/55-59
61. cochrane.ab.
62. embase.ab.
63. (psychlit or psyclit).ab.
64. (psychinfor or psycinfo).ab.
65. or/61-64
66. reference list$.ab.
67. bibliograph$.ab.
68. hand search.ab.
69. relevant journals.ab.
70. manual search$.ab.
71. or/66-70
72. selection criteria.ab.
73. data extraction.ab.
74. 72 or 73
75. review/
76. 74 and 75
77. comment/
78. letter/
79. editorial/
80. animal/
81. human/
82. 80 not (81 and 80)
83. or/77-79,82
84. 60 or 65 or 71 or 76
85. 84 not 83
86. randomized controlled trials as topic/
87. randomized controlled trial/
88. random allocation/
89. double blind method/
90. single blind method/

91. clinical trial/
92. (clinical adj trial$).tw.
93. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
94. placebos/
95. placebo$.tw.
96. randomly allocated.tw.
97. (allocated adj2 random$).tw.
98. or/86-97
99. case report.tw.
100. case study.tw.
101. letter/
102. historical article/
103. 99 or 100 or 101 or 102
104. 98 not 103
105. (ae or to or po or co).fs.
106. (safe or safety).ti,ab.
107. side effec*.ti,ab.
108. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
109. exp Product Surveillance, Postmarketing/
110. exp "Drug-Related Side Effects and Adverse Reactions"/
111. exp Adverse Drug Reaction Reporting Systems/
112. exp Clinical Trials, Phase IV as Topic/
113. exp Poisoning/
114. (toxicity or complication* or noxious or tolerability).ti,ab.
115. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114
116. 54 and (85 or 104 or 115)
117. limit 116 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
118. limit 117 to (adult <18 to 64 years> or aged <65+ years>)
119. 116 not 117
120. 119 or 118
121. limit 120 to (book or book series or conference abstract or conference proceeding or "conference review" or editorial or letter or note or short survey or trade journal)
122. 120 not 121
123. 122 and (104 or 115)
124. 122 and 85
125. 123 not 124
126. from 125 keep 1-461