The management of lower urinary tract symptoms in men

DRAFT VERSION – 1ST version

METHODS, EVIDENCE & GUIDANCE

Produced by the National Clinical Guideline Centre

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Foreword

'As man draws near the common goal

Can anything be sadder

Than he who, master of his soul

Is servant to his bladder'

Anon

A number of terms such as "prostatism", "symptoms of benign prostatic hyperplasia (BPH)", and "clinical BPH" have been used historically to describe male lower urinary tract symptoms (LUTS). It is widely acknowledged that symptoms do not relate to the underlying pathophysiology in many patients; indeed the phrase "the bladder is an unreliable witness" was coined 4 decades ago to acknowledge this. The term lower urinary tract symptoms (LUTS) is an umbrella term that was introduced 15 years ago in order to dispel the popular perception that urinary symptoms in the male invariably arise from the prostate. The Department of Health and NICE are the first governmental agencies to have acknowledged this by supporting the development of this national guideline for the management of male LUTS and avoiding the use of the global term 'BPH'.

The prevalence and severity of male LUTS increase with age and the progressive growth of the aged population group has emphasised the importance to our society of appropriate and effective management of male LUTS. LUTS comprise storage symptoms (i.e., daytime urinary frequency, nocturia, urgency, urinary incontinence), voiding symptoms (i.e., slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble), and post micturition symptoms (i.e., sensation of incomplete emptying, post micturition dribble).

It has been reported that 90% of men aged 50 to 80 years suffer from potentially troublesome LUTS and whist many men have both storage and voiding symptoms with voiding symptoms being the most common; storage symptoms represent the most bothersome LUTS. The most troublesome symptom – incontinence, is associated both with increasing age as a consequence of more severe bladder overactivity and prostatic surgery for either benign or malignant disease. It has been reported that the prevalence of storage symptoms increases from 3% in men 40 to 44 years of age to 42% in those ≥75 years.

In the management of male LUTS we need to clearly recognise that we are dealing with a complex functional unit comprising the bladder, bladder neck/prostate and urethra. LUTS may result from a complex interplay of pathophysiological influences including prostatic pathology and bladder dysfunction in men which adds complexity to their management. The use of incorrect and inconsistent terminology may lead to confusion between clinicians and patients

and result in the less than optimal management of the conditions underlying male LUTS. Since there is a danger that terminology may lead thought rather than facilitating and serving it, it is helpful to reflect on the current terminology associated with male LUTS.

- "Benign prostatic hyperplasia" (BPH) should be reserved for histopathologically confirmed hyperplastic changes (i.e. abnormality/changes at the cell level) in the prostate. The prevalence of BPH increases with age and whilst it is often associated with LUTS, only 25% to 50% of men with BPH have LUTS.
- "Benign prostatic enlargement" (BPE) refers to an increase in size of prostate gland due to BPH. Only about half of men with BPH will develop BPE.
- "Bladder outlet obstruction" (BOO) is an urodynamically diagnosed condition characterised by increased detrusor pressure and reduced urine flow rate.
- "Lower urinary tract symptoms suggestive of BOO" is a term used when a man complains predominantly of voiding symptoms in the absence of infection or obvious pathology other than possible causes of outlet obstruction. This term should be used until BOO is confirmed; approximately 50% of men with LUTS do not have BOO.
- "Overactive bladder" (OAB) has been introduced to describe a common association of storage LUTS, with the exclusion of stress (weak sphincter) and overflow (chronic retention) associated incontinence and is characterised by urinary urgency, with or without urinary urgency incontinence, usually with frequency and nocturia. Overactive bladder symptoms can be caused solely by bladder dysfunction.
- Detrusor overactivity (DO) is urodynamically characterised by involuntary detrusor contractions during the bladder filling phase and occurs in approximately two thirds of those presenting with OAB symptoms and 50% of those with BOO.

There is a clear association between LUTS and sexual dysfunction, including erectile dysfunction, ejaculatory dysfunction, decreased sexual activity and decreased sexual desire. Clearly, lifestyle and psychosocial factors (e.g. depression) consequent upon LUTS may precipitate sexual dysfunction. In this guideline, we will not deal with the primary management of sexual dysfunction but the potential sexual dysfunction associated with the various therapies, both medical and surgical used in the management of LUTS

There are many challenges and methodological obstacles encountered in the progression of the enormous body of work which underpins the development of a complex clinical guideline, particularly one encompassing the whole of male LUTS and all that this involves. Indeed when the topic was first conceived and brought to gestation two years ago it was considered to represent the amalgamation of two separate guideline topics. This guideline stands as a testament to the dedication, knowledge, effort, commitment and quality of the NCGC staff, and the expertise of their leadership in the collaborating centre. They patiently educated and guided myself and the other clinician members and patient representatives on the guideline development group as to the 'process'. Simultaneously they provided both general and specific guidance allowing the GDG to not only understand complex analyses, in particular relating to the evaluation of cost effectiveness; developed original cost-effectiveness analyses, evaluated the clinically relevant information and effortlessly and conscientiously reviewing an enormous body of information. My colleagues on the GDG deserve praise for their expertise, perseverance and insightfulness and in particular from me for the friendship and strong support they have accorded me.

This guideline reviews a number of important aspects of the management of male LUTS:

• diagnostic tests available for evaluation and identification of underlying pathophysiology

- the potential role of the conservative and lifestyle measures

- pharmacotherapy using agents to relax the prostatic muscle, shrink the hyperplastic prostatic tissue or relax the bladder either as monotherapy or in combination

- minimally invasive procedures and other surgical options

Despite meticulous methodology and attention to detail there are areas of uncertainty where no controlled trials (RCT) of sufficient quality exist. In such situations we took account of what is currently perceived to be best practice, potential adverse events and the patients' perception in the interpretation of evidence by the GDG. Even within the boundaries of the evidence there are often uncertainties, and the same considerations were taken into account when formulating the recommendations.

Our panel believes that a comprehensive, practical and effective approach to the management of male LUTS must emphasise the pre-eminent importance of patient perceived outcomes, consider the lower urinary tract as an integrated functional unit and ensure that significant symptoms and the underlying pathology are identified and treated appropriately. Effective therapy depends on accurate identification and diagnosis of the underlying of the problem. One should remember the ancient Chinese proverb that the 'bladder is the mirror of the soul' and that LUTS can result from not only bladder dysfunction, prostatic pathology but also from a number of other pathophysiological processes, e.g., metabolic, hormonal, cardiac, and respiratory. This avoids a local prostate focused approach resulting in a more appropriate recognition of clinical scenarios and will allow clinicians of all disciplines to more effectively take account of patients' expectations and goals and provide a successful outcome for the therapy of male LUTS.

Professor Christopher Chapple,

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Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel will be added when available.

Stakeholder Involvement

To be added after consultation.

1 Abbreviations

5ARI	5-alpha reductase inhibitor
AB	Alpha blockers
Anti-Ch	Anticholinergics
AUA	American Urological Association
AUASS	American Urological Association Symptom Score
b.d.	To be taken twice a day *(bis die)*
BNF	British National Formulary
BNI	Bladder Neck Incision
BF	Biofeedback
BPH	Benign prostatic hyperlasia
BPE	Benign prostatic enlargement
BOO	Bladder outlet obstruction
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CUA	Cost-utility analysis
DH	Department of Health
DRE	Digital rectal examination
ED	Erectile dysfunction
ES	Electrical stimulation
eGFR	Estimated glomerular filtration rate
GDG	Guideline Development Group
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline Review Panel
HIFU	High Intensity Focused Ultrasound
HoLAP	Holmium Laser Ablation of the Prostate
HoLEP	Holmium Laser Enucleation of the prostate
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
IQR	Inter-quartile range
IPSS	International Prostate Symptom Score
ISC	Intermittent self-catheterisation

ITT	Intention to treat
LOS	Length of Stay
LR-	Likelihood ratio negative
LR+	Likelihood ratio positive
LUTS	Lower urinary tract symptoms
LY	Life-year
MD	Mean difference
MHRA	Medicines and Healthcare Products Regulatory Agency
N	Number of patients
NCGC (ACC)	National Clinical Guideline Centre (for Acute and Chronic Conditions)
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NPV	Negative predictive value
NSAIDS	Non-steroidal anti-inflammatory drugs
OAB	Overactive bladder
OP	Open prostatectomy
OR	Odds ratio
PASA	NHS Purchasing and Supply Agency
PDE5I	Phosphodiesterase 5 Inhibitors
PFMT	Pelvic floor muscle training
PICO	Framework incorporating patients, interventions, comparison and outcome
PMD	Post micturition dribble
PPIP	Patient and Public Involvement Programme
PPV	Positive Predictive Value
PSA	Prostate specific antigen
PVP	Photoselective vapourisation of the prostate
PVR	Post void residual
PVM	Post-void milking
Qmax	Maximum urinary flow rate
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SA	Sensitivity analysis
SD	Standard deviation
SMD	Standardised mean difference
SUI	Stress urinary incontinence
TEAP	Transurethral ethanol ablation of the prostate
TUIP	Transurethral incision of the prostate
TUMT	Transurethral microwave thermotherapy
TUNA	Transurethral needle ablation
TUVP	Transurethral vapourisation of the prostate
TUVRP	Transurethral vapourisation resection of the prostate
TURP	Transurethral resection of the prostate
UI	Urinary incontinence

Vs Versus

1

1 Glossary of terms

Absolute risk reduction (Risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Active surveillance	This includes reassurance and life-style advice without immediate treatment.
Acute retention of urine	Painful inability to pass urine and the presence of a distended, tender palpable bladder
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation.[176]
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Alpha Blocker	A drug that blocks alpha adrenoceptors, the cell-bound receptors that are activated by release of norepinephrine from nerves within the sympathetic nervous system. Adrenoceptors may be found on smooth (involuntary) muscle, and if norepinephrine activates them, muscle contraction results. Alpha blockers may therefore produce relaxation of some smooth muscles.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of	An international collaboration of researchers and policy makers

Guidelines Research and Evaluation, (AGREE)	whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org/). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.
Artificial sphincter	The artificial urinary sphincter consists of an implanted inflatable cuff which is implanted around the urethra, usually at the bulb and sometimes around the prostatic apex.
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Biofeedback	The technique by which information about a normally unconscious physiological process is presented to the patient and/or the therapist as a visual, auditory or tactile signal.
Bladder diary	A diary that records voiding times and voided volumes, leakage episodes, pad usage and other information such as fluid intake, degree of urgency, and degree of incontinence. See also frequency-volume chart.
Bladder neck incision (BNI)	Incision in one or both side of the urethra, from bladder neck to verumontanum, usually for men with small prostates.
Bladder outlet obstruction (BOO)	The generic term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urine flow rate.
Bladder sensation	Normal: The individual is aware of bladder filling and increasing sensation up to a strong desire to void. Increased: The individual feels an early and persistent desire to void. Reduced: The individual is aware of bladder filling but does not feel a definite desire to void. Absent: The individual reports no sensation of bladder filling or desire to void. Non-specific: The individual reports no specific bladder sensation, but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity.
Bladder training	Bladder training (also described as bladder retraining, bladder drill, bladder re-education, bladder discipline) actively involves

	the individual in attempting to increase the interval between the desire to void and actual void.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Bothersome symptoms	LUTS that are troublesome and have an impact on quality of life.
Botulinum toxin	A potent neurotoxin derived from the bacterium Clostridium botulinum. It can be injected directly into part of the urinary tract e.g. bladder wall. This can be performed as a day case procedure using a flexible cystoscope.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Catheterisation	A technique for bladder emptying employing a catheter to drain the bladder or a urinary reservoir. Intermittent catheterisation: drainage or aspiration of the bladder or a urinary reservoir. Indwelling catheterisation: a catheter remains in the bladder, urinary reservoir or urinary conduit for a period of time longer than one emptying. Urethral, suprapublic, intermittent, indwelling?
Chronic retention of urine	A non-painful bladder, which fails to empty and remains palpable or percussable after the patient has passed urine, with a post voiding residual of more than 1 litre. Such patients may be incontinent especially at night-time.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical impact The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.

Clinical question In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.

Clinician A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.

Cluster A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.

Cochrane Library A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.

Cochrane Review A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Cohort study A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Co-morbidity Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.

Comparability Similarity of the groups in characteristics likely to affect the study results (such as health status or age).

Compliance The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.[176]

Concordance This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.[176]

Conference proceedings Compilation of papers presented at a conference.

Confidence interval (CI) A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is

	repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Containment products	Materials or devices which are used to collect urine in patients suffering from incontinence i.e. external collection devices, pads, indwelling catheters.
Continuous urinary incontinence	The complaint of continuous leakage.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible interval	The Bayesian equivalent of a confidence interval.
Cystoplasty	An operation to increase the capacity of the bladder, usually performed using a bowel segment that is incorporated into the wall of the bladder like a patch.
Cystoscopy	A diagnostic procedure where a telescope (cystoscope) is used to look inside the bladder. It is also possible to collect urine samples, and to examine the prostate gland.
Daytime frequency	The number of voids recorded during waking hours and includes the last void before sleep and the first void after waking and rising in the morning.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Detrusor overactivity (DO)	An urodynamic observation characterised by involuntary detrusor contractions during the filling phase of cystometry. These contractions may be spontaneous or provoked. See also urodynamics.
Digital Rectal Examination (DRE)	A routine test that is used to detect abnormalities of the prostate gland. The doctor or nurse inserts a gloved and lubricated finger (digit) into the patient's rectum, which lies just behind the prostate.
Dipstick test	A test using a small, chemically treated strip that is dipped into a urine sample; when testing for protein, an area on the strip changes colour depending on the amount of protein (if any) in the urine.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.

Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.
Drop-out	A participant who withdraws from a clinical trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effect size.	This term is usually used in meta-analysis to denote treatment effect, or estimate of effect. It also refers to standardised mean difference (SMD), obtained by dividing the mean difference with the pooled standard deviation. This is the meaning usually referred to in GRADE.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Electrical stimulation	The application of electrical current to stimulate the pelvic viscera or their nerve supply.
Enuresis	Involuntary loss of urine at night
Endoscopy	The visualization of the interior of organs and cavities of the body with a medical telescope.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).

Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Frequency – volume chart (FVC)	A chart that records voided volumes and times of voiding (day and night) for at least 24 hours. See also bladder diary.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See 'Reference standard'.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Haematuria	The presence of blood in the urine. Macroscopic haematuria is visible to the naked eye, while microscopic haematuria is only visible with the aid of a microscope.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative

	healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Hesitancy	The term used when an individual describes difficult in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
High intensity focused ultrasound (HIFU)	High-intensity focused ultrasound (HIFU) uses ultrasound as the energy source, which, when tightly focused, can cause coagulative necrosis of tissue. Ultrasound can be delivered to a precisely located focal zone of 2 × 10 mm leading to a rapid rise in temperature of up to 80–100°C using short exposure duration.
Holmium laser enucleation of prostate (HoLEP)	A holmium laser is used to remove the prostatic tissue and seal blood vessels. HoLEP is sometimes performed as a day procedure in the hospital.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypothesis	A supposition made as a starting point for further investigation.
Imprecision	Imprecision is one of the quality elements considered under the GRADE system. Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.

$ICER=(Cost_A – Cost_B) / (Effectiveness_A – Effectiveness_B)$.

Inconsistency Inconsistency is one of the elements of quality considered under the GRADE system. Inconsistency refers to the unexplained heterogeneity in the results observed.

Index In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.

Indirectness Indirectness is one of the elements of quality considered under the GRADE system. Indirectness of evidence refers to the difference in study population, intervention, comparator and outcomes between the available evidenced and the clinical question or population addressed in the guideline recommendations.

Indication (specific) The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Intention-to-treat analysis (ITT analysis) An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Intermediate outcomes Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study. The reduction of prostate volume which in turn is related to the reduced risk of acute urinary retention.

Intermittent stream (Intermittency) The term used when the individual describes urine flow, which stops and starts on one or more occasions, during micturition.

Internal validity The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.

International Prostate Symptom Score (IPSS) An 8 question (7 symptom questions: 3 dealing with storage symptoms and 4 with voiding symptoms + 1 quality of life question) questionnaire used to assess the symptoms of lower urinary tract symptoms and impact on the patient's quality of life. A score from 0- 8 is categorised as mild symptoms, 8-19 as moderate symptoms and 20-35 as severe symptoms.

Intervention Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.

Intraoperative	The period of time during a surgical procedure.
Kappa statistic	An index which compares the agreement against that which might be expected by chance
Laser coagulation	Laser induced necrosis of prostatic tissue is achieved either by surface application of the laser to the prostatic urethra in a technique termed visual laser ablation of the prostate (VLAP) or by inserting specially designed laser fibres into the prostatic tissue via the urethra, termed interstitial laser coagulation (ILC)
Laser vapourisation	Laser induced vapourisation of the prostatic tissue. See also holmium laser enucleation of the prostate (HoLEP).
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio (LR)	The ratio of the probability that a person with a condition has a specified test result to the probability that a person without the condition has the same specified test result. For positive test results, this is referred to as "Likelihood ratio positive", LR+. For negative test result, this is known as "Likelihood ration negative", LR-.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Markov model	A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Maximum urinary flow rate (Qmax)	See Qmax
Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data

	pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Mid-stream urine (MSU) sample	This involves taking a 'middle' sample while the urine is being voided, avoiding the initial and end stages of the void. This reduces the risk of sample contamination from bacteria present in the distal urethra, as these bacteria are washed away with the initial urine flow.
Minimal important difference (MID)	This is the smallest change which can be recognised by a patient as being clinically significant
Mixed urinary incontinence (MUI)	Involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing
Male sling	A surgically-implantable device designed to relieve incontinence by supporting the urethra.
Marketing authorisation	An authorisation that covers all the main activities associated with the marketing of a medicinal product. Medicines that meet the standards of safety, quality and efficacy set by the Medicines and Healthcare products Regulatory Agency (MHRA) are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold.
Mulitchannel cystometry	Cystometry is the measure of intravesical pressure that can be carried out through a single recording channel (simple cystometry) or, more commonly, by multichannel cystometry, which involves the synchronous measurement of both bladder and rectal pressure. The aim is to replicate the patient's symptoms by filling the bladder and observing pressure changes or leakage caused by provocation tests. See also urodynamics.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Myectomy	The whole of the overactive detrusor muscle above the bladder "equator" is removed by stripping it surgically from the underlying mucosa.
Narrative summary	Summary of findings given as a written description.
Negative likelihood ratio (LR-)	The ratio of the probability that a person with a condition has a negative test result to the probability that a person without the condition has negative test result. Likelihood ratio negative, LR - = (1-sensitivity)/specificity See "likelihood ratio" and "positive likelihood ratio".
Negative predictive value (NPV)	Proportion of patients with a negative test result who do not have the disease = TN/(FP+TN)
Neuromodulation	The term neuromodulation can apply to any method of electrical modulation of nerve activity. In the context of male LUTS, it means the modulation of the sacral reflex pathway upon which

	overactive detrusor function depends.
Nocturia	The complaint that the individual has to wake at night one or more times to void, with each void preceded and followed by sleep See also frequency.
Nocturnal enuresis	The complaint of loss of urine occurring during sleep.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Older people	People over the age of 65 years.
Open prostatectomy	Surgical removal of the prostate through an incision made in the lower abdomen. This leaves behind only the capsule of the prostate.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Overactive bladder (OAB) syndrome	Urgency, with or without urge(ncy) urinary incontinence, usually with frequency and nocturia. OAB wet is where (urgency) incontinence is present, and OAB dry is where incontinence is absent.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC)	Subrapubic pain associated with other lower urinary tract symptoms, usually increased frequency (but not urgency), and nocturia
Patient reported outcomes (PRO) or Patient Reported Outcomes Measures	These terms covers a whole range of potential types of measurements (e.g. symptoms severity or bother, health related quality of life, satisfaction with treatment) but is used specifically to refer to questionnaires designed to obtain the perspective of

(PROMS)	the patient rather than the perspective of clinicians or carers. PRO data may be collected via self-administered questionnaires completed by the patient themselves or via interviewer-administered questionnaires. These questionnaires should be developed and validated before use.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Peak urinary flow rate	See Qmax
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Pelvic floor muscle training (PFMT)	Repetitive selective voluntary contraction and relaxation of specific pelvic floor muscles.
Perioperative	The period from admission through surgery until discharge, encompassing preoperative and post-operative periods.
Polyuria	The measured production of more than 3.0 litres of urine in 24 hours.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.
Positive likelihood ratio (LR+)	The ratio of the probability that a person with a condition has a positive test result to the probability that a person without the condition has positive test result. Positive Likelihood Ratio, LR+ = sensitivity/(1-specificity) See "likelihood ratio" and "negative likelihood ratio".
Positive Predictive Value (PPV)	Proportion of patients with a positive test result who have the disease = TP/(TP+FP)
Post micturition	Immediately after voiding when the bladder returns to storage function.
Post micturition dribble (PMD)	The term used when an individual describes the involuntary loss of urine immediately after he has finished passing urine, usually after leaving the toilet.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post void milking	Post void milking is a technique used to eliminate post micturition dribble (PMD) may be caused by the urethra being emptied

(PVM)	incompletely by the muscles surrounding it. This technique involves drawing the tips of the fingers behind the scrotum and pushing up and forward to expel the pooled urine.
Post-void residual urine (PVR)	The volume of urine left in the bladder immediately after voiding.
Preoperative	Pertaining to the period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product. A drug may be "licensed" for several conditions. When a drug is referred to as "unlicensed" for a particular indication, that means that the may have a marketing authorisation for other conditions, but not for the condition discussed. This is also known as "off label" use.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prompted voiding	Prompted voiding teaches people to initiate their own toileting through requests for help and positive reinforcement from carers. It has been used in institutionalised patients with cognitive and mobility problems. They are asked regularly if they wish to void and only assisted to the toilet when there is a positive response.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*.
Prostate specific antigen (PSA)	A protein produced by the cells of the prostate gland. It is often elevated in the presence of prostate cancer and in other prostate disorders. It has been suggested that serum PSA is correlated with prostate volume in men with LUTS and that it can therefore be used for this purpose in clinical decision-making in specialist practice, provided that prostatic cancer has been excluded.
Pyuria	The presence of pus cells (white blood cells) in the urine. This can be indicative of urine infection.
Qmax (maximum urinary flow rate)	The rate of urine flow is calculated as millilitres of urine passed per second (ml/s). At its peak, the flow rate measurement is recorded and referred to as the Qmax. The higher the Qmax, the better the patients flow rate.

Qualitative research	Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*.
Review of the literature	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Secondary benefits	Benefits resulting from a treatment in addition to the primary,

	intended outcome.
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis (SA)	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Slow stream	Reported by the individual as his perception of reduced urine flow, usually compared to previous performance or in comparison to others.
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of those without disease who have negative test results. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.

Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Storage	During which passive filling of the bladder occurs either naturally from urine produced by the kidneys or artificially during a urodynamic study.
Storage symptoms	Experienced during the storage or filling phase of the bladder, and include urgency, daytime frequency, incontinence and nocturia.
Stress urinary incontinence (SUI)	The complaint of involuntary leakage on effort or exertion or on sneezing or coughing.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Terminal dribble	A prolonged final part of micturition, when the flow has slowed to a trickle/dribble.
Timed voiding	Timed voiding (scheduled, routine or regular toileting) is a passive toileting assistance programme that is initiating and maintained by a care giver, e.g. for patients who cannot participate in independent toileting. Toileting is fixed by time or event, on a regular schedule to match the patient's voiding pattern.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Transurethral ethanol ablation of the prostate (TEAP)	Transurethral ethanol ablation of the prostate (TEAP) is chemical ablation of prostatic tissue using dehydrated ethanol. This results in the development of intraprostatic necrotic areas due to dehydration, protein degeneration and thrombotic closure of arterioles and venules. Delivery of absolute ethanol into the prostate can be achieved by injection via a transperineal, transrectal or transurethral route.

Transurethral resection of the prostate (TURP)	The removal of the prostate in pieces using electrocautery via the water pipe (urethra)
Transurethral vaporesection of the prostate (TUVRP)	Thick band-like loop electrode at high power used to remove prostate tissue in a similar manner to TURP but combining vapourisation and coagulation at the cutting edge.
Transurethral vapourisation of prostate (TUVP)	Utilizes the heat from high-voltage electric current to ablate prostatic tissue and seal blood vessels.
Transurethral needle ablation of prostate (TUNA)	Delivery of radio frequency energy, via a modified urethral catheter attached to a generator, to destroy (ablate) prostate tissue. Two adjustable needles located at the end of the catheter are inserted into the prostate under endoscopic control. The radio frequency waves generate ionic agitation of molecules within the prostate, which in turn produces a localised heating effect of up to 115°C, resulting in areas of tissue death.
Transurethral microwave thermotherapy (TUMT)	Microwave energy is used in transurethral microwave thermotherapy (TUMT), achieving temperatures of 45–70°C in the prostate depending on the device and power setting. Microwaves induce oscillation of water molecules causing heat generation and inducing death of prostatic tissue.
Transurethral incision of the prostate (TUIP)	Incision in one or both side of the urethra, from bladder neck to verumontanum, usually for men with small prostates.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Urgency	The complaint of 'a sudden compelling desire to pass urine which is difficult to defer'.
Urgency incontinence	Involuntary leakage accompanied by or immediately preceded by urgency
Urinalysis	A first line investigation that can be performed in any setting, using dipsticks that can be used to detect blood, sugar, protein, specific gravity and nitrites.
Urinary incontinence (UI)	The 'complaint of any involuntary urinary leakage'.
Urodynamics (UD)	The term 'urodynamics' encompasses a number of varied physiological tests of bladder and urethral function that aim to demonstrate the basis of an underlying abnormality of storage or voiding. The term is often used loosely to mean multichannel cystometry. See also cystometry and uroflowmetry. Videourodynamics involves synchronous radiographic screening of the lower urinary tract with multichannel cystometry, and is so called because originally the information was recorded to videotape. Ambulatory urodynamics involves multichannel cystometry carried out with physiological bladder filling rates

and using portable recording devices that enable the patient to move around more or less normally during the test.

Uroflowmetry Uroflowmetry entails voiding into a recording device that measures the volume of urine passed, and the rate of urine flow.

Utility A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

Vesico-urethral Relating to, or connecting the urinary bladder and the urethra.

Voiding The phase during which the bladder expels its contents.

Voiding symptoms Symptoms that occur during the voiding phase; previously called obstructive symptoms and include hesitancy, straining and poor urinary stream. See also straining, hesitancy and terminal dribble.

1 Introduction

1.1 What is a guideline?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guidelines Centre for Acute and Chronic conditions (NCGC)
- The NCGC establishes a guideline development group

- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence
- the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies
- the **quick reference guide** presents recommendations in a suitable format for health professionals
- information for the public (‘**understanding NICE guidance’**) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE www.NICE.org.uk.

1.2 The need for this guideline

Lower urinary tract symptoms (LUTS) are a collection of symptoms related to problems with the voiding, storage and post-micturition of urine. They generally arise as a result of abnormalities or inadequate functioning of the prostate, urethra, bladder or sphincters. The bladder is frequently said to be an ‘unreliable witness’ for a number of reasons. Firstly, lower urinary tract symptoms are not disease specific and diverse patho-physiologies can produce similar lower urinary tract symptoms. Secondly, patients describe symptoms in different ways and this is influenced both by what they feel and how they interpret the experience. Lastly, clinicians take histories in different ways and interpret the clinical picture based on their own experience and prejudices.

In men, benign prostate enlargement, which is secondary to benign prostatic hyperplasia and causes bladder outlet obstruction, is frequently considered to be the major cause of LUTS. However, many other conditions can cause LUTS, including detrusor muscle weakness or overactivity, prostatitis, urinary tract infection, malignancy and neurological disease. In acknowledgement of the non-specific nature of many male LUTS, this clinical guideline will advise on the effective evidence-based management of male LUTS in general, with a specific focus on LUTS associated with benign prostatic disease (presumed benign prostatic hyperplasia).

The International Continence Society (ICS) have categorised LUTS into 3 groups (Table 1-1) related to their timing within the bladder (filling and voiding) cycle. The 3 stages of the bladder cycle are:

- Storage - during which filling of the bladder occurs either naturally from urine produced by the kidneys or artificially during cystometry.

- Voiding - during which the bladder actively expels its contents.
- Post micturition - immediately after voiding when the bladder returns to storage function.

Table 1-1: Lower Urinary Tract Symptoms

Storage	Voiding	Post Micturition
• Urgency • Increased Daytime Frequency • Nocturia • Urinary Incontinence • Altered Bladder Sensations	• Hesitancy • Intermittency • Slow Stream • Splitting or Spraying • Straining • Terminal Dribble	• Feeling of incomplete emptying • Post micturition dribble

LUTS are a major burden for the ageing male population. Approximately 30% of men aged 50 and older have moderate to severe LUTS. This is a very large group potentially requiring treatment. Age is an important risk factor for LUTS and the prevalence of LUTS increases as men get older. Other risk factors include increased size of the prostate gland and bladder decompensation. Ethnicity may also be a risk factor: men of black origin seem to be more likely to need surgery for prostate enlargement than men of white origin. Men of Asian origin seem to be less likely than men of white origin to need surgery[153].

Because prevalence increases with age, the figure above will continue to rise with increasing life expectancy and the resulting growth of the elderly population. This will place increasing demands on health service resources in the coming years. The past 25 years have seen an increase in the use of pharmacotherapy for LUTS, with a considerable decline in surgical rates. Nevertheless, in England, for the year 2003–2004, there were almost 30,000 endoscopic resections of the male bladder outlet, accounting for more than 138,000 bed days. Although transurethral resection of the prostate is often effective in reducing symptoms in men, it is associated with considerable morbidity and a significant overall annual cost. In addition, a significant proportion of men (25–30%) do not benefit from prostatectomy and have poor post-surgical outcome with no improvement of symptoms. Some failures can be attributed to poor surgical technique, whereas others may be due to incorrect diagnosis of the cause of LUTS. Therefore, to minimise the number of unnecessary operations, predicting the outcome of transurethral resection of the prostate is important.

According to expert opinion, most UK clinicians carry out uroflowmetry and, in appropriate patients in secondary care, multichannel cystometry is done before surgical intervention in units with access to the equipment. However, experts agree that there is wide variation in clinical practice in the UK. This is due to individual clinicians' belief in the value of multichannel cystometry, and also due to staffing issues and access to the technology. There are many national and international guidelines concerned with the management of men with LUTS; however, these vary in quality. This NICE clinical guideline will address the variations in practice to allow equitable and appropriate treatment for all affected men.

1.3 The National Collaborating Centre for Acute Care/ National Clinical Guidelines Centre

This guideline was commissioned by NICE and developed by the National Collaborating Centre for Acute Care (NCC-AC). On 1st April 2009 the NCC-AC merged with 3 other collaborating centres to form the National Clinical Guidelines Centre for Acute and Cronic Conditions (NCGC). The development of this guideline was therefore started at the NCC-AC and completed at the NCGC. The centre is one of four centres funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work.

1.4 Remit

The following remits were received by the NCC-AC from the Department of Health as part of NICE's 14th and 16th wave programmes of work.

The Department of Health asked the Institute:

"To prepare a clinical guideline on the management of benign prostatic hyperplasia"

"To prepare a guideline on the assessment, investigation, management and onward referral of men with lower urinary tract symptoms (including male incontinence) within primary care."

It was agreed that due to the overlap of these two topics the NCC-AC would develop one guideline on lower urinary tract symptoms, which would cover the management of benign prostatic hyperplasia.

1.5 What the guideline covers

The guideline covers men (18 and over) with a clinical working diagnosis of LUTS. In addition, the guideline will cover men who have a higher prevalence of LUTS or may be at higher risk including older men and men who are of black origin. Options for conservative, pharmacological, surgical, and complementary or alternative treatments are considered in terms of clinical and cost effectiveness. Further details of the scope of the guideline can be found in Appendix A.

1.6 What the guideline does not cover

The guideline does not cover women or men under the age of 18 years.

1.7 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Collaborating Centre for Acute Care (NCC-AC) and latterly the National Clinical Guidelines Centre (NCGC) and thus supported the development of this guideline. The GDG was convened

by the NCC-AC and chaired by Professor Christopher Chapple in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCC-AC/ NCGC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the evidence and drafted the guideline. The glossary to the guideline contains definitions of terms used by staff and the GDG.

2 Methodology

2.1 Guideline methodology

The Male Lower Urinary Tract Symptoms (LUTS) guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The guidelines manual'[184]. The versions of the guideline manual used for each stage of guideline development are detailed in Table 2-2.

Table 2-2: Version of NICE guideline used

Stage of development	Version of NICE Guidelines Manual Used
Scope	April 2007
Formation of GDG	April 2007
Review of evidence and drafting of recommendations	April 2007 Pilot for GRADE
Consultation	January 2009[184]

2.2 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the review team and refined and validated by the guideline development group (GDG). The questions were based on the scope (Appendix A). Further information on the outcome measures examined follows this section.

2.2.1 Questions on diagnosis

The clinical questions were:

- What is the sensitivity and specificity of urinalysis to detect each relevant condition (diabetes, bladder cancer, UTI, stones, renal disease)?
- In men with LUTS, does performing a PSA test affect patient outcomes versus not performing the diagnostic test?
- In men with LUTS, does completing IPSS score affect patient outcomes (including futile treatment and missed treatment opportunities) versus not completing scores?
- In men with LUTS, what is the effectiveness of a DRE versus no DRE in changes to patient treatment/outcomes?

- In men with LUTS, what is the effectiveness of frequency volume chart versus no frequency volume chart in changes to patient treatment/outcomes?

- In men with LUTS, what is the effectiveness of urinary flow rate versus no urinary flow rate in relationship to patient treatment/outcomes?

- What is the sensitivity and specificity of a maximum urinary flow rate in predicting bladder outlet obstruction as defined by pressure flow studies in men with LUTS?

- In men with LUTS, what is the effectiveness of post void residual measurement versus no post void residual measurement in relationship to patient treatment/outcomes?

- What is the sensitivity and specificity of post void residual measurement in predicting urodynamic diagnosis as defined by pressure flow studies in men with LUTS?

- In men with LUTS, what is the effectiveness of performing multichannel cystometry tests versus not performing the diagnostic test?

- In men with LUTS how does performing cystoscopy affect patient outcomes versus not performing the diagnostic test?

- In men with LUTS how does performing transabdominal ultrasound affect patient outcomes versus not performing the diagnostic test?

- In men with LUTS how does measuring renal function affect patient outcomes versus not performing the diagnostic test?

- In men with LUTS how does measuring incontinence (pad test) affect patient outcomes versus not performing the diagnostic test?

- In men with LUTS how does performing plain abdominal x-ray affect patient outcomes versus not performing the diagnostic test?

- In men with LUTS how does performing intravenous urogram affect patient outcomes versus not performing the diagnostic test?

2.2.2 Questions on prognosis

- How does baseline PSA predict symptom progression?

2.2.3 Questions on monitoring

- In men with LUTS who are not on treatment, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

- In men with LUTS who take alpha blockers, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

- In men with LUTS who take 5-alpha reductase inhibitors, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

- In men with LUTS who take anticholinergics, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

- In men with LUTS who take phosphodiesterase 5 inhibitors, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

- In men with LUTS who take combination therapy, what are the most clinically effective and cost effective recall intervals for detecting progression of symptoms?

2.2.4 Questions on conservative interventions

- In men who report LUTS, what is the effect of pelvic floor muscle training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of electrical stimulation or biofeedback with or without pelvic floor muscle training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of bladder training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of post void milking versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of timing of fluid intake versus no change in timing of fluid intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of reducing alcohol / caffeine / artificial sweeteners / carbonated drink intake versus no reduction in their intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of one type of product versus no product or other conservative therapy on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of intermittent catheters compared to indwelling catheters on patient related and biometric outcomes and adverse events?

- In men who report LUTS, what is the effect of acupuncture versus no acupuncture or other conservative therapy on patient related and biometric outcomes and adverse events?

2.2.5 Questions on medical and surgical interventions

These questions aimed to determine which are the most effective pharmacological, laser and non-laser surgical treatments for men with lower urinary tract symptoms. They included:

- What is the effectiveness and comparative effectiveness of medications in reducing symptoms for managing lower urinary tract symptoms?
- What is the effectiveness of alpha blockers in treating men after acute urinary retention?
- In all patients associated with LUTS what is the effectiveness and comparative effectiveness of surgery in reducing LUTS?
- What is the effectiveness of medications compared to surgical therapies in managing LUTS?
- What is the effectiveness of medications compared to conservative therapies in managing LUTS?

2.2.6 Question on provision of information

- Does provision of information about management of LUTS improve patient outcomes?

2.2.7 Questions on complementary and alternative medicines

- What is the effectiveness of complementary and alternative therapies in managing LUTS?

2.3 Patients covered by this guideline

We searched for studies of adult men (age 18 years and older) with lower urinary tract symptoms.

2.4 Outcomes

2.4.1 Diagnostic test accuracy outcomes

The accuracy outcomes reported in this guideline are:

- Specificity
- Sensitivity
- Likelihood ratios
- Pre and post test probabilities

- Negative predictive value (NPV) and positive predictive value (PPV)

Some of these outcomes (when not reported in the papers) were calculated by the NCGC team based on the data presented in the papers.

2.4.2 Prognostic outcomes

The main outcome considered for prognostic studies was:

- Correlation of PSA at baseline with IPSS at follow up

If these were not available, we also looked for the differences in IPSS at follow up for groups with different baseline PSA levels where the population was similar in other aspects (e.g. placebo arm of randomised controlled trials)

2.4.3 Clinical effectiveness of interventions and outcomes of some diagnostic tests:

We looked for the following primary outcomes in all questions related to clinical-effectiveness of interventions:

- Symptom scores (validated scores of International Prostate Symptom Score (IPSS) or the American Urological Association (AUA) Symptom Score were used)
- Quality of life question included from the IPSS score
- Maximum urinary flow rate (Qmax)
- Incontinence episodes

The GDG decided that to assess effectiveness of pharmacological treatments a minimum of 1 month follow up would be required for all the interventions except for 5-alpha reductase inhibitors which would require 3 months.

The GDG decided that to assess effectiveness of surgical treatments a minimum of 3 months follow up would be required since in practice they would not consider a treatment a success unless it had been shown to be effective over at least this period.

We looked for the following secondary outcomes:

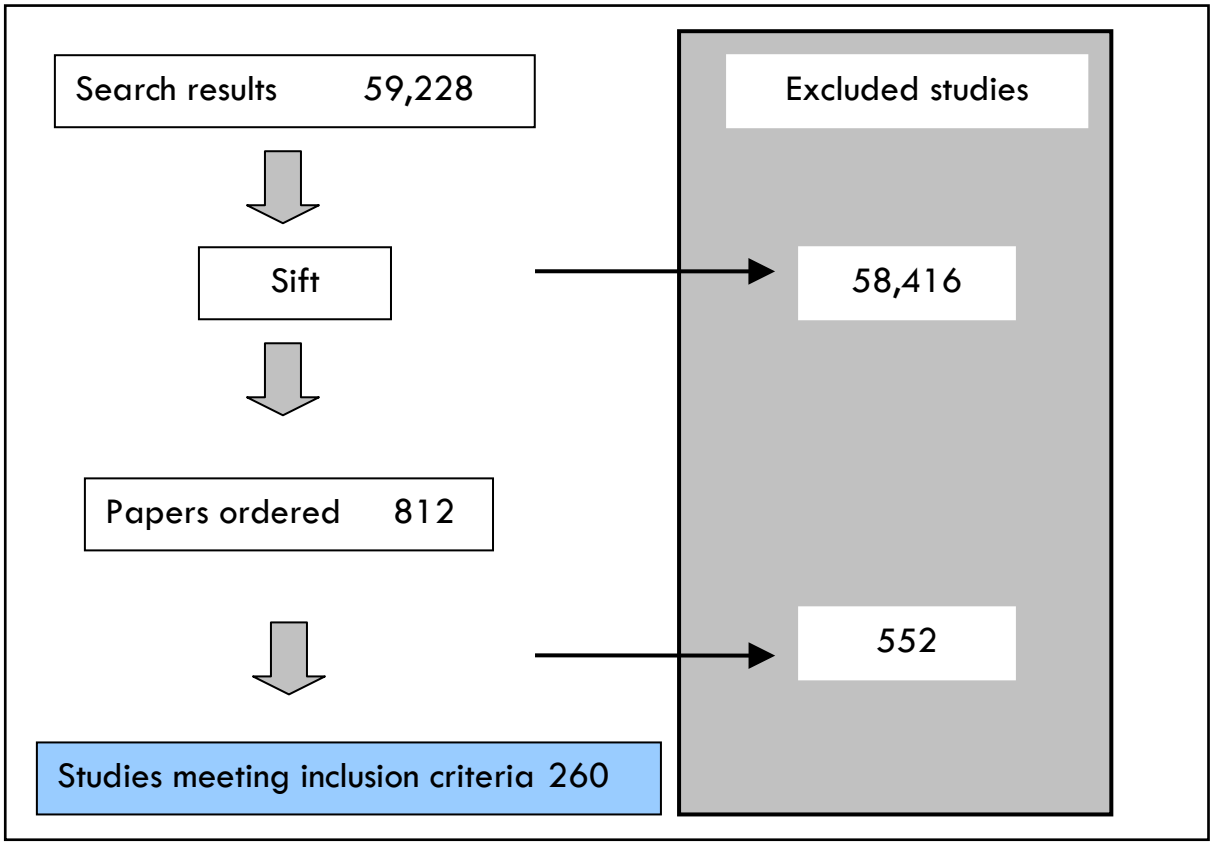
- Adverse events. These include sexual adverse events (impotence or erectile dysfunction, ejaculatory disorders, gynaecomastia or breast enlargement, decreased libido), urological events (urinary retention), and other adverse events relevant to the interventions considered (postural hypotension, vertigo, syncope, dry mouth, constipation, diarrhoea, dizziness, headache, fatigue, somnolence). Adverse events specific to surgical procedures were incontinence, Strictures, transurethral resection (TUR) syndrome, blood transfusions, re-operation rates, and all cause mortality
- Patient views for diagnostic studies and conservative interventions.

2.5 Literature search

2.5.1 Clinical literature search

The aim of the literature search was to find 'evidence within the published literature,' to answer the clinical questions identified. We searched clinical databases using relevant medical subject headings and free-text terms. Search filters were used to limit searches to particular study types where applicable. Non-English language studies and abstracts were not excluded from the search but the articles were not reviewed.

We performed initial searches for each section when the literature was needed for the review. Each search was updated twice nearer the end of guideline development period: once at the beginning of April and then finally, 17 June 2009. No papers after this date were considered.



The search strategies can be found in Appendix C.

The following databases were searched:

- The Cochrane Library up to Issue 2 2009
- Medline 1950-2009 (OVID)
- Embase 1980-2009 (OVID)

- Cinahl 1982-2009 (Dialog Datastar, later NLH Search 2.0, update searches in EBSCO) - searched for questions relating to patient education and views only.

- PsycINFO 1800s-2009 (NLH Search 2.0, update searches in Ovid) - searched for questions relating to patient education and views only.

There was no systematic attempt to search for grey literature or unpublished literature although all stakeholder references were followed up. We searched for guidelines and reports via relevant urological websites including those listed below.

- Constituent websites of the Guidelines International Network (www.g-i-n.net)

- National Guideline Clearing House (www.guideline.gov/)

- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)

- National Institutes of Health Consensus Development Program (consensus.nih.gov/)

- National Library for Health (www.library.nhs.uk/)

The results of the searches with the final number of studies meeting the inclusion criteria for the clinical questions are shown in the diagram above.

2.5.2 Economic literature search

We obtained published economic evidence from a systematic search of the following databases:

- The Cochrane Library up to Issue 3 2008

- Medline 1950-2009 (OVID)

- Embase 1980-2009 (OVID)

- Health economic and evaluations database (HEED) up to August 2008 (access was no longer available after that date).

The information specialists used the same search strategy as for the clinical questions, using an economics filter in the place of a systematic review or randomised controlled trial filter. Each database was searched from its start. Each search was updated twice nearer the end of guideline development period: once at the beginning of April and then finally, 17 June 2009. Papers identified after this date were not considered. Search strategies can be found in Appendix C.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of an included intervention, quality of life literature and literature relating to economic modelling. A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

2.6 Assessing quality of evidence

Two stages of quality assessment were conducted. At the first stage, studies found through the systematic search are quality assessed and only included in the review and

meta-analysis if they met some or all of the quality criteria. Data from these studies are then extracted and the outcomes of interest are then pooled. At the second stage, the quality of evidence for each of these outcomes is then quality assessed using elements of the GRADE system.

2.6.1 Quality assessment for inclusion of studies

All studies are quality assessed before being included as part of the systematic review. The criteria for assessment for different types of studies are listed below.

2.6.1.1 Diagnosis

To grade individual studies according to diagnostic accuracy we used the hierarchy of evidence recommended in the Guidelines Manual April 2007 which was developed by NICE using 'The Oxford Centre for Evidence-based Medicine Levels of Evidence' (2001) and the Centre for reviews and Dissemination 'Report Number 4 (2001)[182]. See Table 2-3 below.

We included studies applying both tests (the test of interest and the reference standard) to a consecutive group of patients to answer clinical questions on diagnostic accuracy. Studies included were randomised controlled trials or cross-sectional studies.

Table 2-3: Levels of evidence for studies of accuracy of diagnostic tests (reproduced by kind permission from the NICE guidelines manual (April 2007))

Level of evidence	*Type of evidence*
1a	Systematic review with homogeneity (a) of level-1 studies (b)
1b	Level-1 studies (b)
II	Level-2 studies (c) Systematic reviews of level-2 studies
III	Level-3 studies (d) Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

(a) Homogeneity indicates there are no or minor variations in the directions and degrees of results between individual studies included in the systematic review

(b) Level-1 studies:
1. Use a blind comparison of the test with a reference standard (gold standard)
2. Are conducted in a sample of patients that reflects the population to whom the test would apply

(c) Level-2 studies have only **one** of the following:
1. Narrow population (sample does not reflect the population to whom the test would apply)
2. A poor reference standard (where tests are not independent)
3. The comparison between the test and reference standard is not masked
4. A case-control study design

(d) Level-3 studies have **two** or **three** of the above features

2.6.1.2 Prognosis

Prospective cohort studies were included for the prognostic questions. We also considered data from the placebo arm of randomised controlled trials which analysed the link between PSA level at baseline and the IPSS outcomes at the study end points.

The prospective cohort studies' quality was assessed using the quality checklist in the NICE Guidelines Manual April 2007[182]. The main criteria considered in assessing study quality were:

- An appropriate and clearly focused question was addressed
- The cohort(s) being studied are selected from source populations that are comparable in all respects other than the factor under investigation
- The inclusion or participation rate was reported
- The likelihood that some eligible subjects might have the outcome at the time of enrolment assessed had been taken into account in the analysis
- The drop out rate was reported and acceptable
- Comparison by the prognostic status is made between participants who completed the study and those lost to follow up
- The outcomes were clearly defined
- The assessment of outcome was blind to exposure status or acknowledged where this was not possible
- The methods of assessment used for the prognostic factor and the outcomes were valid and reliable
- The main potential confounders are identified and taken into account adequately in the design and analysis
- Confidence intervals or standard deviation were provided

2.6.1.3 Intervention and monitoring studies

For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta-analysis or randomised (double blinded) controlled trial was identified, we did not search for studies of a weaker design. The quality assessment criteria as listed in the NICE Guidelines Manual 2007 were used to assess systematic reviews, meta-analysis, and randomised controlled trials.

For systematic reviews and meta-analysis, the main criteria considered were:

- An appropriate and clearly focused question was addressed
- Methodology was well described
- The literature search was sufficiently robust to identify all the relevant studies
- The individual study quality included in the review was assessed and taken into account
- The studies were sufficiently similar to make combining them reasonable

For randomised controlled trials, the main criteria considered were:

- An appropriate and clearly focused question was addressed
- Appropriate randomisation allocation and concealment methods were used
- Subjects, investigators and outcomes assessors were masked about treatment allocation
- The intervention and control groups are similar at baseline
- The only difference between group is the type of intervention received
- All outcomes are measured in a standard and reliable method
- Drop out rates reported and are acceptable, and all participants are analysed in the groups to which they were randomly allocated the treatment
- For multi-centred trials, results are comparable between sites

Only studies which fulfilled some to all of the criteria included were included in the evidence review.

2.6.2 GRADE (Grading of Recommendations Assessment, Development and Evaluation)

The evidence for outcomes from studies which passed the quality assessment were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess pooled outcome data using individual study quality assessments and results from meta-analysis.

The summary of findings was presented as two separate tables in this guideline. The "Clinical Study Characteristics" table includes details of the quality assessment while the "Clinical Summary of Findings" table includes pooled outcome data, an absolute measure of intervention effect calculated and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate pooled sample size for continuous outcomess. For binary outcomes such as number of patients with an adverse event, the event rates (n/N) are shown with percentages. Reporting or publication bias was considered in the quality assessment but not included in the Clinical Study Characteristics table because this was a rare reason for downgrading an outcome in this guideline.

Each outcome was examined separately for the quality elements listed and defined in Table 2-4 and each graded using the quality levels listed in Table 2-5. The main criteria considered in the rating of these elements are discussed in the literature reviewing process (see section 2.9 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. Then, an overall quality of evidence for each outcome was applied by selecting from the options listed in Table 2-6.

The GRADE toolbox is currently designed only for randomised controlled trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Table 2-4: Descriptions of quality elements in GRADE

Quality element	*Description*
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the clinical question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2-5: Levels for quality elements in GRADE

Level	*Description*
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 2-6: Overall quality of outcome evidence in GRADE

Level	*Description*
High	Further research is *very unlikely* to change our confidence in the *estimate of effect*
Moderate	Further research is *likely* to have an important impact on our confidence in the *estimate of effect* and may change the estimate
Low	Further research is *very likely* to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	*Any estimate of effect is very uncertain*

2.6.3 NICE Economic Profile

Since GRADE was not originally designed for economic evidence, the NICE economic profile has been used to present cost and cost-effectiveness estimates from published

studies or analyses conducted for the guideline. As for the clinical evidence, the economic evidence has separate tables for the quality assessment and for the summary of results. The quality assessment is based on two criteria – limitations and applicability (Table 2-7) and each criterion is graded using the levels in Table 2-8 and Table 2-9.

Table 2-7: Description of quality elements for economic evidence in NICE economic profile

Quality element	*Description*
Limitations	This criterion relates to the methodological quality of cost, cost-effectiveness or net benefit estimates.
Applicability	This criterion relates to the relevance of the study to the specific guideline question and NICE Reference Case.

Table 2-8: Levels for limitations for economic evidence in NICE economic profile

Level	*Description*
Minor limitations	The study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.
Serious limitations	The study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness
Very serious limitations	The study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.

Table 2-9: Levels for applicability for economic evidence in NICE economic profile

Level	*Description*
Directly applicable	The applicability criteria are met, or one or more criteria are not met but this is not likely to change the cost-effectiveness conclusions.
Partially applicable	One or more of the applicability criteria are not met, and this might possibly change the cost-effectiveness conclusions.
Not applicable	One or more of the applicability criteria are not met, and this is likely to change the cost-effectiveness conclusions.

An overall score of the evidence is not given as it is not clear how the quality elements could be summarised into a single quality rating.

A summary of results is presented for each study including:

- incremental cost
- incremental effectiveness
- incremental cost-effectiveness ratio
- uncertainty

2.7 Literature reviewing process

2.7.1 Clinical literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more of the outcomes listed in section 2.4. Selected studies were ordered and assessed in full by the NCGC team using agreed inclusion/exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design[182]. Further references suggested by the guideline development group were assessed in the same way.

2.7.2 Economic literature reviewing process

Economic studies identified in the systematic search were excluded from the review if:

- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper)
- The study population did not comply with the inclusion criteria as established in the clinical effectiveness review methods
- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios)
- The study was a non-UK cost-analysis
- The study was a letter or written in a foreign language

Included papers were reviewed by a health economist. In the evidence tables, costs are reported as in the paper. However, where costs were in a currency other than pounds sterling, the results were converted into pounds sterling using the appropriate purchasing power parity for the study year.

We have included studies from all over the world in our review, however, we use overseas studies with caution since resource use and especially unit costs vary considerably. Particular caution is applied to studies with predominantly private health insurance (for example, USA or Switzerland) where unit costs may be much higher than in the UK and to developing countries where costs may be much lower.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost–utility analysis (that is, cost–effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We found one 'cost benefit analysis' (study that puts a monetary value on health gain) but it was not included for methodological reasons.

Models are analogous to systematic reviews because they pool evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in

economic GRADE tables, evidence tables and write-up may not necessarily imply statistical significance.

2.7.3 Cost-effectiveness modelling

The details of the economic models are described in Appendix F.

2.8 Methods of combining studies

Where possible, meta-analyses were conducted to combine the results of studies for each clinical question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: number of incontinent patients or adverse events, and the continuous outcome for endpoint or change from baseline IPSS score, QOL question from IPSS score and Qmax was analysed using an inverse variance method for pooling weighted mean differences. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.05$ or an I-squared inconsistency statistic of $\geq 50\%$ to indicate significant heterogeneity.

Where significant heterogeneity was present we carried out predefined subgroup analyses for: the severity or main type of symptoms experienced by participants recruited into the studies, treatment protocols and length of follow-up. Sensitivity analysis based on the quality of studies was also carried out if there were differences (e.g. open label vs. masked studies). Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The standard deviations of continuous outcomes were required for imputation for meta-analysis. However, this was not reported in many studies. In such cases, calculation based on methods outlined in section 7.7.3 of the Cochrane Handbook (February 2008) 'Data extraction for continuous outcomes' were applied to estimate the standard deviations if p values of the difference between two means, 95% confidence intervals or standard error of the mean (SEM) had been reported[96]. Where p values were reported as "less than", a conservative approach was undertaken. For example, if p value was reported as "$p \leq 0.001$", the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (February 2008) 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

2.9 Grading of quality of evidence for outcomes

After results were pooled, the overall quality of evidence for each outcome was considered using the GRADE system. The following is the procedure adopted when using GRADE

1. The evidence for all outcomes start with a HIGH quality rating as only RCTs were considered.

2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below.

3. The downgrade marks are then summed. Each quality element being considered as having "serious" or "very serious" risk of bias were rated down -1 or -2 points respectively. All studies started as HIGH and the quality became MODERATE, LOW or VERY LOW when 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes whenever possible.

The details of criteria used for each of the main quality element are discussed further in the following sections 2.9.1 to 2.9.4.

2.9.1 Study limitations

The main limitations considered are listed in the following table. The GDG accepted that investigator blinding in surgical intervention studies was impossible and participant blinding was also impossible to achieve in most situations. Nevertheless, open-label studies for surgery were downgraded to maintain a consistency in quality rating across the guideline and the recognition that most of the important outcomes considered were subjective or patient reported (IPSS, IPSS-QoL, adverse events) and therefore highly subjected to bias in an open label setting. Table 2-10 listed the limitations considered for randomised controlled trials.

Table 2-10: Study limitations of randomised controlled trials

Limitation	*Explanation*
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • carry-over effects in cross-over trials • recruitment bias in cluster-randomised trials

2.9.2 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.05$ or I square $>50\%$), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. On top of the I-square and Chi square values the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. In this situation, the quality of evidence would not be downgraded.

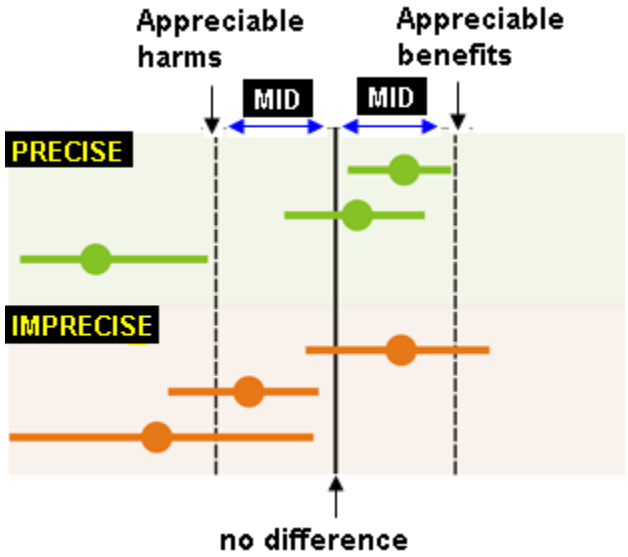
2.9.3 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. It was also looked at carefully in surgical intervention procedures where the specific technique used and local protocol may affect the outcomes (e.g. blood transfusions). This rating was reevaluated when recommendations had been made, for example, an outcome based on studies limited to patients with large prostates were downgraded during review but no longer downgraded when recommendation specific to patients with large prostates were made.

2.9.4 Imprecision

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered. Where the minimal important difference (MID) of an outcome is known, the optimal information size (OIS), i.e. the sample size required to detect the difference with 80% power and $p \leq 0.05$ was calculated and used as the criteria. The criteria applied for imprecision are based on the confidence intervals for pooled outcomes as illustrated in Figure 2-1 and outlined in Table 2-11.

Figure 2-1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results. Figure adapted from GRADEPro software.

Table 2-11: Criteria applied to determine precision

Criteria for downgrading an outcome for imprecision
1. Total (cumulative) sample size is lower than the calculated optimal information size (OIS).
2. 95% confidence interval crosses the minimal important difference (MID), either for benefit of harm. If the MID is not known or the use of different outcomes measures required calculation of a standardised mean difference(SMD), the outcome will be considered for downgrading if the upper or lower confidence limit crosses a SMD of 0.5 in either direction. For dichotomous outcomes, GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk of less than 0.75 (for risk reduction) or relative risk greater than 1.25 (for risk increase).

The following are the MID for the outcomes and the methods used to calculate the OIS in this guideline.

(a) IPSS/AUA -7: The MID used was 3 points, based on a study which found a change of 3 points was correlated with “slight” improvement, 5 points corresponded to “moderate” improvement and 8 points related to “marked” improvement (as reported by the patients) [21]. The SD used for the OIS calculation was 5, based on the SD observed in the study and as observed in the larger studies we reviewed. Based on these assumptions, the OIS was 90, ie 45 participants per treatment arm.

(b) IPSS-QoL: Unlike IPSS, there were no studies evaluating the MID for this question. Some phytotherapy studies had used the change of 1 point as the MID but the reasons for choosing this value was not explained[37,243]. In this guideline, 0.5 point was chosen based on the following considerations which all converged on this figure:

- In other well studied questions with similar 7 point Likert scales, the MIDs are usually around 0.5 [211]
- The rule of thumb that the MID is approximately 0.5 of the standard deviation[211]
- The rule of thumb that the MID is approximately one standard error of measurement[211]

Based on these assumptions, the OIS was estimated as 128, i.e. 64 participants per treatment arm.

(c) QMax: The minimal clinical difference was unknown from the patient's perspective. A consensus during a GDG meeting suggested that a change of 2ml/s is usually considered as important enough to guide treatment decision. A standard deviation of 4 ml/s was taken from the power calculation used in Van Melick et al., 2003 which compared laser surgeries against TUVRP and TURP[258]. Based on these assumptions, the OIS was estimated as 126, ie 63 participants per treatment arm.

2.10 Development of the recommendations

Over the course of the guideline development process, the GDG was presented with the following:

- Evidence tables of the clinical and economic evidence reviewed. All evidence tables are in appendix D
- Summary of clinical evidence and quality (as presented in section write ups)
- Forest plots of meta-analyses (appendix E)
- A description of the methods and results of the cost-effectiveness analysis (appendix F)

Recommendations were drafted on the basis of this evidence whenever it was available.

When clinical and economic evidence was poor or absent, the GDG drafted recommendations based on their expert opinion.

The GDG added supporting recommendations whenever it was necessary in order to improve clinical practice. The supporting recommendations were not derived from clinical questions and were based on GDG expert opinion.

The development of the recommendations required several steps:

- Whenever possible, a preliminary draft recommendation was presented by NCGC staff after each summary of evidence presentation during GDG meetings. This draft was discussed and modified by the group to form the first draft recommendation.

- Where necessary, NCGC staff suggested modifications to the draft recommendations as a result of the discussion and in the light of NICE guidance on writing recommendations.

- Towards the end of the guideline development process, a list of all the draft recommendations was sent to the GDG members. The GDG members independently completed a consensus exercise to feedback comments and level of agreement on each recommendation. This procedure allowed the NCGC to verify the level of agreement between the GDG members.

- All GDG feedback was collated and circulated again to the GDG. The recommendations which did not have unanimous agreement were discussed again during a GDG meeting before being finalised.

- During the writing up phase of the guideline, the GDG could further refine each recommendation working in subgroups on each chapter.

- NCGC staff verified the consistency of all recommendations across the guideline.

The GDG then developed care pathway algorithms according to the recommendations.

2.11 Research Recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

2.12 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- have a high impact on outcomes that are important to patients
- have a high impact on reducing variation in care and outcomes
- lead to a more efficient use of NHS resources

- promote patient choice
- promote equalities

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Relates to an intervention that is not part of routine care
- Requires changes in service delivery
- Requires retraining staff or the development of new skills and competencies
- Highlights the need for practice to change
- Affects and needs to be implemented across various agencies or settings (complex interactions)
- May be viewed as potentially contentious, or difficult to implement for other reasons

2.13 Validation of the guideline

The first draft of this guideline will be posted on the NICE website for consultation between 28th August – 23rd October 2009 and registered stakeholders were invited to comment. The GDG will respond to comments and an amended version of the guideline will be produced.

2.14 Related NICE guidance

NICE has developed/is developing the following guidance (details available from www.nice.org.uk):

- Urinary incontinence: the management of urinary incontinence in women. NICE clinical guideline 40 (2006)
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005)
- Prostate cancer: diagnosis and treatment. NICE clinical guideline 58 (2008).
- Potassium-titanyl-phosphate (KTP) laser vapourisation of the prostate for benign prostatic obstruction. NICE interventional procedure guidance 120 (2005)
- Holmium laser prostatectomy. NICE interventional procedure guidance 17 (2003)
- Transurethral radiofrequency needle ablation of the prostate. NICE interventional procedure guidance 15 (2003)
- Transurethral electrovapourisation of the prostate. NICE interventional procedure guidance 14 (2003).

- Laparoscopic prostatectomy for benign prostatic obstruction. NICE interventional procedure guidance 275 (2008).

- Insertion of extraurethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in men. NICE interventional procedure guidance 224 (2007).

- Suburethral synthetic sling insertion for stress urinay incontinence in men. NICE interventional procedure guidance 256 (2008).

2.15 Updating the guideline

This guideline will be updated when appropriate. The decision to update will balance the need to reflect changes in the evidence against the need for stability, as frequent changes to the recommendations would make implementation difficult. We check for new evidence three years after publication, to decide whether all or part of the guideline should be updated. In exceptional circumstances, if important new evidence is published at other times, we may conduct a more rapid update of some recommendations. Any update will follow the methodology outlined in the NICE guidelines manual[184].

3 Summary of recommendations

Below are the recommendations that the GDG selected as the key priorities for implementation followed by the complete list of recommendations and research recommendations.

3.1 Key priorities for implementation

The GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients (**A**)
- Have a high impact on reducing variation in care and outcomes (**B**)
- Lead to a more efficient use of NHS resources (**C**)
- Promote patient choice (**D**)
- Promote equalities (**E**).

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Relates to an intervention that is not part of routine care (**U**)
- Requires changes in service delivery (**V**)
- Requires retraining staff or the development of new skills and competencies (**W**)
- Highlights the need for practice to change (**X**)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (**Y**)
- May be viewed as potentially contentious, or difficult to implement for other reasons (**Z**).

The following recommendations were selected as being key priorities for implementation. For each key recommendation, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.

- At initial assessment, offer men with LUTS an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.

(Selection criteria: A, B, C, F. Implementation support: W)

- At initial assessment, offer men with LUTS a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a digital rectal examination (DRE).

(Selection criteria: A, B, C, F.)

- At initial assessment, ask men with bothersome LUTS to complete a urinary frequency volume chart.

(Selection criteria: B, C, F. Implementation support: X)

- Refer men for specialist assessment if they have LUTS complicated by recurrent or persistent urinary tract infection, retention, renal impairment that is suspected to be caused by lower urinary tract dysfunction, or suspected urological cancer.

(Selection criteria: A, B, F. Implementation support: Y)

- Offer men with urinary incontinence management (for example, pads or collecting devices) to achieve social continence until a diagnosis and management plan has been discussed.

(Selection criteria: A, B, D. Implementation support: W, X, Y, Z.)

- Offer men with storage LUTS suggestive of overactive bladder (OAB) supervised bladder training, advice on fluid intake, lifestyle advice and, if needed, containment products.

(Selection criteria: A, B, C, D, F. Implementation support: W, X, Y.)

- If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a centre specialising in the technique.

(Selection criteria: A, B, C. Implementation support: X, Z.)

- If offering surgery for managing voiding LUTS presumed secondary to BPE, do not offer minimally invasive treatments (including transurethral needle ablation [TUNA], transurethral microwave thermotherapy [TUMT], high-intensity focused ultrasound [HIFU], transurethral ethanol ablation of the prostate [TEAP] and laser coagulation) as an alternative to TURP, TUVP or HoLEP.

(Selection criteria: A, B, C. Implementation support: W, Z.)

- Ensure men with LUTS have access to care that can help with:
  - their emotional and physical conditions and
  - relevant physical, emotional, psychological, sexual and social issues.

- Provide men with LUTS maintenance products at point of need and access to relevant support groups.

(Selection criteria: A, B, C, D, E. Implementation support: W, Y.)

3.2 Complete list of recommendations

3.2.1 Recommendations on diagnosis

Initial assessment:

- At initial assessment, offer men with LUTS an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.

- At initial assessment, offer men with LUTS a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a digital rectal examination (DRE).

- At initial assessment, ask men with bothersome LUTS to complete a urinary frequency volume chart.

- At initial assessment, offer men with LUTS a urine dipstick test to detect blood, glucose, protein, leucocytes and nitrites in the urine.

- At initial assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:

  - their LUTS are suggestive of bladder outlet obstruction secondary to BPE or
  - their prostate feels abnormal on DRE or
  - they are concerned about prostate cancer.

- Manage suspected prostate cancer in men with LUTS in line with 'Prostate cancer: diagnosis and management' (NICE clinical guideline 58) and 'Referral guidelines for suspected cancer' (NICE clinical guideline 27).

- At initial assessment, offer men with LUTS a serum creatinine test only if there are any indications of renal impairment (for example, palpable bladder, nocturnal enuresis, recurrent urinary tract infection or history of renal stones).

- Do not offer cystoscopy to men with uncomplicated LUTS (that is, without evidence of bladder abnormality) at initial assessment.

- Do not offer imaging of the upper urinary tract to men with uncomplicated LUTS at initial assessment.

- Do not offer flow-rate measurement to men with LUTS at initial assessment.

- Do not offer a post void residual volume measurement to men with LUTS at initial assessment.

- At initial assessment, give reassurance, offer advice on lifestyle interventions (for example, fluid intake) and information on their condition to men whose LUTS are not bothersome or complicated. Offer review if symptoms change.

- Refer men for specialist assessment if they have bothersome LUTS that have not responded to conservative management or drug treatment.

- Refer men for specialist assessment if they have LUTS complicated by recurrent or persistent urinary tract infection, retention, renal impairment that is suspected to be caused by lower urinary tract dysfunction, or suspected urological cancer.

- Offer men considering any treatment for LUTS an assessment of their baseline symptoms with a validated symptom score (for example, the International Prostate Symptom Score [IPSS]).

Specialist assessment:

- Offer men with LUTS having specialist assessment an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.

- Offer men with LUTS having specialist assessment a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a DRE.

- Ask men with LUTS to complete a urinary frequency volume chart at specialist assessment.

- At specialist assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:
  - their LUTS are suggestive of bladder outlet obstruction secondary to BPE or
  - their prostate feels abnormal on DRE or
  - they are concerned about prostate cancer.

- Offer cystoscopy to men with LUTS having specialist assessment only when clinically indicated, for example if there is a history of any of the following:
  - recurrent infection
  - sterile pyuria

- haematuria
- profound symptoms
- pain.

➢ Offer imaging of the upper urinary tract to men with LUTS having specialist assessment only when clinically indicated, for example, if there is a history of any of the following:

- chronic retention
- haematuria
- recurrent infection
- sterile pyuria
- profound symptoms
- pain.

➢ Offer men with LUTS who are having specialist assessment a measurement of flow rate and post void residual volume.

➢ Consider offering multichannel cystometry for men with LUTS who are considering surgery.

➢ Offer pad tests to men having specialist assessment only if the degree of urinary incontinence needs to be measured.

3.2.2 Recommendations on conservative management

➢ Explain to men with post micturition dribble how to perform urethral milking.

➢ Offer men with urinary incontinence management (for example, pads or collecting devices) to achieve social continence until a diagnosis and management plan has been discussed.

➢ Offer a choice of containment products to manage urinary incontinence based on individual circumstances and in consultation with the man.

➢ Offer men with storage LUTS suggestive of overactive bladder (OAB) supervised bladder training, advice on fluid intake, lifestyle advice and, if needed, containment products.

➢ Inform men with LUTS and proven bladder outlet obstruction that bladder training is less effective than surgery.

➢ Offer supervised pelvic floor muscle training to men with stress urinary incontinence caused by prostatectomy. Advise them to continue the exercises for at least 3 months before considering other options.

➢ Refer for specialist assessment men with stress urinary incontinence arising from causes other than prostatectomy (for example, radiotherapy or pelvic fracture urethral distraction injuries).

- Consider permanent use of absorbent products for men with LUTS only after assessment and exclusion of other methods of management.

- Do not routinely offer penile clamps to men with urinary incontinence.

- Consider offering sheath appliances for managing urinary incontinence in men if there is no indication for indwelling catheterisation.

- Consider offering bladder catheterisation (intermittent or indwelling urethral or suprapubic) to men with LUTS that cannot otherwise be corrected by less invasive measures such as external collection devices (for example, pubic pressure urinal, sheath appliances).

- Consider offering long-term indwelling urethral catheterisation to men:
  - for whom surgery is not appropriate
  - who are unable to manage intermittent self-catheterisation
  - with skin wounds, pressure ulcers or irritation that are being contaminated by urine
  - who are distressed by bed and clothing changes
  - who express a preference for this form of management.

- If offering long-term indwelling catheterisation, discuss the practicalities, benefits and risks with the man and, if appropriate, his carer.

- Explain to men that indwelling catheters for urgency incontinence may not result in continence or the relief of recurrent infections.

- Consider offering indwelling suprapubic catheters as an alternative to long-term urethral catheters.

3.2.3 Recommendations on drug treatment

- Offer men with bothersome LUTS drug treatment only when conservative management options have been unsuccessful or are not appropriate.

- Take into account comorbidities and current treatment when offering men drug treatment for LUTS.

- Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS.

- Offer an anticholinergic to men to manage the symptoms of OAB.

- Offer a 5-alpha reductase inhibitor to men with LUTS who have prostates estimated to be larger than 30 g or PSA greater than1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men).

- Consider offering a combination of an alpha blocker and a 5-alpha reductase inhibitor to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or PSA greater than 1.4 ng/ml.

- Consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker alone.

- Consider offering a late afternoon diuretic[a] for men with nocturnal polyuria.

- Consider offering oral desmopressin[b] for men with nocturnal polyuria if they have not benefited from other treatments. Measure serum sodium at 3 days after the first dose.

3.2.4 Recommendations on review

- Review men taking alpha blockers at 4-6 weeks and then every 6-12 months.

- Review men taking 5–alpha reductase inhibitors at 3-6 months and then every 6-12 months.

- Review men taking anticholinergics every 4-6 weeks until stable, and then every 6-12 months.

- Review men taking an alpha blocker and a 5-alpha reductase inhibitor at 4-6 weeks and then every 6-12 months.

- Review men taking an anticholinergic and an alpha blocker at 4-6 weeks until stable, and then every 6-12 months.

- Discuss active surveillance (reassurance and lifestyle advice without immediate treatment and with regular follow-up) or active intervention (conservative management, drug treatment or surgery) for:
  - men with mild or moderate bothersome LUTS
  - men whose LUTS fail to respond to drug treatment.

3.2.5 Recommendations on surgery for voiding symptoms

- Offer surgery only to men with severe voiding symptoms, or men with voiding symptoms for whom drug treatment and conservative management options have been unsuccessful or are not appropriate. Discuss the alternatives to and outcomes from surgery.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a centre specialising in the technique.

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[a] At the time of publication (July 2009), diuretics (for example, furosemide) did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[b] At the time of publication (July 2009), desmopressin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

- Offer transurethral incision of the prostate (TUIP) as an alternative to TURP, TUVP or HoLEP to men with a prostate estimated to be smaller than 30 g.

- Offer open prostatectomy as an alternative to TURP, TUVP or HoLEP to men with prostates estimated to be larger than 80 g.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, do not offer minimally invasive treatments (including transurethral needle ablation [TUNA], transurethral microwave thermotherapy [TUMT], high-intensity focused ultrasound [HIFU], transurethral ethanol ablation of the prostate [TEAP] and laser coagulation) as an alternative to TURP, TUVP or HoLEP.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer botulinum toxin as part of a clinical trial.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer laser vapourisation[c], bipolar TUVP or monopolar or bipolar transurethral vapourisation resection of the prostate (TURVP) as part of a clinical trial.

3.2.6 Recommendations on surgery for storage symptoms

- Consider offering surgery only to men whose storage symptoms have not responded to conservative management and drug treatment. Discuss the alternatives of containment or surgery. Inform men being offered surgery that effectiveness, side effects and long-term risks are uncertain.

- If considering offering surgery for storage LUTS, refer men to a urologist to discuss:
  - the surgical and non-surgical options appropriate for their circumstances and
  - the potential benefits and limitations of each option, particularly long-term results.

- Consider offering cystoplasty to manage detrusor overactivity only to men whose symptoms have not responded to conservative management or drug treatment and who are willing to self-catheterise. Before offering cystoplasty, discuss serious complications (that is, bowel disturbance, metabolic acidosis, mucus production and/or mucus retention in the bladder, urinary tract infection and urinary retention).

- Consider offering bladder wall injection with botulinum toxin[d] only to men with detrusor overactivity whose symptoms have not responded to conservative management and drug treatments and who are willing to self catheterise.

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[c] Current evidence on the safety and short-term efficacy of potassium-titanyl-phophate (KTP) laser vaporisation of the prostate for benign prostatic obstruction appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance. (NICE interventional procedure guidance120). However, research is necessary to understand its role compared with other treatments.

- Consider offering implanted sacral nerve root stimulation to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.

- Do not offer myectomy to men to manage detrusor overactivity.

- Consider offering intramural injectables, implanted adjustable compression devices and male slings[e] to manage stress urinary incontinence only as part of a clinical trial.

- Consider offering urinary diversion to manage intractable urinary tract symptoms only to men whose symptoms have not responded to conservative management and drug treatments, and if cystoplasty or sacral root stimulation are not appropriate or unacceptable.

- Consider offering implantation of an artificial sphincter to manage stress urinary incontinence only to men whose symptoms have not responded to conservative management and drug treatments.

3.2.7 Recommendations on treating urinary retention

- Immediately catheterise men with acute retention.

- Consider offering self- or carer-administered intermittent urethral catheterisation as an alternative to indwelling catheterisation for men with chronic or acute urinary retention.

- Offer an alpha blocker to men for managing acute urinary retention before removal of the catheter.

- Carry out a serum creatinine test and imaging of upper urinary tract in men with chronic urinary retention.

- Catheterise men who have impaired renal function or hydronephrosis secondary to chronic urinary retention.

- Consider offering intermittent or indwelling catheterisation before surgery in men with chronic urinary retention.

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[d] At the time of publication (July 2009), botulinum toxin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[e] Current evidence on the safety and efficacy of suburethral synthetic sling[183] insertion for stress urinary incontinence in men appears adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance (NICE interventional procedure guidance 256). However, research is necessary to understand its role compared with other treatments.

- Consider offering surgery without catheterisation to men who have chronic urinary retention and other bothersome LUTS but no impairment of renal function or upper renal tract abnormality.

- Consider intermittent self-catheterisation as an alternative to TURP in men with chronic retention if there is evidence of poor bladder function.

- Continue or start long-term catheterisation in men with chronic retention for whom surgery is unsuitable.

- Provide active surveillance (imaging and creatinine) to men with non-bothersome LUTS secondary to chronic retention who have not had their bladder drained.

3.2.8 Recommendations on alternative and complementary therapies

- Do not offer homeopathy, phytotherapy or acupuncture for treating LUTS in men.

3.2.9 Recommendations on providing information

- Ensure that, if appropriate, men's carers are informed and involved in managing their LUTS and can give feedback on treatments.

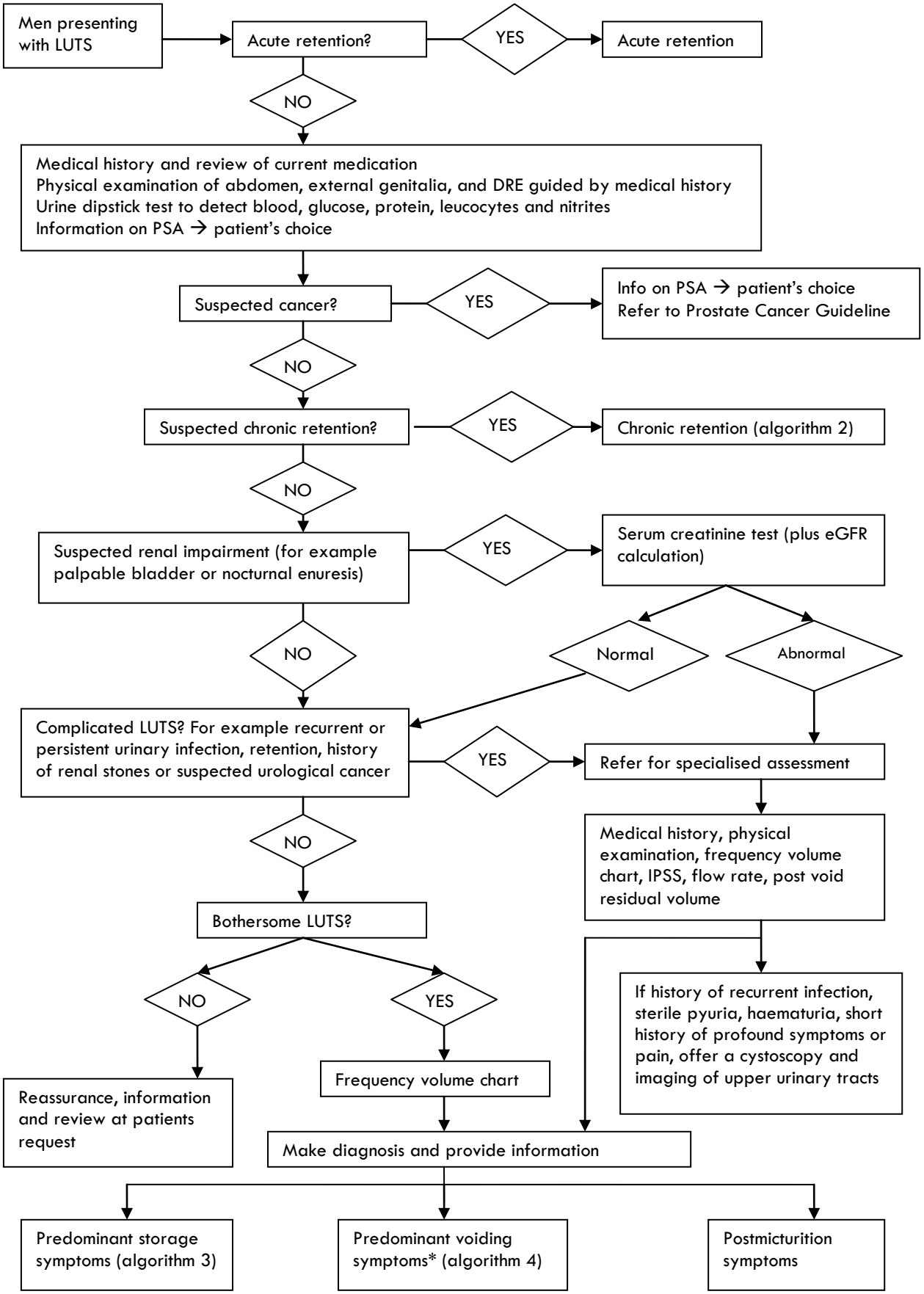
- Ensure men with LUTS have access to care that can help with:
  - their emotional and physical conditions and
  - relevant physical, emotional, psychological, sexual and social issues.

- Provide men with LUTS maintenance products at point of need and access to relevant support groups.

3.3 Algorithms

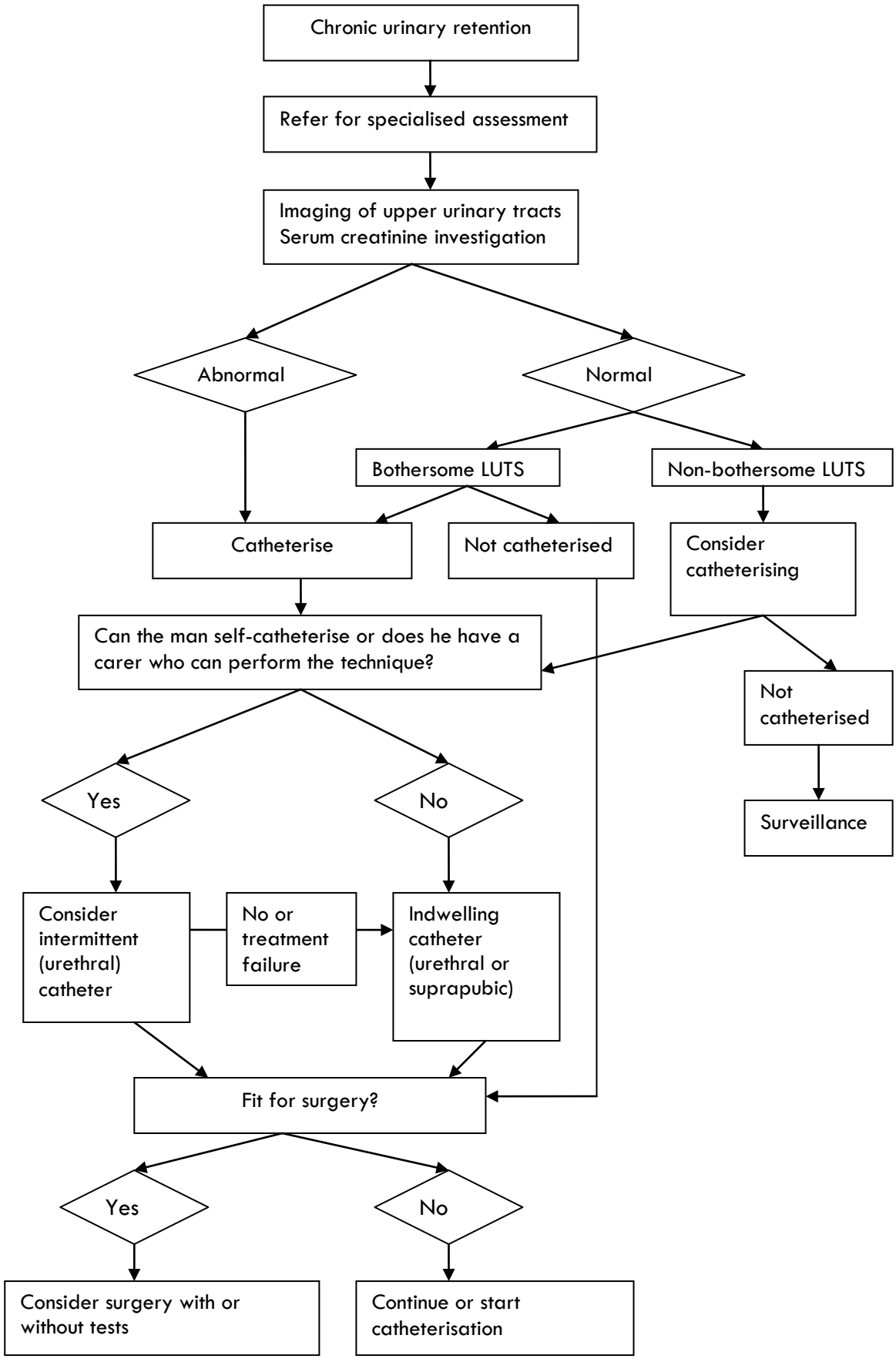
The GDG developed a care pathway algorithm according to the recommendations, where decision points are represented with boxes linked with arrows.

1 **Algorithm 1: Diagnosis**

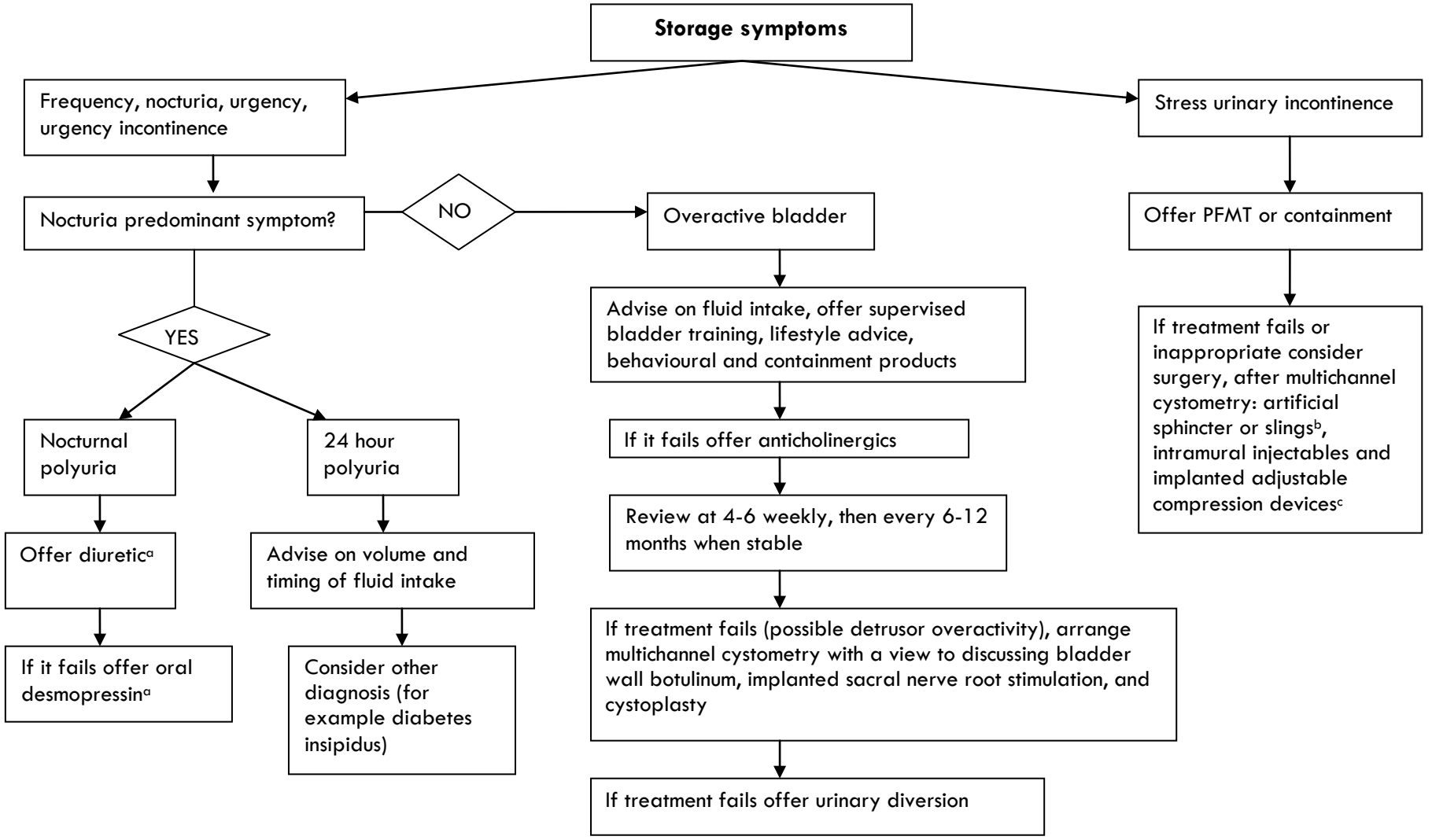


2

Algorithm 2 – Chronic urinary retention (specialist care)



Algorithm 3: Storage symptoms

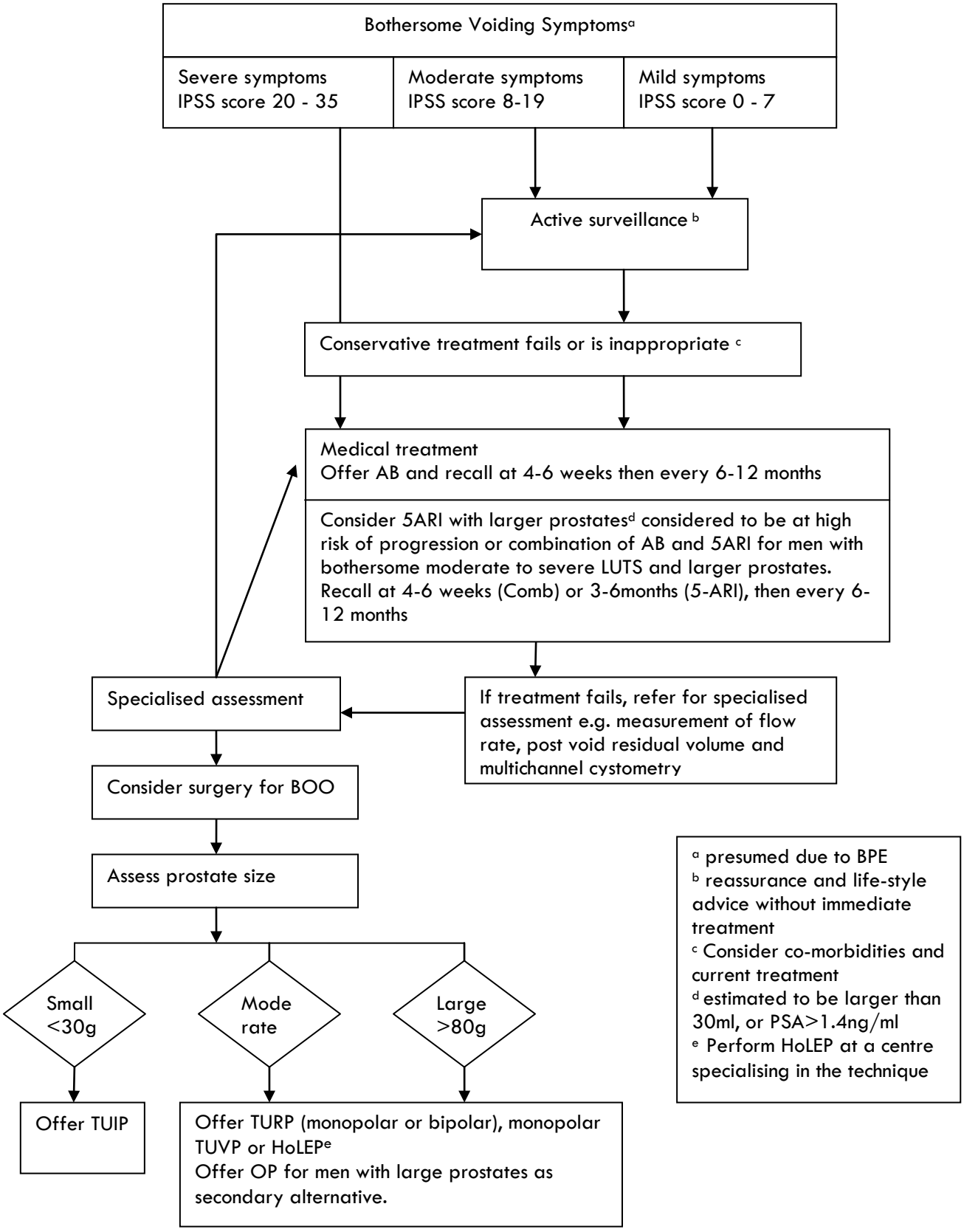


[a] The use of diuretics (e.g.furosemide) and desmopressin for nocturnal polyuria in men is outside the UK marketing authorisation for these products. Informed consent should be obtained and documented. For desmopressin, measure serum sodium at 3 days following the first dose.

[b] Clinicians should clearly explain to patients that the procedure is not always successful, particularly in men with severe stress urinary incontinence or those who have been previously treated with radiotherapy. Patients should also be made aware that the benefits of the procedure may decrease over time (Interventional Procedure guidance 256).

[c] Current evidence on the safety and efficacy of insertion of extraurethral retropubic adjustable compression devices for stress urinary incontinence in men is not adequate for this procedure to be used without special arrangements for consent and for audit or research (Interventional Procedure guidance 224).

Algorithm 4: Predominant voiding symptoms



3.4 Research recommendations

The GDG identified the following priority areas for research:

- Multichannel cystometry
- Catheters
- Products
- Green light laser prostatectomy
- Male slings

3.4.1 Research recommendation on multichannel cystometry

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of multichannel csytometry in improving patient related outcomes in men being considered for bladder outlet surgery?

Why this is important

This research would clarify whether this test could improve the outcome of surgery. If the result is positive, this could improve the chance of a good outcome from surgery. The study should be a randomised controlled trial comparing multichannel cystometry before surgery to no intervention in men awaiting bladder outlet surgery.

3.4.2 Research recommendation on catheters

The GDG recommended the following research question:

- What are the clinical and cost effectiveness and associated adverse events of intermittent catheterisation compared to indwelling catheterisation (suprapubic or urethral) for men with voiding difficulty and chronic retention of urine?

Why this is important

The number of patients in this group is steadily increasing as more radical prostatectomies are carried out and the population ages. Current practice varies widely across the UK with no established standard of good practice. This research could establish the best approach to management in these men and so bring more effective, patient-focused treatment that is more cost effective. The study should be a randomised controlled trial comparing intermittent catheterisation, indwelling suprapubic and indwelling urethral catheterisation. Outcomes of interest would be quality of life, healthcare resource utilisation, adverse events (including leakage, skin breakdown, infection, erosion and death).

3.4.3 Research recommendation on products

The GDG recommended the following research question:

- What is the clinical and cost effectiveness and associated adverse events of absorbent pads compared to sheath collectors for men with urinary incontinence to improve symptoms and quality of life?

Why this is important

The number of patients in this group is steadily increasing as more radical prostatectomies are carried out and the population ages. Current practice varies widely across the UK with no established standard of good practice. This research could establish the best approach to continence management in these men and so bring more effective, patient-focused treatment that is more cost effective. It is rare that any element of bladder training or recognition and treatment of bladder dysfunction are recognised as part of continence management. Evidence-based guidance on selecting the most suitable containment product and its subsequent management will benefit the quality of life of patients, use skilled nurse/carer resources more efficiently and reduce the costs of waste of unsuitable or sub-optimal product use. The study should be a randomised controlled trial reporting symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events.

3.4.4 Research recommendation on green light laser prostatectomy

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of green light laser prostatectomy compared to TURP in men with moderate to severe bothersome LUTS considering surgery for bladder outlet obstruction?

Why this is important

The evidence base is inadequate to give clear guidance. This research would help plan future guidance on the use of green light laser prostatectomy for men with LUTS who are having surgery. The potential advantages of reduced blood loss, shorter hospital stay and earlier return to normal activities make Green Light Laser prostatectomy attractive to patients and healthcare providers although there is uncertainty around degree of symptom improvement and improvement in quality of life in the short and longer term. The study design should be a randomised controlled trial.

3.4.5 Research recommendation on male slings

The GDG recommended the following research question:

- In men with mild to moderate post prostatectomy urinary incontinence, what is the clinical and cost effectiveness of a male sling or an extraurethral non-circumferential compression device, when assessed by symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events?

Why this is important

Guidance is needed on the most suitable surgical options for this growing group of men who, until recently, have had no acceptable treatment option other than insertion of an artificial urinary sphincter. However many men consider this treatment to be too invasive

and too prone to complication or failure, and therefore depend on containment alone for control of their urinary incontinence. A number of new interventions have been devised but it is uncertain which of these offers the best outcomes. This research could lead to clear recommendations and effective treatment for the majority of these men. A randomised controlled trial comparing up to three current interventions; retrobulbar "non compressive" male sling, adjustable compression sling, and extraurethral non circumferential compression device is recommended.

3.4.6 Additional research recommendations

The following four research questions were selected by the group but were not prioritiesed in the top five recommendations for research.

3.4.6.1 Biofeedback and Electrical stimulation

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pelvic floor muscle training (PFMT) with biofeedback and/or PFMT with electrical stimulation to PFMT alone in reducing symptom progression for men with storage symptoms?

Why this is important

There is a lack of evidence that either electrical stimulation or biofeedback help to alleviate symptoms in men with lower urinary tract symptoms despite both treatments being offered in certain healthcare settings. The answer to this research question would provide data on the clinical and cost effectiveness of these interventions. If biofeedback or electrical stimulation is not beneficial it should not be offered, as costly in staff time and outlay of equipment. If the interventions are effective they will be beneficial by improving the patient's quality of life and reducing cost to the NHS in managing incontinence. It should then be made more freely available and budgeted into service provision. The study design should be a randomised controlled trial. Outcomes of interest would be symptoms score, quality of life, incontinence, adverse events, duration and cost of treatment and reduction of other incontinence management costs (e.g. pads).

3.4.6.2 Lifestyle interventions:

The GDG recommended the following research question:

- What lifestyle elements in men with lower urinary tract symptoms predict symptom progression?

Why this is important

Lower urinary tract symptoms are a common and probably under-reported cause of morbidity in men. Current diagnosis and treatment is a lengthy process often of trial and error. If basic lifestyle changes can improve this, the economic and quality of life benefits, affecting up to 25% of men, will be significant. Current evidence for lifestyle impact is of poor quality and a better understanding of incidence, causes and outcome will simplify and improve diagnosis and treatment. The study design to answer the question should be a prospective cohort study that will determine different lifestyle elements (e.g. diet) and whether they are linked to causing LUTS or the progression of LUTS.

3.4.6.3 Non-steriodal anti-inflammatory drugs (NSAIDS)

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of NSAIDS compared to placebo in reducing symptom progression for men with lower urinary tract symptoms?

Why this is important

There is increasing evidence that prostatic inflammation may play a major role in benign prostatic disease progression. A recent study [156] found that men with inflammation at baseline had a 5.6% incidence of retention compared to 0% for men without retention over the four year study. Preliminary studies have suggested that NSAIDS may be beneficial in men with LUTS particularly with the bothersome symptoms of nocturia. As there is a lack of evidence the role of NSAIDS in men with LUTS (especially those over 70 years) cannot be clearly defined. The study design to answer the question should be a randomised controlled trial and the outcomes of interest are symptom progression and progression to surgery or acute urinary retention.

3.4.6.4 Phosphodiesterase 5-inhibitors (PDE5I)

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of PDE5I and PDE5I/alpha blocker combinations compared to placebo in men with LUTS?

Why this is important?

Epidemiological studies have indicated that the association between LUTS and erectile dsyfunction is more than a co-incidence of age, with a possible cause and effect relationship. The two conditions share several patho-physiological processes. Studies of all three PDE-5 inhibitors (sildenafil, vardenafil and tadalafil) have shown improvements in both LUTS and erectile dsyfunction in men with significant problems in both disease areas. The greatest improvements occurred with the combination of an alpha blocker and PDE-5 inhibitor when compared with either drug alone. Trials of PDE-5 inhibitors alone have shown significant improvements in LUTS symptom scores, but there was no significant improvement in flow rates with PDE-5 inhibitors when compared with placebo. Well designed, placebo-controlled studies are needed to confirm the impact of these drugs, alone or in combination with alpha blockers, to be able to make future recommendations for men with LUTS.

4 Diagnosis of men with lower urinary tract symptoms

4.1 Introduction

Diagnosis of the underlying cause of lower urinary tract symptoms (LUTS) in men is clearly of paramount importance and is central to clinical treatment. A differential diagnosis allows focused investigation and management prior to a firm diagnosis being reached and a management plan formulated. This chapter deals with the necessary steps, in addition to symptom history; for which there is no evidence of efficacy in terms of altering outcome, but upon which modern medicine is founded.

A careful history with emphasis on allocating symptoms to the appropriate stage of the bladder cycle is an important starting point. Failure to store urine can either be due to overactivity of the bladder, underactivity of the bladder with overflow, or weakness of the bladder outlet. Likewise while voiding symptoms tend to be associated in many people's minds with bladder outlet obstruction, they can of course occur in the context of poor bladder emptying (poor contractility).

4.2 Urinalysis

Urinalysis is used as a first line investigation and can be performed in any setting using dipsticks. These can be used to identify haematuria, glycosuria, proteinuria, pyuria, specific gravity and the presence of urinary nitrites and leucocyte esterase. The detection of haematuria relies on the peroxidase properties of haemoglobin. Thus, free red blood cells, haemoglobinuria and myoglobinuria will give positive results. Dipstick haematuria may require further investigation. Nitrites in the urine on stick testing may indicate infection (some bacteria convert nitrates into nitrites). A false-positive result can be given by hypochlorite solutions, oxidizing agents and bacterial peroxidases. Protein may indicate infection and/or renal impairment, blood or leucocytes may indicate infection or malignancy, and glucose may indicate diabetes mellitus.

A dipstick test whilst suggestive of pathology is useful as a screening test and abnormal findings need to be confirmed by a mid stream specimen of urine (MSU). An MSU may define any infection that is present and allow antibacterial sensitivities of any organisms to be determined.

A mid-stream urine (MSU) sample is the usual method of collecting urine from adults and every effort should be made to ensure this is sterile (retract male foreskin and clean

meatus). After voiding has started, use a sterile pot to catch an MSU sample. If difficulty persists, catheterisation may occasionally be needed to obtain a sterile sample.

However, an MSU sample is not always the most appropriate collection method, as the initial voided and terminal urine samples are more important for determining infections of the urethra and prostate. For urinary tuberculosis, the first daily void (early morning urine) has the highest concentration of the Mycobacterium and is the collection of choice. It should be repeated at least three times and if urothelial malignancy is suspected, a separate sample may be sent for urinary cytology.

The MSU sample should be sent to the microbiology department as soon as possible for microscopy and culture (and if any growth, sensitivities). Microscopy may reveal bacteria, blood cells (leucocytes and erythrocytes) and cellular casts (always abnormal and suggestive of renal disease). All of these features can suggest the site and nature of any pathology.

4.2.1 What is the sensitivity and specificity of urinalysis to detect each relevant condition (diabetes, bladder cancer, urinary tract infections, stones, renal disease)?

See Evidence Table 1, Appendix D.

4.2.1.1 Clinical evidence

Table 4-12: Urinalysis – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Bladder Cancer[70]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Urinary tract infection[70]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Urinary calculi (stones)[70]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Diabetes	0					
Renal Disease	0					

(a) It was not reported whether investigators and patients were masked to the results of the earlier tests.
(b) This study analysed erythrocyte sediment following a positive urine dipstick result.
The study population was outpatients from a urology department (secondary care setting) rather than a primary care setting where this test would be used in practice.

Table 4-13: Urinalysis - Clinical summary of findings

Outcome	*Prevalence (%)*	*Sensitivity (%)*	*Specificity (%)*	*NPV (%)*	*PPV (%)*	*Likelihood Ratio (+ve)*	*Likelihood Ratio (-ve)*	*Quality*
Bladder tumours	0.4	66.7	68.9	99.8	0.9	2.15	0.48	Low
Urinary tract infection	2.3	58.8	69.4	92.4	9.4	1.92	0.59	Low
Urinary calculi (stones)	6.5	28.6	68.6	93.2	6.0	0.91	1.04	Low

4.2.1.2 Economic evidence

No studies were identified.

4.2.1.3 Evidence statement(s)

Clinical Red blood cell detection is not a sensitive or specific test to detect bladder cancer, urinary tract infection or urinary calculi.

Economic No economic studies were identified.

4.2.2 Recommendations and link to evidence

Recommendation	**At initial assessment, offer men with LUTS a urine dipstick test to detect blood, glucose, protein, leucocytes and nitrites in the urine.**
Relative values of different outcomes	The GDG considered that detection of diabetes, bladder cancer, renal disease, urinary tract infections and urinary tract stones were the primary outcomes of the test.
Trade off between clinical benefits and harms	The test is non-invasive and has no known side effects. The benefit of detecting cases of bladder cancer was considered to be very important.
Economic considerations	There are costs associated with additional specialised tests required after a positive result of this test. However, missed cases are associated with costs and health detriment that is likely to outweigh the cost of false positives.
Quality of evidence	One low quality study was found in an indirect population.
Other considerations	This recommendation is linked to the one on medical history as specific pre-existing conditions may have an impact on the interpretation of results of urinalysis.

4.3 Prostate specific antigen (PSA)

PSA is a protein produced by cells of the prostate gland, and is measured as nanograms of PSA per millilitre (ng/mL) of blood. PSA, a member of the human kallikrein family, is produced and secreted by the ductal epithelium of the prostate. It liquefies the seminal coagulum and frees any entrapped spermatozoa. In the normal physiological state, the epithelial basement membrane of the prostatic ducts acts as a barrier, preventing escape of PSA into the systemic circulation. It is normal for men to have a low level of PSA in their blood, however prostate cancer or benign (not cancerous) conditions can increase a man's PSA level. As men age, both benign prostate conditions and prostate cancer become more common. The most frequent benign prostate conditions are prostatitis (inflammation of the prostate, also known as chronic pelvic pain syndrome) and benign prostatic hyperplasia (BPH, enlargement of the prostate). It is important to realise that both prostatic inflammation and trauma associated with urinary infections, retention and catheterisation can all lead to spurious rises in PSA level.

4.3.1 How does baseline PSA predict symptom progression?

See Evidence Table 2, Appendix D.

4.3.1.1 Clinical evidence

We searched for longitudinal studies that analysed changes of symptom scores in relation to baseline PSA. Healthy men, and men with LUTS on medication, were included in this review.

Table 4-14: PSA - Summary of findings

Study	Study design	Population	Intervention & comparison	Analysis	Outcome
Crawford2006, [49] *analysing data from* ***McConnell 2003*** [154,156]	Longitudinal follow up of the placebo arm of an RCT with 4 years follow up	Men with BPH and moderate to severe symptom (AUASS) mean 17 (range of 8-20). The average age was 62 years. (N=737)	None (placebo arm)	Patients in the placebo arm of the trial were divided into high (≥1.6ng/ml) vs. low (<1.6ng/ml) PSA at the median baseline level. Overall BPH progression was defined as the first occurrence of an increase of at least 4 points in the AUASS, AUR, urinary incontinence or renal insufficiency or recurrent urinary tract infection.	Baseline PSA level was associated with symptom progression. At 4 years, the cumulative probability and incidence rate of overall BPH progression was significantly higher in the baseline high PSA group (p<0.001). Incidence rate of ≥ 4 points increase in AUASS was significantly higher in the high PSA group (4.5 vs. 2.8 events/100 person year). The incidence rate of acute urinary retention and invasive therapy was also significantly higher in the group with higher baseline PSA.
Carter 2005 [39]	Longitudinal cohort study.	Healthy men less than 70 years (N=704).	None	Regression analysis (mixed effect Poisson model) for change in PSA percentile group and symptom score (IPSS score) with time.	No correlation (analysis not shown).
O'Leary 2003 [196]	Analysis from 3 RCTs with a 2 year follow up.	Men with BPH (N=4335) with moderate to severe symptoms.	Dutasteride vs. placebo	Logistic regression model to identify predictors for men most likely to be bothered at the end of the study.	PSA at baseline was not one of the factors which predicted bother (as measured by item 3 of BII - Benign Prostatic Hyperplasia Impact Index).
Roehrborn 1999 [220]	RCT with follow up of 4 years.	Men with clinical BPH with moderate to severe symptoms (N=3040)	Finasteride vs. placebo	Mean change in quasi-AUA symptom score over time. Analysis of variance within PSA tertiles and between treatment group.	Baseline PSA predicts deterioration of symptoms in untreated patients. Baseline PSA predicts improvement of symptoms for those patients treated with finasteride relative to placebo Baseline PSA does not predict improvement of symptoms in the finasteride treatment group alone.
Roehrborn 2006 [219]	RCT	Men at risk of progression events from LUTS/BPH (N=1522)	Alfuzosin vs. placebo	Analysis of baseline PSA as predictor of IPSS using logistic regression expressed as hazard ratios.	PSA levels were not found to be a significant predictor of IPSS worsening in the intervention or placebo arm

4.3.1.2 Economic evidence

No studies were identified.

4.3.1.3 Evidence statement(s)

Clinical Data suggesting that PSA has prognostic value in predicting symptom progression were inconsistent.

Economic No economic studies were identified

4.3.2 In men with LUTS, does performing a PSA test affect patient outcomes versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.3.3 Recommendations and link to evidence

Recommendation	**At initial assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:** • **their LUTS are suggestive of bladder outlet obstruction secondary to BPE or** • **their prostate feels abnormal on DRE or** • **they are concerned about prostate cancer.**
Recomemendation	**Manage suspected prostate cancer in men with LUTS in line with 'Prostate cancer: diagnosis and management' (NICE clinical guideline 58) and 'Referral guidelines for suspected cancer' (NICE clinical guideline 27).**
Recommendation	**At specialised assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:** • **their LUTS are suggestive of bladder outlet obstruction secondary to BPE or** • **their prostate feels abnormal on DRE or** • **they are concerned about prostate cancer.**
Relative values of different outcomes	Symptom progression was considered the most important outcome.
Trade off between clinical benefits and harms	The GDG felt that although it was important not to miss a case of prostate cancer it was essential to acknowledge that this test lacks accuracy and may cause more harm than benefit in terms of unnecessary worry for the patient. Therefore, the GDG decided that these men should be given information about the test so that they could make an informed decision whether to go ahead with the test.
Economic considerations	There is a trade-off between the cost of performing PSA and the useful information that this test could provide.
Quality of evidence	There was no evidence comparing LUTS outcomes for men that

had a PSA test compared to those that had not.

The ideal analysis for the prognostic question would be regression analysis identifying the link of baseline PSA levels with progression while controlling for other variables. This was performed in only some of the studies reviewed [39,196,219]. Data suggesting that PSA has prognostic value in predicting symptom progression were inconsistent.

Other considerations

Because PSA levels tend to increase with age, the use of age-specific PSA reference ranges has been suggested as a way of increasing the accuracy of PSA tests. However, age-specific reference ranges have not been generally favoured because their use may lead to missing or delaying the detection of prostate cancer in as many as 20 percent of men in their 60s and 60 percent of men in their 70s. Another complicating factor is that studies to establish the normal range of PSA values have been conducted primarily in white men.

4.4 Symptom Scores

The International Prostate Symptom Score (IPSS) is an 8 question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of benign prostatic hyperplasia (BPH). Created in 1992 by the American Urological Association, it originally lacked the 8th quality of life question, hence its original name: the American Urological Association symptom score (AUA-7). An example of the IPSS questionnaire can be found in Appendix H.

The IPSS was designed to be completed by the patient, with speed and ease in mind. Hence, it can be used in both urology clinics as well as the clinics of primary care physicians (i.e. by general practitioners) for the diagnosis of LUTS. The IPSS can also be performed multiple times to compare the progression of symptoms and their severity over months and years.

4.4.1 In men with LUTS, does completing symptom scores affect patient outcomes (including futile treatment and missed treatment opportunities) versus not completing scores?

No clinical or economic studies were identified.

4.4.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.4.2 Recommendations and link to evidence

Recommendation	**Offer men considering any treatment for LUTS an assessment of their baseline symptoms with a validated symptom score (for example, the International Prostate Symptom Score [IPSS]).**
Relative values of different outcomes	Response to treatment and improvement in symptoms were considered the most important outcomes.
Trade off between clinical benefits and harms	The consensus of the group was that it was not essential for all men with LUTS to complete a symptom score. They felt that this was time consuming and did not add much to the medical history taking at initial assessment. The test was considered beneficial at the stage when men were considering treatment. This would then provide a baseline score to monitor their response to treatment.
Economic considerations	The assessment of the baseline symptoms does not need expensive equipment or considerable staff time.
Quality of evidence	No clinical or economic evidence was found.
Other considerations	The GDG considered the difficulties in completing the symptom score for men who are blind, have learning disabilities or when English is not their first language. There is a Braille version of the IPSS which could be used and a translator could be provided for men if required.

4.5 Digital Rectal Examination (DRE)

A digital rectal examination is essential to assess the prostate. The symmetry, size, firmness, surface smoothness, tenderness and the midline groove should all be assessed. The examination is usually performed with the patient in the left lateral position. The index finger is gently inserted into the rectum. Force is not needed, as the external anal sphincter will relax with gentle pressure. The prostate is palpable anteriorly. Training and experience will teach the difference between a soft smoothly enlarged benign feeling prostate and the hard, woody irregular carcinoma. In addition, the rectum and pelvis should be assessed. Faecal loading or impaction, rectal tumours and other pelvic masses may all be palpated when present.

4.5.1 In men with LUTS, what is the effectiveness of a DRE versus no DRE in changes to patient treatment/outcomes?

No clinical or economic studies were identified.

4.5.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.5.2 Recommendations and link to evidence

Recommendation	**At initial assessment, offer men with LUTS a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a digital rectal examination (DRE).**
Recommendation	**Offer men with LUTS having specialist assessment a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a DRE.**
Relative values of different outcomes	The GDG considered that a diagnosis was not possible without a history and examination.
Trade off between clinical benefits and harms	Performing a digital rectal examination is good practice to identify abnormalities of the prostate and associated conditions which might affect bladder function. In practice this test is not being done regularly and the group felt that is was important to raise awareness of its importance. A focused physical examination is important so that abnormalities of the abdomen and external genitalia are not missed and left untreated. The harms are the short-term complications of embarrassment and transient discomfort.
Economic considerations	Physical examination (including DRE) has clinician time costs, very inexpensive disposables, and the cost of further assessments. Experience in its performance is required but the clinical benefit should outweigh direct cost.
Quality of evidence	No clinical or economic evidence was found.
Other considerations	None.

4.6 Frequency Volume charts (voiding diaries, bladder diaries / charts)

Voiding diaries are simple, non-invasive tools that are frequently part of the initial evaluation of patients complaining of LUTS, particularly those who have storage symptoms such as increased urinary frequency and incontinence. These diaries give an indication of the voiding pattern, the severity of symptoms and they add objectivity to the history. They may also give an indication of the impact on the patient's life and may show 'coping strategies' that the patient has adopted to help manage their symptoms. Voiding diaries are also useful in identifying abnormalities of renal origin such as abnormal production of urine related to the circadian rhythm.

A number of different diaries have been defined by the International Continence Society (ICS):

- **Micturition Time Chart** – records only the times that voids occur with no volumetric data.
- **Frequency/Volume Chart (FVC)** – records the time and volume of each micturition.

- **Bladder Diary –** records the time and volume of each micturition and may also include other data such as incontinence episodes, pad usage, fluid intake and urgency.

The patient is asked to record as accurately as possible the time of events such as voids and incontinence episodes on the chart and to measure the volume voided using a graduated container (jug). They are also asked to record the time they are awake and asleep. Patients must be instructed to continue their normal activities during the course of the assessment, so as to obtain an accurate representation of their normal lower urinary tract function. The ICS has recommended that voiding diaries are performed for at least 24 hours, although in practice a period of 3-7 days is usually chosen. Most patients find diaries acceptable for use over short periods.

Frequent findings include:

- **Normal frequency and voided volumes.**

- **Increased frequency and normal volumes** – an increased 24-hour production of urine, suggesting a high fluid intake. This may be related to diabetes mellitus or diabetes insipidus, but is more usually habitual.

- **Reduced volumes with minimal variation in the volume voided** – suggesting bladder wall pathology such as carcinoma in situ or painful bladder syndrome/interstitial cystitis or carcinoma in situ.

- **Reduced volumes with variation in the volume voided** - suggestive of underlying detrusor overactivity as the bladder contracts at variable degrees of distension before maximum capacity, erroneously informing the patient that it is full; resulting in urinary frequency and low and variable voided volumes.

- **Increased nocturnal production** – (nocturnal polyuria- defined as nightime output of more than 35% of the 24hr output), suggestive of fluid retaining states, hormonal fluid balance abnormality or idiopathic in origin. This is a commonly occurring bothersome symptom caused by physiological problems rather than lower urinary tract disease processes.

4.6.1 In men with LUTS, what is the effectiveness of frequency volume chart versus no frequency volume chart in changes to patient treatment/outcomes?

No clinical or economic studies were identified.

4.6.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.6.2 Recommendations and link to evidence

Recommendation	**At initial assessment, ask men with bothersome LUTS to complete a urinary frequency volume chart.**
Recommendation	**Ask men with LUTS to complete a urinary frequency volume chart at specialist assessment.**
Relative values of different outcomes	The GDG considered that an improvement in symptoms was the most important outcome.
Trade off between clinical benefits and harms	The group felt that this test is important to build on information obtained from the medical history. This test has no side effects or harms associated with it but is time consuming for the patients so whether this chart is accurately completed will depend on how bothersome the symptoms are to the patient. This chart will help the clinician to make an accurate diagnosis of the underlying cause of the symptoms.
Economic considerations	There are no costs to the healthcare system associated with completing a frequency volume chart whilst this test adds important information for the diagnosis and subsequent treatment.
Quality of evidence	No clinical or economic studies were found.
Other considerations	Patient preference will play a role in whether the men are bothered enough by their symptoms to complete this test at primary care. Learning difficulties, dyslexia, blindness and language barriers were equality issues of concern to the group that may affect mens' ability to complete a frequency volume chart. Likewise, men who have either physical or cognitive impairment may need assistance in the completion of a chart. It is important for a carer to be instructed in helping complete the voiding diary if possible.

4.7 Pad tests

Pad testing is a non-invasive, objective method for detecting and quantifying urinary incontinence. It is easy to perform and interpret and provides a great deal of useful information.

The principal aim of the test is to determine the amount of urine lost during a specified period (e.g. one hour), as degree of incontinence is frequently unclear from the history. Therefore, this test provides quantification to both the clinician and patient alike regarding the severity of incontinence. In addition, the test may be useful to confirm the presence of incontinence when other tests have failed to demonstrate any urinary leakage.

4.7.1 In men with LUTS how does measuring incontinence (pad test) affect patient outcomes versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.7.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.7.2 Recommendations and link to evidence

Recommendation	**Offer pad tests to men having specialist assessment only if the degree of urinary incontinence needs to be measured.**
Relative values of different outcomes	The GDG considered that an improvement in symptoms was the most important outcome.
Trade off between clinical benefits and harms	The test has no side effects or harms but takes time. The GDG recommended that this test should not be routinely offered because of the absence of evidence and they were unsure of the benefit it offered.
Economic considerations	The costs associated with a pad test are those associated with the cost of pads; incurred by the patient using the time to do the test, and those associated with the healthcare professionals who explain and supervise the test, and then deal with the pads and patient afterwards. There is a trade-off between the cost of performing a pad test and the information it could provide. This test is likely to add useful information only in special cases.
Quality of evidence	No clinical or economic evidence was found.
Other considerations	No specific values have been defined for men as male incontinence is uncommon and any amount leaked would be considered to be significant.

4.8 Renal function

Serum creatinine is the most reliable routinely available biochemical estimation of renal filtration and function. The serum urea concentration is less reliable, being affected by hydration, dietary protein intake and tubular reabsorption of urea. Creatinine is produced by the metabolism of skeletal muscle at a constant daily rate. Thus, variations in its serum concentration are due to changes in its excretion by the kidney. However, alterations in serum creatinine will not be seen until at least 50% of the renal function has been lost. Most laboratories now report eGFR alongside their measurements of blood creatinine levels. However, more exact glomerular filtration rate (GFR) estimation can be

obtained (when needed) by measuring the creatinine clearance (from 24-hour total urine creatinine and serum creatinine concentration).

4.8.1 In men with LUTS how does measuring renal function affect patient outcomes versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.8.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.8.2 Recommendations and link to evidence

Recommendation	**At initial assessment, offer men with LUTS a serum creatinine test only if there are any indications of renal impairment (for example, palpable bladder, nocturnal enuresis, recurrent urinary tract infection or history of renal stones).**
Relative values of different outcomes	The GDG considered that an improvement in symptoms was the most important outcome.
Trade off between clinical benefits and harms	The group felt in the absence of evidence detecting a benefit this test should not be routinely offered.
Economic considerations	There are costs associated with this test which does not add any important information except in the case of clinically suspected renal impairment.
Quality of evidence	No clinical or economic studies were found.
Other considerations	The results of testing need to be interpreted with regard to the age, sex and race of the man.

4.9 Urinary flow rate

Uroflowmetry is a non invasive and inexpensive test that gives useful information regarding voiding function by measuring the rate of flow of voided urine. It can often be used to suggest the presence of bladder outlet obstruction (BOO) or a poorly functioning detrusor.

Uroflowmetry is performed using a flowmeter, a device that measures the quantity of fluid (volume or mass) voided per unit of time; in this case the measurement is expressed in millilitres per second (ml/s). Patients are instructed to void normally, either sitting or standing, with a comfortably full bladder and should be provided with private and comfortable surroundings so as to reduce the inhibitory effects of the test environment. Uroflowmetry can be carried out in combination with measurement of post void residual

(PVR) urine. The patient should be asked if the void was representative of their usual voiding. It is important that the flowmeter is regularly calibrated as per the manufacturer's instructions to maintain accuracy of the readings. A flow rate based upon a voided volume of under 150 ml is insufficient for reliable interpretation.

Men under 40 years of age generally have maximum flow rates over 25 ml/s. Flow rates decrease with age and men over 60 years of age with no urinary obstruction usually have maximum flow rates over 15 ml/s.

Uroflowmetry is useful in the assessment of voiding function for a wide range of urological conditions. The observed flow pattern should be assessed, as well as any absolute values obtained. The results must always be interpreted within the context of the clinical situation, recognising the limitations of the study.

4.9.1 In men with LUTS, what is the effectiveness of urinary flow rate versus no urinary flow rate in relationship to patient treatment/outcomes?

No clinical or economic studies were identified.

4.9.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.9.2 Recommendations and link to evidence

See recommendations and link to evidence in section 4.10.4

4.9.3 What is the sensitivity and specificity of a maximum urinary flow rate in predicting bladder outlet obstruction as defined by pressure flow studies in men with LUTS?

See Evidence Table 3, Appendix D, and Forest Plots in Figures E-1 and E-2, Appendix E.

4.9.3.1 Clinical evidence

Table 4-15: Accuracy of urinary flow rate – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Diagnostic accuracy at Qmax <10 mL/s[197,206,213,214]	4	Cross-sectional study	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness (c)	Serious imprecision (d)
Diagnostic accuracy at Qmax <12 mL/s[213]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Diagnostic accuracy at Qmax <15 mL/s[197,206,213,214]	4	Cross-sectional study	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness(c)	Serious imprecision (d)

a) *There was no indication of whether the tests were performed independently, in a masked fashion or time interval between tests for three of the studies*[206,213,214]*. Number of voids was not reported for one study*[206]*, and two studies did not report test equipment and methods*[197,214]*. Three studies reported missing data*[206,213,214]*.*

b) *There were variations between studies in number of voids, patient population and classification scheme used to determine obstruction.*

c) *All studies were in a secondary care setting with high prevalence.*

d) *Most studies had a sample size of around 150 except for a large multi-centre study with nearly 900 patients*[214]*.*

Table 4-16: Accuracy of urinary flow rate - Clinical summary of findings

Outcome	*Sensitivity %*	*Specificity %*	*NPV %*	*PPV %*	*Prevalence %*	*Likelihood Ratio (+ve)*	*Likelihood Ratio (-ve)*	*Quality*
Diagnostic accuracy at Qmax <10 mL/s	Range: 47 to 69	Range: 57 to 87	Range: 46 to 72	Range: 69 to 85	Range: 47 to 65	Range: 1.56 to 3.83	Range: 0.44 to 0.76	Low
Diagnostic accuracy at Qmax <12 mL/s	65	74	58	79	61	2.53	0.47	Low
Diagnostic accuracy at Qmax <15 mL/s	Range: 81 to 99	Range: 31 to 53	Range: 58 to 97	Range: 59 to 74	Range: 47 to 65	Range: 1.31 to 1.82	Range: 0.03 to 0.49	Low

4.9.3.2 Economic evidence

No studies were identified.

4.9.3.3 Evidence statement(s)

Clinical The range of sensitivities are higher for increasing values of Qmax but the range of specificities are lower for corresponding values of Qmax. The range of values for sensitivity of 47% to 99% indicate that the urinary flow rate has variable diagnostic worth in detecting true cases of obstruction, and the range of values for specificity of 31% to 87% show that the urinary flow rate has variable diagnostic worth in detecting true cases of no obstruction. However, the variance in values may reflect the

differences across study populations in prevalence of obstruction, test conditions and Qmax thresholds.

The range of likelihood ratios for a positive test for obstruction (LR+) are between 1.6 and 3.8 suggesting that urinary flow rate misdiagnoses a variable proportion of patients as unobstructed when they are obstructed when compared to the suggested standard of LR+=10 for a test with good discriminatory power. However, the variance in values reflects the differences across studies in prevalence of obstruction, test conditions and Qmax thresholds.

The range of likelihood ratios for a negative test for obstruction (LR-) are between 0.03 and 0.5 suggesting that urinary flow rate misdiagnoses a variable proportion of patients as obstructed when they have no obstruction compared to the suggested standard of 0.1 for a test with good discriminatory power. However the variance in values reflects the differences across studies in prevalence of obstruction, test conditions and Qmax thresholds.

Economic No economic studies were identified.

4.9.4 Recommendations and link to evidence

See recommendations and link to evidence in section 4.10.4.

4.10 Post void residual (PVR) measurement

Portable ultrasound devices can be used to scan and calculate the volume of urine in the bladder (whether in retention or post-void residual). Whilst these devices are easy to use, they are less accurate than bladder volume measurements made by a trained sonographer or radiologist using diagnostic quality ultrasound equipment. More accurate assessment of post void residuals can be obtained by catheterisation, but this is invasive and patients generally dislike this means of assessing residual urine.

4.10.1 In men with LUTS, what is the effectiveness of post void residual measurement versus no post void residual measurement in relationship to patient treatment/outcomes?

No clinical or economic studies were identified.

4.10.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.10.2 Recommendations and link to evidence

See recommendations and link to evidence in section 4.10.4.

4.10.3 What is the sensitivity and specificity of post void residual measurement in predicting urodynamic diagnosis as defined by pressure flow studies in men with LUTS?

See Evidence Table 4, Appendix D.

4.10.3.1 Clinical evidence

Table 4-17: Accuracy of post void residual measurement – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Diagnostic accuracy at PVR >50 mL[197]	1	Diagnostic study A	No serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)

(a) *Study reported details of equipment and methods for measuring PVR but not for pressure flow test.*
(b) *The study was conducted in a secondary care setting with high prevalence.*
(c) *One study with 160 patients*

Table 4-18: Accuracy of post void residual measurement - Clinical summary of findings

Outcome	*Sensitivity %*	*Specificity %*	*NPV %*	*PPV %*	*Prevalence %*	*Likelihood Ratio (+ve)*	*Likelihood Ratio (-ve)*	*Quality*
Diagnostic accuracy at PVR >50 mL	72	42	52	63	47	1.25	0.66	Moderate

4.10.3.2 Economic evidence

No economic studies were identified.

4.10.3.3 Evidence statement (s)

Clinical The value for sensitivity shows that post void residual volume measurement has little value in detecting true positive cases of obstruction since elevation of PVR may reflect poor detrusor function as much as obstruction.

The likelihood ratio for a positive test is just above 1 suggesting that post void residual volume measurement has little value in detecting true positive cases of obstruction compared to the suggested standard of 10 for a test with good discriminatory power.

The likelihood ratio for a negative test is below 1 suggesting that the post void residual volume measurement has little value in detecting true negative cases of no obstruction compared to the suggested standard of 0.1 for a test with good discriminatory power.

Economic No economic studies were identified.

4.10.4 Recommendations and link to evidence

Recommendation	**Do not offer flow-rate measurement to men with LUTS at initial assessment.**
Recommendation	**Do not offer a post void residual volume measurement to men with LUTS at initial assessment.**
Recommendation	**Offer men with LUTS who are having specialist assessment a measurement of flow rate and post void residual volume.**
Relative values of different outcomes	The GDG considered that increasing the chance of an accurate diagnosis upon which to base management was the most important outcome when comparing test vs. no test. The GDG considered that an accurate diagnosis of obstruction was the primary outcome for the test accuracy.
Trade off between clinical benefits and harms	The group felt that at specialised assessment the benefit of correctly diagnosing obstruction was important for considering treatment options. Evidence showed very little benefit in having a post void residual measurement at initial assessment. The GDG considered that this test is important to be completed at specialised assessment as it adds information to other tests to give an overall diagnosis.
Economic considerations	There is a trade-off between the cost of performing these tests and the information it adds. The clinical evidence shows that it is of no benefit in routine assessment, so it is not cost-effective. However it could be useful and cost-effective in specialised assessment, although evidence is lacking.
Quality of evidence	All studies were performed at secondary care setting with high prevalence and should be used to inform recommendations for this setting. There was no evidence to suggest that this test was useful at initial assessment.
Other considerations	The ability of those with physical disability to perform these tests may need specific consideration. Scanning inaccuracies can occur for post void residual measurement as this test is operator and patient dependent. The most accurate assessment is via catheterisation.

4.11 Multichannel cystometry

Cystometry may be used when invasive treatment is being considered, or for equivocal or more complex cases. The principal benefit of cystometry, over other urodynamic techniques such as uroflowmetry in men with LUTS, is that simultaneous measurement of bladder pressure and flow rate allows the best assessment of the presence or absence of bladder outlet obstruction. If simultaneous imaging is done (videourodynamics), the site of bladder outlet obstruction can be localised accurately to the bladder neck, the prostate or the urethra. In addition, cystometry provides useful information regarding the function of the lower urinary tract during both the storage and voiding phases of the bladder cycle and in many instances can support a definitive pathophysiological

diagnosis for the patient's LUTS. Cystometry can help inform decisions about future management, including possible surgery for bladder outlet obstruction or detrusor overactivity, and the management of men with neurological lower urinary tract dysfunction.

Cystometry should allow definition of the behaviour of the bladder during both the storage and voiding phases. In the normal physiological situation the bladder fully relaxes during storage and contracts forcefully during voiding. It is therefore difficult otherwise to assess whether the detrusor is underactive during storage or overactive during voiding, unless cystometry is done. Likewise it should be possible to define the behaviour of the urethra during both phases. During storage the bladder outlet should be closed and can therefore not be overactive, whereas during voiding it should be fully open and can therefore not be underactive (incompetent). Any other combinations of bladder and urethral activity are therefore abnormal.

Multichannel cystometry may also help to characterise bladder compliance, sensation and capacity.

Performing an invasive procedure is a balance of the possible benefits vs. the possible risks and these must be explained to the patient during informed consent for the procedure and appropriate advice given should adverse events occur.

4.11.1 In men with LUTS, what is the effectiveness of performing multichannel cystometry tests versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.11.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.11.2 Recommendations and link to evidence

Recommendation	**Consider offering multichannel cystometry for men with LUTS who are considering surgery.**
Relative values of different outcomes	The GDG considered that improving the chance of an accurate diagnosis and identifying potential complications was the most important outcome when considering surgical treatment for men with LUTS.
Trade off between clinical benefits and harms	The clinical benefit of cystometry is that a diagnosis of the underlying cause of LUTS may be established. This allows surgery to relieve bladder outlet obstruction to be used only in men who actually have bladder outlet obstruction. In addition, it confirms the indication for surgery for detrusor overactivity only in men who actually have detrusor overactivity. This should reduce the number of men who have an unsatisfactory outcome from surgery. The harms are the short-term complications of embarrassment,

transient discomfort, haematuria and urinary tract infection.

Economic considerations	There are costs associated with this test, but the information it provides is important to reduce unnecessary surgery and save future costs.
Quality of evidence	No clinical or economic studies were found.
Other considerations	None.

4.12 Cystoscopy

The lower urinary tract is easily accessible to endoscopic assessment. Modern fibreoptic technology has allowed the production of flexible, small-calibre instruments yielding high-quality images. Thus, flexible urethrocystoscopy is a routine investigation, performed in all urological outpatient departments, allowing straightforward endoscopic assessment of the lower urinary tract, in a broadly similar way to the endoscopic assessment of the gastrointestinal and respiratory tracts. Many units have open access clinics where flexible endoscopy is performed for the investigation of haematuria and recurrent urinary tract infections, combined with a kidneys–ureter–bladder (KUB) radiograph and abdominal ultrasound. The follow-up of transitional cell carcinoma of the bladder is frequently performed by flexible endoscopic means. Rigid cystoscopy, requiring anaesthesia, is still indicated when the view is likely to be poor or biopsies are required.

Flexible cystoscopy is done using topical urethral local anaesthesia, which most men find produces mild to moderate discomfort, but some find painful. There is usually discomfort passing urine for a few days afterwards, often some blood in the urine during this period, and it is occasionally complicated by urinary tract infection or acute retention.

4.12.1 In men with LUTS how does performing cystoscopy affect patient outcomes versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.12.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.12.2 Recommendations and link to evidence

Recommendation	**Do not offer cystoscopy to men with uncomplicated LUTS (that is, without evidence of bladder abnormality) at initial assessment.**
Recommendation	**Offer cystoscopy to men with LUTS having specialist assessment only when clinically indicated, for example if there is a history of any of the following:** • **recurrent infection** • **sterile pyuria** • **haematuria** • **profound symptoms** • **pain.**
Relative values of different outcomes	The GDG considered that an improvement in symptoms was the most important outcome.
Trade off between clinical benefits and harms	The clinical benefit is that cystoscopy can allow diagnosis of the cause of LUTS in some men, and of other clinical problems. The harm associated with cystoscopy is discomfort, subsequent dysuria and bleeding, and the possibility of urinary tract infection or acute retention.
Economic considerations	There are significant costs associated with cystoscopy. Only in presence of other indications are they warranted.
Quality of evidence	No clinical or economic studies were found.
Other considerations	None.

4.13 Imaging (transabdominal ultrasound, intravenous urogram or plain abdominal x-ray)

Ultrasound has become widely used in the assessment of many urological problems, because it produces high-quality images of all of the urinary tract except the normal ureter, it involves no radiation, it can be carried out by suitably trained non-medical staff, and it is highly acceptable to patients. This technique gives good structural detail of the kidneys, and allows good assessment of bladder volume, but does not give reliable detail of bladder pathology. Ultrasound does not identify stones in the ureter reliably; consequently it is often combined with a plain abdominal radiograph that includes the kidneys, ureters and bladder. This involves a very small dose of radiation. Intravenous urography (IVU) produces imaging of the entire urinary tract, albeit with the need for radiation and intravenous contrast, and thus has small risks of radiation exposure, allergic reactions and contrast-induced nephrotoxicity, and it cannot be done in patients with moderate or more severe renal impairment.

4.13.1 In men with LUTS how does performing imaging (transabdominal ultrasound, intravenous urogram or plain abdominal x-ray) affect patient outcomes versus not performing the diagnostic test?

No clinical or economic studies were identified.

4.13.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

4.13.2 Recommendations and link to evidence

Recommendation	**Do not offer imaging of the upper urinary tract to men with uncomplicated LUTS at initial assessment.**
Recommendation	**Offer imaging of the upper urinary tract to men with LUTS having specialist assessment only when clinically indicated, for example, if there is a history of any of the following:** • **chronic retention** • **haematuria** • **recurrent infection** • **sterile pyuria** • **profound symptoms** • **pain.**
Relative values of different outcomes	The GDG considered that an improvement in symptoms was the most important outcome.
Trade off between clinical benefits and harms	These additional tests are not warranted in routine assessment unless clinically indicated because of the low likelihood of finding pathology directly linked to the presenting LUTS, the cost of the imaging and the risks associated with the investigations (e.g. radiation dose).
Economic considerations	There are significant costs associated with imaging. Only in presence of other indications are they warranted.
Quality of evidence	No clinical or economic studies were found.
Other considerations	None.

4.14 Supporting recommendations on diagnosis

Recommendation	**At initial assessment, offer men with LUTS an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.**
Recommendation	**Offer men with LUTS having specialist assessment an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.**
Trade off between clinical benefits and harms	Taking a medical history for every patient is essential to gather information about co-morbidities and possible underlying causes of the LUTS.
Economic considerations	The cost associated with this assessment is that incurred by the time required by the patient and the healthcare professional who takes the history.
Other considerations	Sexual problems are important to men but may be under-reported as men may be embarrassed to discuss such issues. Therefore, providing adequate opportunity to discuss sexual problems is important.

Recommendation	**At initial assessment, give reassurance, offer advice on lifestyle interventions (for example, fluid intake) and information on their condition to men whose LUTS are not bothersome or complicated. Offer review if symptoms change.**
Trade off between clinical benefits and harms	The benefit of giving reassurance and information is essential for these men with non-bothersome symptoms who may be concerned of underlying causes. These benefits outweigh the time spent with the patient.
Economic considerations	The cost associated with this assessment is that incurred by the time required by the patient and the healthcare professional who offers the advice.
Other considerations	None.

Recommendation	**Refer men for specialist assessment if they have bothersome LUTS that have not responded to conservative management or drug treatment.**
Recommendation	**Refer men for specialist assessment if they have LUTS complicated by recurrent or persistent urinary tract infection, retention, renal impairment that is suspected to be caused by lower urinary tract dysfunction, or suspected urological cancer.**
Trade off between clinical benefits and harms	It is important that these patients have specialised assessment so that they can receive the appropriate treatment.
Economic considerations	Timely diagnosis of other conditions is crucial for initiating an appropriate treatment and extend/improve the quality of the patient's life.
Other considerations	This recommendation links to the NICE guidance on 'Referral guidelines for Suspected Cancer'.

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4.15 Summary of recommendations on diagnosis

Initial assessment:

- At initial assessment, offer men with LUTS an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.

- At initial assessment, offer men with LUTS a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a digital rectal examination (DRE).

- At initial assessment, ask men with bothersome LUTS to complete a urinary frequency volume chart.

- At initial assessment, offer men with LUTS a urine dipstick test to detect blood, glucose, protein, leucocytes and nitrites in the urine.

- At initial assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:
  - their LUTS are suggestive of bladder outlet obstruction secondary to BPE or
  - their prostate feels abnormal on DRE or
  - they are concerned about prostate cancer.

- Manage suspected prostate cancer in men with LUTS in line with 'Prostate cancer: diagnosis and management' (NICE clinical guideline 58) and 'Referral guidelines for suspected cancer' (NICE clinical guideline 27).

- At initial assessment, offer men with LUTS a serum creatinine test only if there are any indications of renal impairment (for example, palpable bladder, nocturnal enuresis, recurrent urinary tract infection or history of renal stones).

- Do not offer cystoscopy to men with uncomplicated LUTS (that is, without evidence of bladder abnormality) at initial assessment.

- Do not offer imaging of the upper urinary tract to men with uncomplicated LUTS at initial assessment.

- Do not offer flow-rate measurement to men with LUTS at initial assessment.

- Do not offer a post void residual volume measurement to men with LUTS at initial assessment.

- At initial assessment, give reassurance, offer advice on lifestyle interventions (for example, fluid intake) and information on their condition to men whose LUTS are not bothersome or complicated. Offer review if symptoms change.

- Refer men for specialist assessment if they have bothersome LUTS that have not responded to conservative management or drug treatment.

- Refer men for specialist assessment if they have LUTS complicated by recurrent or persistent urinary tract infection, retention, renal impairment that is suspected to be caused by lower urinary tract dysfunction, or suspected urological cancer.

- Offer men considering any treatment for LUTS an assessment of their baseline symptoms with a validated symptom score (for example, the International Prostate Symptom Score [IPSS]).

Specialist assessment:

- Offer men with LUTS having specialist assessment an assessment of their general medical history to identify possible causes and comorbidities. This should include a review of current medication.

- Offer men with LUTS having specialist assessment a focused physical examination guided by their medical history, an examination of the abdomen and external genitalia, and a DRE.

- Ask men with LUTS to complete a urinary frequency volume chart at specialist assessment.

- At specialist assessment, offer men with LUTS information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if:
  - their LUTS are suggestive of bladder outlet obstruction secondary to BPE or
  - their prostate feels abnormal on DRE or
  - they are concerned about prostate cancer.

- Offer cystoscopy to men with LUTS having specialist assessment only when clinically indicated, for example if there is a history of any of the following:
  - recurrent infection
  - sterile pyuria
  - haematuria
  - profound symptoms
  - pain.

- Offer imaging of the upper urinary tract to men with LUTS having specialist assessment only when clinically indicated, for example, if there is a history of any of the following:
  - chronic retention
  - haematuria
  - recurrent infection
  - sterile pyuria
  - profound symptoms
  - pain.

- Offer men with LUTS who are having specialist assessment a measurement of flow rate and post void residual volume.

- Consider offering multichannel cystometry for men with LUTS who are considering surgery.

- Offer pad tests to men having specialist assessment only if the degree of urinary incontinence needs to be measured.

4.16 Research recommendation on diagnosis

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of multichannel csytometry in improving patient related outcomes in men being considered for bladder outlet surgery?

Why this is important

This research would clarify whether this test could improve the outcome of surgery. If the result is positive, this could improve the chance of a good outcome from surgery. The study should be a randomised controlled trial in men awaiting bladder outlet surgery comparing multichannel cystometry to no intervention, before surgery.

5 Conservative management for men with lower urinary tract symptoms

5.1 Introduction

Lower urinary tract symptoms (LUTS) which include storage, voiding and post micturition symptoms can often be treated by conservative measures. In this chapter we consider the clinical and cost-effectiveness of conservative management for men with LUTS. These include lifestyle interventions, physical, behavioural and non-therapeutic interventions (products that collect or contain leakage).

We searched for randomised controlled trials (RCT) comparing the effectiveness of different conservative managment for lower urinary tract symptoms. The interventions we included in our search were pelvic floor muscle training (PFMT), biofeedback, electrical stimulation, bladder training, post-void urethral milking (PVM), fluid change, reduced fluid, products or catheters. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box filled with "**Yes**" represents where evidence was found and is reviewed in this chapter. A box filled with "**No**" represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

PFMT	No								
Biofeedback	No								
Electrical Stimulation	No	No							
Bladder training	No	No	No						
PVM	No	No	No	No					
Fluid change	No	No	No	No	No				
Reduced fluid	No	No	No	No	No	No			
Product	No	No	No	No	No	No	No		
Catheters	No	No	No	No	No	No	No	No	
NT/ active observation	**Yes Page 107**	**Yes Page 111**	**Yes Page 113**	No	**Yes Page 116**	No	No	**Yes Page 119**	**Yes Page 124**
	PFMT	BF	ES	Bladder training	PVM	Fluid change	Fluid reduction	Products	Catheters

Key: BF= Biofeedback, ES= electrical stimulation, NT= no treatment or intervention; PFMT= Pelvic Floor Muscle Training, PVM= post-void urethral milking

5.2 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training (PFMT) involves recruiting pelvic floor muscles for muscle strengthening and skill training. Contraction of pelvic floor muscles causes inward lift of the muscles, with resultant increase in urethral closure pressure, stabilisation and resistance to downward movement. There are many variations on PFMT protocols and unanswered questions regarding when PFMT should be initiated and for how long it should be maintained. Men value the support they receive from the nurse or physiotherapist and the individual instruction and planned follow up is likely to be an important factor affecting the success PFMT.

5.2.1 In men who report LUTS, what is the effect of pelvic floor muscle training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

Eight of the studies found were conducted in men who received prostatectomy for prostate cancer [33,76,80,146,151,168,199,255]. Another two RCTs investigated PFMT before surgery in men undergoing TURP [205,249]. One study was conducted in men with post-micturition dribbling who had no history of stress or urgency incontinence [203]. These studies have variations in the number and duration of training sessions provided, recommended type and intensity of exercise to practice at home, when these were initiated (pre or post surgery) and the type of intervention received by the control group.

See Evidence Table 5, Appendix D and Forest Plots in Figures E-3 to E-5, Appendix E.

5.2.1.1 Clinical evidence

Table 5-19: Pelvic Floor Muscle Training vs. control group - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Men with post-prostatectomy incontinence						
Incontinence at 0 - 3 months follow up [33,76,80,146,151,168,199,255]	8	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Incontinence at 3 - 6 months follow up[33,76,80,146,168,199,255]	7	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Incontinence at 6 - 12 months follow up[33,76,146,199,255]	5	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost(g) per 24 hour pad test at 0 - 3 months follow up [76,151,168]	3	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost (g) per 24 hour (pad test) at 3 - 6 months follow up[76,168]	2	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost (g) per 24 hour (pad test) at 6 - 12 months follow up[76]	1	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness (d)	Serious imprecision (e)
Men with post-TURP incontinence						
Incontinence at 0 - 3 months follow up[205,249]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Incontinence at > 3 months follow up	0	RCT				
Men with post-micturition dribbling (PMD)						
Decrease in mean urine loss adjusted for initial pad weight gain (g) in men with PMD at 0 – 3 months[203]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (f)	Very serious imprecision (e)
Adverse events	0	RCT				

(a) *Data from studies are supplemented by data from the Cochrane systematic reviews Hunter 2007*[104].

(b) *4 studies*[80,199,203,205] *do not report randomisation method and 8 studies*[76,80,146,151,199,203,205,249] *do not report allocation concealment. Masking of outcome assessment was not performed or unclear in all but 5 of the studies*[33,146,168,203,255]*. Drop out rate was high or unexplained in 5 studies*[33,80,146,151,249]*. Standard deviations reported for mean urine loss in 4 studies*[76,151,168,203] *were very high indicating possible skewed data. One study* [203] *did not report standard deviations for adjusted mean improvement in pad weight gain.*

(c) *Significant statistical heterogeneity is noted and is not explained by subgroup analysis, for example: timing of exercises (pre- or post-operative) or treatment duration (months). Other factors such as number of exercises performed or their intensity may also contribute to differences. The control arms also received different amount and type of additional written or verbal instructions. Different definitions for incontinence were used.*

(d) *Patients in studies* [33,76,80,146,151,168,199,255] *under went prostatectomy for localised prostate cancer and therefore likely to experience more severe incontinence as a result of surgery compared to men with overactive bladder or those following a TURP. However this is unlikely to significantly reduce the applicability of the results.*

(e) *Confidence intervals cross MID despite adequate cumulative sample size for some outcomes. 1 study*[203] *has 15 only patients or less in each arm.*

(f) *The study was conducted in men with PMD without a history of incontinence or surgeries. The data were only considered for making recommendation specifically for this group of patients.*

Table 5-20: Pelvic Floor Muscle Training vs. Control group - Clinical summary of findings

Outcome	PFMT*	Control *	Relative risk	Absolute effect	Quality
Men with Incontinence after prostatectomy					
Incontinence at 0 - 3 months follow up (a)	154/392 (39.3%)	249/389 (64.0%)	0.67 [0.42 to 1.05]	211 fewer per 1000 [371 fewer to 32 more]	Very Low
Incontinence at 3 - 6 months follow up (a)	71/365 (19.5%)	144/365 (39.5%)	0.50 [0.26 to 0.97]	198 fewer per 1000 [12 to 292 fewer]	Very Low
Incontinence at 6 - 12 months follow up (a)	38/330 (11.5%)	82/329 (24.9%)	0.42 [0.22 to 0.80]	144 fewer per 1000 [50 to 194 fewer]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 0 - 3 months follow up	197	195	Not applicable	Mean difference (MD): -10.24 [-19.13 to -1.35]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 3 - 6 months follow up	170	171	Not applicable	MD: -18.79 [-23.99 to -13.58]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 6 - 12 months follow up	150	150	Not applicable	MD: -14.40 [-18.27 to -10.53]	Very Low
Men with Incontinence after TURP					
Incontinence after TURP at 0 - 3 months follow up	4/56 (7.1%)	6/50 (12%)	0.58 [0.97 to 1.96]	50 fewer per 1000 [4 fewer to 115 more]	Low
Men with post micturition dribbling PMD					
Decrease in mean urine loss adjusted for initial pad weight gain (g) in men with PMD at 0 – 3 months	13	15	Not applicable	Not estimable p<0.001 reported in study	Very Low
Adverse events	0	0			

(a) Data were analysed using random effects due to unexplained heterogeneity.

** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

5.2.1.2 Economic evidence

No economic studies were identified.

5.2.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between the PFMT and the control group in number of men who were incontinent after prostatectomy when the outcomes are reported at 3 months or less.

Fewer men in the PFMT group were incontinent after prostatectomy compared to the control group when the outcomes are reported after 3 months but less than one year.

The PFMT group had more reduction in mean urine loss compared to the control group in men who received prostatectomy for all intervals where the outcome was reported.

There is no statistically significant difference between the PFMT and no control group in the reduction of incontinence after TURP when the outcomes are reported at 3 months or less.

The PFMT group had more reduction in mean urine loss adjusted for initial pad weight compared to the control group in men with post micturition dribble when the outcomes were reported between 0 – 3 months.

Economic No economic studies were identified.

5.2.2 Recommendations and link to evidence

Recommendation	**Offer supervised pelvic floor muscle training to men with stress urinary incontinence caused by prostatectomy. Advise them to continue the exercises for at least 3 months before considering other options.**
Recommendation	**Refer for specialist assessment men with stress urinary incontinence arising from causes other than prostatectomy (for example, radiotherapy or pelvic fracture urethral distraction injuries).**
Relative values of different outcomes	The GDG considered incontinence whether patient is continent or not irrespective of the degree of incontinence as being an important outcome since the definition of degree of incontinence and the impact that has on an individual patient is not standardised. Number of episodes of incontinence and the time at which they occur would be a more useful outcome. The amount (mean grammes) of urine loss was considered less useful by the GDG. This is a subjective impact of amount of urine leaked per day upon the individual and it is difficult to establish a minimal clinically important difference.
Trade off between clinical benefits and harms	There are no harms associated with pelvic floor muscle exercises providing the patient is taught to perform the exercises correctly. Incontinence can substantially reduce quality of life and the group considered its prevention clinically important.
Economic considerations	There are costs associated to NHS in terms of time spent on pelvic floor exercise instruction by the healthcare professional. However these could be offset by minimising the costs of products for incontinence management if the conservative strategy is successful.
Quality of evidence	The quality of evidence for each outcome pooled was low to very low due to limitations in study design, imprecision and high statistical heterogeneity probably arising from differences between studies due to different protocols for treatment (such as timing and duration of PFMT sessions, definition of incontinence, type and amount of information to the control arm). There was also considerable indirectness. All of the longer term evidence for PFMT was in men following radical prostatectomy for localised prostate cancer, these patients tend to experience more severe incontinence due to surgery and have fewer prior symptoms compared to the guideline population of men with LUTS due to other causes, such as overactive bladder or weakened muscles.
Other considerations	Maintaining motivation and adherence to treatment programmes may be difficult; in order to get improvement, treatment must be continued for several months. There was no significant difference between patients receiving PFMT and no

intervention when outcomes were measured within 3 months.

The implementation of this recommendation depends on the local availability of people capable of training and on the availability of patient information.

It is uncertain whether certain groups of patients, for example cognitively impaired patients may benefit equally from PFMT training.

There is no evidence for patients with stress urinary incontinence arising from non-prostatectomy reasons such as trauma or radiotherapy. These patients should be referred to specialists for individual assessment.

5.3 Biofeedback

Biofeedback (BF) uses specialised equipment to provide a visual, auditory or tactile representation of pelvic floor muscle function which the patient can use to aid pelvic floor muscle training.

5.3.1 In men who report LUTS, what is the effect of biofeedback versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

All three RCTs indentified for biofeedback were conducted in men who had prostatectomy for localised prostate cancer [19,78,265].

All of these studies were different in how biofeedback sessions were performed and the type of intervention provided to the "control" group. One of these studies compared patients instructed pre-operatively (one session) with graded PFMT using biofeedback against patients who only received written and brief verbal instructions on how to perform PFMT [19]. Another study compared patients receiving biofeedback sessions against those who were trained in PFMT without the biofeedback technique [78]. The third study included electrical stimulation (ES) and randomised patients into three arms: PFMT only, PFMT + ES and PFMT + ES + BF arms; the PFMT + ES + biofeedback arm was compared against PFMT + ES [265].

See Evidence Table 5, Appendix D and Forest Plots in Figure E-6 in Appendix E.

5.3.1.1 Clinical evidence

Table 5-21: Biofeedback vs. Control – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Incontinence at 0 - 3 months follow up[19,265]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Incontinence at 3 - 6 months follow up[19,78]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Incontinence at 6 - 12 months follow up[265]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Quality of life (IPSS question)	0	RCT				
Adverse events	0	RCT				

(a) *Data from studies are supplemented by data from a Cochrane systematic reviews Hunter 2007[104]*
(b) *2 studies[19,78] do not report randomisation method or allocation concealment. 2 studies[78,265] do not report masking of outcome assessment or were unclear. One study[265] has a high attrition rate. Although there is no statistical heterogeneity, differences between studies are noted in the intervention received by the control group, timing of interventions, number of exercises performed and intensity, treatment duration and amount of supplementary written and verbal information provided.*
(c) *All patients underwent prostatectomy for localised prostate cancer and therefore likely to experience more severe incontinence as a result of surgery compared to men with overactive bladder or those following a TURP. However this is unlikely to significantly reduce the applicability of the results.*
(d) *Confidence intervals are wide making estimate of effect uncertain.*

Table 5-22: Biofeedback vs. Control – Clinical summary of findings

Outcome	*Biofeedback*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Incontinence at 0 – 3 months follow up	31/96 (32.3%)	33/96 (34.4%)	0.94 [0.63 to 1.39]	21 fewer per 1000 [127 fewer to 134 more]	Low
Incontinence at 3 – 6 months follow up	10/78 (12.8%)	2/64 (3.1%)	3.41 [0.87 to 13.44]	75 more per 1000 [4 fewer to 386 more]	Low
Incontinence at 6 – 12 months follow up	5/46 (10.9%)	8/46 (17.4%)	0.63 [0.22 to 1.77]	64 fewer per 1000 [136 fewer to 134 more]	Low

5.3.1.2 Economic evidence

No economic studies were identified.

5.3.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between the biofeedback and the control group in number of men who were incontinent after prostatectomy at all intervals (0 to 12 months) where the outcomes were reported.

Economic No economic studies were identified.

5.3.2 Recommendations and link to evidence

See research recommendations in section 5.12.3.

5.4 Electrical stimulation

Electrical stimulation has been evaluated in a number of clinical settings in patients with both urge and stress urinary incontinence and in those with voiding difficulty. Electrical stimulation can be administered by probes being inserted into the rectum and an electrical impulse applied to either stimulate the pelvic floor muscles via their nerve supply, or to modulate the reflex activity. It is also often used as an aid to enhance the effectiveness of pelvic floor muscle training by helping patients to learn to recognise their pelvic floor muscles.

Implantable sacral root neuromodulation is covered in section 9.2 on Surgery for Storage Symptoms (Neuromodulation and sacral nerve stimulation). A variation of the implanted spinal cord stimulation technique (The Brindley Anterior Sacral Root Stimulator) which can be used for patients with spinal injury is not considered and reviewed in this guideline.

5.4.1 In men who report LUTS, what is the effect of electrical stimulation versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

Two RCTs on electrical stimulation were found and both compared ES with PFMT against PFMT in patients who received prostatectomy [168,265]. However, the number of sessions, intensity of instructions and training methods differed. See Evidence Tables 5, Appendix D, Forest Plots in Figures E-7, Appendix E, and Economic Evidence Table 53, Appendix D.

5.4.1.1 Clinical evidence

Table 5-23: Electrical stimulation plus PFMT vs. Control – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Incontinence at 0 - 3 months follow up[168,265]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Incontinence at 3 - 6 months follow up	0					
Incontinence at 6 - 12 months follow up[265]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (c)	Serious imprecision (d)
Quality of life (IPSS question)	0					
Adverse events	0					

(a) *Studies are supplemented by data from the Cochrane systematic reviews Hunter 2007*[104]
(b) *Both studies report randomisation method and allocation concealment but neither study reports masked outcome assessment and there was serious attrition from one study*[265]*. Although there is no statistical heterogeneity, differences between studies are noted in timing, intensity and duration of sessions, treatment duration and amount of supplementary written and verbal information provided.*
(c) *All patients underwent prostatectomy for localised prostate cancer and are likely to experience more severe incontinence as a result of surgery compared to men with overactive bladder or those following a TURP. However this is unlikely to significantly reduce the applicability of the results.*
(d) *Confidence intervals cross MID making estimate of effect uncertain.*

Table 5-24: Electrical stimulation plus PFMT vs. Control - Clinical summary of findings

Outcome	Electrical stimulation	Control	Relative risk	Absolute effect	Quality
Incontinence at 0 - 3 months follow up	21/68 (30.9%)	29/67 (43.3%)	0.70 [0.45 to 1.08]	130 fewer per 1000 [238 fewer to 35 more]	Low
Incontinence at 6 - 12 months follow up	8/46 (17.4%)	11/47 (23.4%)	0.74 [0.33 to 1.68]	61 fewer per 1000 [157 fewer to 159 more]	Low

5.4.1.2 Economic evidence

One economic study[75] was identified and included in the review of economic evidence. It is a within group comparison reporting clinical outcomes and the cost of ten sessions of maximal functional electrical stimulation. Please see Evidence table 53 in Appendix D for further details.

Table 5-25: stimulation vs. Control - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Fehrling2007[75]	Serious limitations (a)	Partially applicable (b)	

(a) *Within group comparison; not a full economic evaluation; outcomes are not clear-cut; only the cost of the intervention is considered; mixed male and female population (31/29); many outcome data were not reported.*
(b) *Study conducted in Sweden.*

Table 5-26: Electrical stimulation vs. Control - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Fehrling2007[75]	£2,640 (a,b)	Not estimable (c)	Not applicable (d)	Not reported

(a) *Cost converted from 2007 Euro (Germany) using the Purchasing Power Parities 1€=£0.754*
(b) *Cost of 10 sessions.*
(c) *Outcomes reported are: a) number of patients with the following degree of leakage: No leakage, Minor, Moderate, Severe, Not Reported; b) number of patients with either 2-4, 4-6, 6-8, 8-10, >10 voids per day or number of voids not reported. Please see evidence table 53, Appendix D for further details.*
(d) *The study reports the cost per successfully treated patient (£12,820) but it does not say how success was defined.*

5.4.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between electrical stimulation plus PFMT and the control group in number of men who were incontinent after prostatectomy at all intervals where the outcomes were reported.

Economic Electrical stimulation is associated with high costs. This evidence has serious limitations and partial applicability.

5.4.2 Recommendations and link to evidence

See research recommendations in section 5.12.3.

5.5 Bladder training

Bladder retraining is thought to be useful in managing the symptoms of urinary urgency and frequency. It is used to describe the educational and behavioural approach to re-establish bladder control and restore a normal bladder pattern by actively involving the individual in attempting to increase the interval between the desire to void and the actual void. This may occur by mandatory schedules in which the individual may not use the toilet between set times for voiding, or a self-scheduled regimen where the patient gradually increases their inter-voiding times, and may use the toilet between times if urgency becomes unbearable.

5.5.1 In men who report LUTS, what is the effect of bladder training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

No clinical or economic studies were identified.

5.5.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

5.5.2 Recommendations and link to evidence

Recommendation	**Offer men with storage LUTS suggestive of overactive bladder (OAB) supervised bladder training, advice on fluid intake, lifestyle advice and, if needed, containment products.**
Relative values of different outcomes	Improved quality of life from improved continence and a reduction in urinary urgency and frequency are important benefits to patients.
Trade off between clinical benefits and harms	Bladder training is a non-invasive therapy with no systemic side effects. Discomfort during delayed voiding is a possible harm generated by this therapy but this is largely outweighed by the potential clinical benefits. Providing the patient is advised the correct target fluid intake, no harm is likely to result. Caffeine withdrawal symptom is possible, but patients can be advice to cut back gradually rather than stopping them suddenly. The GDG considered the benefit from reducing urinary frequency and urgency is worth the inconvenience.
Economic considerations	There are costs associated with the time spent by healthcare professionals on supervising bladder training, and healthcare professionals may need to spend more time explaining the lifestyle modifications. However these could be offset by minimising the costs of products for incontinence management if the conservative strategy is successful.
Quality of evidence	No clinical or economic studies were found in men with LUTS.

Other considerations

Due to the lack of evidence, this recommendation was developed based on expert opinion and consideration of the recommendations and evidence in the NICE Urinary Incontinence Guideline for women.

The female urinary incontinence guideline recommended that 'bladder training lasting for a minimum of 6 weeks should be offered as first-line treatment to women with urge or mixed urinary incontinence(UI), and advised fluid intake modification.

The difference between the recommendation for women with UI and recommendation for men with LUTS reflects the lack of evidence in men on the effects of bladder training.

This recommendation is also linked to the education recommendations as any person assessing men with LUTS should be aware of this technique.

The implementation of bladder training recommendation depends on the local availability of people capable of training and on the availability of patient information.

Advice on fluid intake and lifestyle modification would be easy to implement but requires a good explanation from the clinician so that the concept is clearly understood by the patient. Training for carers will also be required. The patient's religious belief needs to be considered by the clinician as certain practices such as fasting may affect the ability to carry this out.

For some patients with cognitive impairment bladder training is not feasible, and advice on fluid intake and lifestyle modification require assistance from family members and carers. Alternative methods of behavioural modification are more appropriate for those patients.

5.6 Post void milking

Post void milking is a technique used to eliminate post micturition dribble (PMD) which is not associated with obstruction but may be caused by the urethra being emptied incompletely by the muscles surrounding it. This technique involves drawing the tips of the fingers behind the scrotum and pushing up and forward to expel the pooled urine.

5.6.1 In men who report LUTS, what is the effect of post void milking versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

See Evidence Table 6, Appendix D.

One small RCT with three arms comparing post-void milking, PFMT and no intervention in men with post-micturition dribbling was found.

5.6.1.1 Clinical evidence

Table 5-27: Post void milking vs. No Intervention – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Decrease in mean urine loss adjusted for initial pad weight gain (g) at 0 – 3 months[203]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

a) *The study is supplemented by data from the Cochrane systematic reviews Hunter 2007[104].*
b) *The study[203] does not report randomisation method or allocation concealment. Standard deviations reported for the unadjusted mean urine loss in were very high indicating possible skewed data. In addition mean improvement in pad weight gain adjusted for initial pad weight again gain were not reported with standard deviations so an absolute effect between interventions could not be calculated.*
c) *The study has 15 only patients or less in each arm.*

Table 5-28: Post void milking vs. no intervention - Clinical summary of findings

Outcome	*Post void milking*	*No intervention*	*Relative risk*	*Absolute effect*	*Quality*
Decrease in mean urine loss adjusted for initial pad weight gain (g) at 0 – 3 months	15	15	Not applicable	Not estimable p<0.01 reported in study, favouring post void milking	Very Low

5.6.1.2 Economic evidence

No economic studies were identified.

5.6.1.3 Evidence statement (s)

Clinical Post void urethral milking is more effective than no treatment in decreasing mean urine loss adjusted for initial pad weight in men with post micturition dribble at 0 – 3 months follow up.

Economic No economic studies were identified.

5.6.2 Recommendations and link to evidence

Recommendation	**Explain to men with post micturition dribble how to perform urethral milking.**
Relative values of different outcomes	Post-micturition urine loss measured by pad testing was the important and relevant outcome as reduced post-micturition dribbling is the desired effect of the technique.
Trade off between clinical benefits and harms	Being a safe and simple (easy to learn) procedure, the benefits largely outweigh the harms which are mainly represented by embarrassment.
Economic considerations	There are costs associated with the time spent by healthcare professionals on offering advice about urethral milking. However, these could be offset by minimising the costs of other types of management if the conservative strategy is successful.

Quality of evidence	The evidence was in one small study of very low quality. Two different ways of analysing the efficacy (urine loss) was used: mean urine loss adjusted for baseline level and unadjusted for baseline level. Only the adjusted mean reached statistical significance in this very small study.
Other considerations	It would be very easy to implement if not already used in practice. There are leaflets available and many clinicians are aware of this technique. The technique is easy to learn and patients usually can master the technique in one session. The clinical benefits (reduced urine loss) can be immediately observable in patients who had learned the technique.

5.7 Fluid intake

Advice on moderation of fluid intake is given by most services treating LUTS. There is much confusion over how much people should drink but there is some consensus that fluid intake should be based on body weight. However, patients (particularly those with storage LUTS) will often reduce their fluid intake excessively as a coping strategy, resulting in worsened symptoms and increased risk of infection.

5.7.1 In men who report LUTS, what is the effect of timing of fluid intake versus no change in timing of fluid intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

No clinical or economic studies were identified.

5.7.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

5.7.2 Recommendations and link to evidence

See recommendations and link to evidence in section 5.5.2.

5.8 Reduction in alcohol/caffeine/artificial sweeteners/carbonated drink

Advice on the modification of the type of fluids consumed is commonly provided to men with LUTS. Reduction in the intake of fluids containing alcohol, caffeine and artificial sweeteners together with avoidance of carbonated drinks is often advised by clinicians in the hope that this will reduce LUTS.

5.8.1 In men who report LUTS, what is the effect of reducing alcohol/caffeine/artificial sweeteners/carbonated drink intake versus no reduction in their intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

No clinical or economic studies were identified.

5.8.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

5.8.2 Recommendations and link to evidence

See recommendations and link to evidence in section 5.5.2.

5.9 Products

Products designed to contain or divert the urine leaked during an episode of incontinence are widely used in men with LUTS involving incontinence. Many types and brands of products are available both on prescription and on general sale. Penile clamps are devices designed to fit around and compress the penis to prevent urine loss. The patient releases the clamp when they wish to void urine.

5.9.1 In men who report LUTS, what is the effect of one type of product (pads, pants, bedpants, penile sheaths appliances and penile clamps) versus no product or other conservative therapy on patient related and biometric outcomes and adverse events?

Only one small cross-cross over RCT which compared the effectiveness of 3 types of penile clamps in reducing urine loss was found [169]

See Evidence Table 7, Appendix D, and Economic Evidence Table 53, Appendix D.

5.9.1.1 Clinical evidence

Table 5-29: Penile clamp vs. no penile clamp – Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Incontinence (mean urine loss, g) - Cunningham clamp [169]	1	RCT	Serious limitations (a, b)	No serious inconsistency	Serious indirectness (c)	Very serious imprecision (d)
Incontinence (mean urine loss, g) - C3 clamp [169]	1	RCT	Serious limitations (a, b)	No serious inconsistency	Serious indirectness (c)	Very serious imprecision (d)
Incontinence (mean urine loss, g) - U-Tex Clamp [169]	1	RCT	Serious limitations (a, b)	No serious inconsistency	Serious indirectness (c)	Very serious imprecision (d)
Adverse events	0					

[a] *This is a cross-over, open label trial. Blinding would not have been possible for this intervention. The average number of days for follow up in each type of clamp was about 4 days.*
[b] *Parametric test (analysis of variance) had been used despite the small sample size (n=12)*
[c] *This study was conducted in men with radical prostatectomy.*
[d] *Small study population (12 men in cross-over trial).*

Table 5-30: Penile clamp vs. no penile clamp - Clinical summary of findings

Outcome	Penile Clamp	No intervention	Relative risk	Absolute effect	Quality
Incontinence (mean urine loss, g) – Cunningham clamp	12	12	Not applicable	MD-105.7 [180.7 to 30.7 lower]	Very Low
Incontinence (mean urine loss, g) - C3 clamp	12	12	Not applicable	MD -90.5 [165.8 to 15.2 lower]	Very Low
Incontinence (mean urine loss, g) - U-Tex clamp	12	12	Not applicable	MD -69.5 [152.3 lower to 7 higher]	Very Low

5.9.1.2 Economic evidence

We found one economic study[71] comparing different types of products for incontinence (inserts, diapers, pull-ups, T-shaped, washables). This study[71] was a HTA on absorbent products for urinary/faecal incontinence based on three RCTs. We have included only one of the three RCTs according to the male/female ratio of patients enrolled.

In this study[71] patients living in the community setting were asked to rate their preference for one product through a Visual Analogue Scale (VAS) from 0 to 100. Patients were also asked to state whether they would be willing to buy the product if they had to bear its cost. The ranges of the proportion of patients willing to buy the product were: inserts 33% - 39%; diapers 50% - 52%; pull-ups 39% - 43%; T-shaped 33% - 39%; washables 38% - 53%.

Please see Economic Evidence Table 53, Appendix D for further details.

Table 5-31: Absorbent products - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Fader 2008[71]	Serious limitations (a)	Partially applicable (b)	HTA on absorbent products for urinary/faecal incontinence. Considered to have some usefulness in informing GDG decision making

(a) Not a full economic evaluation. Effectiveness was not measured in terms of any of the clinical outcomes included in our Guideline. Nevertheless this study was included because it supports our recommendations.
(b) The study included also women and men with faecal incontinence.

Table 5-32: Absorbent products - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Fader 2008[71]	(a)	(a, b)	Not applicable (b)	The monthly costs had the following ranges: for day use £34 - £73, for night use £43 - £64. The VAS scores had the following ranges: for day use 34 – 64, for night use 43 – 73. Different types of products within the same category have different costs and performance. The results are very sensitive to these variations.

(a) The study is not easily accommodated by the economic profile tables and the details of the study are reported in the text below.
(b) The outcome reported was a measure of preference towards a product rather than a health outcome.

5.9.1.3 Patient views

One study reported the patient view on penile clamps. Three other studies reported the patient preferences on various absorbent products for urinary incontinence.

Table 5-33: Patient view on products

Study	Study design	Setting	Population	Intervention	Comparison	Outcomes
Moore 2004[169]	RCT, cross-over, open label – Self reported questionnaire	Canada	Post-radical prostatectomy (n=12)	3 types of penile clamps: Cunningham, C-3 and U-Tex	Other penile clamp designs, and without penile clamps	The Male Continence Device Satisfaction Questionnaire was completed for each type of clamp. The number of patients who ranked a product "positively" was 10/12 for Cunningham, 2/12 for C3 and 0/12 for U-Tex clamps respectively (a).
Macualay 2004 & 2004A[143,144]	Pre & post test interview, questionnaire, diary	UK, London	Patients with moderate or severe urinary incontinence and mobile (n=14, 10 men)	Washable products	Disposable products	Important attributes of a product were high absorbency without leakage, discreteness, comfort, fits well. Pads designed for women were not anatomically suitable for men. For washable products, the privacy and practicalities of washing were concerns for men.
Fader 2006[72]	RCT, multicentre, cross over.	UK, London	Men with light urinary incontinence using or suitable for using absorbent products (n=74)	Incontinence products of various designs: pouch, leaf, Pantegral and pads. All pouches and leaf products which were available in UK in 2003 were compared		Prioritisation of product characteristics were ability to hold urine (absorb without leak), comfort, fit – flattering designs, discreteness and ability to stay in place. When going out, lack of a sanitary bin equivalent to discard disposable product in public toilets could be a problem. For washable products, it was inconvenient to bring a soiled product home.
Fader2008[71]	RCT, cross over study. A validated questionnaire for pad performance and diaries for leakage were used. An interview and VAS scale was used to determine performance	UK	85 (49 men, 36 women) participants with moderate to heaving incontinence with good mobility and independence of daily living activities.	Two or three products from each of the four main disposable designs and one washable design (total of 14 test products) were tested. This includes pads, pull-ups, T shapes, washables and disposable diapers.		This study found that men and women have different preferences of products. The suitability of products may depend on time of use (day vs. night) due to the position of the penis and whether when going out or staying at home. For overall acceptability, men preferred pull ups or diapers to pads. Washable diapers were most popular among men for use at night.
Paterson 2003[202]	Focus groups & 4 interviews. Qualitative, thematic analysis. Needs, issues and concerns of patients and carers were explored.	Australia	Patients or carers (n=82), who were members of an incontinence advocacy group	Incontinence products		Key factors found to influence selection of products were availability, cost, quality, comfort and design. Most consumers said they had selected from a limited range of products as they had limited product knowledge in the early stages.

(a) This was based on the reply to a single question "What is your overall opinion of the penile compression device?" These are the patients who "ranked positively" (the clamp). Answer options to the questionnaire was not provided.

5.9.1.4 Evidence statement (s)

Clinical Penile clamps are more effective than no clamps in reducing urine leakage.

No studies reported outcomes for pads, pants, bedpants or penile sheaths.

Patient views Some designs of penile clamps (e.g. Cunningham clamp) are associated with better patient satisfaction than others (e.g. C-3 clamp)

For absorbent products, the attributes such as high absorbency with low leakage, discreteness, comfort and proper fit were considered by patients as important.

Men and women have different preference for types of products. Pads designed for women were not anatomically suitable for men.

For washable products, the privacy and practicalities of washing were concerns for men.

Economic The cost-effectiveness of products is uncertain.

5.9.2 Recommendations and link to evidence

Recommendation	**Offer a choice of containment products to manage urinary incontinence based on individual circumstances and in consultation with the man.**
Recommendation	**Offer men with urinary incontinence management (for example, pads or collecting devices) to achieve social continence until a diagnosis and management plan has been discussed.**
Recommendation	**Do not routinely offer penile clamps to men with urinary incontinence.**
Recommendation	**Consider permanent use of absorbent products for men with LUTS only after assessment and exclusion of other methods of management.**
Relative values of different outcomes	The important outcome is restoring quality of life by containing the urine leakage in a way which is socially acceptable to patients. Leakage, skin integrity and urinary tract infection are important.
Trade off between clinical benefits and harms	The harms considered by the GDG were urinary infection, stone formation, skin problems and damage from improper use of penile clamps, sheaths and catheters. Other than penile clamps, it was felt that the benefits of using these products for management of symptoms outweighed the harms but should remain a personal preference.
Economic considerations	According to GDG judgement, prices for these relatively low cost products will vary considerably locally. Their utility will vary by patient, and recommending a choice of products appear to be the most practical way to offer cost effective management of LUTS patients given the evidence available.

Quality of evidence	One small cross over trial for penile clamps was found. Thus, the strength of evidence for penile clamps was of very low quality.
Other considerations	Early implementation of continence support with appropriate products should be made available to all patients, taking into account personal preferences and clinical experience. Pads or incontinence products should be offered as early as possible, even if a definite diagnosis has not yet been reached. Men may have different preferences of product types due to anatomical differences. Product preference also depends on lifestyle and severity of the incontinence. A patient may also prefer different types of product for night time vs. day time use and when going out vs. staying in. There can be important differences between different product designs in terms of leakage performance.

5.10 Catheters

Urinary catheterisation is the insertion of a catheter through the urethra or abdominal wall (suprapubic) into the urinary bladder for withdrawal of urine. Catheters may be used as a short-term measure whilst men are awaiting curative treatment for LUTS and as a long term solution where persistent LUTS (either incontinence or urinary retention) are causing incontinence, infection or renal dysfunction and where an operative solution is not feasible. Their use is associated with an increased risk of adverse events including recurrent urinary infections, trauma to the urethra, pain and stone formation.

There are a number of types of catheters. The least invasive is a sheath appliance attached to a collection system (also known as a condom catheter), but this cannot be used for complete urinary retention. Intermittent catheterisation involves the passage of a single-use catheter by the patient or carer to empty the bladder. This is associated with lower risks than continuous indwelling catheterisation but is dependent on the man, or his carer, being able to learn the technique.

Long-term indwelling catheters are divided into urethral and suprapubic types. The urethral catheters have the advantage of easier initial insertion but suprapubic catheters may provide benefits in the long term such as reduced impact on sexual function, reduced infection and easier replacement.

5.10.1 In men who report LUTS, what is the effect of intermittent catheters compared to indwelling catheters on patient related and biometric outcomes and adverse events?

See Evidence Table 8, Appendix D.

5.10.1.1 Clinical evidence

No studies were identified.

5.10.1.2 Patient views

Table 5-34: Catheter patient views

Study	*Study design*	*Setting*	*Population*	*Intervention*	*Comparisons*	*Outcomes*
Saint 1999 [226]	Qualitative study – interviews	University affiliated Veterans Affairs medical centre, US.	Men using catheter in US hospital (N=104)	Condom catheter	Indwelling catheter	Condom catheter was significantly more conformable, less painful, and less restrictive than the indwelling catheter. Also more convenient and causing less embarrassment (not significant).
Jakobsson 2002[107]	Qualitative study – questionnaire	Urological clinic in Sweden.	Men with BPH (n=37) and men with prostate cancer (n=71)	Indwelling catheter experience	None	23.9% of men with BPH and 29.9% of men with prostate cancer had little or less information than wanted about wearing a catheter. 22.6% of men with BPH and 23.9% of cancer group had little or less information than wanted about handling a catheter. Men expressed discomfort in wearing a catheter when resting and moving and also when handling the catheter.
Shaw2008[233]	Qualitative study – interviews	Continence and urology service, Cardiff	Men (n=8) and women (n=7) – results reported for men's comments only	Experience of learning clean intermittent self-catheterisation	None	Comments included the negative impact of difficulty experienced with travelling and carrying the equipment. Men's catheters are longer and this led to difficulties in carrying them discreetly. Additional comments included the physical impacts of clean intermittent self catheterisation.
Logan 2008[138]	Qualitative study – interviews [same study as Shaw 2008]	Continence and urology service, Cardiff	Men (n=8) and women (n=7) – results reported for men's comments only.	Experience of learning clean intermittent self-catheterisation	None	Themes from interviews included: Technical difficulties and time to build confidence varies. Fear of contamination and infection. At start found it emotionally and technically difficult. Concerned at first time inserting catheter due to psychological issues and fear of causing internal damage.

5.10.1.3 Economic evidence

No economic studies were identified.

5.10.1.4 Evidence statement (s)

Clinical No studies were identified.

Patient views The condom catheter is more comfortable, less painful and less restrictive than indwelling catheters.

There is no statistically significant difference between condom catheters

and indwelling catheters in convenience and embarrassment.

Men with LUTS reported a request for more information on handling and wearing an indwelling catheter.

Comments about learning clean intermittent self catheterisation included fear of contamination and infection, initial concerns as technically and emotionally difficult and difficulties with travel.

Economic No economic studies were identified.

5.10.2 Recommendations and link to evidence

Recommendation	**Consider offering bladder catheterisation (intermittent or indwelling urethral or suprapubic) to men with LUTS that cannot be corrected by less invasive measures such as external collection devices (for example, pubic pressure urinal, sheath appliances).**
Recommendation	**Explain to men that indwelling catheters in urgency incontinence may not result in continence or the relief of recurrent infections.**
Recommendation	**Consider offering long-term indwelling urethral catheterisation to men:** • **for whom surgery is not appropriate** • **who are unable to manage intermittent self-catheterisation** • **with skin wounds, pressure ulcers or irritation that are being contaminated by urine** • **who are distressed by bed and clothing changes** • **who express a preference for this form of management.**
Recommendation	**If offering long-term indwelling catheterisation, discuss the practicalities, benefits and risks with the man and, if appropriate, his carer.**
Recommendation	**Consider offering indwelling suprapubic catheters as an alternative to long-term urethral catheters.**
Recommendation	**Consider offering sheath appliances for managing urinary incontinence in men if there is no indication for indwelling catheterisation.**
Relative values of different outcomes	Alleviation of acute retention and prevention of incontinence, infection or renal dysfunction from persistent retention is important. Recurrent urinary tract infections, haematuria, trauma to the urethra, pain and stone formation are important adverse events.
Trade off between clinical benefits and harms	Harms include incorrect use of catheter, and complications such as recurrent urinary tract infections, trauma to the urethra, accidental removal, recurrent blockage and stone formation. Patients may also be in pain or discomfort. The benefits will be the alleviation of acute retention and prevention of

	incontinence and they outweigh the harms if the catheters are used correctly.
Economic considerations	All these devices involve costs in terms of supervision and management of complications associated with the device. Their cost-effectiveness is very uncertain.
Quality of evidence	No clinical or economic studies were found.
Other considerations	The duration of catheterisation and the ability of patients to self-catheterise and availability of support from carers are important considerations. Patients should be made aware that suprapubic catheters are associated with urinary tract infections, calcification and long-term supervision and follow-up. Indwelling catheters are available in male and female lengths. There have been reports of female length catheters being used in male patients and the Foley balloon consequently being inflated in the male urethra with resulting trauma to the urethra. Care must be taken to select catheters of the correct length.

5.11 Summary of recommendations

- Explain to men with post micturition dribble how to perform urethral milking.

- Offer men with urinary incontinence management (for example, pads or collecting devices) to achieve social continence until a diagnosis and management plan has been discussed.

- Offer a choice of containment products to manage urinary incontinence based on individual circumstances and in consultation with the man.

- Offer men with storage LUTS suggestive of overactive bladder (OAB) supervised bladder training, advice on fluid intake, lifestyle advice and, if needed, containment products.

- Offer supervised pelvic floor muscle training to men with stress urinary incontinence caused by prostatectomy. Advise them to continue the exercises for at least 3 months before considering other options.

- Refer for specialist assessment men with stress urinary incontinence arising from causes other than prostatectomy (for example, radiotherapy or pelvic fracture urethral distraction injuries).

- Consider permanent use of absorbent products for men with LUTS only after assessment and exclusion of other methods of management.

- Do not routinely offer penile clamps to men with urinary incontinence.

- Consider offering sheath appliances for managing urinary incontinence in men if there is no indication for indwelling catheterisation.

- Consider offering bladder catheterisation (intermittent or indwelling urethral or suprapubic) to men with LUTS that cannot otherwise be corrected by less invasive measures such as external collection devices (for example, pubic pressure urinal, sheath appliances).

- Consider offering long-term indwelling urethral catheterisation to men:
  - for whom surgery is not appropriate
  - who are unable to manage intermittent self-catheterisation
  - with skin wounds, pressure ulcers or irritation that are being contaminated by urine
  - who are distressed by bed and clothing changes
  - who express a preference for this form of management.

- If offering long-term indwelling catheterisation, discuss the practicalities, benefits and risks with the man and, if appropriate, his carer.

- Explain to men that indwelling catheters for urgency incontinence may not result in continence or the relief of recurrent infections.

- Consider offering indwelling suprapubic catheters as an alternative to long-term urethral catheters.

5.12 Research recommendations on conservative managment

5.12.1 Catheters

The GDG recommended the following research question:

- What are the clinical and cost effectiveness and associated adverse events of intermittent catheterisation compared to indwelling catheterisation (suprapubic or urtheral) for men with voiding difficulty and chronic retention of urine?

Why this is important

The number of patients in this group is steadily increasing as more radical prostatectomies are carried out and the population ages. Current practice varies widely across the UK with no established standard of good practice. This research could establish the best approach to management in these men and so bring more effective, patient-focused treatment that is more cost effective. The study should be a randomised controlled trial comparing intermittent catheterisation, indwelling suprapubic and indwelling urethral catheterisation. Outcomes of interest would be quality of life, healthcare resource utilisation, adverse events (including leakage, skin breakdown, infection, erosion and death).

5.12.2 Products

The GDG recommended the following research question:

- What is the clinical and cost effectiveness and associated adverse events of absorbent pads compared to sheath collectors for men with urinary incontinence to improve symptoms and quality of life?

Why this is important

The number of patients in this group is steadily increasing as more radical prostatectomies are carried out and the population ages. Current practice varies widely across the UK with no established standard of good practice. This research could establish the best approach to continence management in these men, and so bring more effective, patient-focused treatment that is more cost effective. It is rare that any element of bladder training or recognition and treatment of bladder dysfunction are recognised as part of continence management. Evidence-based guidance on selecting the most suitable containment product and its subsequent management will benefit the quality of life of patients, use skilled nurse/carer resources more efficiently and reduce the costs of waste of unsuitable or sub-optimal product use. The study should be a randomised controlled trial reporting symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events.

5.12.3 Biofeedback and Electrical stimulation

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pelvic floor muscle training (PFMT) with biofeedback and/or PFMT with electrical stimulation to PFMT alone in reducing symptom progression for men with storage symptoms?

Why this is important

There is a lack of evidence that either electrical stimulation or biofeedback help to alleviate symptoms in men with lower urinary tract symptoms despite both treatments being offered in certain healthcare settings. The answer to this research question would provide data on the clinical and cost effectiveness of these interventions. If biofeedback or electrical stimulation is not beneficial it should not be offered, as costly in staff time and outlay of equipment. If the interventions are effective they will be beneficial by improving the patient's quality of life and reducing cost to the NHS in managing incontinence. It should then be made more freely available and budgeted into service provision. The study design should be a randomised controlled trial. Outcomes of interest would be symptoms score, quality of life, incontinence, adverse events, duration and cost of treatment and reduction of other incontinence management costs (e.g. pads).

5.12.4 Lifestyle interventions:

The GDG recommended the following research question:

- What lifestyle elements in men with lower urinary tract symptoms predict symptom progression?

Why this is important

Lower urinary tract symptoms are a common and probably under-reported cause of morbidity in men. Current diagnosis and treatment is a lengthy process often of trial and error. If basic lifestyle changes can improve this, the economic and quality of life benefits, affecting up to 25% of men, will be significant. Current evidence for lifestyle impact is of poor quality and a better understanding of incidence, causes and outcome will simplify and improve diagnosis and treatment. The study design to answer the question should be a prospective cohort study that will determine different lifestyle elements (e.g. diet) and whether they are linked to causing LUTS or the progression of LUTS.

6 Drug treatment for men with lower urinary tract symptoms

6.1 Introduction

In this chapter we consider the clinical and cost-effectiveness of drug treatment of lower urinary tract symptoms (LUTS). A number of medical treatments have been investigated for the treatment of LUTS. These include alpha blockers, 5α-reductase inhibitors (5-ARI) and numerous plant extracts. Aromatase inhibitors are only used in older clinical trials and will not be reviewed. There are considerable data on the safety and efficacy of alpha blockers and 5-ARIs and these data will be critically reviewed. Data on plant extracts are examined in the chapter on complementary treatments (chapter 14).

In the late 1980s there were a number of non-selective alpha blockers available that had been introduced to treat hypertension. They were also found to be effective in LUTS/BPH treatment but they were associated with significant side effects; particularly those of postural hypotension and dizziness. During the 1990's a number of more selective alpha blockers and two 5-alpha reductase inhibitors (5-ARIs) were released.

Drug treatment is frequently initiated in primary care by general practitioners; particularly the use of alpha blockers and to a lesser extent 5-alpha reductase inhibitors. They are frequently started on the basis of symptoms alone without much in the way of investigation. A trial of medical therapy may be a reasonable option for a man with LUTS.

6.2 Matrix of treatment comparisons

We searched for RCTs comparing the effectiveness of different pharmacological interventions for lower urinary tract symptoms. The interventions we included in our search were alpha blockers, 5α-reductase inhibitors (5-ARI), anticholinergics (Anti-Ch), phosphodiesterase 5 inhibitors (PDE5-I), diuretics, desmopressin, non-steroidal anti-inflammatory drugs and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box filled with "Yes" represents where evidence was found and is reviewed in this chapter. A box filled with "No" represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

Alpha blockers								
5-ARI	**Yes P136**							
Anticholinergics	**Yes P141**	No						
PDE5-I	**Yes P144**	No	No					
Diuretics	No	No	No	No				
Desmopressin	No	No	No	No	No			
NSAIDS	No	No	No	No	No	No		
Placebo	**Yes P132**	**Yes P145**	**Yes P149**	**Yes P152**	**Yes P154**	**Yes P155**	No	
Combination treatments*	**Yes P159**	**Yes P159**	**Yes P159**	**Yes P159**	No	No	No	**Yes P159**
	Alpha blockers	5-ARI	Anti-Ch	PDE5-I	Diuretics	Desmo-pressin	NSAIDS	Placebo

5-ARI = 5-alpha reductase inhibitors, Anti-Ch= Anticholinergics, NSAIDS= Non steroidal anti-inflammatory drugs, PDE5- I = phosphodiesterase-5-inihibitors

** Combinations considered were alpha blocker plus 5-ARI, alpha-blocker plus anticholinergic and alpha-blocker plus PDE5-I.*

6.3 Alpha blockers

The prostate and bladder neck have an important α-adrenergic innervations which provides the 'dynamic' component of bladder outlet obstruction. This is caused by the smooth muscle that contributes 40% of the content of benign prostatic hyperplasia responsible for enlargement of the prostate. Alpha blockers are thought to work by relaxing this muscle thereby reducing this resistance and improving symptoms and flow rate.

We reviewed alpha blockers (alfuzosin, doxazosin, tamsulosin and terazosin) which are commonly used and excluded studies with indoramin, prazosin and phenoxybenzamine hydrochloride as these are older drugs that are now little used. The GDG decided to review only doses and formulations of drugs which are currently licensed for use in the UK for the treatment of LUTS. Therefore, alfuzosin was included for doses of 7.5 and 10mg but one study reporting a 15mg arm was not included in the meta-analysis. Doxazosin doses from 2-8mg were included. Tamsulosin studies with 0.4mg doses were included but 0.2 and 0.8mg were excluded as they are not licensed in the UK. Terazosin studies with 5 or 10mg doses were included. Please see the footnotes of Table 6-35: Alpha blocker vs. Placebo - Clinical study characteristics for details of analysis.

6.3.1 Alpha blockers vs. placebo

See Evidence Table 9, Appendix D, Forest Plots in Figures E-8 to E-15, Appendix E and Economic Evidence Table 53, Appendix D.

6.3.1.1 Clinical evidence

Table 6-35: Alpha blocker vs. Placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score 42,60,121,130,132,156,166,172,218,219,223,256	12	RCT	No serious limitations	No serious inconsistency(b)	No serious indirectness	Serious imprecision(c)
Qmax4,29,43-45,65,85,117,121,130-132,137,150,166,172,218,219,223,229,256	21	RCT	No serious limitations	Serious inconsistency(b)	No serious indirectness	No serious imprecision(d)
Quality of life (IPSS question)42,130,218,219,256	5	RCT	Serious limitations (a)	No serious inconsistency(b)	No serious indirectness	Serious imprecision(c)
Dizziness3,14,29,36,42,44,45,59,65,74,85,93,115,121,130-132,137,150,156,166,172,192,210,218,219,223,256	28	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	No serious imprecision
Fatigue (asthenia) 3,14,29,36,44,65,74,85,93,115,121,130-132,156,166,172,192,210,218,219,223,256	23	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Headache3,14,29,36,44,65,74,85,93,115,130-132,137,166,172,192,210,218,219,256	21	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Postural hypotension14,60,65,74,93,121,131,132,156,166,192,210,219,223,256	15	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Rhinitis44,65,115,130,132,172,218	7	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Erectile dysfunction29,121,132,156,192,210,218,256	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Abnormal ejaculation42,44,115,121,130,132,156,166,172,193,219,223	12	RCT	No serious limitations	Serious inconsistency (b)	No serious indirectness	Serious imprecision(c)
Withdrawal due to adverse events3,14,29,42-44,60,74,85,93,115,121,130-132,137,166,192,210,218,219,223,241	23	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(c)

(a) *Serious study limitations as more than half of the studies have not reported the method of randomisation or allocation concealment.*

(b) *Heterogeneity was detected in the pooled results. Random effects analyses were conducted in these outcomes. Outcome may not be downgraded if the inconsistently was due to the difference in magnitude of benefits or harms, but all studies consistently showed harms or benefits.*

(c) *Confidence interval crossed the MID, and this adds to the uncertainty about the benefit or harm of one intervention over the other.*

(d) *The size of the benefit/arm was small, and did not reach clinical significance*

Table 6-36: Alpha blocker vs. Placebo - Clinical summary of findings

Outcome	Alpha blocker*	Placebo*	Relative risk	Absolute effect	Quality
Symptom score (a), (b)	5109	4226	Not applicable	Mean difference (MD) -2.55 [-3.17, -1.92]	Moderate
Qmax(ml/s)(a),(c)	3472	2982	Not applicable	MD 1.23 [0.90, 1.55]	Moderate
Quality of life (IPSS question) (a),(d)	2407	1672	Not applicable	MD -0.41 [-0.57, -0.25]	Low
Dizziness (a)	643/7949 (8.1%)	266/5855 (4.5%)	Relative risk (RR) 1.91 [1.54, 2.36]	41 more per 1000 [25 to 61 more]	Low
Fatigue (asthenia)	353/6600 (5.4%)	159/5333 (3.0%)	RR 1.89 [1.57, 2.27]	27 more per 1000 [17 to 38 more]	High
Headache	285/4636 (6.2%)	195/3316 (5.9%)	RR 1.11 [0.93, 1.32]	6 more per 1000 [4 fewer to 19 more]	Moderate
Postural Hypotension	126/5116 (2.5%)	32/4140 (0.8%)	RR 3.09 [2.12, 4.50]	17 more per 1000 [9 to 28 more]	Moderate
Rhinitis	101/1660 (6.1%)	68/1465 (4.6%)	RR 1.45 [1.08, 1.95]	21 more per 1000 [4 to 44 more]	Moderate
Erectile dysfunction/ impotence	72/2382 (3.0%)	46/2055 (2.2%)	RR 1.44 [1.00, 2.07]	10 more per 1000 [0 to 24 more]	Low
Abnormal ejaculation (a)	123/5655 (2.2%)	32/4549 (0.7%)	RR 2.98 [1.20, 7.40]	14 more per 1000 [1 to 45 more]	Low
Withdrawal due to adverse events	476/6622 (7.2%)	287/4709 (6.1%)	RR 1.37 [1.19, 1.58]	23 more per 1000 [12 to 35 more]	Moderate

** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

Notes about analysis of results:

(a) These outcomes were analysed using random effects analysis. . All analyses were conducted using the fixed effect model except where indicated

(b) For symptoms scores, Chapple 2005:Tamsulosin combined 0.4mg arms and excluded 0.8mg arm; Roehrborn 2001: Alfuzosin 10mg arm included and 15mg arm excluded; Vankerrebroeck 2000: Alfuzosin 10mg and 7.5mg arm combined; Wilt 2002: tamsulosin included 0.4mg arm and excluded 0.8mg arm.

(c) For Qmax: Wilt 2002 as above, Gillenwater1995: Doxazosin 2, 4,8mg arms combined and 12mg excluded; Roehrborn 2001 and Vankerrebroeck 2000 as above.

(d) Quality of life: as above.

(e) Cochrane systematic review for Wilt on tamsulosin used 0.4mg and not 0.8mg data. For adverse events, asthenia and withdrawal due to adverse events the reviewers went back to the original studies to retrieve the data for 0.4mg as the results were combined in the Cochrane review. Chapple 1996 did not report this outcome separately.

6.3.1.2 Economic evidence

We found several economic studies comparing alpha blockers with placebo or active surveillance. Some of them[11,157] were excluded because the clinical data for the two arms were obtained from studies with different populations. A UK cost-benefit analysis[263] was excluded because of its uncertain methodology (arbitrary choice of attributes, probabilities not obtained from a systematic review, etc).

Three studies were included: a cost-consequences analysis[98] based on a RCT, a UK cost consequences analysis[109] based on a decision model, and a cost-utility analysis[58] based on a decision analysis.

Please see Economic Evidence Table 53 in Appendix D for further details.

Table 6-37: Alpha blockers vs. Placebo - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Hillman1996[98]	Serious limitations (a)	Partially applicable (b)	Comparator was placebo. Based on a RCT[223] included in our clinical review (see 6.3.1.1).
Johnson1999[109]	Serious limitations (c)	Directly applicable	Comparator was watchful waiting followed by medical treatment if necessary. Based on the AHCPR Guideline[154].
DiSantostefano2006[58]	Minor limitations	Partially applicable (d)	Comparator was watchful waiting. Based on the AHCPR Guideline[154].

(a) *Short follow-up (12 months). Complications were not considered. Funding from manufacturer of Alpha-Blockers.*
(b) *Study older than 10 years conducted in the USA.*
(c) *Funding from manufacturer of Alpha-Blockers. Not a full economic evaluation.*
(d) *Study conducted in the USA.*

Table 6-38: Alpha blockers vs. Placebo - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Hillman1996[98]	Alpha blockers are cost saving (a)	Alpha blockers significantly improved IPSS and IPSS QoL	Alpha blockers are dominant	One-way SA: results not sensitive to outlier costs, costs assigned by patient-reported events, cost of patients completing a full year of therapy, costs of improperly randomised patients.
Johnson1999[109]	£636 (b)	Alpha blockers improve discontinuation, symptoms, response-year gained (c)	Not reported	One-way SA: results not sensitive to cost of surgery, response rates, discontinuation rates, response degree, and time horizon.
Moderate symptoms				
DiSantostefano2006[58]	£1,420 (d, e, f, g)	0.08 QALYs (f, g)	£17,752/QALY (g)	One-way SA: results not sensitive to patient age. Alpha-blockers are not cost-effective when using the lower bound of utility weights. PSA: for a WTP=$50,000, AB have 70% probability f being cost-effective.
Severe symptoms				
DiSantostefano2006[58]	£1,429 (d, e, f, g)	0.09 QALYs (f, g)	£15,877/QALY (g, h)	One-way SA: results not sensitive to utility weights and patient age.

(a) *Cost of visits (home, GP and urologist), inpatient care, medication.*
(b) *Cost of GP and urologist consultations, laboratory procedures, examination, medications, surgical procedures, complications.*
(c) *Statistical significance not reported. Not clear how the outcome 'response-years gained' was calculated.*
(d) *2004 USD converted using the PPP 1$=£0.632*
(e) *Cost of visits, tests, drugs, operations, complications (strictures, and artificial urinary sphincter)*
(f) *Assumes 70% compliance to medical treatment.*
(g) *Results reported for the scenario where patients can switch treatment.*
(h) *In the study, TURP was the most cost-effective intervention for this group (see 12.1.1.2).*

6.3.1.3 Evidence statement (s)

Clinical

Alpha blockers are more effective than placebo in improving symptom scores.

Alpha blockers are more effective than placebo in improving Qmax (ml/s).

Alpha blockers are more effective than placebo in improving quality of life (IPSS question).

More men treated with alpha blockers than placebo experienced dizziness, fatigue (asthenia), postural hypotension, rhinitis, erectile dysfunction and abnormal ejaculation.

There is no statistically significant difference between alpha blockers and placebo in men experiencing headaches.

More men treated with alpha blockers than placebo withdrew due to adverse events.

Economic

Alpha blockers are cost-effective compared to placebo/no treatment in patients with moderate and severe symptoms.

This evidence has minor limitations and partial applicability.

6.3.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13.

6.3.2 Alpha blockers vs. 5-alpha reductase inhibitors (5-ARI)

Alpha blockers are the commonest first line medical therapy because of their rapid onset of action on symptoms, due to their mode of action of reducing contraction of the smooth muscle within the benign hyperplastic tissue of an enlarged prostate. They are most commonly used in men with mild to moderate bothersome LUTS. Their influence on the natural history of the condition is far less certain, based on our understanding of the mechanism of action of these agents.

5-alpha reductase inhibitors (5-ARI) act on the 5-alpha reductase enzyme which converts testosterone into the more potent androgen, dihydrotestosterone within the prostatic cells themselves. Because of their mechanism of action, the 5-ARIs are much slower in their onset of action but appear to have a more significant impact on the long-term natural history of the disease, effectively reducing prostate volume.

These two classes of drugs therefore have different mechanisms and time courses of action and need evaluation at different time points to assess their relative value. Studies of 5-ARIs and combination studies of alpha-blockers plus 5-ARIs are studied after longer follow-up periods than alpha blockers because the effects of the drug require 3-6 months to become measurable; this is true of symptom improvement, flow rate and prostate volume effects. Additional benefits have been recorded up to 2 and 4 years of follow-up.

6.3.2.1 Clinical evidence

See Evidence Table 10, Appendix D, Forest Plots in Figures E-16 to E-25, Appendix E and Economic Evidence Table 53, Appendix D.

1 **Table 6-39: Alpha blockers vs. 5-ARI - Clinical study characteristics**

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months [57,216]	2	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness	Serious imprecision(b)
Symptom score 1 year [121,132]	2	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness	Serious imprecision(b)
Symptom score at 2 years [224]	1	RCT	No serious limitations	No serious inconsistency(a,c)	No serious indirectness (c)	No serious imprecision(i))
Symptom score at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness	Serious imprecision(i)
Quality of Life (IPSS question) at 6 months [216]	1	RCT	Serious limitation(d)	No serious inconsistency	No serious indirectness	Serious imprecision(i)
Qmax(ml/s) at 6 months [57,216]	2	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness	Serious imprecision(i)
Qmax(ml/s) at 1 year [121,132]	2	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness	Serious imprecision(b)
Qmax(ml/s) at 2 years [224]	1	RCT	No serious limitations	No serious inconsistency(a)	No serious indirectness(c)	Serious imprecision(i)
Prostate volume (ml) at 6 months [57]	1	RCT	Serious limitations(d)	No serious inconsistency	No serious indirectness	No serious imprecision(e)
Prostate volume (ml) at 1 year [132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision(e)
Prostate volume (ml) at 2 years [224]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness(c)	No serious imprecision(e)
Prostate volume (ml) at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision(e)
PSA (ng/ml) at 6 months [57]	1	RCT	Serious limitations(d)	No serious inconsistency	No serious indirectness	No serious imprecision(e)
PSA (ng/ml) at 1 year[121]	1	RCT	Serious limitations(d)	No serious inconsistency	No serious indirectness	No serious imprecision(e)
Syncope (up to one year follow up)[121,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Postural hypotension[57,121,132]	3	RCT	No serious limitations	Very serious inconsistency (f)	No serious indirectness	Serious imprecision(b)
Orthostatic hypotension[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Dizziness[57,121,132,156,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Vertigo[121]	1	RCT	Serious limitations(d)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Headache[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Asthenia/fatigue [57,121,132,156]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Somnolence [57,121,156]	3	RCT	Serious limitations(d)	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Rhinitis[132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Decreased libido[121,132,156,224]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Impotence or erectile dysfunction[57,121,156,216,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Gynaecomastia[224]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)
Urinary retention[57,156]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Ejaculatory abnormality or retrograde ejaculation [57,121,132,156,216,224]	6	RCT	No serious limitations	Very serious inconsistency(g)	No serious indirectness	Serious imprecision(b)
Withdrawal due to adverse events [57,121,132,156,224]	5	RCT	No serious limitations	Serious inconsistency(h)	No serious indirectness	Very serious imprecision (b)

(a) *The treatment effects observed suggested the duration of treatment and follow-up are factors which potentially affect the direction and magnitude of difference, consistent with known mechanism of actions. Therefore, the quality of evidence was not downgraded.*

(b) *The confidence intervals of treatment effects crossed the MID(s).*

(c) *The direction of effect is not consistent with other studies comparing alpha-blocker vs. 5-ARI at both longer and shorter durations of followed up. The study had enrolled patients with large prostate (mean volume of 55ml). The population is applicable to the recommended populations.*

(d) *Only RCT(s)[57,121,216] which did not report randomisation allocation and concealment method was found or contributed more than 50% of weight of the pooled results.*

(e) *Precision was considered but the magnitude of reduction in prostate volume or PSA level that is important to patients or associated with differences in symptoms and prognosis is unknown.*

(f) *There was substantial heterogeneity in this outcome (postural hypotension). Chi square =4.56, df=2 (P=0.10), I square = 56%. This is not statistically significant using random effect analysis but significantly favoured alpha reductase inhibitors using a fixed effect analysis (RR: 3.39, 95% CI 1.80 to 6.40). (See Appendix E, Forest Plot E-23).*

(g) *Random effects analyses were used for the results of this outcome. There was substantial heterogeneity (The Chi square = 13.35, df=5 (P=0.02), I square = 63%) in the ejaculatory abnormality outcome, and random effect analysis was used. Subgroup analysis showed the RR for the tamsulosin trials were 2.03, 95% CI 1.02 to 4.04 (favouring 5-ARI) while the RR for the subgroup of alfuzosin, doxazosin and terazosin was 0.18, 95% CI 0.06 to 0.55 (favouring alpha-blocker, see Appendix E, Forest Plot E-24.*

(h) *There was substantial heterogeneity for this outcome and random effects analysis was conducted. Criteria for withdrawing patients due to adverse events were not reported in the papers reviewed, and there may be differences between the protocols used in different trials. (See Appendix E, Forest Plot E-25).*

(i) *The size of the benefit/arm was small, and did not reach clinical significance.*

Table 6-40: Alpha blockers vs. 5-ARI – Clinical summary of findings

Outcome	Alpha blockers	5-ARI	Relative risk	Absolute effect	Quality
Symptom score at 6 months	557	548	Not applicable	MD -0.91 [-1.58 to -0.24]	Moderate
Symptom score at 1 year	525	499	Not applicable	MD -2.52 [-3.15 to -1.89]	Moderate
Symptom score at 2 years	1611	1623	Not applicable	MD 0.6 [0.19 to 1.01]	High
Symptom score at 4 years	756	768	Not applicable	MD -1.00 [-1.54, -0.46]	Moderate
Quality of Life (IPSS question) at 6 month	196	204	Not applicable	MD -0.1 [-0.34 to 0.14]	Low
Qmax(ml/s) at 6 months	554	548	Not applicable	MD 0.12 [-0.41 to 0.66]	Moderate
Qmax(ml/s) at 1 year	525	491	Not applicable	MD 1.53 [0.92 to 2.15]	Moderate
Qmax(ml/s) at 2 years	1611	1623	Not applicable	MD -1.00 [-1.33 to -0.67]	Moderate
Prostate volume (ml) at 6 months	358	344	Not applicable	MD 4.1 [1.93 to 6.27]	Moderate
Prostate volume(ml) at 1 year	271	252	Not applicable	MD 6.60 [2.97 to 10.23]	High
Prostate volume(ml) at 2 years	1611	1623	Not applicable	MD 15.30 [14.18 to 16.42]	High
Prostate volume(ml) at 4 years	755	761	Not applicable	MD 10.76 [9.22 to 12.30]	High
PSA(ng/ml) at 6 months	358	344	Not applicable	MD 1.80[1.45 to 2.14]	Moderate
PSA(ng/ml) at 12 months	250	239	Not applicable	MD1.50 [1.28 to 1.72]	Moderate
Syncope (up to 1 year follow up)	5/580 (0.9%)	3/574 (0.5%)	RR 1.57 [0.41 to 6]	3 more per 1000 [3 fewer to 25 more]	Moderate
Postural hypotension (a)	41/938 (4.4%)	12/918 (1.3%)	RR 2.87 [0.91 to 9.06]	24 more per 1000 [1 fewer to 105 more]	Very Low
Orthostatic hypotension	146/663 (22.0%)	89/654 (13.6%)	RR 1.66 [1.33 to 2.07]	90 more per 1000 [45 to 146 more]	High
Dizziness	159/3305 (4.8%)	64/3309 (1.9%)	RR 2.47 [1.88 to 3.26]	28 more per 1000 [17 to 43 more]	High
Vertigo	8/275 (2.9%)	6/264 (2.3%)	RR 1.28 [0.45 to 3.64]	6 more per 1000 [13 fewer to 61 more]	Low
Headache	25/663 (3.8%)	23/654 (3.5%)	RR 1.09 [0.63 to 1.9]	3 more per 1000 [13 fewer to 32 more]	Moderate
Asthenia/fatigue	75/1694 (4.4%)	37/1686 (2.2%)	RR 2.00 [1.38 to 2.92]	22 more per 1000 [8 to 42 more]	High
Somnolence	12/1389 (0.9%)	10/1376 (0.7%)	RR 1.14 [0.52 to 2.51]	1 more per 1000 [3 fewer to 11 more]	Low
Rhinitis	20/305 (6.6%)	8/310 (2.6%)	RR 2.54 [1.14 to 5.68]	40 more per 1000 [4 to 122 more]	Moderate
Decreased libido	47/2947 (1.6%)	70/2965 (2.4%)	RR 0.67 [0.47 to 0.97]	8 fewer per 1000 [1 to 13 fewer]	Moderate
Impotence or erectile dysfunction	95/3196 (3%)	145/320 3 (4.5%)	RR 0.65 [0.51 to 0.84]	16 fewer per 1000 [7 to 22 fewer]	Moderate
Gynaecomastia	13/1611 (0.8%)	29/1623 (1.8%)	RR 0.45 [0.24 to 0.87]	10 fewer per 1000 [2 to 14 fewer]	Moderate
Urinary retention	11/1114 (1%)	7/1112 (0.6%)	RR 1.58 [0.62 to 4.07]	3 more per 1000 [2 fewer to 18 more]	Moderate
Ejaculatory abnormality(a)	27/3501 (0.8%)	31/3513 (0.9%)	RR 0.59 [0.18 to 1.94]	4 fewer per 1000 [7 fewer to 8 more]	Very Low
Withdrawals due to adverse events (a)	143/2748 (5.2%)	161/274 5 (5.2%)	RR 0.99 [0.69 to 1.42]	1 fewer per 1000 [18 fewer to 25 more]	Very Low

(a) Random effects analyses were conducted for these outcomes.

6.3.2.2 Economic evidence

We found several economic studies comparing alpha-blockers with 5-alpha reductase inhibitors. Some of them[11,157,254] were excluded because the clinical data for the two arms were obtained from studies with different populations (e.g. men with larger prostates only in the 5-ARI arm). One study[47] was excluded because results were poorly reported. A UK cost-benefit analysis[263] was excluded because of its uncertain methodology (arbitrary choice of attributes, probabilities not obtained from a systematic review).

Two studies were included: a UK cost consequences analysis[109] based on a decision model, and a cost-utility analysis[58] based on a decision analysis. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 6-41: Alpha-blockers vs. 5-alpha reductase inhibitors - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Johnson1999[109]	Serious limitations (a)	Directly applicable	Comparator was watchful waiting followed by medical treatment if necessary. Based on the AHCPR Guideline[154].
DiSantostefano2006[58]	Minor limitations	Partially applicable (b)	Comparator was watchful waiting. Based on the AHCPR Guideline[154].

(a) *Funding from manufacturer of Alpha-Blockers. Not a full economic evaluation.*
(b) *Study conducted in the USA.*

Table 6-42: Alpha blockers vs. 5-alpha reductase inhibitors - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Johnson1999[109]	Cost saving (a)	AB improve discontinuation, symptoms, response-year gained (b)	AB dominant	One-way SA: results not sensitive to cost of surgery, response rates, discontinuation rates, response degree, and time horizon.
Moderate symptoms				
DiSantostefano2006[58]	AB cost saving (c, d, e)	0.05 QALYs (d, e)	AB dominant (e)	PSA: for a WTP=$50,000, AB have 70% probability of being cost-effective. Same results if patients continue on initial treatment unless TURP is required.
Severe symptoms				
DiSantostefano2006[58]	AB cost saving (c, d, e)	0.05 QALYs (d, e)	AB dominant (e, f)	Same results if patients continue on initial treatment unless TURP is required.

(a) *Cost of GP and urologist consultations, laboratory procedures, examination, medications, surgical procedures, complications.*
(b) *Statistical significance not reported. Not clear how the outcome 'response-years gained' was calculated.*
(c) *Cost of visits, tests, drugs, operations, complications (strictures, and artificial urinary sphincter)*
(d) *Assumes 70% compliance to medical treatment.*
(e) *Results reported for the scenario where patients can switch treatment.*
(f) *In the study, TURP was the most cost-effective intervention for this group*

6.3.2.3 Evidence statement (s)

Clinical Alpha blockers are more effective than 5-ARIs in improving symptom scores at 6 months, 1 year and 4 years treatment periods.

5-alpha reductase inhibitors are more effective than alpha blockers in improving symptom scores at 2 years (men with larger prostates).

There is no statistically significant difference between alpha blockers and 5-ARIs in improving quality of life (IPSS question) score at 6 months follow-up.

There is no statistically significant difference between alpha blockers and 5-ARIs in improving Qmax (ml/s) at 6 months follow-up.

Alpha blockers are more effective than 5-ARIs in improving Qmax (ml/s) at 1 year follow up.

5-alpha reductase inhibitors are more effective than alpha blockers in improving Qmax (ml/s) at 2 year follow up (men with larger prostates).

5-alpha reductase inhibitors are more effective than alpha-blockers in reducing prostate volume at 6 months, 1, 2 and 4 years follow-up.

5-alpha reductase inhibitors are more effective than alpha blockers in reducing PSA at 6 months and 1 year follow up.

More men treated with alpha blockers than 5-ARIs experienced orthostatic hypotension, dizziness, fatigue (asthenia) or rhinitis.

Fewer men treated with alpha blockers than 5-ARIs experienced decreased libido, impotence or erectile dysfunction, gynaecomastia (breast enlargement).

There is no statistically significant difference between alpha blockers and 5-ARIs in number of men experiencing syncope, somnolence, postural hypotension, vertigo, headaches, ejaculatory abnormality, urinary retention or withdrew from study due to adverse events.

Economic Alpha blockers are less costly and more effective than 5-ARIs. This evidence has minor limitations and direct applicability.

6.3.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.3.3 Alpha blockers vs. anticholinergics

Alpha blockers reduce all the symptoms of LUTS attributed to BPH, as measured in the International Prostate Symptom Scores (IPSS). Anticholinergics are indicated for the more bothersome storage symptoms such as frequency and urgency which may be the main presenting symptoms in some patients with LUTS or still a problem despite the used of alpha blockers. Comparing these two classes of drugs therefore is worthwhile.

See Evidence Table 11, Appendix D, Forest Plot in Figures E-39, Appendix E.

6.3.3.1 Clinical evidence

Table 6-43: Anticholinergics vs. Alpha blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Qmax at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision(c), (d)
Urgency incontinence episodes/24h[115]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c),(e)
Urgency/24h[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/24h[115]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/night[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Ejaculation Failure[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Urinary Retention[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Fatigue[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Somnolence[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dizziness[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Nasal Congestion[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Diarrhoea[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Constipation[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dyspepsia[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Headache[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dry Mouth[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Withdrawal due to adverse events[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)

a) *There was incomplete or unclear reporting for many outcomes. This study [114,115] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but statistical significance of differences between agents were not reported. Only the statistical significance ($p<0.05$ or $p<0.01$) of the combination vs. placebo comparison was indicated in the paper for some of the outcomes. Actual values and standard deviations of these outcomes were also not reported. It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was shown.*

b) *Patients recruited in this study have higher IPSS (mean IPSS ~20) and significant storage symptoms. There is no serious indirectness of evidence because the recommendation was made for patients with these symptoms (OAB).*

c) *Confidence intervals for continuous outcomes unknown but unlikely to be precise based on the graphs, while those for adverse events met the criteria for downgrading.*

d) *Number of patients with Qmax measurements at follow up was not reported.*

e) *Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries were filled for 5 days before visit.*

Table 6-44: Anticholinergics vs. Alpha blockers - Clinical summary of findings

Outcome	Anti-Ch	Alpha blocker	Relative risk	Absolute effect	Quality
Symptom score at 3 months	197	206	Not applicable	MD 0.90 p value NR (a)	Low
Quality of life (IPSS question) at 3 months	198	206	Not applicable	MD 0.00 p value NR (a)	Low
Qmax at 3 months	NR (b)	NR (b)	Not applicable	MD -0.38 p >0.3	Low
Urgency incontinence episodes/24h	46	48	Not applicable	MD -0.13 p value NR (a)	Low
Urgency/24h	205	209	Not applicable	MD -0.50 P value NR (a)	Low
Frequency/24h	205	209	Not applicable	MD 0.1 p value NR (a)	Low
Frequency per night	205	209	Not applicable	MD 0.18 p value NR (a)	Low
Ejaculation Failure	0/217 (0.0%)	4/215 (1.9%)	RR 0.11 [0.01 to 2.03]	17 fewer per 1000 [18 fewer to 19 more]	Low
Urinary Retention	2/217 (0.9%)	0/215 (0.0%)	RR 4.98 [0.24 to 102.59]	Not estimable	Low
Fatigue	2/217 (0.9%)	3/215 (1.4%)	RR 0.66 [0.11 to 3.91]	5 fewer per 1000 [12 fewer to 41 more]	Low
Somnolence	2/217 (0.9%)	5/215 (2.3%)	RR 0.4 [0.08 to 2.02]	14 fewer per 1000 [21 fewer to 24 more]	Low
Dizziness	3/217 (1.4%)	12/215 (5.6%)	RR 0.25 [0.07 to 0.87]	42 fewer per 1000 [7 fewer to 52 fewer]	Low
Nasal Congestion	0/217 (0%)	3/215 (1.4%)	RR 0.14 [0.01 to 2.72]	12 fewer per 1000 [14 fewer to 24 more]	Low
Diarrhoea	7/217 (3.2%)	6/215 (2.8%)	RR 1.16 [0.39 to 3.38]	4 more per 1000 [17 fewer to 66 more]	Low
Constipation	9/217 (4.1%)	2/215 (0.9%)	RR 4.46 [0.97 to 20.4]	32 more per 1000 [0 fewer to 180 more]	Low
Dyspepsia	2/217 (0.9%)	1/215 (0.5%)	RR 1.98 [0.18 to 21.69]	5 more per 1000 [4 fewer to 103 more]	Low
Headache	2/217 (0.9%)	9/215 (4.2%)	RR 0.22 [0.05 to 1.01]	33 fewer per 1000 [40 fewer to 0 more]	Low
Dry Mouth	16/217 (7.4%)	15/215 (7%)	RR 1.06 [0.54 to 2.08]	4 more per 1000 [32 fewer to 75 more]	Low
Withdrawal due to adverse events	5/217 (2.3%)	4/215 (1.9%)	RR 1.24 [0.34 to 4.55]	4 more per 1000 [12 fewer to 66 more]	Low

(a) Statistical significance was of difference unknown. The study only reported outcomes as graphs and p values, standard errors or standard deviations were not reported. Values reported were adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre.

(b) Number of patients with Qmax measurements at follow up not reported.

6.3.3.2 Economic evidence

No economic studies were identified.

6.3.3.3 Evidence statement (s)

Clinical There is no statistically significant difference between anticholinergics and alpha blockers in improving Qmax.

There is no statistically significant difference between anticholinergics and alpha blockers in number of patients with ejaculation failure, urinary retention, fatigue, somnolence, rhinitis, diarrhoea, dyspepsia, constipation, headache, dizziness, dry mouth or adverse events which resulted in study withdrawal.

Economic No economic studies were identified.

6.3.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.3.4 Alpha blockers vs. phosphodiesterase 5 inhibitors (PDE5-I)

Several epidemiological studies have indicated that the association between LUTS and erectile dysfunction is more than a coincidence of age, with a possible cause and effect relationship. LUTS is more common in men with erectile dysfunction and there is a strong relationship between the severity of LUTS and the degree of erectile difficulty.

See Evidence Table 12, Appendix D, Forest Plots in Figures E-44 to E-48, Appendix E.

6.3.4.1 Clinical evidence

Table 6-45: PDE5-I vs. Alpha blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question)	0	RCT				
Qmax at 3 months[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Voiding frequency at 3 months[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Nocturia at 3 months[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Flushing[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Dizziness[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Dyspepsia[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Withdrawals due to adverse events[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)

(a) *Only one small (each study arm had 20-21 patients), open label study was found. This study also did not report method of randomisation allocation and concealment. The outcomes have a very high risk of bias, especially when subjective outcomes or outcomes collected based on patient responses were considered.*

(b) *Serious imprecision because of the very small sample size, or confidence intervals crossed MID.*

Table 6-46: PDE5-I vs. Alpha blockers - Clinical summary of findings

Outcome	PDE5-I	Alph a blockers	Relative risk	Absolute effect	Quality
Symptom score at 3 months	21	20	Not applicable	0.30 [-2.12 to 2.72]	Very Low
Qmax at 3 months	21	20	Not applicable	-0.20 [-1.64 to 1.24]	Very Low
Voiding frequency at 3 months	21	20	Not applicable	1.40 [0.23 to 2.57]	Very Low
Nocturia at 3 months	21	20	Not applicable	0.30 [-0.25 to 0.85]	Very Low
Flushing	1/21 (4.8%)	0/20 (0.0%)	2.86 [0.12 to 64.4]	Not estimable	Very Low
Dizziness	0/21 (0.0%)	2/20 (10.0%)	0.19 [0.01 to 3.75]	81 fewer per 1000 [99 fewer to 275 more]	Very Low
Dyspepsia	1/21 (4.8%)	0/20 (0.0%)	2.86 [0.12 to 64.4]	Not estimable	Very Low
Withdrawals due to adverse events	2/21 (9.5%)	2/20 (10.0%)	0.95 [0.15 to 6.13]	5 fewer per 1000 [85 fewer to 513 more]	Very Low

6.3.4.2 Economic evidence

No economic studies were identified.

6.3.4.3 Evidence statement (s)

Clinical There is no statistically significant difference between PDE5-I and alpha blockers in improving symptom score, Qmax, or nocturia at 3 months follow up.

Alpha blockers are more effective than PDE5-I in decreasing urinary frequency at 3 months follow up.

There is no statistically significant difference between PDE5-land alpha blockers in number of patients with flushing, dizziness, dyspepsia or withdrew from study due to adverse events.

Economic No economic studies were identified.

6.3.4.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.4 5-Alpha reductase inhibitors(5-ARI)

The rationale of 5-ARI usage is that development and growth of the prostate is dependent on the presence of androgens and dihydrotestosterone (DHT) in particular. The enzyme 5α-reductase converts testosterone to DHT within the prostate cell. The use of 5-ARIs therefore reduces levels of DHT which results in prostate volume reduction; as it is predominantly an intracellular effect it reduces the chance of sexual dysfunction, compared to systemic castration. Decreasing prostate volume decreases the static component of bladder outlet obstruction (BOO).

6.4.1 5-Alpha reductase inhibitors vs. placebo

See Evidence Table 13, Appendix D, Forest Plots in Figures E-26 to E-36, Appendix E and Economic Evidence Table 53, Appendix D.

6.4.1.1 Clinical evidence

Table 6-47: 5-ARI vs. Placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[34,204]	2	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	Serious imprecision (e)
Symptom score at 6 months [34,204]	2	RCT	Serious limitations (a)	Serious inconsistency(c)	No serious indirectness	Serious imprecision (e)
Symptom score at 1 year[5,34,132,155,187,204]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision (f)
Symptom score at 2 years[155,187,221]	3	RCT	No serious limitations	Serious inconsistency(d)	No serious indirectness	No serious imprecision (f)
Symptom score at 3 years [155]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision(f)
Symptom score at 4 years or more[155,156]	2	RCT	No serious limitations	Serious inconsistency(d)	No serious indirectness	No serious imprecision (f)
Quality of life (IPSS question)	0	RCT				
Qmax at 3 months[187]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision (f)
Qmax at 6 months[24]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	No serious imprecision (f)
Qmax at 1 year[5,13,88,132,155,187,204]	7	RCT	Serious limitations (a)	Serious inconsistency (d)	No serious indirectness	No serious imprecision (f)
Qmax at 2 years[13,155,187,221]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision (f)
Qmax at 3 years [155]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Qmax at 4 years or more [155]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Prostate volume at 1 year [88,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Prostate volume at 2 years [13,221]	2	RCT	No serious limitations	Serious inconsistency (d)	No serious indirectness	No serious imprecision
PSA (ng/ml) at 2 year [221]	1	RCT	No serious limitations	No serious inconsistency (g)	No serious indirectness	No serious imprecision
Decreased libido [24,34,88,132,147,155,187,221,248]	9	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Dizziness [88,132]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Ejaculation disorder [34,88,132,147,155,187,221,248]	8	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Fatigue[147]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Gynaecomastia[155,221]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Impotence[24,34,77,88,132,147,155,187,204,221,248]	11	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary retention[34,77,147,155,248]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Withdrawal due to adverse events [5,13,24,34,77,88,132,147,155,187,221,248]	12	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision (f)

(a) *7 studies did not report sequence generation, allocation concealment and blinding methods [5,13,24,34,88,204,248]. One had unclear blinding methods [132] while another did not report allocation concealment and blinding methods [155]. One of these studies did not report sequence generation, allocation concealment and blinding clearly, and outcomes data was not fully reported [77].*

(b) *There was substantial heterogeneity detected: Chi² = 3.08, df = 1 (P = 0.08); I² = 68%.The results were statistically significant using fixed effect analysis (0.94, 95% CI-1.62to -0.26) but not significant using random effects analysis.*

(c) *There was substantial heterogeneity was detected: Chi Heterogeneity: Tau² = 1.68; Chi² = 3.29, df = 1 (P = 0.07); I² = 70%. The results were statistically significant using fixed effect analysis (-1.01, 95% CI -1.70 to -0.31) but not significant using random effects analysis.*

(d) *Substantial unexplained heterogeneity was detected and random effects analysis was conducted.*

(e) *The upper or lower end of the confidence interval crossed MID.*

(f) *There were no statistically significant difference or the size of the benefit/harm was small, and the upper and lower end of confidence interval did not cross the MIDs of both benefit and harm.*

(g) *Five studies reported PSA change from baseline. Four studies reported median % of change [13,24,77,187]. Only 1 study reported mean with standard deviation [221].*

Table 6-48: 5-ARI vs. Placebo - Clinical summary of findings

Outcome	5-ARI	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 3 months(a)	1821	644	Not applicable	-1.38 [-3.10, 0.33]	Very Low
Symptom score at 6 months(a)	1821	644	Not applicable	1.63 [-3.72, 0.46]	Very Low
Symptom score at 1 year	3774	2545	Not applicable	-0.84 [-1.13, -0.56]	Moderate
Symptom score at 2 years(a)	3630	3562	Not applicable	-1.78 [-2.34, -1.23]	Moderate
Symptom score at 3 years	1047	961	Not applicable	-1.80 [-2.32, -1.28]	High
Symptom score at ≥ 4 years(a)	1733	1590	Not applicable	-1.45 [-2.91, 0.02]	Moderate
Qmax(ml/s) at 3 months	310	303	Not applicable	0.05 [-0.77, 0.87]	High
Qmax(ml/s) at 6 months	87	81	Not applicable	0.50 [0.08, 0.92]	Moderate
Qmax(ml/s) at 1 year (a)	2186	2136	Not applicable	1.15 [0.77, 1.52]	Low
Qmax(ml/s) at 2 years	3571	3490	Not applicable	1.55 [1.32, 1.77]	High
Qmax(ml/s) at 3 years	691	608	Not applicable	1.80 [1.25, 2.35]	Moderate
Qmax(ml/s) at 4 years plus	588	496	Not applicable	1.80 [1.21, 2.39]	Moderate
Prostate volume (ml)at 1 year	509	521	Not applicable	-9.18 [-11.01,-7.35]	High
Prostate volume (ml)at 2 year (a)	2364	2355	Not applicable	-22.60 [-37.56, -7.63]	Moderate
PSA (ng/ml) at 2 years	2167	2158	Not applicable	-3.60 [-3.72, -3.48]	High
Decreased libido	448/9815 (4.6%)	191/7433 (2.6%)	1.87 [1.58, 2.21]	23 more per 1000 [15 to 31 more]	High
Dizziness	26/607 (4.3%)	24/605 (4.0%)	1.07 [0.63, 1.81]	3 more per 1000 [15 fewer to 32 more]	Low
Ejaculation disorder	231/9721 (2.4%)	50/7345 (0.7%)	3.39 [2.48, 4.63]	17 more per 1000 [10 to 25 more]	High
Fatigue	11/1577 (0.7%)	24/1591 (1.5%)	0.46 [0.23, 0.94]	8 fewer per 1000 [1 to 12 fewer]	Moderate
Gynaecomastia	58/3670 (1.6%)	18/3671 (0.5%)	3.21 [1.90, 5.44]	11 more per 1000 [4 o 22 more]	High
Impotence	719/10126 (7.1%)	291/7749 (3.8%)	1.96 [1.71, 2.25]	36 more per 1000 [27 to 48 more]	High
Urinary retention	107/6886 (1.6%)	164/4534 (3.6%)	0.48 [0.37, 0.61]	19 fewer per 1000 [14 to 23 fewer]	Moderate
Withdrawal due to adverse events	795/10498 (7.6%)	692/8082 (8.6%)	1.00 [0.91, 1.11]	1 more per 1000 [8 fewer to 9 more]	High

(a) *These outcomes were analysed using random effects analyses.*

6.4.1.2 Economic evidence

We found few economic studies comparing 5-alpha reductase inhibitors with placebo or active surveillance. One study[11] was excluded because the clinical data for the two arms were obtained from studies with different populations. Another study[18] was excluded because results were poorly reported. A UK cost-benefit analysis[263] was excluded because of its uncertain methodology (arbitrary choice of attributes, probabilities not obtained from a systematic review, etc).

Three studies, all based on decision models, were included: a UK cost consequences analysis[109], and two cost-utility analyses[58,157]. Please see Economic Evidence table 53 in Appendix D for further details.

Table 6-49: 5-ARI vs. Placebo - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Johnson 1999[109]	Serious limitations (a)	Directly applicable	Comparator was watchful waiting followed by medical treatment if necessary. Based on the AHCPR Guideline[154].
McDonald 2004 [157]	Serious limitations (b)	Partially applicable (c)	Comparator was watchful waiting. Based on the PLESS study[155]
DiSantostefano 2006[58]	Minor limitations	Partially applicable (d)	Comparator was watchful waiting. Based on the AHCPR Guideline[154].

(a) Short follow-up (12 months). Complications were not considered. Funding from manufacturer of alpha blockers.
(b) Funding from manufacturer of 5-ARI.
(c) Study conducted in Canada. Patients in the PLESS study had a large prostate (55mL on average).
(d) Study conducted in the USA.

Table 6-50: 5-ARI vs. Placebo - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Johnson 1999[109]	929 (a)	5-ARI improve discontinuation, number of patients with improved symptoms, response-year gained (b).	Not reported	One-way SA: results not sensitive to cost of surgery, response rates, discontinuation rates, response degree, and time horizon.
McDonald 2004 [157]	2,050 (c, d)	0.101 QALYs	£20,297/QALYs (c)	Considering only patients with PSA>3.2ng/ml, ICER=£18,397/QALY.
Moderate symptoms				
DiSantostefano 2006[58]	2,826 (e, f, g, h)	0.03 QALYs (g, h)	£94,200/QALY (h, i)	Similar results if patients continue on initial treatment unless TURP is required.
Severe symptoms				
DiSantostefano 2006[58]	2,834 (e, f, g, h)	0.04 QALYs (g, h)	£70,850/QALY (h, l)	Similar results if patients continue on initial treatment unless TURP is required.

(a) Cost of GP and urologist consultations, laboratory procedures, examination, medications, surgical procedures, complications.
(b) Statistical significance not reported. Not clear how the outcome 'response-years gained' was calculated.
(c) 2003 Can$ converted using the PPP 1$=£0.524
(d) Cost of drugs (including 10% pharmacy mark-up charge and dispensing fee), visits, hospitalization, surgery, complications, tests.
(e) 2004 USD converted using the PPP 1$=£0.632
(f) Cost of visits, tests, drugs, operations, complications (strictures, and artificial urinary sphincter)
(g) Assumes 70% compliance to medical treatment.
(h) Results reported for the scenario where patients can switch treatment.
(i) In the study 5-ARI were dominated by AB (see 6.3.2.2)
(j) In the study, TURP was the most cost-effective intervention for this group (see12.1.1.2)

6.4.1.3 Evidence statement (s)

Clinical There was no statistically significant difference between 5-ARI and placebo in symptom score improvement.

5-Alpha reductase inhibitors are more effective than placebo in improving symptom at 1 to more than 4 years follow up.

There is no statistically significant difference between 5-ARI and placebo Qmax improvement at 3 months follow up.

5-Alpha reductase inhibitors are more effective than placebo in improving Qmax at 6 months or longer follow up periods.

5-Alpha reductase inhibitors are more effective than placebo in reducing prostate volume.

5-Alpha reductase inhibitors are more effective than placebo in reducing PSA level at 2 years follow up.

Significantly more men treated with 5-ARI compared to placebo experienced decreased libido, ejaculation disorders, gynaecomastia and impotence.

There is no significant difference between 5-ARI and placebo in number of men experiencing dizziness or that withdrew from studies due to adverse events.

Significantly fewer men treated with 5-ARI compared to placebo experienced fatigue or urinary retention.

Economic 5-Alpha reductase inhibitors are not cost-effective in the general population of men with LUTS.

This evidence has minor limitations and partial applicability.

6.4.2 5-Alpha reductase inhibitors vs. alpha blockers

Evidence reported in alpha blockers vs. 5-alpha reductase inhibitor section 6.3.2.

6.4.2.1 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.5 Anticholinergics

Bladder contraction is mediated via the parasympathetic cholinergic nerves. Blockade of these nerves therefore may reduce bladder overactivity underlying the storage symptoms of the overactive bladder such as urgency, frequency, nocturia and incontinence. Cholinergic blockade may, in sufficient amounts, lead to a reduction in both normal and involuntary bladder contractions, but at currently recommended therapeutic doses acts primarily on the latter. Anticholinergics may also reduce the sensation of urgency during bladder filling and therefore increase the functional bladder capacity.

6.5.1 Anticholinergics vs. placebo

See Evidence Table 14, Appendix D, Forest Plots in Figures E-37 to E-38, Appendix E.

6.5.1.1 Clinical evidence

Table 6-51: Anticholinergics vs. Placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Qmax at 3 months[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c), (d)
Urgency incontinence episodes/24h[115]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c),(e)
Urgency/24h[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/24h[115]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/night[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Ejaculation Failure[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Urinary Retention[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Fatigue[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Somnolence[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dizziness[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Rhinitis[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Diarrhoea[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Constipation[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dyspepsia[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Headache[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dry Mouth[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Withdrawals due to adverse events[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)

(a) *There was incomplete or unclear reporting for many outcomes. This study [114,115] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance ($p<0.05$ or $p<0.01$) of combination vs. placebo was indicated in the paper for some of the outcomes. Actual values and standard deviations were not reported. It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was reported.*

(b) *Patients recruited in this study have higher IPSS scores than most trials (mean IPSS ~20) and significant storage symptoms. Anticholinergics were licensed for storage symptoms. Recommendation was made for patients with OAB – no indirectness of evidence.*

(c) *Confidence intervals for continuous outcomes unknown, while those for adverse events met the criteria for downgrading.*

Table 6-52: Anticholinergics vs. Placebo - Clinical summary of findings

Outcome	Anti-Ch	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 3 months	197	206	Not applicable	MD -0.60 Not stats sig. (a)	Low
Quality of life (IPSS question) at 3 months	198	206	Not applicable	MD -0.20 Not stat sig (a)	Low
Qmax at 3 months	NR (b)	NR (b)	Not applicable	MD -0.07 P >0.3	Low
Urgency incontinence episodes/24h (c)	48	43	Not applicable	MD -0.52 p value 0.008 (a)	Low
Urgency/24h	209	210	Not applicable	MD -0.30 Not stats sig. (a)	Low
Frequency/24h	209	212	Not applicable	MD -0.30 Not stats sig. (a)	Low
Frequency/night	209	212	Not applicable	MD 0.04 Not stats sig. (a)	Low
Fatigue	2/217 (0.9%)	6/220 (2.7%)	RR 0.34 [0.07 to 1.66]	18 fewer per 1000 [25 fewer to 18 more]	Low
Somnolence	2/217 (0.9%)	2/220 (0.9%)	RR 1.01 [0.14 to 7.13]	0 more per 1000 [8 fewer to 56 more]	Low
Dizziness	3/217 (1.4%)	2/220 (0.9%)	RR 1.52 [0.26 to 9.01]	5 more per 1000 [7 fewer to 73 more]	Low
Rhinitis	0/217 (0%)	2/220 (0.9%)	RR 0.2 [0.01 to 4.2]	7 fewer per 1000 [9 fewer to 29 more]	Low
Diarrhoea	7/217 (3.2%)	3/220 (1.4%)	RR 2.37 [0.62 to 9.03]	19 more per 1000 [5 fewer to 109 more]	Low
Constipation	9/217 (4.1%)	5/220 (2.3%)	RR 1.82 [0.62 to 5.36]	19 more per 1000 [9 fewer to 99 more]	Low
Dyspepsia	2/217 (0.9%)	5/220 (2.3%)	RR 0.41 [0.08 to 2.07]	13 fewer per 1000 [21 fewer to 24 more]	Low
Headache	2/217 (0.9%)	7/220 (3.2%)	RR 0.29 [0.06 to 1.38]	23 fewer per 1000 [30 fewer to 12 more]	Low
Dry Mouth	16/217 (7.4%)	5/220 (2.3%)	RR 3.24 [1.21 to 8.7]	51 more per 1000 [5 more to 175 more]	Low
Ejaculation Failure	0/217 (0%)	0/220 (0%)	Not estimable	0 fewer per 1000 [0 fewer to 0 fewer]	Low
Urinary Retention	2/217 (0.9%)	3/220 (1.4%)	RR 0.68 [0.11 to 4.01]	4 fewer per 1000 [12 fewer to 41 more]	Low
Withdrawal due to adverse events	5/217 (2.3%)	7/220 (3.2%)	RR 0.72 [0.23 to 2.25]	9 fewer per 1000 [24 fewer to 40 more]	Low

(a) Not stat sig. = no statistically significant difference, i.e. P >0.05, Values reported are adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre. The study reported outcomes as graphs only and there were no p values or standard deviations for comparison to calculate confidence intervals.

(b) NR = not reported. Number of patients with Qmax measurements at follow up not reported

(c) Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries filled for 5 days before visit.

6.5.1.2 Economic evidence

No economic studies were identified.

6.5.1.3 Evidence statement (s)

Clinical Anticholinergics are more effective than placebo in reducing the number of urinary urgency incontinence episodes per 24 hours at 3 months follow up.

There is no statistically significant difference between anticholinergics and placebo in improvement of symptom score, quality of life scores, Qmax (ml/s), urinary urgency per 24 hours, frequency per 24 hours, and frequency at night.

There is no statistically significant difference between anticholinergics and placebo in number of men experiencing, constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache, nasal congestion or withdrew from study due to adverse events.

Significantly more patients treated with anticholinergics experiencing dry mouth compared to placebo.

Economic No economic studies were identified.

6.5.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.5.2 Anticholinergics vs. alpha blockers

Evidence reported in alpha blocker vs. anticholinergic section 6.3.3.

6.5.2.1 Recommendations and link to evidence

Evidence reported in alpha blocker vs. anticholinergic section 6.3.3.

6.6 Phosphodiesterase 5 inhibitors (PDE5-I)

Nitric oxide (NO) is a mediator of the relaxation of isolated bladder and urethral smooth muscle, and could also relax prostatic smooth muscle tone. A reduction in pelvic NO synthase and NO and decreased cyclic guanosine monophosphate (cGMP) results from a variety of systemic diseases that also result in erectile dysfunction. It has been suggested that PDE5 inhibitors could, in addition to improving erectile dysfunction, relax bladder and prostatic smooth muscle, and thereby improve both storage, voiding and post-micturition LUTS.

6.6.1 Phosphodiesterase 5 inhibitors (PDE5-I) vs. placebo

See Evidence Table 15, Appendix D, Forest Plots in Figures E-40 to E-43, Appendix E.

6.6.1.1 Clinical evidence

Table 6-53: Phosphodiesterase 5 inhibitors vs. placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom scores [161,162,222,244]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life[161,162,222]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax[161,162,222,244]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision (c)
Rhinitis[161]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Flushing[161,244]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Headache[161,162,222,244]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Back pain[162,222,244]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Gastrointestinal reflux[222,244]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Dyspepsia[161,162,222,244]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Allocation concealment and method of randomisation were unclear in at least half of the studies.*
(b) *Studies were not combined as the analysis as adjusted means were reported and factors used for adjustment not clearly reported. All the studies were imprecise and crossed the MID.*
(c) *There were no statistical significant difference in treatment effects and confidence intervals did not cross MID in 3 of the four studies.*

Table 6-54: Phosphodiesterase 5 inhibitors vs. placebo - Clinical summary of findings

Outcome	*PDE5I*	*Placebo*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score (a)	105 136 182 844	110 138 178 210	Not applicable	MD -2.30 [-3.66, -0.94] MD -2.10 [-3.87, -0.33] MD -4.40 [-6.86, -1.94] MD -2.52 [-3.60, -1.44]	Low
Quality of life (IPSS question) (a)	182 136 844	178 138 210	Not applicable	MD -0.66 [-1.17, -0.19] MD -0.40 [-0.68, -0.12] MD -0.36 [-0.6, -0.12]	Low
Qmax (a)	105 116 182 844	110 121 178 210	Not applicable	MD 0.60 [0.01, 1.19] MD -0.40 [-1.79, 0.99] MD 0.15 [-2.52, 2.82] MD 0.41 [-0.46, 1.28]	Moderate
Rhinitis	8/189 (4.2%)	3/180 (1.7%)	RR 2.54 [0.68, 9.42]	26 more per 1000 [5 fewer to 143 more]	Moderate
Flushing	16/297 (5.4%)	2/293 (0.7%)	RR 7.96 [1.84, 34.37]	49 more per 1000 [6 to 234 more]	High
Headache	67/1279 (5.2%)	15/647 (2.3%)	RR 2.68 [1.59, 4.53]	39 more per 1000 [14 to 81 more]	Moderate
Back pain	35/1090 (3.2%)	2/467 (0.4%)	RR 6.06 [1.63, 22.50]	20 more per 1000 [3 to 86 more]	Moderate
Gastrointestinal reflux	16/952 (1.7%)	0/324 (0%)	RR 6.98 [0.88, 55.31]	Not estimable	Low
Dyspepsia	54/1279 (4.2%)	2/647 (0.3%)	RR 10.04 [3.27, 30.81]	27 more per 1000 [7 to 89 more]	Moderate

(a) The results for each of the 4 studies are reported separately for the symptom score, quality of life (IPSS question) and Qmax outcomes. Studies were not combined as the analysis used adjusted means and the factors used for adjustment were not clearly reported.

6.6.1.2 Economic evidence

No economic studies were identified.

6.6.1.3 Evidence statement (s)

Clinical PDE5-I is more effective than placebo in improving symptom scores.

There is no statistically significant difference between PDE5-I and placebo in improving Qmax.

PDE5-I is more effective than placebo in improving the quality of life (IPSS question).

More men treated with PDE5-I compared to placebo experienced headaches, back pain, flushing and dyspepsia.

There is no statistically significant difference between PDE5-I and placebo in men experiencing rhinitis and gastrointestinal reflux.

Economic No economic studies were identified.

6.6.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.6.2 Phosphodiesterase 5 inhibitors (PDE5-I) vs. alpha blockers

The evidence for this can be found in section 6.3.4.

6.6.2.1 Recommendations and link to evidence

See research recommendation in section 6.16.

6.7 Diuretics

Diuretics such as furosemide are not licensed for the treatment of LUTS.

However, furosemide has been suggested as a therapeutic modality in men with LUTS and nocturnal polyuria (men with LUTS who produce >35% of their 24 hour urine production during the night time hours). A diuretic in the late afternoon which produces a diuresis in the early evening should reduce nocturnal production of urine and subsequently reduce nocturnal frequency.

6.7.1 Diuretics vs. placebo

See Evidence Table 16, Appendix D.

6.7.1.1 Clinical evidence

Table 6-55: Diuretics vs. Placebo – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score [212]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question)	0	RCT				
Night time frequency	0	RCT				
Night time voided volume, ml [212]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Adverse events	0	RCT				

(a) *One small study*[212] *with limitations in study design as method of randomisation and allocation concealment were not reported.*

(b) *Imprecision due to small numbers (N=43) reported from single study.*

Table 6-56: Diuretics vs. Placebo – Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score	21	22	Not applicable	+1 (p=0.9)	Low
Night time voided volume (ml)	21	22	Not applicable	-0.5 (p=0.06)	Low

6.7.1.2 Economic evidence

No economic studies were identified.

6.7.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between diuretics and placebo in improving symptoms score.

Diuretics are more effective than placebo in reducing night time frequency.

Economic No economic studies were identified.

6.7.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.8 Desmopressin

Desmopressin is not licensed for the treatment of LUTS. However, this drug is sometimes used for patients with nocturia, which is a very bothersome symptom for patients.

6.8.1 Desmopressin vs. placebo

See Evidence Table 17, Appendix D, Forest Plot in Figure E-49, Appendix E.

6.8.1.1 Clinical evidence

Table 6-57: Desmopressin vs. placebo - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Nocturnal frequency: FV chart – 1 week[35]	1	RCT(a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
24h vol (ml): FV chart – 1 week[35]	1	RCT(a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Proportion of night time volume(%): FV chart – 1 week[35]	1	RCT(a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
24h vol (ml): 24-hr collection-last day[35]	1	RCT(a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Nocturnal %: 24-hr collection-last day[35]	1	RCT(a)	Very serious limitations(b))	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Hyponatraemia & hypoosmolaemia[35]	1	RCT (a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dry throat & cough[35]	1	RCT (a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Increased sputum[35]	1	RCT (a)	Very serious limitations(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Fluid retention & hyponatraemia[35]	1	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[35]	1	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Flu like illness[35]	1	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) *Cross over study - Patients were randomised and treated for 2 weeks before crossing over. FV charts recorded for one week, during second week of treatment. 24-h urine recorded on the last day treatment period*
(b) *There was no washout period. Reports for the first and second treatment periods were not reported separately. Paired t-tests used for a small sample size, non-parametric test may be more appropriate.*
(c) *Small sample size – less than OIS or confidence intervals crossed MID.*

Table 6-58: Desmopressin vs. placebo - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk	Absolute effect	Quality
Nocturnal frequency-FV chart – 1 week	18	18	Not applicable	MD -0.4 P: Not sig(a)	Very Low
24h vol (ml): FV chart – 1 week	18	18	Not applicable	MD -146.1 P: Not sig (a)	Very Low
Proportion of night time volume (%): FV chart – 1 week	18	18	Not applicable	MD -6.4 P: <0.05(a)	Very Low
24h vol (ml):24-hr collection-last day	18	18	Not applicable	MD 18.4 P: Not sig(a)	Very Low
Nocturnal %:24-hr collection-last day	18	18	Not applicable	MD -11.4 P: <0.001(a)	Very Low
Hyponatraemia & hypoosmolaemia	1/20 (5%)	0/20 (0%)	RR 3 [0.13 to 69.52]	Not estimable	Very Low
Dry throat & cough	1/20 (5%)	0/20 (0%)	RR 3 [0.13 to 69.52]	Not estimable	Very Low
Increased sputum	1/20 (5%)	0/20 (0%)	RR 3 [0.13 to 69.52]	Not estimable	Very Low
Fluid retention & hyponatraemia	1/20 (5%)	0/20 (0%)	RR 3 [0.13 to 69.52]	Not estimable	Very Low
Headache	0/20 (0%)	1/20 (5%)	RR 0.33 [0.01 to 7.72]	33 fewer per 1,000 [50 to 336 fewer]	Very Low
Flu like illness	0/20 (5%)	1/20 (5%)	RR 0.33 [0.01 to 7.72]	33 fewer per 1,000 [50 to 336 fewer]	Very Low

(a) *P values were calculated using paired t-test, as reported by authors.*

6.8.1.2 Economic evidence

No economic studies were identified.

6.8.1.3 Evidence statement (s)

Clinical

There is no statistical significant difference between desmopressin 20mcg nasal spray compared to placebo in reducing nocturnal frequency as recorded using a 1-week frequency-volume chart.

There is no statistical significant difference between desmopressin 20mcg nasal spray and placebo in 24-hour volume as recorded using a 1-week frequency-volume chart and 24-hour urine collection.

Desmopressin 20mcg nasal spray significantly reduced the proportion of night time volume as recorded using a 1-week frequency volume chart and 24-hour urine collection.

There is no significant difference in adverse events reported between desmopressin 20mcg nasal spray and placebo.

Economic

No economic studies were identified.

6.8.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.9 Non-steroidal anti-inflammatory drugs (NSAIDS)

Non-steroidal anti-inflammatory drugs (NSAIDS) are inhibitors of the enzyme cyclooxygenase. This inhibition reduces production of prostaglandins and other mediators of inflammation. They have a wide range of uses (mostly in pain reduction in musculoskeletal disease, or pain associated with inflammation) and have been used (off-label) to treat detrusor overactivity, particularly in relation to nocturia.

Human bladder epithelium has the ability to synthesize eicosanoids and these agents can be liberated from bladder muscle and epithelium in response to different types of trauma, it is still unclear whether prostaglandins contribute to the pathogenesis of detrusor overactivity. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. A further potential mode of action is via a direct effect on the kidneys where prostaglandins are involved in the homeostasis of glomerular filtration rate. Clinical evidence for this therapeutic approach is scarce.

6.9.1 NSAIDS vs. placebo

See Evidence Table 18, Appendix D, Forest Plots in Figures E-50 to E-53, Appendix E.

6.9.1.1 Clinical evidence

One RCT was which compared a cyclooxygenase 2 (COX-2) selective inhibitor against placebo was identified.

Table 6-59: NSAIDS vs. placebo - Clinical study characteristics

Outcomes	No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptom score at follow up 1 month [73]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question)	0					
Qmax at follow up (1 month) [73]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Nocturia frequency - 1 month [73]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mild gastric discomfort[73]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a) *Only one very small study with unknown randomisation and allocation concealment methods. The study length of follow up was only one month.*

(b) *The confidence interval crossed MID or sample size was smaller than the optimal information size to detect a significant difference*

Table 6-60: NSAIDS vs. placebo - Clinical summary of findings

Outcomes	NSAIDS	Placebo	Relative Risk	Absolute Risk	Quality
Symptom score at follow up -1 month	40	40	Not applicable	MD -2.5 [-4.34 to -0.66]	Low
Qmax at follow up -1 month	40	40	Not applicable	MD 0.6 [-0.54 to 1.74]	Low
Nocturia frequency at follow up-1 month	40	40	Not applicable	MD -2.62 [-3.45 to -1.79]	Moderate
Mild gastric discomfort	4/40 (10%)	0/40 (0%)	RR 9.0 [0.5 to 161.86]	Not estimable	Low

6.9.1.2 Economic evidence

No economic studies were identified.

6.9.1.3 Evidence statement (s)

Clinical NSAIDS are more effective than placebo in improving symptoms score and reducing nocturia.

There is no statistically significant difference between NSAIDS and placebo in improving Qmax (ml/s).

There is no statistically significant difference in number of men experiencing adverse effects such as mild gastric discomfort.

Economic No economic studies were identified.

6.9.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.10 Combination therapy (Alpha blockers plus 5-alpha reductase inhibitors)

The combination of alpha blockers and 5-ARIs has been shown to be more effective than either drug alone. This effect almost certainly works with any combination of these two drug modalities although doxazosin combined with finasteride and tamsulosin with dutasteride have been most investigated. Both the magnitude of the improvement and the speed of the symptom improvement are much more marked with alpha-blockers than with 5-ARIs. However prevention of progression to either retention or surgery is noted with 5-ARIs. Therefore when selecting treatment for an individual patient the presence or severity of symptoms, and particularly their bothersomeness, should indicate the initial need for treatment and the presence or absence of risk factors for progression should guide both the doctor and patient to the appropriate treatment option.

6.10.1 Alpha blockers plus 5-alpha reductase inhibitors(5-ARI) vs. alpha-blockers

See Evidence Table 19, Appendix D, Forest Plots in Figures E-54 to E-60, Appendix E, Economic Evidence Table 53, Appendix D, and Economic Model, Appendix F.

6.10.1.1 Clinical evidence

Table 6-61: Alpha-blockers plus 5-ARI vs. alpha blockers vs. - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months[57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Symptom score at 1 year [121,132]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Symptom score at 2 years [224]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness (d)	Serious imprecision (c)
Symptom score at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0	RCT	-	-	-	-
Qmax(ml/s) at 6 months [57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Qmax(ml/s) at 1 year[121,132]	2	RCT	Serious limitations(a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Qmax(ml/s) at 2 years[224]	1	RCT	No serious limitations	No serious inconsistency (b)	No Serious indirectness (d)	No serious imprecision (c)
Prostate volume (ml) at 6 months [57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume(ml) at 1 year[132]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume(ml) at 2 year[224]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness (d)	No serious imprecision (f)
Prostate volume(ml) at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
PSA(ng/ml) at 6 months[57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
PSA(ng/ml) at 1 year[121]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Syncope[121,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Postural hypotension[57,121,132]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Orthostatic hypotension[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c),
Dizziness[57,121,132,156,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c),
Vertigo[121]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Fatigue (Asthenia)[57,121,132,156]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c),
Somnolence[57,121,156]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Rhinitis[132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Decreased libido[57,121,132,156,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Ejaculatory abnormality/ retrograde ejaculation[57,121,132,156,224]	5	RCT	No serious limitations	Serious inconsistency (e)	No serious indirectness	No serious imprecision
Impotence / erectile dysfunction[57,121,156,224]	4	RCT	No serious limitations	Serious inconsistency (g)	No serious indirectness	No serious imprecision
Breast enlargement[224]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Acute urinary retention[57,156]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Withdrawals due to adverse events[57,121,132,224]	4	RCT	No serious limitations	Serious inconsistency (g)	No serious indirectness	Serious imprecision (c)

(a) *RCT(s) with which did not report randomisation allocation and concealment methods [57,121] contributed entirely or more than 50% of the weight of the pooled outcome.*

(b) *Treatment effects observed at different time points differed, suggesting the duration of treatment and follow-up as a likely factor which affect the direction and effect size. This observation would be consistent with current knowledge of the pharmacology (mechanism of action) of these classes of drugs. Therefore, the quality was not downgraded.*

(c) *Outcomes were downgraded when the confidence intervals crossed the MID. It was not downgraded if the size of the benefit/harm was small or not statistically significant, and the confidence intervals did not reach cross MID.*

(d) *The study which contributed data to this time point had large prostate size, with a mean of 55ml. There is no indirectness of evidence based on the recommendation made (for men with larger prostates).*

(e) *There were variations in the terms used to describe and report the sexual side effects such as retrograde ejaculation, reduced semen volume ejaculatory abnormalities; erectile dysfunction and impotence.*

(f) *It is unknown what magnitude of reduction in prostate volume or PSA level is important enough to be noticeable by patients or associated with differences in symptoms and prognosis.*

(g) *Substantial heterogeneity detected. Random effects analysis was conducted.*

Table 6-62: Alpha blockers plus 5-ARI vs. alpha blockers - Clinical summary of findings

Outcome	Alpha blocker + 5-ARI	Alpha blocker	Relative risk	Absolute effect	Quality
Symptom score at 6-months	349	358	Not applicable	MD 0.2 [-0.64 to 1.04]	Moderate
Symptom score at 1 year	543	525	Not applicable	MD -0.15 [-0.77 to 0.48]	High
Symptom score at 2 years	1610	1611	Not applicable	MD -1.9 [-2.31 to -1.49]	Moderate
Symptom score at 4 years	786	756	Not applicable	MD -0.8 [-1.37 to -0.23]	Moderate
Qmax(ml/s) at 6 months	349	344	Not applicable	MD 0.5 [-0.19 to 1.19]	Moderate
Qmax(ml/s) at 1 year	542	525	Not applicable	MD 0.33[-0.28 to 0.94]	Moderate
Qmax(ml/s) at 2 years	1610	1611	Not applicable	MD 1.5 [1.17 to 1.83]	High
Prostate volume (ml) at 6 months	349	358	Not applicable	MD -4.7 [-6.67 to -2.73]	Moderate
Prostate volume(ml) at 1 year	275	271	Not applicable	MD -7.5 [-11.13 to -3.87]	High
Prostate volume(ml) at 2 years	1610	1611	Not applicable	MD -14.7 [-15.82 to -13.58]	High
Prostate volume(ml) at 4 years	778	755	Not applicable	MD -9.91 [-11.41,-8.42]	High
PSA(ng/ml) at 6 months	349	358	Not applicable	MD -1.5 [-1.83 to -1.17]	Moderate
PSA(ng/ml) at 1 year	265	250	Not applicable	MD: -1.60 [-1.83 to -1.37]	Moderate
Syncope	11/595 (1.8%)	5/580 (0.9%)	RR 2.14 [0.75 to 6.14]	10 more per 1000 [2 fewer to 46 more]	Moderate
Postural hypotension	41/1730 (2.4%)	45/1694 (2.7%)	RR 0.89 [0.59 to 1.34]	3 fewer per 1000 [11 fewer to 9 more]	Moderate
Orthostatic hypotension	129/658 (19.6%)	146/663 (22%)	RR 0.87 [0.73 to 1.05]	29 fewer per 1000 [59 fewer to 11 more]	Moderate
Dizziness	144/3340 (4.3%)	159/3305 (4.8%)	RR 0.89 [0.72 to 1.1]	5 fewer per 1000 [13 fewer to 5 more]	Moderate
Vertigo	39/286 (13.6%)	43/275 (15.6%)	RR 0.87 [0.58 to 1.3]	20 fewer per 1000 [66 fewer to 47 more]	Low
Headache	21/658 (3.2%)	25/663 (3.8%)	RR 0.84 [0.47 to 1.48]	6 fewer per 1000 [20 fewer to 18 more]	Moderate
Fatigue(Asthenia)	73/1730 (4.2%)	61/1683 (3.6%)	RR 1.16 [0.84 to 1.6]	6 more per 1000 [6 fewer to 22 more]	Moderate
Somnolence	11/1421 (0.8%)	12/1389 (0.9%)	RR 0.89 [0.4 to 1.96]	1 fewer per 1000 [5 fewer to 9 more]	Low
Rhinitis	24/309 (7.8%)	20/305 (6.6%)	RR 1.18 [0.67 to 2.1]	12 more per 1000 [22 fewer to 73 more]	Moderate
Decreased libido	86/3340(2.6 %)	49/3305 (1.5%)	RR 1.74 [1.23 to 2.46]	11 more per 1000 [3 to 22 more]	High
Ejaculatory abnormality or retrograde ejaculation	102/3340 (3.1%)	21/3305 (0.6%)	RR 4.75 [2.99 to 7.53]	23 more per 1000 [12 to 39 more]	Moderate
Impotence or erectile dysfunction	180/3031 (5.9%)	89/3000 (3%)	RR 2.01 [1.57 to 2.58]	30 more per 1000 [17 to 47 more]	Moderate
Breast enlargement	23/1610 (1.4%)	29/1611 (1.8%)	RR 0.79 [0.46 to 1.37]	4 fewer per 1000 [10 fewer to 7 more]	Moderate
Acute urinary retention	5/1135 (0.4%)	11/1114 (1%)	RR 0.44 [0.15 to 1.27]	6 fewer per 1000 [8 fewer to 3 more]	Moderate
Withdrawals due to adverse events (a)	131/2533 (5.2%)	124/2549 (4.9%)	RR 1.08 [0.85 to 1.37]	4 more per 1000 [7 fewer to 18 more]	Moderate

(a) Outcome was analysed using random effects due to heterogeneity

6.10.1.2 Economic evidence

We found two studies[58,157] comparing a combination of alpha blockers and 5-alpha-reducatse inhibitors with alpha blockers. However, both were excluded because either the clinical data for the two arms were obtained from studies with different populations[157] or the clinical data for the combination arm was based on expert opinion[58].

It was thus decided to build an original economic model in order to formulate a recommendation. Please see cost-effectiveness analysis in Appendix F for further details.

Table 6-63: Alpha blockers plus 5-ARI vs. alpha blockers - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCGC Combination Model (Appendix F)	Minor limitations	Direct applicability	

Table 6-64: Alpha blockers plus 5-ARI vs. alpha blockers - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
NCGC Combination Model (Appendix F)	2,587 (a)	-0.0072 QALY	Comb dominated	95% CI: £3,273/QALY – Comb dominated. AB have a 90% probability of being cost-effective at a willingness to pay = £20,000/QALY

(a) Costs of treatment, surgery if treatment fails and complications (AUR).

6.10.1.3 Evidence statement (s)

Clinical

Alpha blockers plus 5-ARI combinations are more effective than alpha blockers in improving symptom scores at 2 and 4 years follow up.

There is no statistical difference between alpha blockers plus 5-ARI combination and alpha blockers in improving symptom score at 6 months and 1year follow up periods.

There is no statistical difference between alpha blockers plus 5-ARI combinations and alpha blockers in improving Qmax (ml/s) at 6 months and 1year follow up periods.

Alpha blocker plus 5-ARI combinations are more effective than alpha blockers in improving Qmax (ml/s) at 2 and 4 years follow up.

Alpha blockers plus 5-ARI combinations are more effective than alpha blockers in reducing prostate volume at 6 months, 1 year, 2 years and 4 years follow up.

Alpha blockers plus 5-alpha reductase inhibitor combinations are more effective than alpha blockers in reducing PSA levels at 6 months and 1 year follow up.

More men treated with alpha blockers plus 5-ARI combinations compared to alpha blockers experienced adverse effects such as decreased libido, ejaculatory abnormalities or erectile dysfunction (impotence).

There is no significant difference between combination therapy of alpha blockers plus 5-ARI vs. alpha-blocker in the number of men experiencing adverse effects such as syncope, orthostatic hypotension, dizziness, vertigo, headache, fatigue (asthenia), breast enlargement, acute urinary retention, postural hypotension, somnolence or rhinitis.

Economic

Alpha blockers are more cost-effective compared to a combination of alpha-blockers and 5-ARI. This evidence has minor limitations and direct applicability.

6.10.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.10.2 Alpha blockers plus 5-alpha reductase inhibitors (5-ARI) vs. 5-alpha reductase inhibitors

See Evidence Table 19, Appendix D, Forest Plots in Figures E-61 to E-69, Appendix E.

6.10.2.1 Clinical evidence

Table 6-65: Alpha blockers plus 5-ARI vs. 5-ARI - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months [57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Symptom score at 1 year [121,132]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 2 years [224]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness (d)	No serious imprecision (c)
Symptom score at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Quality of life (IPSS-Question)	0	RCT	-	-	-	-
Qmax(ml/s) at 6 months [57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Qmax(ml/s) at 1 year[121,132]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Qmax(ml/s) at 2 years[224]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness (d)	No serious imprecision (c)
Prostate volume (ml): 6 months [57]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Prostate volume(ml): 1 year [132]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Prostate volume(ml): 2 year [224]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness (d)	No serious imprecision (c)
Prostate volume(ml): 4 year [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
PSA(ng/ml): 6 months[57]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
PSA(ng/ml): 12 months[121]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (c)
Syncope[121,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Postural hypotension[57,121,132,156]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Orthostatic hypotension[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[57,121,132,156,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Vertigo[121]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[57,132]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Fatigue (Asthenia)[57,121,132,156]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Somnolence[57,121,156]	3	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Rhinitis[132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Decreased libido[57,121,132,156,224]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Ejaculatory abnormality or retrograde ejaculation[57,121,132,156,224]	5	RCT	No serious limitations	Very serious inconsistency (e),(f),(g)	No serious indirectness	Serious imprecision (c)
Impotence or erectile dysfunction [57,121,156,224]	4	RCT	Serious limitations(g)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Breast enlargement (gynaecomastia)[224]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Acute urinary retention[57,156]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Study withdrawals due to adverse events[57,121,224]	4	RCT	No serious limitations	Serious inconsistency (e)	No serious indirectness	Serious imprecision (c)

(a) *RCT(s) with which did not report randomisation allocation and concealment methods [57,121] contributed entirely or more than 50% of the weight of the pooled outcome.*

(b) *The magnitude of treatment effects observed at different time points differed, suggesting the duration of treatment and follow-up as a likely factor which affect the direction and effect size. This observation would be consistent with current knowledge of the pharmacology (mechanism of action) of these classes of drugs. Therefore, the quality was not downgraded.*

(c) *Outcomes were downgraded when the confidence intervals crossed the MID. It was not downgraded if the size of the benefit/harm was small or not statistically significant, and the confidence intervals did not reach cross MID.*

(d) *The study which contributed data to this time point had large prostate size, with a mean of 55ml. However, recommendations were made for men with large prostates and therefore there is no indirectness of evidence.*

(e) *There was substantial heterogeneity and random effects analyses were conducted.*

(f) *When random effect analysis was used conducted, the RR changed from 3.50 (2.33, 5.26) to not statistically significant. Subgroup analysis conducted to investigate the source of heterogeneity found the RR for the tamsulosin trial as 6.85, 95% CI 3.54 to 13.27 (favouring alpha reductase inhibitors) while RR for RR for the other alpha-blockers was RR 1.76 (1.01 to 3.06).*

(g) *There were variations in the terms used to describe and report the sexual side effects such as retrograde ejaculation, reduced semen volume ejaculatory abnormalities; erectile dysfunction and impotence.*

Table 6-66: Alpha blockers plus 5-ARI vs. 5-ARI- Clinical summary of findings

Outcome	Alpha-blockers + 5-ARI	5-ARI	Relative risk	Absolute effect	Quality
Symptom score at 6 months	349	344	Not applicable	MD -0.9 [-1.74 to -0.06]	Moderate
Symptom score at 1 year	543	499	Not applicable	MD -2.67 [-3.31 to -2.67]	Moderate
Symptom score at 2 years	1610	1623	Not applicable	MD -1.3 [-1.71 to -0.89]	High
Symptom score at 4 years	786	768	Not applicable	MD -1.8 [-2.33 to -1.27]	High
Qmax(ml/s) at 6 months	349	344	Not applicable	MD 0.5 [-0.19 to 1.19]	Moderate
Qmax(ml/s) at 1 year	542	491	Not applicable	MD 1.87 [1.26 to 2.48]	Moderate
Qmax(ml/s) at 2 years	1611	1623	Not applicable	MD 0.5 [0.17 to 0.83]	High
Prostate volume (ml) at 6 months	349	344	Not applicable	MD -0.6 [-2.65 to 1.45]	Moderate
Prostate volume(ml) at 1 year	275	252	Not applicable	MD -0.9 [-4.53 to 2.73]	High
Prostate volume(ml) at 2 years	1610	1623	Not applicable	MD 0.6 [-0.32 to 1.52]	High
Prostate volume(ml) at 4 years	778	768	Not applicable	MD 0.85 [-0.54 to 2.24]	High
PSA(ng/ml) at 6 months	349	344	Not applicable	MD 0.30 [0.03 to 0.57]	High
PSA(ng/ml) at 1 year	265	239	Not applicable	MD -0.10 [-0.36 to 0.16]	High
Syncope	11/595 (1.8%)	3/574 (0.5%)	RR 3.2 [0.96 to 10.64]	11 more per 1000 [0 fewer to 48 more]	Moderate
Postural hypotension	41/1730 (2.4%)	15/1686 (0.9%)	RR 2.69 [1.5 to 4.82]	15 more per 1000 [4 to 34 more]	High
Orthostatic hypotension	129/658 (19.6%)	89/654 (13.6%)	RR 1.45 [1.16 to 1.82]	61 more per 1000 [22 to 112 more]	Moderate
Dizziness	144/3340 (4.3%)	64/3309 (1.9%)	RR 2.2 [1.66 to 2.91]	23 more per 1000 [13 to 36 more]	High
Vertigo	8/286 (2.8%)	6/264 (2.3%)	RR 1.23 [0.43 to 3.5]	5 more per 1000 [13 fewer to 58 more]	Low
Headache	21/658 (3.2%)	23/654 (3.5%)	RR 0.91 [0.51 to 1.63]	3 fewer per 1000 [17 fewer to 22 more]	Moderate
Fatigue(Asthenia)	75/1730 (4.3%)	36/1686 (2.1%)	RR 2.02 [1.38 to 2.95]	21 more per 1000 [8 to 41 more]	High
Somnolence	11/1421 (0.8%)	10/1376 (0.7%)	RR 1.03 [0.45 to 2.34]	0 more per 1000 [4 fewer to 9 more]	Low
Rhinitis	24/309 (7.8%)	8/310 (2.6%)	RR 3.01 [1.37 to 6.6]	52 more per 1000 [10 to 146 more]	Moderate
Decreased libido	86/3340 (2.6%)	76/3309 (2.3%)	RR 1.13 [0.83 to 1.53]	3 more per 1000 [4 fewer to 12 more]	Moderate
Ejaculatory abnormality or retrograde ejaculation (a),(b)	102/3340 (3.1%)	29/3323 (0.9%)	RR 2.13 [0.84 to 5.42]	10 more per 1000 [1 fewer to 40 more]	Very Low
Impotence or erectile dysfunction	180/3031 (5.9%)	138/2999 (4.6%)	RR 1.29 [1.04 to 1.6]	13 more per 1000 [2 to 28 more]	Low
Breast enlargement (gynaecomastia)	23/1610 (1.4%)	29/1623 (1.8%)	RR 0.8 [0.46 to 1.38]	4 fewer per 1000 [10 fewer to 7 more]	Moderate
Acute urinary retention	5/1135 (0.4%)	7/1112 (0.6%)	RR 0.7 [0.22 to 2.19]	2 fewer per 1000 [5 fewer to 7 more]	Moderate
Withdrawal due to adverse events (a)	131/2533 (5.2%)	167/2470 (6.8%)	RR 0.79 [0.54 to 1.17]	14 fewer per 1000 [31 fewer to 12 more]	Low

(a) Outcome was analysed using random effects due to heterogeneity

(b) See notes in the Clinical study characteristics table and Forest plots in Figure E-68 in appendix for subgroup analysis.

6.10.2.2 Economic evidence

We found two studies[58,157] comparing a combination of alpha blockers and 5-alpha-reducatse inhibitors with 5-alpha-reductase inhibitors. However, both were excluded because either the clinical data for the two arms were obtained from studies with different populations[157] or the clinical data for the combination arm was based on expert opinion[58].

It was not necessary to build an original economic model since neither of the two interventions is cost-effective when compared with alpha blockers. Please see 6.3.2.2 and 6.10.1.2.

6.10.2.3 Evidence statement (s)

Clinical

Combination treatment of alpha blocker plus 5-ARI is more effective than 5-ARI in improving symptom score at 6 months, 1, 2 and 4 years follow up.

There are no statistically significant differences between combination treatment of alpha blocker plus 5-ARI and 5-ARI in improving Qmax (ml/s) at 6 months follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than 5-ARI in improving Qmax (ml/s) at 1 and 2 years follow up.

There is no statistically significant difference between combination treatment of alpha blocker plus 5-ARI and 5-ARI in reducing prostate volume at 6 months, 1 year, 2 years and 4 years follow up.

5- Alpha reductase inhibitors are more effective than combination treatment of alpha blocker plus 5-ARI and in reducing PSA levels at 6 months follow up.

There is no statistically significant difference between combination treatment of alpha blocker plus 5-ARI and 5-ARI in reducing PSA levels at1 year follow up.

More men treated with a combination of alpha blockers plus 5-ARI compared to 5-ARI experienced adverse effects such as postural hypotension, dizziness, fatigue (asthenia), orthostatic hypotension, rhinitis or erectile dysfunction (impotence).

There is no statistically significant difference between combination of alpha blockers plus 5-ARI and 5-ARI in number of men experiencing adverse effects such as syncope, vertigo, headache acute urinary retention, ejaculatory disorders, somnolence, decreased libido, or withdrawal from study due to adverse reactions.

Economic

No economic studies were included which compared combination of Alpha blockers plus 5-ARI with 5-ARI.

6.10.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.10.3 Alpha blockers plus 5-ARIvs. placebo

See Evidence Table 19, Appendix D, Forest Plots in Figures E-70 to E-77, Appendix E.

6.10.3.1 Clinical evidence

Table 6-67: Alpha blockers plus 5-ARI vs. Placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score t 6-months	0	RCT				
Symptom score at 1 year [121,132]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 2 years	0	RCT				
Symptom score at 4 years [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0	RCT	-			
Qmax(ml/s) at 1 year[121,132]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
PSA(ng/ml)at 1 year[121]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume (ml) at 1 year [132]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume (ml) at 4 year [156]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Syncope[121,132]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Postural hypotension[121,132,156]	3	RCT	No serious limitations	Serious inconsistency (d)	No serious indirectness	No serious imprecision
Orthostatic hypotension [132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[121,132,156]	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Vertigo[121]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Fatigue(Asthenia)[121,132,156]	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Somnolence[121,156]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Rhinitis[132]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Decreased libido[121,132,156]	3	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Ejaculatory abnormality/ retrograde ejaculation[121,132,156]	3	RCT	Serious limitations (e)	No serious inconsistency	No serious indirectness	No serious imprecision
Impotence or erectile dysfunction[121,156]	2	RCT	Serious limitations (e)	No serious inconsistency	No serious indirectness	No serious imprecision
Withdrawals due to adverse events[121,132]	2	RCT	No serious limitations	Serious inconsistency (d)	No serious indirectness	Serious imprecision (c)

(a) *RCT(s) with which did not report randomisation allocation and concealment methods [121] contributed entirely or more than 50% of the weight of the pooled outcome.*
(b) *Treatment effects observed at different time points differed, suggesting the duration of treatment and follow-up as a likely factor which affect the direction and effect size. This observation would be consistent with current knowledge of the pharmacology (mechanism of action) of these classes of drugs. Therefore, the quality was not downgraded.*
(c) *Outcomes were downgraded when the confidence intervals crossed the MID. It was not downgraded if the size of the benefit/harm was small or not statistically significant, and the confidence intervals did not reach cross MID.*
(d) *There were substantial heterogeneity and random analysis was conducted.*
(e) *There were variations in the terms used to describe and report the sexual side effects such as retrograde ejaculation, reduced semen volume ejaculatory abnormalities; erectile dysfunction and impotence.*
(f) *It is unknown what magnitude of reduction in prostate volume or PSA level is important enough to be noticeable by patients or associated with differences in symptoms and prognosis.*

Table 6-68: Alpha blockers plus 5-ARI vs. placebo - Clinical summary of findings

Outcome	Alpha-blockers + 5-ARI	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 1 year	543	518	Not applicable	MD -3.37 [-4.01 to -2.72]	Moderate
Symptom score at 4 years	786	737	Not applicable	MD -2.5 [-3 to -2]	Moderate
Qmax(ml/s) at 1 year	542	517	Not applicable	MD 2.13 [1.51 to 2.76]	Moderate
PSA(ng/ml) at 1 year	265	253	Not applicable	MD-1.60 [-1.85, -1.35]	Moderate
Prostate volume (ml) at 1 year	275	258	Not applicable	MD -7.5 [-11.5 to -3.5]	Moderate
Prostate volume (ml) at 1 year	778	736	Not applicable	MD -8.58 [-10.08 to -7.08]	High
Syncope	11/595 (1.8%)	1/574 (0.2%)	RR 7.35 [1.35 to 40.0]	13 more per 1000 [1 to 78 more]	Moderate
Postural hypotension(a)	39/1381 (2.8%)	9/1311 (0.7%)	RR 3.35 [1.11 to 10.15]	16 more per 1000 [1 to 63 more]	Moderate
Orthostatic hypotension	121/309 (39.2%)	92/310 (29.7%)	RR 1.32 [1.06 to 1.65]	95 more per 1000 [18 to 193 more]	Moderate
Dizziness	110/1381 (8%)	44/1311 (3.4%)	RR 2.41 [1.73 to 3.36]	48 more per 1000 [25 to 80 more]	High
Vertigo	39/286 (13.6%)	20/269 (7.4%)	RR 1.83 [1.1 to 3.06]	61 more per 1000 [7 to 152 more]	Low
Headache	16/309 (5.2%)	10/305 (3.3%)	RR 1.58 [0.73 to 3.42]	19 more per 1000 [9 fewer to 80 more]	Moderate
Fatigue(Asthenia)	73/1381 (5.3%)	34/1311 (2.6%)	RR 2.08 [1.41 to 3.08]	28 more per 1000 [11 to 54 more]	High
Somnolence	10/1072 (0.9%)	6/1006 (0.6%)	RR 1.52 [0.58 to 3.99]	3 more per 1000 [3 fewer to 18 more]	Moderate
Rhinitis	24/309 (7.8%)	14/305 (4.6%)	RR 1.69 [0.89 to 3.21]	32 more per 1000 [5 fewer to 102 more]	Moderate
Decreased libido	24/1381 (1.7%)	10/1311 (0.8%)	RR 2.31 [1.12 to 4.8]	10 more per 1000 [1 to 30 more]	Moderate
Ejaculatory abnormality or retrograde ejaculation	31/1381 (2.2%)	9/1311 (0.7%)	RR 3.33 [1.6 to 6.93]	16 more per 1000 [4 to 42 more]	Moderate
Impotence or erectile dysfunction	35/1072 (3.3%)	12/1006 (1.2%)	RR 2.74 [1.44 to 5.21]	21 more per 1000 [5 to 51 more]	Moderate
Withdrawals due to adverse events(a)	59/574 (10.3%)	35/574 (6.1%)	RR 2.22 [0.56 to 8.8]	74 more per 1000 [27 fewer to 476 more]	Low

(a) Random effects analysis was conducted

6.10.3.2 Economic evidence

We found two studies [58,157] comparing a combination of alpha blockers and 5-ARI with no intervention. However, both were excluded because either the clinical data for the two arms were obtained from studies with different populations [157] or the clinical data for the combination arm was based on expert opinion [58].

It was not necessary to build an original economic model since none of the two interventions are cost-effective when compared with alpha blockers. Please see 6.3.2.2 and 6.10.1.2.

6.10.3.3 Evidence statement (s)

Clinical Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in improving symptom score at 1and 4 years follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in improving Qmax (ml/s) at1 year follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in reducing prostate volume at 1 year and 4 years follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in reducing PSA level at1 year follow up.

Significantly more men treated with a combination of alpha blockers plus 5-ARI compared to placebo experienced adverse effects such as syncope, dizziness, fatigue (asthenia), erectile dysfunction (impotence), ejaculatory abnormality, postural hypotension, orthostatic hypotension or decreased libido and vertigo.

There is no statistically significant difference between men treated with a combination of alpha blockers plus 5-ARI compared to placebo in number of men experiencing adverse effects such as headache, rhinitis, somnolence, or withdrawal from study due to adverse reactions.

Economic No economic studies were included which compared combination treatment of alpha blocker plus 5-ARI with placebo.

6.10.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.11 Combination therapy (Alpha blocker plus anticholinergics)

Alpha blockers work on all the symptoms of lower urinary tract symptoms attributed to BPH, as measured with the IPSS. Anticholinergics are indicated for the more bothersome storage symptoms such as urgency, frequency and incontinence which may be the main presenting symptoms in some patients with LUTS or remain a problem after therapy with alpha blockers.

Investigating whether any additional benefits can be gained when using a combination of these two classes and whether these are worth the potentially more severe or numerous side-effects is important.

6.11.1 Alpha blockers plus anticholinergics vs. alpha blockers

See Evidence Table 20, Appendix D, Forest Plots in Figures E-78 to E-82, Appendix E.

6.11.1.1 Clinical evidence

Table 6-69: Alpha blockers plus anticholinergics vs. alpha blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptoms score at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life IPSS question at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax(ml/s) at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency incontinence episodes/24h [115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency episodes/24h[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/24h[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/night[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Constipation[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Diarrhoea[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dry mouth[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Dyspepsia[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Ejaculation failure[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Fatigue[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Somnolence[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Nasal congestion[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) *There was incomplete or unclear reporting for many outcomes. This study [114,115] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance ($p<0.05$ or $p<0.01$) of combination vs. placebo was indicated in the paper for some of the outcomes. (Actual values and standard deviations of these outcomes were also not reported.*

(b) *It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was reported. All efficacy outcomes were rated "very serious imprecision" as it was unclear whether the combination strategy was more effective than any of the monotherapies There is very high uncertainty in the results.*

(c) *Serious to very serious imprecision as confidence interval crossed the MID(s).*

(d) *Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries filled for 5 days before visit.*

Table 6-70: Alpha blockers plus anticholinergics vs. alpha blockers - Clinical summary of findings

Outcome	Alpha-blockers + Anti-Ch	Alpha-blockers	Relative risk	Absolute effect	Quality
Symptoms score at 3 months	203	197	Not applicable	-0.4 p value NR(a)	Very Low
Quality of life (IPSS question) at 3 months	205	198	Not applicable	-0.2 p value NR(a)	Very Low
Qmax(ml/s) at 3 months	NR(b)	NR(b)	Not applicable	0.29 p value NR(a)	Very Low
Urgency incontinence episodes/24h	47	46	Not applicable	-0.17 p value NR(a)	Very Low
Urgency episodes/24h	211	205	Not applicable	-0.9 p value NR(a)	Very Low
Frequency/24h	211	205	Not applicable	-0.7 p value NR(a)	Very Low
Frequency/night	209	205	Not applicable	-0.05 p value NR(a)	Very Low
Constipation	8/225 (3.6%)	2/215 (0.9%)	RR 3.82 [0.82 to 17.8]	25 more per 1000 [2 fewer to 151 more]	Low
Diarrhoea	5/225 (2.2%)	6/215 (2.8%)	RR 0.8 [0.25 to 2.57]	17 fewer per 1000 [63 fewer to 132 more]	Low
Dizziness	6/225 (2.7%)	12/215 (5.6%)	RR 0.48 [0.18 to 1.25]	29 fewer per 1000 [46 fewer to 14 more]	Low
Dry mouth	47/225 (20.9%)	15/215 (7%)	RR 2.99 [1.73 to 5.19]	139 more per 1000 [51 to 293 more]	Moderate
Dyspepsia	3/225 (1.3%)	1/215 (0.5%)	RR 2.87 [0.3 to 27.35]	9 more per 1000 [3 fewer to 132 more]	Very Low
Ejaculation failure	7/225 (3.1%)	4/215 (1.9%)	RR 1.67 [0.5 to 5.63]	13 more per 1000 [10 fewer to 88 more]	Low
Urinary retention	2/225 (0.9%)	0/215 (0%)	RR 4.78 [0.23 to 98.97]	0 more per 1000 [0 fewer to 0 more]	Very Low
Fatigue	2/225 (0.9%)	3/215 (1.4%)	RR 0.64 [0.11 to 3.78]	5 fewer per 1000 [12 fewer to 39 more]	Low
Somnolence	4/225 (1.8%)	5/215 (2.3%)	RR 0.76 [0.21 to 2.81]	6 fewer per 1000 [18 fewer to 42 more]	Low
Headache	14/225 (6.2%)	9/215 (4.2%)	RR 1.49 [0.66 to 3.36]	21 more per 1000 [14 fewer to 99 more]	Low
Nasal congestion	10/225 (4.4%)	3/215 (1.4%)	RR 3.19 [0.89 to 11.42]	31 more per 1000 [2 fewer to 146 more]	Low

(a) *The study reported outcomes as graphs only and there were no p values or standard deviations for comparison. Therefore confidence intervals could not be obtained. These values were adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre.*

(b) *Numbers of patients with Qmax measurements at follow up were not reported.*

6.11.1.2 Economic evidence

No economic studies were identified.

6.11.1.3 Evidence statement (s)

Clinical Significantly more men treated with a combination of alpha blockers plus anticholinergics compared to alpha blockers experienced dry mouth.

There is no statistically significant difference between a combination of alpha blockers plus anticholinergics compared to alpha blockers in number of men experiencing constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache and nasal congestion.

Economic No economic studies were identified.

6.11.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.11.2 Anticholinergics added on to alpha blockers vs. alpha blockers

One study which investigated the benefits of adding anticholinergics to patients who did not achieve adequate control with alpha blockers [145].

See Evidence Table 20, Appendix D, Forest Plots in Figures E-79 to E-82, Appendix E.

6.11.2.1 Clinical evidence

Table 6-71: Anticholinergics added on to alpha blockers vs. alpha blockers- Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months)[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Qmax(ml/s) at 3 months[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Dry mouth- 3 months follow up[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	No serious imprecision
Infections and infestations- 3 months follow up[145]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Renal and urinary adverse events- 3 months follow up[145]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Constipations- 3 months follow up[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Nervous system disorders- 3 months follow up[145]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Acute urinary retention- 3 months follow up[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Withdrawals due to adverse events[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Obstruction - Qmax<5ml/s at end point(12 weeks)[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Retention - PVR >300ml at end-point(12 weeks)[145]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)

(a) *Only one study where rrandomisation allocation and concealment methods were not reported was found* [145]. *Patient characteristics at screening visit (before receiving alpha-blocker) were not described.*

(b) *Only about half of all patients who were screened and received alpha-blockers were eligible to be randomised and the breakdown of reasons for ineligibility for randomisation was not reported.*

(c) *The confidence interval crossed minimum important difference.*

(d) *Adverse events not well defined.*

Table 6-72: Anticholinergics added on to alpha blockers vs. alpha blockers - Clinical summary of findings

Outcome	Anti-Ch add on	Alpha blockers	Relative risk	Absolute effect	Quality
Symptom score at 3 months	209	209	Not applicable	MD -1.7 [-2.92 to -0.48]	Very Low
Quality of life (IPSS-question) at 3 months	209	209	Not applicable	MD -0.5 [-0.78 to -0.22]	Very Low
Qmax(ml/s) at 3 months	209	209	Not applicable	MD -0.30 [-1.78 to1.18]	Very Low
Dry mouth- 3 months follow up	32/209 (15.3%)	10/209 (4.8%)	RR 3.2 [1.62 to 6.34]	106 more per 1000 [30 to 256 more]	Low
Infections and infestations- 3 months follow up	18/209 (8.6%)	22/209 (10.5%)	RR 0.82 [0.45 to 1.48]	19 fewer per 1000 [58 fewer to 50 more]	Very Low
Renal and urinary adverse events- 3 months follow up	10/209 (4.8%)	10/209 (4.8%)	RR 1 [0.43 to 2.35]	0 fewer per 1000 [27 fewer to 65 more]	Very Low
Constipations- 3 months follow up	1/209 (0.5%)	4/209 (1.9%)	RR 0.25 [0.03 to 2.22]	14 fewer per 1000 [18 fewer to 23 more]	Very Low
Nervous system disorders- 3 months follow up	8/209 (3.8%)	9/209 (4.3%)	RR 0.89 [0.35 to 2.26]	5 fewer per 1000 [28 fewer to 54 more]	Very Low
Acute urinary retention- 3 months follow up	0/209 (0%)	0/209 (0%)	Not estimable	Not estimable	Very Low
Withdrawals due to adverse events	21/209 (10%)	20/209 (9.6%)	RR 1.05 [0.59 to 1.88]	5 more per 1000 [39 fewer to 84 more]	Very Low
Obstruction - Qmax<5ml/s at end point(12 weeks)	14/209 (6.7%)	13/209 (6.2%)	RR 1.08 [0.52 to 2.24]	5 more per 1000 [30 fewer to 77 more]	Very Low
Retention - PVR >300ml at end-point(12 weeks)	8/209 (3.8%)	12/209 (5.7%)	RR 0.67 [0.28 to 1.6]	19 fewer per 1000 [41 fewer to 34 more]	Very Low

6.11.2.2 Economic evidence

No economic studies were identified.

6.11.2.3 Evidence statement (s)

Clinical An anticholinergic added to an alpha blocker is more effective than alpha blockers alone in improving symptom scores and quality of life (IPSS question).

More men treated with a combination of anticholinergic drug added on to an alpha blocker compared to alpha blockers experienced dry mouth.

There is no statistically significant difference between anticholinergic drug added on to alpha blocker compared to alpha blockers in number of men experiencing adverse events which led to withdrawal from study, infections and infestations, constipations, nervous system disorders, acute urinary retention or renal and urinary adverse events.

Economic No economic studies were identified.

6.11.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.11.3 Alpha blockers plus anticholinergics vs. anticholinergics

See Evidence Table 20, Appendix D, Forest Plot in Figure E-83, Appendix E.

6.11.3.1 Clinical evidence

Table 6-73: Alpha blockers plus anticholinergics vs. anticholinergics - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptoms score at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life IPSS question at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax(ml/s) at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency incontinence episodes/24h [115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency episodes/24h[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/24h[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/night[115]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Constipation[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Diarrhoea[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Dizziness[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Dry mouth[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Dyspepsia[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c
Ejaculation failure[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Urinary retention[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Fatigue[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Somnolence[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(c)
Headache[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Nasal congestion[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) *There was incomplete or unclear reporting for many outcomes. This study [114,115] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance ($p<0.05$ or $p<0.01$) of combination vs. placebo was indicated in the paper for some of the outcomes. (Actual values and standard deviations of these outcomes were also not reported.*

(b) *It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was reported. All efficacy outcomes were rated "very serious imprecision" as it was unclear whether the combination strategy was more effective than any of the monotherapies There is very high uncertainty in the results.*

(c) *Serious to very serious imprecision as confidence interval crossed the MID(s), increasing the uncertainty of the results.*

(d) *Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries filled for 5 days before visit.*

Table 6-74: Alpha blockers plus anticholinergics vs. anticholinergics - Clinical summary of findings

Outcome	*Alpha blockers + Anti-Ch*	*Anti-Ch*	*Relative risk*	*Absolute effect*	*Quality*
Symptoms score at 3 months	203	206	Not applicable	-1.3 p value NR(a)	Very Low
Quality of life (IPSS question) at 3 months	205	206	Not applicable	-0.2 p value NR(a)	Very Low
Qmax(ml/s) at 3 months	NR(b)	NR(b)	Not applicable	0.67 p value NR(a)	Very Low
Urgency incontinence episodes/24h	47	48	Not applicable	-0.04 p value NR(a)	Very Low
Urgency episodes/24h	211	209	Not applicable	-1.4 p value NR(a)	Very Low
Frequency/24h	211	209	Not applicable	-0.8 p value NR(a)	Very Low
Frequency/night	209	217	Not applicable	-0.23 p value NR(a)	Very Low
Constipation	8/225 (3.6%)	9/217 (4.1%)	RR 0.85 [0.34 to 2.17]	6 fewer per 1000 [27 fewer to 49 more]	Low
Diarrhoea	5/225 (2.2%)	7/217 (3.2%)	RR 0.69 [0.22 to 2.13]	10 fewer per 1000 [25 fewer to 36 more]	Low
Dizziness	6/225 (2.7%)	3/217 (1.4%)	RR 1.92 [0.49 to 7.58]	13 more per 1000 [7 fewer to 91 more]	Low
Dry mouth	47/225 (20.9%)	16/217 (7.4%)	RR 2.82 [1.65 to 4.82]	134 more per 1000 [48 more to 282 more]	Moderate
Dyspepsia	3/225 (1.3%)	2/217 (0.9%)	RR 1.44 [0.24 to 8.53]	4 more per 1000 [7 fewer to 69 more]	Low
Ejaculation failure	7/225 (3.1%)	0/217 (0%)	RR 14.4 [0.83 to 250.65]	Not estimable	Low
Urinary retention	2/225 (0.9%)	2/217 (0.9%)	RR 0.96 [0.14 to 6.75]	0 fewer per 1000 [8 fewer to 53 more]	Low
Fatigue	2/225 (0.9%)	2/217 (0.9%)	RR 0.96 [0.14 to 6.75]	0 fewer per 1000 [8 fewer to 53 more]	Low
Somnolence	4/225 (1.8%)	2/217 (0.9%)	RR 1.92 [0.36 to 10.38]	8 more per 1000 [6 fewer to 86 more]	Low
Headache	14/225 (6.2%)	2/217 (0.9%)	RR 6.72 [1.55 to 29.22]	53 more per 1000 [5 more to 260 more]	Moderate
Nasal congestion	10/225 (4.4%)	0/217 (0%)	RR 20.16 [1.19 to 342]	Not estimable	Low

6.11.3.2 Economic evidence

No economic studies were identified.

6.11.3.3 Evidence statement (s)

Clinical More men treated with a combination of alpha blockers plus anticholinergics than anticholinergics alone experienced dry mouth.

There is no statistically significant difference between combination treatment of alpha blockers plus anticholinergics compared to anticholinergics in number of men experiencing adverse events such as constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache or nasal congestion.

Economic No economic studies were identified.

6.11.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.11.4 Alpha blockers plus anticholinergics vs. placebo

See Evidence Table 20, Appendix D, Forest Plot in Figure E-84, Appendix E.

6.11.4.1 Clinical evidence

Table 6-75: Alpha blockers plus anticholinergics vs. placebo - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptoms score at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life (IPSS question) at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax(ml/s) at 3 months [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency incontinence episodes/24h [115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency episodes/24h[115]	1	RCT	Serious limitations (a)(c)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/24h[115]	1	RCT	Serious limitations (a)(c)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Frequency/night[115]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Constipation	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Diarrhoea	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Dizziness	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Dry mouth	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Dyspepsia	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Ejaculation failure	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary retention	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Fatigue	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Somnolence	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Headache	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Nasal congestion	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)

(a) *This study [114,115] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance of results for combination vs. placebo was reported for the effectiveness results. The standard deviations of these outcomes were also not reported and therefore not able to tell whether the combination strategy was more effective than monotherapy.*

(b) *Although reported as statistically significant efficacy outcomes downgraded as it was unknown whether the confidence intervals crossed the MIDs and mean difference of treatment effects were smaller than MIDs.*

(c) *The confidence intervals crossed the MID.*

Table 6-76: Alpha blockers plus anticholinergics vs. placebo - Clinical summary of findings

Outcome	*Alpha-blockers + Anti-Ch*	*placebo*	*Relative risk*	*Absolute effect*	*Quality*
Symptoms score at 3 months	203	213	Not applicable	MD-0.9 P value <0.01 (a)	Very Low
Quality of life (IPSS question) at 3 months	205	213	Not applicable	MD-0.4 p value = 0.003 (a)	Very Low
Qmax(ml/s) at 3 months	NR(b)	NR(b)	Not applicable	MD 0.60 p value = 0.003 (a)	Very Low
Urgency incontinence episodes/24h	47	43	Not applicable	MD-0.57 p value = 0.005 (a)	Very Low
Urgency episodes/24h	211	210	Not applicable	MD -0.8 p value =0.03 (a)	Very Low
Frequency/24h	211	212	Not applicable	MD -1.1 p value < 0.001(a)	Low
Frequency/night	209	212	Not applicable	MD -0.2 p value =0.02 (a)	Very Low
Constipation	8/225 (3.6%)	5/220 (2.3%)	RR 1.56 [0.52 to 4.71]	13 more per 1000 [11 fewer to 85 more]	Low
Diarrhoea	5/225 (2.2%)	3/220 (1.4%)	RR 1.63 [0.39 to 6.74]	9 more per 1000 [9 fewer to 80 more]	Low
Dizziness	6/225 (2.7%)	2/220 (0.9%)	RR 2.93 [0.6 to 14.38]	17 more per 1000 [4 fewer to 120 more]	Low
Dry mouth	47/225 (20.9%)	5/220 (2.3%)	RR 9.19 [3.73 to 22.68]	188 more per 1000 [63 more to 499 more]	Moderate
Dyspepsia	3/225 (1.3%)	5/220 (2.3%)	RR 0.59 [0.14 to 2.43]	9 fewer per 1000 [20 fewer to 33 more]	Low
Ejaculation failure	7/225 (3.1%)	0/220 (0%)	RR 14.67 [0.84 to 255.28]	Not estimable	Low
Urinary retention	2/225 (0.9%)	3/220 (1.4%)	RR 0.65 [0.11 to 3.86]	5 fewer per 1000 [12 fewer to 40 more]	Low
Fatigue	2/225 (0.9%)	6/220 (2.7%)	RR 0.33 [0.07 to 1.6]	18 fewer per 1000 [25 fewer to 16 more]	Low
Somnolence	4/225 (1.8%)	2/220 (0.9%)	RR 1.96 [0.36 to 10.57]	9 more per 1000 [6 fewer to 86 more]	Low

6.11.4.2 Economic evidence

No economic studies were identified.

6.11.4.3 Evidence statement (s)

Clinical A combination for alpha blockers plus anticholinergics are more effective than placebo in improving symptom score, quality of life (IPSS question), urgency incontinence episodes, urgency episodes and frequency, frequency of micturition at night, and Qmax.

More patients treated with a combination of alpha blockers plus anticholinergics than placebo experienced dry mouth.

There is no statistically significant difference between combination treatment of alpha blockers plus anticholinergics compared to placebo in number of men experiencing adverse events such as constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache or nasal congestion.

Economic No economic studies were identified.

6.11.4.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.12 Alpha blockers plus Phosphodiesterase 5-inhibitors (PDE5-I)

Several epidemiological studies have indicated that the association between LUTS and ED is more than a co-incidence of age, with a possible cause and effect relationship. LUTS is more common in men with ED and there is a strong relationship between the severity of LUTS and the degree of erectile difficulty. The co-prescription of two active agents for these conditions will improve each condition and the addition of one drug to the other may potentiate the primary response of the first treatment and thereby improve the symptoms and QoL of patients.

6.12.1 Alpha blockers plus PDE5-I vs. Alpha blockers

See Evidence Table 21, Appendix D, Forest Plots in Figures E-85 to E91, Appendix E.

6.12.1.1 Clinical evidence

Table 6-77: Alpha blockers plus PDE5-I vs. alpha blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score (up to 3 months)[112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (c)
Quality of life (IPSS question) up to 3 months [135]	1	RCT	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Very serious imprecision (c)
Qmax(ml/s) at follow up - 3 months [112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (c)
Frequency at follow up - 3 months [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Nocturia at follow up - 3 months [112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[23,112]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Dyspepsia[23,112]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Flushing [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Gastric upset[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Headache[23]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Ejaculation disorder[23]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Altered vision[23]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Diarrhoea[23]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Hypotension[23,112]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Syncope[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

(a) *Three small studies (each arm <30 participants) were found and each of these studies had major limitations [23,112,135]. Two studies were open label with poorly reported randomisation allocation and concealment methods, resulting in very high risk of bias, particularly in subjective and patient reported outcomes measures [112,135]. Another study was a crossover study [23]. Some outcomes only had less than 30 patients per treatment arm.*

(b) *Liguori2009 included patients with severe LUTS, with an average IPSS around 20points [135].*

(c) *Serious to very serious imprecision for all outcomes because of the very small sample size, which was not sufficient to detect a MID in the main outcomes considered.*

Table 6-78: Alpha blockers plus PDE5-I vs. alpha blockers - Clinical summary of findings

Outcome	PDE5-I + alpha blocker	Alpha blockers	Relative risk	Absolute effect	Quality
Symptom score -up to 3 months	69	65	Not applicable	MD -1.29 [-2.73 to 0.15]	Very Low
Quality of life (IPSS question) up to 3 months	21	18	Not applicable	MD -0.3 [-0.87 to 0.27]	Very Low
Qmax(ml/s) at follow up - 3 months	42	38	Not applicable	MD 1.03 [-0.27 to 2.32]	Very Low
Frequency at follow up - 3 months	21	20	Not applicable	MD -0.3 [-1.62 to 1.02]	Very Low
Nocturia at follow up - 3 months	42	38	Not applicable	MD 0.15 [-0.28 to 0.58]	Very Low
Dizziness	1/51 (2%)	3/50 (6%)	RR 0.42 [0.06 to 2.69]	35 fewer per 1000 [56 fewer to 101 more]	Very Low
Flushing	0/21 (0%)	0/20 (0%)	Not estimable	Not estimable	Very Low
Dyspepsia	3/51 (5.9%)	1/50 (2%)	RR 3 [0.33 to 27.23]	40 more per 1000 [13 fewer to 525 more]	Very Low
Gastric upset	2/21 (9.5%)	0/20 (0%)	RR 4.77 [0.24 to 93.67]	Not estimable	Very Low
Headache	12/30 (40%)	0/30 (0%)	RR 25 [1.55 to 403.99]	Not estimable	Very Low
Ejaculation disorder	0/30 (0%)	1/30 (3.3%)	RR 0.33 [0.01 to 7.87]	22 fewer per 1000 [33 fewer to 227 more]	Very Low
Altered vision	0/30 (0%)	1/30 (3.3%)	RR 0.33 [0.01 to 7.87]	22 fewer per 1000 [33 fewer to 227 more]	Very Low
Diarrhoea	0/30 (0%)	1/30 (3.3%)	RR 0.33 [0.01 to 7.87]	22 fewer per 1000 [33 fewer to 227 more]	Very Low
Hypotension	2/51 (3.9%)	1/50 (2%)	RR 2 [0.19 to 20.9]	20 more per 1000 [16 fewer to 398 more]	Very Low
Syncope	0/21(0%)	0/20(0%)	Not estimable	Not estimable	Very Low

6.12.1.2 Economic evidence

No economic studies were identified.

6.12.1.3 Evidence statement (s)

Clinical

There is no statistically significant difference between combination treatment of alpha blockers plus PDE5-I and alpha blockers in improving symptom scores, quality of life (IPSS question), Qmax (ml/s), nocturia or frequency at up to 3 months follow-up.

There is no significant difference between combination of alpha blockers plus PDE5-I compared to alpha blockers in number of men experiencing dizziness, flushing, dyspepsia, gastric upset, ejaculation disorders, altered vision, diarrhoea, hypotension, syncope or adverse events which led to withdrawal from the study.

More men treated with a combination of alpha blockers plus phosphodiesterase inhibitors compared to alpha blockers experienced headaches.

Economic

No economic studies were identified.

6.12.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.12.2 Alpha blockers plus PDE5-I vs. PDE5-I

See Evidence Table 21, Appendix D, Forest Plots in Figures E-91 to E-98, Appendix E.

6.12.2.1 Clinical evidence

Table 6-79: Alpha -blockers plus PDE5-I vs. PDE5-I - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months [112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency(d)	Serious indirectness (b)	Very serious imprecision (c)
Quality of life (IPSS question)- up to 3 months [112,135]	1	RCT	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Very serious imprecision (c)
Qmax(ml/s) at follow up - 3 months[112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Frequency at follow up - 3 months [112,135]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Nocturia at follow up - 3 months [112,135]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Flushing [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Dyspepsia [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Gastric upset [112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Hypotension[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Syncope[112]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

(a) *Only two small (each study arm had 19-21 patients) were found. One was an open label study which did not report method of randomisation generation and concealment of randomisation [112]. This puts the study at a very high level of potential bias, especially when subjective outcomes or outcomes collected based on patient responses were considered.*

(b) *Liguori2009 included patients with severe LUTS, with an average IPSS score around 20points [135].*

(c) *Very serious imprecision was found for all outcomes because of the very small sample size, which was not sufficient to detect a minimal important difference in the main outcomes considered.*

(d) *Substantial heterogeneity was found and random effects analysis was performed.*

Table 6-80: Alpha blockers plus PDE5-I vs. PDE5-I - Clinical summary of findings

Outcome	Alpha blockers + PDE5-I	PDE5-I	Relative risk	Absolute effect	Quality
Symptom score - 3 months (a)	42	40	Not applicable	MD -2.4 [-6.71 to 1.91]	Very Low
Quality of life (IPSS question) -3 months	21	19	Not applicable	MD -0.6 [-1.26 to 0.06]	Very Low
Qmax(ml/s) at follow up - 3 months	42	40	Not applicable	MD 1.76 [0.32 to 3.2]	Very Low
Frequency at follow up – 3 months	21	21	Not applicable	MD -1.7 [-2.89 to -0.51]	Very Low
Nocturia at follow up – 3 months	42	40	Not applicable	MD 0.04 [-0.37 to 0.45]	Very Low
Dizziness	1/21 (4.8%)	0/21 (0%)	RR 3 [0.13 to 69.7]	Not estimable	Very Low
Flushing	0/21 (0%)	1/21 (4.8%)	RR 0.33 [0.01 to 7.74]	32 fewer per 1000 [48 fewer to 324 more]	Very Low
Dyspepsia	0/21 (0%)	1/21 (4.8%)	RR 0.33 [0.01 to 7.74]	32 fewer per 1000 [48 fewer to 324 more]	Very Low
Gastric upset	2/21 (9.5%)	0/21 (0%)	RR 5 [0.25 to 98.27]	Not estimable	Very Low
Hypotension	0/21 (0%)	0/21 (0%)	Not estimable	Not estimable	Very Low
Syncope	0/21 (0%)	0/21 (0%)	Not estimable	Not estimable	Very Low

(a) Analysed using random effects analysis

6.12.2.2 Economic evidence

No economic studies were identified.

6.12.2.3 Evidence statement (s)

Clinical There is no statistically significant difference between combination treatment of alpha blockers plus PDE5-I and PDE5-I in improving symptom scores (IPSS), quality of life (IPSS question), nocturia or frequency at up to 3 months follow-up.

Combination treatment of alpha blocker plus PDE5-I and PDE5-I in improving Qmax (ml/s) at 3 months follow up.

There is no statistically significant difference between combination of alpha blockers plus PDE5-I compared to PDE5-I in number of men experiencing dizziness, flushing, dyspepsia, gastric upset, syncope or hypotension.

Economic No economic studies were identified.

6.12.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 6.13

6.13 Recommendations and link to evidence

Recommendation	**Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS.**
Relative values of different outcomes	Symptom score, quality of life, Qmax and adverse events were considered primary outcomes of interest.
Trade off between clinical benefits and harms	Evidence of an improvement in symptom scores outweighed the adverse events.
Economic considerations	Alpha blockers are cost-effective for men with moderate to severe symptoms. They are more cost-effective than 5-ARI in men with a normal prostate size.
Quality of evidence	Evidence from alpha blockers vs. placebo, 5-ARI, anticholinergics and PDE5-I were considered. *Alpha-blocker vs. placebo:* The quality of evidence for IPSS, and Qmax were of moderate for alpha blocker vs. placebo. *Alpha blocker vs. 5-alpha reductase inhibitors (5-ARIs)* The quality of evidence for IPSS, and Qmax were of moderate to high for alpha blocker vs. 5ARIs. *Alpha blockers vs. PDE5-I or vs. anticholinergic* The quality of evidence for these comparisons mostly ranged from low to very vow quality. There was very little evidence in these comparisons compared to those comparing alpha blockers against placebo or 5-ARIs. The economic evidence considered has minor limitations and it is directly applicable.
Other considerations	Men with LUTS may opt for watchful waiting rather than medical (or surgical) treatment either if the symptoms are not bothersome or if they perceive that potential adverse events of treatment are greater than the benefits of treatment. This is particularly likely if they can be reassured that the likelihood of disease progression is low. This choice is often patient led.

Recommendation	**Offer a 5-alpha reductase inhibitor to men with LUTS who have prostates estimated to be larger than 30 g or PSA greater than 1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men).**
Relative values of different outcomes	Symptom score, quality of life, Qmax and adverse events were primary outcomes of interest. The reduction of LUTS progression and risk of retention or need of surgical intervention. Sexual adverse events are also important to patients.
Trade off between clinical benefits and harms	Evidence of an improvement in symptom scores outweighed the adverse events. Other than in the subgroup of patients with large prostates (at least 30 ml, mean of 55 ml), alpha blocker is more effective in improving symptoms scores and Qmax. 5-ARI was more effective for reducing prostate volume and PSA. There were higher risk of orthostatic hypotension, dizziness, fatigue or asthenia and rhinitis in the alpha blocker group, but higher risk of decreased libido, impotence and breast enlargement in the 5-ARI group.
Economic considerations	5-ARI are more costly and more effective than placebo/watchful waiting; however they might not be cost-effective. They are less cost-effective than alpha blockers in men with a normal prostate size. In a selected population where they are more effective (men with large prostate etc.) 5-ARI could be cost-effective.
Quality of evidence	Evidence from 5ARI vs. placebo, alpha blockers, anticholinergics and PDE5-I were considered. <u>Alpha reductase inhibitors compared to placebo:</u> ▪ Fourteen RCTs comparing 5-ARI vs. placebo were found. Most of these studies recruited men with larger prostates. <u>Alpha reductase inhibitors compared to alpha blockers:</u> ▪ Three out of six double blinded RCTs identified had unclear randomisation and allocation concealment. There were no other major study limitations. There was imprecision for some of the outcomes. ▪ There were no definitions given in the papers on how sexual side-effects (for example impotence or erectile dysfunction and ejaculatory disorders or retrograde ejaculation) were classified and documented, and this may result in inconsistencies observed between studies. ▪ Subgroup analysis of ejaculatory disorders showed difference in direction of effect between tamsulosin (significantly favoring 5 ARIs) and other alpha blockers (significantly favoring alpha blockers). However, this should be interpreted with caution due to the limited number of studies available for this comparison and in context of other comparisons. <u>Combination of alpha blocker plus 5-ARI</u> ▪ Six multi-arm RCTs comparing a combination of alpha

blockers and 5-ARI against single agents or placebo were found. One of these specifically recruited patients with larger prostates and this study showed more benefit from 5-ARI treatment.

The economic evidence has minor limitations but it is only partially applicable.

Other considerations

Prostate size was smaller in men treated by 5-alpha reductase inhibitors compared to placebo at 1 and 2 years follow-up.

Men with higher risk of progression, such as older men with poorer flows, higher symptom scores, greater residuals, larger prostates and higher PSA are more likely to benefit.

Personal preference will be important in choice of treatment. A longer treatment time is required before improvements are observed for 5-ARI, and adherence may become an issue.

Individuals may place different importance or have different susceptibilities (e.g. due to other comorbidities or age) on various types of side-effects.

Recommendation	**Offer an anticholinergic to men to manage the symptoms of OAB.**
Relative values of different outcomes	LUTS symptoms (storage symptoms such as urgency, frequency, nocturia and urgency incontinence), IPSS, quality of life scores and adverse events were important.
Trade off between clinical benefits and harms	Anticholinergics reduced number of urinary incontinence episodes compared to placebo, but not alpha blockers. There were no other improvements noted compared to placebo. This is a very important benefit, and was considered against increased risk of side-effects such as dry mouth.
Economic considerations	It was the GDG opinion that the benefits of this intervention in carefully selected patients where a large post voiding residual and significant obstruction as the predominant problem have been excluded offset its costs.
Quality of evidence	Only studies conducted in men were included. One RCT with 4 arms (anticholinergics, alpha blockers, combination and placebo) conducted in men with moderate to severe LUTS was found. The results of efficacy were reported in graphs, without mean with standard deviations. Only statistical significance of combination vs. placebo was reported. Total numbers of patients was too small to determine adverse events precisely. No economic evidence was found on anticholinergics.
Other considerations	There are concerns that men given anticholinergics may develop urinary retention, but there is no evidence from RCTs to support this. Sexual problems are important to patients but can be under-reported as men may be embarrassed to discuss and some patients may perceive this to be caused by their LUTS treatment. Therefore, adequate opportunity to discuss this is important as this may affect treatment adherence or appropriateness of treatment.

1

Recommendation	**Consider offering a late afternoon diuretic[a] for men with nocturnal polyuria.**
Relative values of different outcomes	Reduced frequency of night time voiding due to nocturnal polyuria was the most important outcome. This outcome could have significant impact on patient's sleep quality and quality of life.
Trade off between clinical benefits and harms	The potential improvement in night time frequency was considered against the potential adverse events such as hypovolaemia and orthostatic hypotension.
Economic considerations	It was the GDG opinion that the benefits of this intervention offset its costs.
Quality of evidence	One small study which did not report method of randomisation or allocation concealment was identified. Adverse events were not reported. No economic evidence was found on diuretics.
Other considerations	Diuretics are not licensed for the treatment of LUTS or polyuria. However, the group felt that this treatment would offer an improvement in quality of life for men with nocturnal polyuria.

1

[a] At the time of publication (July 2009), diuretics (for example, furosemide) did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

Recommendation	**Consider offering oral desmopressin[b] for men with nocturnal polyuria if they have not benefited from other treatments. Measure serum sodium 3 days after the first dose.**
Relative values of different outcomes	Reduced frequency of night time voiding due to nocturnal polyuria was the most important outcome. This outcome could have significant impact on patient's sleep quality and quality of life.
Trade off between clinical benefits and harms	The benefit of reducing night time frequency was considered against the potentially serious side-effect such as hyponatraemia. The risk increases in elderly patients.
Economic considerations	It was the GDG opinion that their use could add some benefits when other treatments have failed at an acceptable cost.
Quality of evidence	Only one small cross-over study which compared desmopressin against placebo RCT in 20 men was identified. The study compared the efficacy and safety of 20microgram desmopressin nasal spray at bed time. There is indirectness of evidence as the bioavailability and pharmacokinetics of the nasal formulation differs from the oral formulation. These may result in different safety and efficacy profiles. For example, the nasal spray formulation was associated with more cases of hyponatraemia (15 per 100000 patients years) compared to the oral formulation (6 per 100000 patient years)[c]. No economic evidence was found on desmopressin.
Other considerations	The use of desmopressin for nocturnal polyuria is outside the marketing authorisation for both the oral and nasal spray forms of the products. Informed consent should be documented. Where treatment is initiated, the oral form should be used, and patients started at the lowest doses, with careful biochemical monitoring to identify early onset of dilutional hyponatraemia.

[b] At the time of publication (July 2009), desmopressin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[c] From the MHRA website: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2030795. Accessed 24 February 2009

Recommendation	**Consider offering a combination of an alpha blocker and a 5-alpha reductase inhibitor to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or PSA greater than 1.4 ng/ml.**
Relative values of different outcomes	The reduction of LUTS, risk of disease progression or need of surgical intervention is important Cardiovascular adverse events can be potentially dangerous. Sexual adverse events are important to patients.
Trade off between clinical benefits and harms	The increased benefits were considered against the higher risk and types of side effects when a combination is used. There were higher risk higher risk of sexual side effects and withdrawal due to adverse events in the 5-ARI group.
Economic considerations	Combinations are not cost-effective compared to alpha blockers in the general population. They might be cost-effective in a selected population where they are more effective (e.g. men with larger prostates).
Quality of evidence	5 double blinded RCTs were were identified. Although two of these studies had unclear randomisation and allocation concealment, there were generally no other major limitations except for lack of precision in some outcomes. The economic evidence has minor limitations and direct applicability.
Other considerations	Using combination treatment increase the risks associated with polypharmacy and may affect adherence to medications. Treatment with alpha reductase alone may require up to 6 months of treatment before improvements are observed. This may discourage adherence to medications. The addition of an alpha blocker may result in observable improvements. Individuals most likely to benefit are those at risk of disease progression. The factors that have been identified and most important in identifying risk of BPH progression are; increasing age particularly patients over 70 years of age, increasing symptom severity (moderate to severe categories) and increasing symptom bother, poor flow rates (particularly below 10mls/sec) and increasing residual volumes after voiding. The two most important predictors are; prostate volume and PSA. Whilst PSA may be seen simply as a proxy for volume, it appears that PSA may be a more specific test than volume and may, in part, be a metabolic marker of progression risk. Individuals may place different importance or are susceptible to various types of side-effects due to their personal and clinical circumstances and these should be considered. Patient severity at baseline should be considered in the decision to offer a combination treatment vs. single agent. GDG also noted that side effects profile within the same class of medication may differ (e.g. ejaculatory disorders for tamsulosin) and different formulations of the same medication may result in different side effects profile.

Recommendation	**Consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker alone.**
Relative values of different outcomes	Nocturia and urgency were considered the most important symptoms for this comparison.
Trade off between clinical benefits and harms	The potential of increased efficacy of combination treatment was considered against increased risk (frequency) and severity of side effects. Although statistically significant improvements among patients who had inadequate response to alpha blockers and significant storage symptoms in the overall IPSS, storage symptoms and quality of life (IPSS question) scores, these were very small and the benefits perceptible to patients were uncertain. All the studies showed an increased risk of dry mouth compared to just using a single agent (Anticholinergic or alpha blocker alone)
Economic considerations	It was the GDG opinion that generally the benefits of this intervention do not offset its costs. However, when alpha blockers alone are not working, adding an anticholinergic could generate benefits at a reasonable cost.
Quality of evidence	Alpha blockers plus anticholinergic vs. anticholinergic or alpha blocker, or placebo ▪ A double-blinded RCT, with 4 treatment arms (combination, alpha blockers, anticholinergics, placebo) was identified. ▪ The sample size would have been sufficiently powered (80%) if difference between groups were more than the MID (IPSS 3 points) for combination vs. alpha blocker or anticholinergic. However, only the statistical significance of combination against placebo was reported. It was unknown whether the other comparisons were statistically significant. ▪ This study recruited only men with severe LUTS (mean baseline IPSS was 20±5) and may have limited applicability to the general population of men with LUTS. Anticholinergic added on to alpha blockers in men who were still symptomatic after treated with alpha blockers ▪ One double blinded RCT investigated the addition of an anticholinergic to men who were still symptomatic ((IPSS ≥13, with IPSS (Storage≥8) to alpha blockers after at least 4 weeks of treatment was identified. ▪ The participant characteristics at screening were unknown and only about half of the men who were screened meet criteria for randomisation after receiving 4 weeks of alpha blocker treatment. ▪ The treatment length (4 weeks for alpha blockers) may not be sufficient to observe the optimal alpha blocker

	treatment effect, with continued improvement still observed in both arms at 3 month follow up. Improvements in symptoms score and quality of life (IPSS question) were were less than the MID. Therefore the benefits perceptible to patients are uncertain. No economic evidence was found on combinations of anticholinergic and alpha blockers.
Other considerations	There were uncertain additional benefits from using combination treatment compared to the increased risk of dry mouth. The risk of dry mouth was about 3 times higher for both the combination study and add-on study compared to alpha blockers.

6.14 Supporting recommendations

Recommendation	**Take into account comorbidities and current treatment when offering men drug treatment for LUTS.**
Trade off between clinical benefits and harms	Pharmacological therapy offers the benefit of potential reduction of symptoms, with minimal changes required in the patients' lifestyle. Unlike surgery, it is non-invasive. This benefit has to be considered against the potential harms from adding a new medication. Harms include adverse reactions and interactions with the other medications the patients take concomitantly. Polypharmacy is an important problem, especially for the elderly patients, and a detailed history of medical and concomitant medications should be taken and considered to ensure safety and efficacy.
Economic considerations	None.
Other considerations	None

6.15 Summary of recommendations

- Take into account comorbidities and current treatment when offering men drug treatment for LUTS.
- Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS.
- Offer an anticholinergic to men to manage the symptoms of OAB.
- Offer a 5-alpha reductase inhibitor to men with LUTS who have prostates estimated to be larger than 30 g or PSA greater than 1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men).
- Consider offering a combination of an alpha blockers and a 5-alpha reductase inhibitor to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or PSA greater than 1.4 ng/ml.

- Consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker alone.
- Consider offering a late afternoon diuretic for men with nocturnal polyuria.
- Consider offering oral desmopressin for men with nocturnal polyuria if they have not benefited from other treatments. Measure serum sodium at 3 days after the first dose.

6.16 Research recommendations on drug treatment

6.16.1 Non-steriodal anti-inflammatory drugs (NSAIDS)

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of NSAIDS compared to placebo in reducing symptom progression for men with lower urinary tract symptoms?

Why this is important

There is increasing evidence that prostatic inflammation may play a major role in benign prostatic disease progression. A recent study [156]) found that men with inflammation at baseline had a 5.6% incidence of retention compared to 0% for men without retention over the four year study. Preliminary studies have suggested that NSAIDS may be beneficial in men with LUTS particularly with the bothersome symptoms of nocturia. As there is a lack of evidence the role of NSAIS in men with LUTS (especially those over 70 years) cannot be clearly defined. The study design to answer the question should be a randomised controlled trial and the outcomes of interest are symptom progression and progression to surgery or acute urinary retention.

6.16.2 Phosphodiesterase 5-inhibitors (PDE5I)

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of PDE5I and PDE5I/alpha blocker combinations compared to placebo in men with LUTS?

Why this is important?

Epidemiological studies have indicated that the association between LUTS and erectile dsyfunction is more than a co-incidence of age, with a possible cause and effect relationship. The two conditions share several patho-physiological processes. Studies of all three PDE-5 inhibitors (sildenafil, vardenafil and tadalafil) have shown improvements in both LUTS and erectile dsyfunction in men with significant problems in both disease areas. The greatest improvements occurred with the combination of an alpha blocker and PDE-5 inhibitor when compared with either drug alone. Trials of PDE-5 inhibitors alone have shown significant improvements in LUTS symptom scores, but there was no significant improvement in flow rates with PDE-5 inhibitors when compared with placebo. Well designed, placebo-controlled studies are needed to confirm the impact of these drugs, alone or in combination with alpha blockers, to be able to make future recommendations for men with LUTS.

7 Review

7.1 Introduction

Following their initial assessment, many men will need to be seen again by a clinician to check on their progress and consider whether a treatment change is required, or if further review is required or can be dispensed with. The intervals that are appropriate for review have not generally been guided by evidence, but rather by clinical "common sense" and experience, sometimes in combination.

It is important to bear in mind that, in the NHS, most men who present with lower urinary tract symptoms (LUTS) will be managed within a primary care setting. The benefits of follow-up, in terms of avoiding continued prescription of ineffective medication, reassurance to the patient and avoiding progression of the pathology that produced the presenting LUTS, need to be balanced against the possible adverse effects of further treatment that might be offered and the cost (including opportunity cost) of follow-up. Follow up needs to be done by an appropriately expert clinician, experienced in the management of men with LUTS.

7.2 Recall intervals for men who are not on treatment

7.2.1 In men with LUTS who are not on treatment, what are the most clinically effective and cost effective recall intervals for review for detecting progression of symptoms?

No clinical or economic evidence was identified.

7.2.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

7.2.2 Recommendations and link to evidence

Recommendations	**Discuss active surveillance (reassurance and lifestyle advice without immediate treatment and with regular follow-up) or active intervention (conservative management, drug treatment or surgery) for:** • **men with mild or moderate bothersome LUTS** • **men whose LUTS fail to respond to drug treatment.**
Relative values of different outcomes	The key outcome was an improvement in symptom scores.
Trade off between clinical benefits and harms	The GDG considered that these men may not want to proceed to active intervention and should be given the opportunity to discuss the benefits and harms of active surveillance. The benefit is that these men do not have to take medication or undergo surgery but the harms are that their symptoms could worsen.
Economic considerations	If symptoms are unlikely to worsen and the man does not want to proceed to active intervention, active surveillance can save resources without decreasing the man's quality of life.
Quality of evidence	No clinical or economic evidence was retrieved.
Other considerations	The GDG felt that patient choice will play a major role in this decision and follow-up should be regular but should be assessed on an individual basis.

7.3 Recall intervals for men receiving medical treatment

7.3.1 In men with LUTS who take alphablockers/5-alpha reductase inhibitors/anticholinergics/phosphodiesterase 5 inhibitors or combination therapy, what are the most clinically effective and cost effective recall intervals for review for detecting progression of symptoms?

No clinical or economic studies were identified.

7.3.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

7.3.2 Recommendations and link to evidence

Recommendations	**Review men taking alpha blockers at 4-6 weeks and then every 6-12 months.**
Recommendation	**Review men taking 5–alpha reductase inhibitors at 3-6 months and then every 6-12 months.**
Recommendation	**Review men taking anticholinergics every 4-6 weeks until stable, and then every 6-12 months.**
Recommendation	**Review men taking an alpha blocker and a 5-alpha reductase inhibitor at 4-6 weeks and then every 6-12 months.**
Recommendation	**Review men taking an anticholinergic and an alpha blocker at 4-6 weeks until stable, and then every 6-12 months.**
Relative values of different outcomes	The key outcome considered was an improvement in symptom scores.
Trade off between clinical benefits and harms	The guideline development group (GDG) considered that the benefit of monitoring a treatment's effectiveness and the opportunity to change treatment outweighed the time and resources involved in monitoring, ensuring maximal adherence to effective treatments, providing the opportunity to stop ineffective interventions and alter treatment according to patient preference.
Economic considerations	There is a trade off between resources used for monitoring and the missed opportunity of treatment change. Since alpha blockers, anticholinergics and combination therapy will certainly have had chance to be effective by 4-6 weeks, the effectiveness of this intervention must be assessed at this early phase to avoid unnecessary treatment if it proves ineffective. Since 5-alpha reductase inhibitors should be effective at 3-6 months, the effectiveness of this intervention must be assessed at this time to avoid unnecessary treatment if it proves ineffective. It would not be cost-effective to schedule an earlier assessment.
Quality of evidence	No clinical or economic evidence was retrieved. The recommendations were formulated using expert opinion and pharmacological trials showing the time course of symptom change. There was evidence of symptom improvement by four weeks in the studies comparing alpha blockers and placebo (see Evidence table 9, Appendix D). There were data which showed the minimum time to observe symptom reduction and time to achieve maximum effect associated with anticholinergic therapy (see Evidence table 14, Appendix D). In studies comparing 5-alpha reductase inhibitors and placebo, improvements began to be observable 3-6 months after the initiation of the therapy (see Evidence table 13, Appendix D).
Other considerations	Sexual problems are important to patients but can be under-

reported as men may be embarrassed to discuss. Adequate opportunity to discuss this is important as this may affect treatment adherence (if these are perceived to be due to side-effects of medications), and appropriateness of treatment.

7.4 Summary of recommendations on review

- Review men taking alpha blockers at 4-6 weeks and then every 6-12 months.
- Review men taking 5–alpha reductase inhibitors at 3-6 months and then every 6-12 months.
- Review men taking anticholinergics every 4-6 weeks until stable, and then every 6-12 months.
- Review men taking an alpha blocker and a 5-alpha reductase inhibitor at 4-6 weeks and then every 6-12 months.
- Review men taking an anticholinergic and an alpha blocker at 4-6 weeks until stable, and then every 6-12 months.
- Discuss active surveillance (reassurance and lifestyle advice without immediate treatment and with regular follow-up) or active intervention (conservative management, drug treatment or surgery) for:
  - men with mild or moderate bothersome LUTS
  - men whose LUTS fail to respond to drug treatment.

8 Surgery for men with voiding symptoms

8.1 Introduction

The goals of treatment for men with bothersome voiding symptoms are to reduce the severity of symptoms together with the bother that they cause, to normalise the dynamics of the lower urinary tract and to resolve or prevent complications. Decisions about treatment options must balance likely benefits with the possible occurrence and severity of side effects. Transurethral resection of prostate (TURP) has been the mainstay of treatment for symptomatic benign prostatic enlargement (BPE) for many years since it combines high effectiveness with a previously acceptable side effect profile. More recently, in the UK, men have tended to seek help earlier in the natural history of the disease and access to secondary health care has improved. This, together with more patients presenting with increasing co-morbidities present in the ageing population at risk, and the desire of health providers to contain costs, has fuelled the search for less morbid invasive treatments. These interventions can be sub-divided into surgical procedures that generally involve removal of prostate tissue requiring general or regional anaesthesia and minimally invasive options, which do not require general anaesthesia and can be carried out in a day case setting.

The availability of different techniques will differ from hospital to hospital depending on the training and experience of the urologists who work there. Decisions about surgical treatment will always be the result of an honest and balanced discussion between surgeon and patient which must include information about the relative benefits and risks of each available procedure. It is particularly important that the surgeon is able to give information about outcomes in his/her own practice, not just evidence from the literature. Some patients may choose the most efficacious procedure, whilst others may be keen to trade efficacy for lower perioperative morbidity and shorter hospital stay.

The population considered in this chapter is men with bothersome lower urinary tract symptoms (LUTS), predominantly voiding symptoms, who have failed to respond to conservative or pharmacological therapy. Some men will have undergone multichannel cystometry and will have been shown to have evidence of bladder outlet obstruction. These men are the most likely to benefit from surgery.

The following surgical interventions were considered by the group:

- **Holmium:YAG Laser Enucleation of Prostate (HoLEP):**
  - Uses Holmium: YAG laser to dissect in the surgical planes and is conceptually the endoscopic equivalent of open prostatectomy.

- The completely resected prostate lobes are pushed into the bladder, morcellated and removed.
- The procedure is carried out under spinal or general anaesthesia with slightly longer operating times but similar post-operative care compared to TURP.
- Useful for large prostates which would previously have required an open prostatectomy.

➢ **Laser coagulation:**

- Laser induced necrosis of prostatic tissue is achieved either by surface application of the laser to the prostatic urethra in a technique termed visual laser ablation of the prostate (VLAP) or by inserting specially designed laser fibres into the prostatic tissue via the urethra, termed interstitial laser coagulation (ILC).
- Typically up to 10 locations can be treated with the procedure lasting 30-60 minutes under local anaesthesia.
- Catheterisation is typically required for between three and seven days.

➢ **Laser vapourisation:**

- Initially neodinium-yttrium-aluminium-garnet (Nd-YAG) was used but this resulted in relatively deep tissue penetration.
- Now KTP (Green light) laser, generated by passing the Nd-YAG generated beam through a potassium-titanyl-phosphate (KTP) crystal, is used. This results in minimal tissue penetration.
- Requires similar anaesthesia and operating conditions to TURP with operating time increased by a factor of approximately 1.5.

➢ **Transurethral microwave thermotherapy (TUMT):**

- Microwave energy used to achieve temperatures of 45 - 70°C in the prostate depending on the device and power setting.
- Treatment lasts 30-60 minutes using local anaesthesia and oral analgesia together with sedation for high energy protocols.
- Requirement for post-operative catheterisation varies from 1-12 weeks depending on the protocol used.

➢ **Transurethral vapourisation of prostate (TUVP):**

- Utilises a standard monopolar electro-diathermy device as for TURP.

- The current is delivered through a grooved ball or modified loop electrode with temperatures up to 300 – 400°C. Further modification has allowed the use of bipolar current enabling use of physiological saline as a safer irrigant with tissue effects occurring at lower temperatures (ranging from 40-70°C).
- Electrode rolled over the prostate to vaporise tissue and coagulate surface reducing blood loss.
- No tissue is available for histological examination.

➢ **Transurethral needle ablation of prostate (TUNA):**

- Radio frequency energy delivered through two adjustable needles which are inserted into the prostate.
- Localised heating up to 115°C, causing tissue death.
- Procedure lasts 30 to 60 minutes under local or regional anaesthesia.
- Indwelling catheter placed for up to 3 days.

➢ **Transurethral incision of the prostate (TUIP):**

- Bilateral or unilateral incisions from bladder neck to verumontanum, usually for small prostates.
- Indwelling catheters usually left in the urethra for less time compared to TURP.

➢ **Botulinum toxin:**

- Injection of botulinum toxin A directly into the prostate.
- Does not usually require an anaesthetic.
- This treatment is still investigational.

➢ **Transurethral vaporesection of the prostate (TUVRP):**

- Thick band-like loop electrode at high power used to resect prostate tissue in a similar manner to TURP but combining vapourisation and coagulation at the cutting edge.

➢ **Stents**

- Devices made of woven braided wire mesh that can be delivered and expanded in the prostatic urethra under endoscopic or radiological control. The proximal end is engaged in the bladder neck and the distal end must lie above the external sphincter to prevent incontinence.

- Requires local anaesthesia.

- **High intensity focused ultrasound (HIFU):**
  - Ultrasound energy used to achieve temperatures of up to 80–100° C.
  - Treatment lasts about 60 minutes under general anaesthetic or sedo-analgesia as a day case procedure.
  - Indwelling catheter required for approximately 2 weeks.
- **Transurethral ethanol ablation of the prostate (TEAP):**
  - Chemical ablation of prostatic tissue using dehydrated ethanol.
  - Delivery of ethanol into the prostate can be achieved either by injecting via a transperineal, transrectal or transurethral (most common) route.
  - Requirement for an indwelling catheter is longer than standard TURP.
- **Open prostatectomy:**
  - Surgical removal of the prostate through an incision made in the lower abdomen leaving behind only the capsule of the prostate.
  - Hospital stay and recovery period after surgery is usually longer than for TURP.
  - A general or spinal anaesthetic is required.
- **Transurethral resection of prostate (TURP):**
  - Diathermy current for prostate resection via a loop electrode.
  - Continuous flow endoscope passed down the urethra with non-ionic fluid irrigant (usually glycine 1.5%).
  - Coagulative haemostasis achieved with a ball diathermy electrode.
  - Indwelling catheter for 24-48 hours.
  - Hospital stay approximately 1-3 days.
- **Bipolar resection of the prostate:**
  - Uses a continuous flow resectoscope with saline irrigation reducing the risks of fluid absorption.

- The cutting loop is similar to the monopolar loop in shape but has the active and return electrode on the same axis, separated by a ceramic insulator.

- The two electrodes form an ionised plasma 'pocket' which can be used to resect or vapourise tissues.

The primary outcomes reported were symptom score, maximum urinary flow rate (Qmax), IPSS quality of life question and adverse events. The adverse events considered to be most important by the GDG were mortality, infection, reoperation, transurethral resections (TUR) syndrome, acute urinary retention, blood transfusion, strictures, retrograde ejaculation and incontinence.

8.2 Matrix of treatments considered in our clinical question

We searched for RCT evidence comparing the effectiveness of different surgical interventions for lower urinary tract symptoms. The interventions we included in our search were TUNA, laser, TUMT, TURP, TUIP, open prostatectomy, botulinum toxin, HoLEP, HIFU, TUVP and no treatment. We looked for any studies that compared the effectiveness of two or more of these treatments as well as comparisons with no treatment. Below is a matrix showing where evidence was identified. A box filled with '**Yes**' represents where evidence was found and is reviewed in this chapter. A box filled with '**No**' represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

TUNA	No									
LASER	**Yes p. 229**	No								
TUMT	No	No	**Yes p 227**							
TURP	**Yes p 245**	**Yes p 252**	**Yes p 215 & p220**	**Yes p 241**						
TUIP	No	No	No	No	**Yes p256**					
OP	No	No	**Yes P224**	No	No	No				
BT	No	No	No	No	No	No	No			
HOLEP	No	No	No	No	**Yes p204**	**Yes p 211**	**Yes p 213**	No		
HIFU	No	No	No	No	No	No	No	No	No	
NT	No	No	No	**Yes p 239**	**Yes p269**	No	No	**Yes p262**	No	No
	TUVP	TUNA	LASER	TUMT	TURP	TUIP	OP	BT	HOLEP	HIFU

TUNA – transurethral needle ablation; TUMT – transurethral microwave thermotherapy; TURP – transurethral resection of the prostate; TUIP – transurethral incision of the prostate; OP – open prostatectomy; BT – botulinum toxin in prostate; HOLEP – holmium laser enucleation of the prostate; HIFU – high intensity focused ultrasound; NT – no treatment (includes sham studies)

In addition we searched for evidence comparing bipolar TURP, bipolar TUVP, TUVRP, stents and TEAP with TURP. Below is a table showing where evidence was identified. A box filled with '**Yes**' represents where evidence was found and is reviewed in this

chapter. A box filled with '**No**' represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

Bipolar TURP	**Yes p272**
Bipolar TUVP	**Yes p 277**
TUVRP	**Yes p263**
Stents	**No**
TEAP	**Yes p277**
	TURP

TUVRP=transurethral vaporesection of the prostate; TEAP= transurethral ethanol ablation of the prostate.

8.3 Holmium laser enucleation of the prostate (HoLEP)

8.3.1 HoLEP vs. TURP

See Evidence Table 22, Appendix D, Forest Plots in Figures E-99 to E-104, Appendix E, Economic Evidence Table 53, Appendix D, and Economic model in Appendix F.

8.3.1.1 Clinical evidence

Table 8-81: HoLEP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Mean symptom score at 3 months follow-up[152,152WESTENBERG2004}][267]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mean symptom score at 6 months follow[9,91,167,264,267]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Mean symptom score at 12 months follow[9,91,167,264,267]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Mean symptom score at 24 months follow[9,264,267]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Mean symptom score at 36 months follow[9]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mean symptom score at 48 months follow[264]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Mean quality of life (IPSS question) at 3 months[264,267]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Mean quality of life (IPSS question) at 6 months[167,264,267]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Mean quality of life (IPSS question) at 12 months[167,264,267]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Mean quality of life (IPSS question) at 24 months[264,267]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mean quality of life (IPSS question) at 36 months	0					
Mean quality of life (IPSS question) at 48 months[264]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Mean Qmax at 3 months[152,152,264,267]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Mean Qmax at longest follow up[9,91,152,152,167,264,267]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
All cause mortality[9,91,264,267]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Infection[264,267]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Re-operation[9,167,264,267]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Transurethral resection syndrome (TUR)[167]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Acute retention[9,91,152,152,167, 264,267]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Blood transfusion[9,91,152,152,167,264,267]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Stricture[9,91,167,264,267]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence[9,91,152,152,167,264]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation[264,267]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

a) *4 studies[9,91,167,264] did not report allocation concealment or masked outcome assessment. One study[91] did report randomisation method used. 2 of the studies[91,167] have incomplete outcome data and do not report reasons for attrition.*

b) *Statistically significant heterogeneity is present*

c) *Imprecision due to the confidence intervals crossing the MID therefore making estimate of effect uncertain. Complication outcomes are downgraded when the 95% confidence intervals around the pooled estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.*

Table 8-82: HoLEP vs. TURP - Clinical summary of findings

Outcome	HoLEP*	TURP*	Relative risk	Absolute effect	Quality
Mean symptom score at 3 months follow-up	104	103	Not applicable	Mean Difference (MD): -0.18 [-1.09, 0.74]	Moderate
Mean symptom score at 6 months follow (a)	283	275	Not applicable	MD: -0.52 [-1.35, 0.31]	Low
Mean symptom score at 12 months follow (a)	269	260	Not applicable	MD: -0.71 [-1.62, 0.20	Low
Mean symptom score at 24 months follow (a)	147	142	Not applicable	MD: -0.80 [-2.73, 1.13]	Low
Mean symptom score at 36 months follow	75	69	Not applicable	MD: -0.60 [-1.61, 0.41]	Moderate
Mean symptom score at 48 months follow	43	30	Not applicable	-1.40 [-3.91, 1.11]	Low
Mean quality of life (IPSS question) at 3 months	89	88	Not applicable	MD: -0.19 [-0.68, 0.30]	Low
Mean quality of life (IPSS question) at 6 months (a)	139	136	Not applicable	MD: 0.06 [-0.49, 0.61]	Very low
Mean quality of life (IPSS question) at 12 months (a)	130	124	Not applicable	MD: -0.01 [-0.96, 0.95]	Very low
Mean quality of life (IPSS question) at 24 months	67	67	Not applicable	MD: -0.01 [-0.40, 0.38]	Moderate
Mean quality of life (IPSS question) at 48 months	43	30	Not applicable	MD: -0.30 [-0.90, 0.30]	Low
Mean Qmax, ml/s at 3 months	104	103	Not applicable	MD: 2.73 [0.30, 5.15]	Low
Mean Qmax, ml/s at longest follow up	257	238	Not applicable	MD: 1.40 [0.89, 1.91]	Moderate
All cause mortality	1/241 (0.4%)	2/239 (0.8%)	Relative Risk (RR): 0.59 [0.08, 4.39]	3 fewer per 1000 (7 fewer to 27 more)	Low
Infection	3/91 (3.3%)	7/89 (7.9%)	RR: 0.45 [0.13, 1.57]	43 fewer per 1000 (69 fewer to 45 more)	Low
Re-operation	13/240 (5.4%)	17/227 (7.5%)	RR: 0.73 [0.37, 1.45]	20 fewer per 1000 (47 fewer to 34 more)	Low
TUR syndrome	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000 (21 fewer to 134 more)	Low
Acute retention	16/308 (5.2%)	22/302 (7.3%)	RR: 0.72 [0.39, 1.32]	20 fewer per 1000 (45 fewer to 23 more)	Low
Blood transfusion	1/308 (0.3%)	10/302 (3.3%)	RR: 0.27 [0.08, 0.89]	24 fewer per 1000 (4 to 30 fewer)	Moderate
Stricture	13/271 (4.8%)	18/257 (7.0%)	RR: 0. 69 [0.34, 1.37]	22 fewer per 1000 (46 fewer to 26 more)	Low
Retrograde ejaculation	36/41 (87.8%)	40/50 (80.0%)	RR: 1.14 [0.95, 1.36]	112 fewer per 1000 (40 fewer to 288 more)	Low
Urinary incontinence	35/267 (13.1%)	26/258 (10.1%)	RR: 1.26 [0.83, 1.91]	26 fewer per 1000 (17 fewer to 92 more)	Low

(a)Random effects analysis used

** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

8.3.1.2 Economic evidence

We found two economic studies[81,140] comparing HoLEP with TURP. The HTA model[140] was of good quality and directly applicable to the NHS setting. However, the GDG disagreed with some assumptions and it was decided that an original model was needed

for the decision-making process. Please see Economic Evidence Table 53 in Appendix D and Economic Model in Appendix F for further details.

Table 8-83: HoLEP vs. TURP- Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Fraundordfer200[81]	Serious limitations (a)	Partially applicable (b)	Based on a RCT included in the clinical evidence[87]
Lourenco2008[140]	Minor limitations (c)	Directly applicable	HTA (model based on a systematic review)
NCGC model (Appendix F)	Minor limitations (d)	Directly applicable	Based on the systematic review (see 8.3.1.1)

(a) *Not a full economic evaluation*
(b) *New Zealand study conducted by experts in HoLEP. In real practice HoLEP might be less successful as it requires high level of skills and experience.*
(c) *Capital cost of TURP was not included. Duration and cost of operations were equal in all the strategies. Training costs were not included. Treatment success was defined as a reduction in IPSS by at least 10% from baseline.*
(d) *Training costs were not included.*

Table 8-84: HoLEP vs. TURP - Economic summary of findings

Study	*Incremental cost (£) per patient*	*Incremental effects*	*ICER*	*Uncertainty*
Fraundordfer2001[81]	saves £277	NA (a)	NA (a)	NR
Lourenco2008[140]	saves £24	0.001 QALY	HoLEP is dominant	NR (b)
NCGC model (Appendix F)	£67 (c, d)	-0.0098 QALY (d)	TURP is dominant (d)	95% CI: HoLEP dominant – TURP dominant. At a willingness to pay of £20,000/QALY, TURP has 45% of probability of being cost-effective, while HoLEP has 55% of probability. Results are sensitive to the cost of procedure and length of stay, decrease of effectiveness when the intervention is performed the second time, probability of incontinence after HoLEP and TURP, utility of incontinence and utility of LUTS. The average result does not change if after HoLEP no other surgical intervention can be performed or HoLEP is performed twice in case of failure.

(a) *Cost-consequences analysis. More than one outcome was reported. Mean change in AUA score from baseline was higher in TURP group (not sig). Qmax was higher in HoLEP (significant).*
(b) *Not reported for single treatment strategies but only for sequences of treatments.*
(c) *Capital cost of HoLEP, costs of intervention, length of stay, and complications (AUR, infections, incontinence, TUR syndrome, strictures, blood transfusions, AUR).*
(d) *Results of probabilistic analysis.*

8.3.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between HoLEP and TURP in improving symptom scores at 3, 6, 12, 24, 36 and 48 months postoperatively.

There is no statistically significant difference between HoLEP and TURP in improving quality of life (IPSS question) at 3, 6, 12, 24, 36 and 48 months postoperatively.

HoLEP is more effective than TURP in improving urinary flow rate at 3 months and longest follow up.

Fewer men treated with HoLEP compared to TURP experienced blood

transfusions.

There is no statistically significant difference between HoLEP and TURP in the number of men experiencing strictures, urinary retention, TUR, reoperations, incontinence, infection, retrograde ejaculation or mortality.

Economic Both HoLEP and TURP are cost-effective. This evidence has minor limitations and direct applicability.

8.3.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.3.2 Thulium laser resection vs. TURP

See Evidence Table 23, Appendix D, Forest Plots in Figures E-105 to E-109, Appendix E.

8.3.2.1 Clinical evidence

Table 8-85: Thulium vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 and 12 months[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question) at 6 months[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question) at 12 months[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question) at 3, 24, 36 and 48 months	0					
Qmax at 3 months	0					
Qmax at longest follow-up [272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary incontinence[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Stricture[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Retrograde ejaculation[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Blood transfusion[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
TUR syndrome[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary tract infection[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary retention[272]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
All cause mortality	0					
Reoperation	0					

(a) The study[272] did not report method of randomisation or allocation concealment

(b) Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (IPSS, Qmax and quality of life) or the 95% CI crossed the MID therefore making estimate of effect uncertain. Complication outcomes are downgraded when the 95 CIs crossed the MIDs or includes both negligible effect and appreciable benefit or appreciable harm.

Table 8-86: Thulium vs. TURP - Clinical summary of findings

Outcome	Thulium	TURP	Relative risk	Absolute effect	Quality
Mean symptom score at 6 months	52	48	Not applicable	MD: 0.20 [-0.83, 1.23]	Moderate
Mean symptom score at 12 months	52	48	Not applicable	MD: -0.40 [-1.50, 0.70]	Moderate
Qmax at long-term follow-up	52	48	Not applicable	MD: -0.40 [-2.84, 2.04]	Low
Quality of life (IPSS question) at 6 months	52	48	Not applicable	MD: 0.20 [-0.21, 0.61]	Low
Quality of life (IPSS question) at 12 months	52	48	Not applicable	MD: 0.10 [-0.23, 0.43]	Moderate
Infection	2/52 (3.8%)	4/48 (8.3%)	RR: 0.46 [0.09, 2.41]	45 fewer per 1000 (76 fewer to 117 more)	Low
TUR syndrome	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000 (21 fewer to 134 more)	Low
Urinary retention	0/52 (0%)	0/48 (0%)	Not estimable	Not estimable	Low
Blood transfusion	0/52 (0%)	2/48 (4.2%)	RR: 0.18 [0.01, 3.76]	34 fewer per 1000 (42 fewer to116 more)	Low
Stricture	1/52 (1.9%)	3/48 (6.3%)	RR: 0.31 [0.03, 2.86]	43 fewer per 1000 (61 fewer to117 more)	Low
Urinary incontinence (stress)	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000 (21 fewer to 134 more)	Low
Retrograde ejaculation	18/33 (54.5%)	20/31 (64.5%)	RR: 0.85 [0.56, 1.27]	97 fewer per 1000 (284 fewer to 174 more)	Low

8.3.2.2 Economic evidence

No economic studies were identified.

8.3.2.3 Evidence statement (s)

Clinical There is no statistically significant difference between thulium laser resection and TURP in improving symptom scores at 6 and 12 months postoperatively.

There is no statistically significant difference between thulium laser resection and TURP in improving maximum urinary flow at long term follow-up.

There is no statistically significant difference between thulium laser resection and TURP in improving quality of life scores (IPSS question) at 6 or 12 months postoperatively.

There is no statistically significant difference between thulium laser and TURP in the number of complications for infection, TUR, urinary retention, transfusion, incontinence or retrograde ejaculation.

Economic No economic studies were identified.

8.3.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.3.3 HoLEP vs. TUIP

No studies comparing HOLEP with TUIP identified in the review. One study compared HoLEP against using holmium laser for bladder neck incision (HoBNI) was found[8]. The GDG opinion is that they expect HoBNI to have outcomes similar to TUIP.

See Evidence Table 24, Appendix D, Forest Plots in Figures E-110 to E-113, Appendix E.

8.3.3.1 Clinical evidence

Table 8-87: HoLEP vs. HoBNI – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[8]	1	RCT	No serious limitations	No serious heterogeneity	No serious indirectness	Very serious imprecision (a)
Symptom score at 6 months[8]	1	RCT	No serious limitations	No serious heterogeneity	No serious indirectness	Very serious imprecision (a)
Symptom score at 12 months[8]	1	RCT	No serious limitations	No serious heterogeneity	No serious indirectness	Very serious imprecision (a)
Quality of life score (IPSS question) at 3 months[8]	1	RCT	No serious limitations	No serious heterogeneity	No serious indirectness	Very serious imprecision (a)
Quality of life (IPSS question) at 6 months[8]	1	RCT	No serious limitations	No serious heterogeneity	No serious indirectness	Very serious imprecision (a)
Mean quality of life (IPSS question) at 12 months[8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Mean Qmax at 3 months[8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Qmax at longest follow up [8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
All cause All cause mortality[8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Urinary retention[8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Re-operation [8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Stricture[8]	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Infection	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Blood transfusion	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
TUR	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Retrograde ejaculation	1	RCT	Serious limitations(a)	No serious heterogeneity	No serious indirectness	Very serious imprecision (b)
Urinary incontinence	Excluded (c)	RCT				

(a) *Only one study with very small number patients was found*[8]*. There were uneven patient drop out rates in this study, which was not fully accounted for. Study randomised 20 patients in each arm but only 12 vs. 16 patients were followed up at 12 months time point. Not all potential adverse events were reported.*
(b) *Confidence intervals crossed MID and study size was smaller than OIS.*
(c) *This outcome which was reported in the study was excluded because the risk of bias was very high. At baseline, 2/20 vs. 11/20 patients in HoLEP and HoBNI groups respectively had incontinence.*

Table 8-88: HoLEP vs. HoBNI - Clinical summary of findings

Outcome	HoLEP	HoBNI	Relative risk	Absolute effect	Quality
Mean symptom score at 3 months	18	18	Not applicable	MD 0.6 [-3.4 to 4.6]	Very Low
Mean symptom score at 6 months	17	17	Not applicable	MD -1.2 [-6.28 to 3.88]	Very Low
Mean symptom score at12 months	16	12	Not applicable	MD 2.8 [-2.43 to 8.03]	Very Low
Mean quality of life (IPSS question) at 3 months	18	18	Not applicable	MD 0 [-0.95 to 0.95]	Very Low
Mean quality of life (IPSS question) at 6 months	17	17	Not applicable	MD -0.1 [-1.08 to 0.88]	Very Low
Mean quality of life (IPSS question) at 12 months	16	12	Not applicable	MD 0.2 [-0.47 to 0.87]	Very Low
Qmax(ml/s) at 3 months	18	18	Not applicable	MD 2.2 [-3.31 to 7.71]	Very Low
Qmax(ml/s) at longest available follow up	16	12	Not applicable	MD 4.2 [-0.38 to 8.78]	Very Low
All cause mortality	1/20 (5%)	1/20 (5%)	RR: 1.00 [0.07, 14.90]	0 fewer per 1000 [46 fewer to 695 more]	Very Low
Urinary retention	0/20 (0%)	2/20 (10%)	RR:0.20 [0.01, 3.92]	80 fewer per 1000 [99 fewer to 292 more]	Very Low
Re-operation	0/20 (0%)	4/20 (20%)	RR: 0.11 [0.01, 1.94]	178 fewer per 1000 [198 fewer to 188 more]	Very Low
Stricture	1/20 (5%)	1/20 (5%)	RR: 1.00 [0.07, 14.90]	0 fewer per 1000 [46 fewer to 695 more]	Very Low

8.3.3.2 Economic evidence

No economic studies were identified.

8.3.3.3 Evidence statement (s)

Clinical There is no statistically significant difference between HoLEP and HoBNI in improving symptom scores at 3, 6 and 12 months post-operatively.

There is no statistically significant difference between HoLEP and HoBNI in improving quality of life scores at 3, 6 and 12 months postoperatively.

There is no statistically significant difference between HoLEP and HoBNI in improving the maximum urinary flow and 3 and 12 months post-operatively.

There is no statistically significant difference between HoLEP and HoBNI in the number of patients experiencing strictures, incontinence, reoperation, infection, retention or mortality.

Economic No economic studies were identified.

8.3.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.3.4 HoLEP vs. OP

See Evidence Table 25, Appendix D, Forest Plots in Figures E-114 to E-117, Appendix E, and Economic Evidence Table 53, Appendix D.

8.3.4.1 Clinical evidence

Table 8-89: HoLEP vs. OP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Mean symptom score at 3, 12 & 24 months[123,174]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mean symptom score at 6 months[123]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Mean symptom score at 36, 48 and 60 months[123]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax at 3 months [123,174]	2	RCT	Serious limitations (a)	Serious inconsistency(c)	No serious indirectness	Serious imprecision (b)
Qmax at longest available follow-up [123,174]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Mean quality of life (IPSS question) at 3, 12 & 24 months[174]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
All cause mortality[123]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Stricture[123,174]	2	RCT	Serous limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Blood transfusion[123,174]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary incontinence, reoperation and retention[123,174]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Infection	0					
TUR syndrome	0					
Retrograde ejaculation	0					

(a) *Neither of the two studies*[123,174] *reported allocation concealment or masked outcome assessment. One study*[174] *had incomplete outcome data and did not report reasons for attrition.*

(b) *Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (IPSS, Qmax and quality of life) or the confidence intervals cross the MID therefore making estimate of effect uncertain. Complications outcomes are downgraded when the 95% confidence intervals around the pooled estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.*

(c) *Unexplained heterogeneity was detected in the pooled results. Random effects analyses were conducted in these outcomes.*

Table 8-90: HoLEP vs. OP - Clinical summary of findings

Outcome	HoLEP	OP	Relative risk	Absolute effect	Quality
Mean symptom score at 3 months	95	89	Not applicable	MD: 0.25 [-0.53, 1.04]	Moderate
Mean symptom score at 6 months	54	50	Not applicable	MD: -0.40 [-1.59, 0.79]	Moderate
Mean symptom score at12 months	97	88	Not applicable	MD: 0.00 [-0.68, 0.69]	Moderate
Mean symptom score at 24 months	88	76	Not applicable	MD: -0.11 [-0.84, 0.63]	Moderate
Mean symptom score at 36 months	48	40	Not applicable	MD: 0.20 [-0.81, 1.21]	Low
Mean symptom score at 48 months	45	36	Not applicable	MD: 0.20 [-0.90, 1.30]	Low
Mean symptom score at 60 months	42	32	Not applicable	MD: 0.00 [-1.13, 1.13]	Low
Mean quality of life (IPSS question) at 3 months	41	39	Not applicable	MD: 0.40 [0.15, 0.65]	Low
Mean quality of life (IPSS question) at 12 months	41	39	Not applicable	MD: -0.07 [-0.46, 0.32]	Low
Mean quality of life (IPSS question) at 24 months	35	30	Not applicable	MD: 0.00 [-0.66, 0.66]	Low
Mean Qmax at 3 months (a)	95	89	Not applicable	MD: -1.09 [-4.52, 2.35]	Low
Qmax at longest follow up	77	62	Not applicable	MD: -0.53 [-3.27, 2.21]	Low
All cause mortality	3/60 (5.0%)	8/60 (13.3%)	RR: 0.38 [0.10, 1.35]	82 fewer per 1000 (120 fewer to 47 more)	Low
Blood transfusion	2/101 (2.0%)	15/99 (15.2%)	RR: 0.16 [0.04, 0.58]	128 fewer per 1000 (64 to 146 fewer)	Moderate
Stricture	4/101 (4.0%)	3/99 (3.0%)	RR: 1.30 [0.30, 5.60]	9 fewer per 1000 (21 fewer to 138 more)	Low
Urinary incontinence	7/101 (6.9%)	9/99 (9.1%)	RR: 0.77 [0.30, 1.97]	21 fewer per 1000 (64 fewer to 88 more)	Low
Reoperation	10/101 (9.9%)	9/99 (9.1%)	RR: 1.10 [0.47, 2.57]	9 fewer per 1000 (48 fewer to 143 more)	Low
Urinary retention	8/101 (7.9%)	5/99 (5.1%)	RR: 1.56 [0.53, 4.62]	29 fewer per 1000 (24 fewer to 185 more)	Low

(a) *Random effects analysis were conducted for this outcome*

8.3.4.2 Economic evidence

We found one economic study[227] comparing HoLEP with open prostatectomy. This was a simple cost analysis based on RCT included in our clinical review [174]. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-91: Laser (HoLEP) vs. OP - Economic study characteristics

Study	Limitations	Applicability	Other Comments
SALONIA[227]	Serious limitations (a)	Partially applicable (b)	Based on a RCT included in our clinical review[174]

(a) *Not a full economic evaluation.*
(b) *Study conducted in Italy.*

Table 8-92: Laser (HoLEP) vs. OP - Economic summary of findings

Study	Incremental cost (£)per patient	Incremental effects	ICER	Uncertainty
SALONIA[227]	HoLEP cost saving (£371) (a)	Not reported	Not applicable	Not reported

(a) *Costs include procedures (operating room time, disposables, blood transfusion) and hospital stay. Medical salaries were not included. Capital cost for HoLEP was 85% of actual capital cost. Holmium fibres were used at least 10 times.*

8.3.4.3 Evidence statement (s)

Clinical There is no statistically significant difference between HoLEP and OP in improving symptom scores at 3, 6, 12, 24, 36, 48 or 60 months postoperatively.

OP is more effective than HoLEP in improving quality of life scores (IPSS question) at 3 months.

There is no statistically significant difference between HoLEP and OP in improving quality of life scores (IPSS question) at 12 and 24 months postoperatively.

There is no statistically significant difference between HoLEP and OP in improving the maximum urinary flow at 3 months or at long term follow-up.

Fewer men treated with HoLEP compared to OP experienced blood transfusions.

There is no statistically significant difference between HoLEP and OP with number of patients who experienced mortality, strictures, incontinence, reoperation or retention.

Economic HoLEP is less costly compared to open prostatectomy. This evidence has serious limitations and partial applicability.

8.3.5 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.4 Laser treatments

8.4.1 Laser (coagulation) vs. TURP

See Evidence Table 26, Appendix D, Forest Plots in Figures E-118 to E-122, Appendix E and Economic Evidence Table 53, Appendix D.

A total of 13 studies for laser coagulation vs. TURP were identified[16,41,48,61,90,120,127,134,149,209,217,231,246]. Two of these studies were foreign language studies identified from the HTA report [120,217]. One study was specifically conducted in patients with acute urinary retention (AUR), and this study had been analysed and reported separately[41].

8.4.1.1 Clinical evidence

Table 8-93: Laser coagulation vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score - 3 months [149,217,231,246]	4	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score - 6 months [61,90,149,217,231,246]	6	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score- 12 months [149]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score- 24 months [149]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question)- 3 months [149]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question)- 6 months [61,90,149]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)- 12 months [149]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question)- 24 months [149]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax at follow up - 3 months [16,149,217,231,246]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Qmax - Longest follow up available (6-24 months) [16,48,61,90,149,217,231,246]	8	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
All cause mortality [16,61,90]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Blood transfusion [16,48,61,90,120,127,149,231]	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
TUR syndrome[48,61,231]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[48,120]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary tract infections [16,61,90,120,134,149]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Retrograde ejaculation [16,120,134,149,231]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Urinary incontinence[48,120,127,149]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Strictures[48,120,134,231]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Reoperation [16,48,90,127,149]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) Method of randomisation allocation and concealment not reported in 5 studies[134,149,209,231,246]. Randomisation concealment was not reported in 1 study[16]. Two papers were identified from the HTA systematic review, and it was uncertain whether randomisation allocation and concealment was reported[120,217]. Patients randomised in a 2:1 ratio in one study [149]. All studies either did not report masking, or stated that no masking was done. Only 2 studies stated that the clinicians assessing the outcomes were different from surgeons performing the surgery.

(b) Substantial unexplained heterogeneity was detected in the pooled results. Random effects analyses were conducted in these outcomes.

(c) Sample size was less than OIS and/or confidence interval of pooled results crossed minimal important difference.

Table 8-94: Laser coagulation vs. TURP - Clinical summary of findings

Outcome	Laser Coagulation	TURP	Relative risk	Absolute effect	Quality
Symptom score - 3 months (a)	88	75	Not applicable	MD 1.74 [-3.33 to 6.80]	Very Low
Symptom score - 6 months (a)	213	197	Not applicable	MD 2.26 [-0.45 to 4.97]	Very Low
Symptom score - 12 months	30	14	Not applicable	MD 8.90 [5.75 to 12.05]	Low
Symptom score - 24 months	30	14	Not applicable	MD 7.00 [4.1 to 9.9]	Low
Quality of life (IPSS question)- 3 months	30	14	Not applicable	MD 1.4 [0.55 to 2.25]	Low
Quality of life (IPSS question)- 6 months (a)	153	132	Not applicable	MD 0.80 [-0.13 to 1.74]	Very Low
Quality of life (IPSS question)- 12 months	30	14	Not applicable	MD 1.6 [0.92 to 2.28]	Low
Quality of life (IPSS question)- 24 months	30	14	Not applicable	MD 1.5 [0.79 to 2.21]	Low
Qmax at follow up - 3 months (a)	164	150	Not applicable	MD -5.75 [-9.42 to -2.09]	Low
Qmax - Longest available follow up (a)	355	347	Not applicable	MD -4.27 [-6.22 to -2.31]	Low
All cause mortality	8/305 (2.6%)	6/310 (0.8%)	RR 1.31 [0.49 to 3.50]	6 more per 1000 [10 fewer to 48 more]	Low
Blood transfusion	1/473 (0.2%)	30/475 (6.3%)	RR 0.12 [0.04 to 0.35]	55 fewer per 1000 [41 to 60 fewer]	Moderate
TUR syndrome	0/124 (0%)	3/133 (2.3%)	RR 0.27 [0.03 to 2.39]	17 fewer per 1000 [22 fewer to 32 more]	Low
Urinary retention	19/145 (13.1%)	9/110 (8.2%)	RR 0.55 [0.27 to 1.12]	37 fewer per 1000 [60 fewer to 10 more]	Low
Urinary tract infections	62/370 (16.8%)	23/362 (6.4%)	RR 2.27 [1.45 to 3.56]	81 more per 1000 [29 to 164 more]	Moderate
Retrograde ejaculation (a)	15/189 (7.9%)	84/177 (47.5%)	RR 0.16 [0.05 to 0.53]	389 fewer per 1000 [223 to 451 fewer]	Low
Urinary incontinence	0/286 (0%)	11/283 (3.9%)	RR 0.16 [0.04 to 0.72]	33 fewer per 1000 [12 to 37 fewer]	Moderate
Strictures	1/195 (0.5%)	14/201 (7%)	RR 0.11 [0.02 to 0.59]	62 fewer per 1000 [29 to 69 fewer]	Moderate
Reoperation	29/311 (9.3%)	2/301 (0.7%)	RR 6.68 [2.44 to 18.24]	40 more per 1000 [10 to 121 more]	Moderate

(b) Random effects analysis were conducted for these outcomes

8.4.1.2 Clinical evidence for the AUR subgroup

Table 8-95: Laser coagulation vs. TURP in AUR patients – Clinical study characteristics

Outcome	*No of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months [41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question) - 6 months [41]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax	0					
All cause mortality[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Blood transfusion[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
TUR syndrome[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary retention[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urinary tract infections[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Retrograde ejaculation[41]	0	RCT				
Urinary incontinence[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Reoperation[41]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Strictures[41]	0	RCT				

(a) *This study was stated as open label study*[41]*. However, clinicians assessing the outcomes were different from surgeons performing the procedures.*

(b) *There was only one study reporting these outcomes. Sample size was smaller than the OIS. The confidence interval of pooled results crossed MID.*

Table 8-96: Laser coagulation vs. TURP in AUR patients - Clinical summary of findings

Outcome	*Laser coagulation*	*TURP*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score - 6 months	54	48	Not applicable	MD 3.4 [-0.1 to 6.9]	Low
Quality of life score (IPSS question)- 6 months	49	45	Not applicable	MD 0.30 [-0.41 to 1.01]	Low
All cause mortality	8/305 (2.6%)	6/310 (1.9%)	RR 1.31 [0.49 to 3.50]	27 fewer per 1000 [49 fewer to 89 more]	Low
Blood transfusion	0/74 (0%)	4/74 (5.4%)	RR 0.11 [0.01 to 2.03]	48 fewer per 1000 [53 fewer to 56 more]	Low
TUR syndrome	0/74 (0%)	2/74 (2.7%)	RR 0.2 [0.01 to 4.1]	22 fewer per 1000 [27 fewer to 84 more]	Low
Urinary retention	1/74 (1.4%)	0/74 (0%)	RR 3 [0.12 to 72.47]	0 more per 1000 [0 fewer to 0 more]	Very Low
Urinary tract infections	3/74 (4.1%)	4/74 (5.4%)	RR 0.75 [0.17 to 3.24]	14 fewer per 1000 [45 fewer to 121 more]	Low
Urinary incontinence	0/286 (0%)	11/283 (3.9%)	RR 0.16 [0.04 to 0.7]	35 fewer per 1000 [41 fewer to 71 more]	Moderate
Reoperation	29/311 (9.3%)	2/301 (0.7%)	RR 6.68 [2.44to 18.24]	84 more per 1000 [2 fewer to 763 more]	Low

8.4.1.3 Economic evidence

One study[189] comparing laser therapy with a noncontact side firing neodymium:YAG probe, standard TURP, and conservative management was identified. This was based on a RCT[61] included in our clinical review (8.4.1.1). Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-97: Laser coagulation vs. TURP - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Noble2002[189]	Serious limitations (a)	Directly applicable	Based on RCT included in clinical evidence[61]

(a) *Resource use data were available only for 30% of the patient population. The conclusions of the study were incorrect. Short follow-up (7.5 months).*

Table 8-98: Laser coagulation vs. TURP - Economic summary of findings

Study	*Incremental cost (£) per patient*	*Incremental effects*	*ICER*	*Uncertainty*
Noble2002[189]	£295	0.028 QALY (a)	£10,536/QALY	One-way sensitivity analysis: cost of probes, their multiple use, and machinery lifetime were varied with no considerable difference in results.

(a) *Only health utilities were higher in the Laser group. Other outcomes were better in the TURP group.*

8.4.1.4 Evidence statement (s)

Clinical Laser coagulation is less effective than TURP in improving symptom scores at 12 months and 2 years post-operatively.

There is no statistically significant difference between laser coagulation and TURP in improving symptom scores at 3 and 6 months.

Laser coagulation is less effective than TURP in improving quality of life (IPSS question) at 3, 12 months and at 2 years post-operatively.

There is no statistically significant difference between laser coagulation and TURP in improving quality of life (IPSS question) at 6 months post-operatively.

No studies report quality of life at 18 months, 3 years, 4 years and 5 years.

Laser coagulation is less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up postoperatively.

There is no statistically significant difference between laser coagulation and TURP in all cause mortality or number of patients who experienced TUR syndrome and urinary retention.

More patients treated with laser coagulation compared to TURP experienced urinary tract infection and reoperations.

Fewer patients treated with laser compared to TURP experienced blood transfusions, strictures, retrograde ejaculation or urinary incontinence.

In AUR patients, here is no statistically significant difference between

laser coagulation and TURP in symptom scores or quality of life at 6 months follow up.

In AUR patients, there is no statistically significant difference between laser coagulation and TURP in all cause mortality or number of patients who experienced TUR syndrome, blood transfusion and urinary retention, urinary tract infections, urinary incontinence or reoperations.

Economic Laser coagulation is cost-effective compared to TURP when health utilities are considered. This evidence is directly applicable but it has serious limitations.

8.4.1.5 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.4.2 Laser vapourisation vs. TURP

See Evidence Table 27, Appendix D, Forest Plots in Figures E-126 to E-131, Appendix E and Economic Evidence Table 53, Appendix D.

8.4.2.1 Clinical evidence

Table 8-99: Laser vapourisation vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[103,118,246]	3	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 6 months[103,246,258]	3	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 1 year [118,235,246,258]	4	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 2 years [118,235]	2	RCT	Very serious limitations (a), (d)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 3 years [118,235,258]	3	RCT	Very serious limitations (a), (d)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 5 years pr more [118,258]	2	RCT	Very serious limitations (a), (d)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 6 months[258]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 1 year[258]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 years [258]	1	RCT	Very serious limitations (a), (d)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 5 years[258]	1	RCT	Very serious limitations (a), (d)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 3 months[103,118,235,246,252]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at longest available follow up[103,118,235,246,252,258]	7	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Blood transfusion[28,38,103,118,170,235,252,253,258,274]	10	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary retention[28,38,103,235,253,258]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary infection[118,235,246,258]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation[103,235,252,253]	4	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Urinary incontinence[38,103,118,170,235]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Reoperations[38,103,118,170,252,253,258,274]	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
TUR syndrome[28,38]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Strictures[28,38,103,118,170,235,253,258,274]	9	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision (c)
All cause mortality[118,252,253,258]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) 7 studies[103,170,246,252,253,258,274] do not report randomisation method. 7 studies[103,170,235,246,252,253,274] do not report allocation concealment. All studies except 2[38,118] do not report masked outcome assessment or it is unclear. 7 studies[28,103,170,235,246,258,274] have incomplete outcome data and do not report reasons for attrition. Standard deviations or p values for outcome data at follow up or change from baseline are not reported in 4 studies [38,170,253,274]. There were differences in laser treatment modality in terms of energy supplied, laser type

(Nd:YAG, KTP, Holmium) and technique (some hybrid vapourisation & coagulation), and differences in prostate size and severity of LUTS between studies.

(b) Substantial unexplained heterogeneity was detected in the pooled results. Random effects analyses were conducted in these outcomes.

(c) The confidence intervals crossed MID and/or the sample size smaller than the MID.

(d) Percentage of drop out from studies increases with longer follow ups.[118,235,258].

Table 8-100: Laser vapourisation vs. TURP - Clinical summary of findings

Outcome	Laser Vapourisation	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months (a)	104	109	Not applicable	MD 1.78 [-2.28 to 5.84]	Very Low
Symptom score at 6 months (a)	81	84	Not applicable	MD 3.32 [0.04 to 6.60]	Very Low
Symptom score at 1 year (a)	139	144	Not applicable	MD 1.43 [-0.39 to 3.25]	Very Low
Symptom score at 2 years	68	71	Not applicable	MD 1.77 [-0.16 to 3.70]	Very Low
Symptom score at 3 years	76	89	Not applicable	MD 2.49 [0.54 to 4.44]	Very Low
Symptom score at 5 years or more	42	47	Not applicable	MD 2.09 [-0.74 to 4.92]	Very Low
Quality of life (IPSS question) score at 6 months	33	37	Not applicable	MD 0.30 [-0.08 to 0.68]	Very Low
Quality of life (IPSS question score at 1 year	37	41	Not applicable	MD 0.00 [-0.38 to 0.38]	Low
Quality of life (IPSS question at 3 years	10	15	Not applicable	MD 0.90 [0.03 to 1.77]	Very Low
Quality of life (IPSS question) at 5 years or longer	17	15	Not applicable	MD 0.10 [-0.77 to 0.97]	Very Low
Qmax at 3 months	169	173	Not applicable	MD -2.49 [-4.35 to –0.64]	Low
Qmax at longest available follow up (a)	42	47	Not applicable	MD -0.15 [-3.96 to 3.65]	Very Low
Blood transfusion	1/430 (0.2%)	25/423 (5.9%)	0.13 [0.04 to 0.40]	51 fewer per 1000 [35 fewer to 57 fewer]	Moderate
Urinary retention	26/288 (9%)	5/296 (1.7%)	4.6 [1.93 to 10.95]	61 more per 1000 [16 more to 169 more]	Moderate
UTI	28/270 (10.4%)	23/273 (8.4%)	1.21 [0.73 to 2.02]	18 more per 1000 [23 fewer to 86 more]	Low
Retrograde ejaculation (a)	25/121 (20.7%)	48/117 (41%)	0.38 [0.11, 1.27]	254 fewer per 1000 [365 fewer to 111 more]	Very Low
Urinary incontinence	3/279 (1.1%)	3/272 (1.1%)	0.09 [0.26 to 3.15]	1 fewer per 1000 [8 fewer to 24 more]	Low
Reoperations	30/342 (8.8%)	20/335 (6%)	1.51 [0.89 to 2.55]	31 more per 1000 [7 fewer to 93 more]	Low
TUR syndrome	0/133 (0%)	1/134 (0.7%)	0.33 [0.01 to 7.93]	5 fewer per 1000 [7 fewer to 49 more]	Low
Strictures	9/404 (2.2%)	27/397 (6.8%)	0.38 [0.19 to 0.74]	42 fewer per 1000 [18 fewer to 55 fewer]	Moderate
All cause mortality	14/164 (8.5%)	16/177 (9%)	0.94 [0.47 to 1.86]	5 fewer per 1000 [48 fewer to 77 more]	Low

(a) Outcomes were analysed usirng random effects analysis.

8.4.2.2 Economic evidence

Three studies were identified that compared Laser vapourisation with TURP[118,140,245]. In a CEA based on a RCT[118] laser treatment was performed using MD60 Nd:YAG while in the HTA Report[140] the type of laser considered was KTP and in the CEA based on a decision analysis[245] photoselective vapourisation represented laser. The study by Stovsky et al. (2006)[245] was eventually excluded because of worse quality and less applicable than the other two studies included. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-101: Laser (vapourisation) vs. TURP - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Keoghane2000[118]	Minor limitations (a)	Directly applicable	Based on a RCT included in the clinical evidence[118]
Lourenco2008[140]	Minor limitations (b)	Directly applicable	HTA (model based on a systematic review). Laser was KTP.

(a) *Surgeons had limited experience with the laser technique which may have caused the high failure rate with this treatment.*
(b) *Cost of equipment was included only for laser. Duration and cost of operations were equal in all the strategies. Training costs not included.*

Table 8-102: Laser (vapourisation) vs. TURP - Economic summary of findings

Study	*Incremental cost (£)per patient*	*Incremental effects*	*ICER*	*Uncertainty*
Keoghane2000[118]	£281 (a)	TURP more effective (b)	TURP is dominant	One-way sensitivity analysis: if inpatient stay after laser is reduced to 1.5 days laser becomes less costly by £50.
Lourenco2008[140]	£49 (c)	TURP more effective – adds 0.004 QALY	TURP is dominant	NR (d)

(a) *Costs included were cost of operation, hospitalisation, outpatient visits, GP and nurse visits, re-operation and capital costs.*
(b) *Both symptom score and Qmax were better with TURP.*
(c) *Costs included were cost of procedure, equipment, short-term complications (acute urinary retention, bladder neck contracture or urethral stricture, blood transfusion, transurethral syndrome, urinary tract infections), long-term complications (incontinence: 95% oxybutinin, 5% artificial sphincter).*
(d) *Not reported for single treatment strategies but only for sequences of treatments.*

8.4.2.3 Evidence statement (s)

Clinical There is no statistically significant difference between laser vapourisation and TURP in improving symptom score at 3 months, 1 year, 2 years and at 5 years or longer follow up.

Laser vapourisation is less effective than TURP in improving symptom score at 6 months and 3 years follow up. .

There is no statistically significant difference between laser vapourisation and TURP in improving IPSS QoL score at 3 months, 1 year and at 5 years or longer follow up.

Laser vapourisation is less effective than TURP in improving IPSS QoL score at 3 years follow up.

Laser vapourisation is less effective than TURP in improving Qmax at 3

months follow up but there is no statistically significant difference at longest available follow up.

Fewer patients treated with laser vapourisation compared to TURP experienced transfusions or strictures

More patients treated with laser vapourisation compared to TURP experienced urinary retention.

There is no statistically significant difference between laser vapourisation and TURP in number of patients with all cause mortality, UTI, reoporation, incontinence, TUR syndrome or retrograde ejaculation.

Economic TURP is less costly and more effective than laser vapourisation. This evidence has minor limitations and direct applicability.

8.4.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.4.3 Laser vs. OP

See Evidence Table 28, Appendix D, Forest Plots in Figures E-132, Appendix E.

8.4.3.1 Clinical evidence

Table 8-103: Laser (photoselective vapourisation) vs. OP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Median (25-75 percentile) symptom score at 3 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) symptom score at 6 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) symptom score at 12 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) symptom score at 18 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) Qmax at 3 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) Qmax at 6 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) Qmax at 12 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) Qmax at 18 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) quality of life (IPSS question) at 3 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) quality of life (IPSS question) at 6 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) IPSS quality of life at 12 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Median (25-75 percentile) quality of life (IPSS question) at 18 months[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Urinary incontinence[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Not estimable
Blood transfusion[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
TUR[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Not estimable
Reoperation[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
UTI[239]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
All cause mortality	0	RCT				
Acute urinary retention	0	RCT				
Stricture	0	RCT				
Retrograde ejaculation	0	RCT				

(a) Imprecision due to only one small study retrieved. Complication outcomes are downgraded when the 95% confidence intervals around the pooled estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.

Table 8-104: Laser (photoselective vapourisation) vs. Open prostatectomy - Clinical summary of findings

Outcome	Laser (PVP)	OP	Relative risk	Absolute effect	Quality
Median (25-75 percentile) symptom score at 3 months	10 [8-12]	10 [7-12]	P=0.743	Not applicable	Moderate
Median (25-75 percentile) symptom score at 6 months	9 [7-12]	9 [7-12]	P=0.224	Not applicable	Moderate
Median (25-75 percentile) symptom score at 12 months	9 [7-12]	8 [7-12]	P=0.128	Not applicable	Moderate
Median (25-75 percentile) symptom score at 18 months	10 [7-12]	8.5 [7-12]	P=0.063	Not applicable	Moderate
Median (25-75 percentile) Qmax at 3 months	16 [14-18]	15.1 [12.6-17]	P=0.255	Not applicable	Moderate
Median (25-75 percentile) Qmax at 6 months	16 [13.9-18.8]	15.6 [12.8-17.1]	P=0.220	Not applicable	Moderate
Median (25-75 percentile) Qmax at 12 months	16 [13.7-19]	15.1 [13-17.5]	P=0.186	Not applicable	Moderate
Median (25-75 percentile) Qmax at 18 months	16 [13.5-18.9]	15 [13-17.4]	P=0.271	Not applicable	Moderate
Median (25-75 percentile) quality of life (IPSS question) at 3 months	1 [1-2]	2 [1-2]	P=0.995	Not applicable	Moderate
Median (25-75 percentile) quality of life (IPSS question) at 6 months	1 [1-2]	1 [0.25-1]	P=0.024	Not applicable	Moderate
Median (25-75 percentile) quality of life (IPSS question) at 12 months	1 [1-2]	1 [1-1]	P=0.035	Not applicable	Moderate
Median (25-75 percentile) quality of life (IPSS question) at 18 months	1 [1-2]	1 [1-1]	P=0.001	Not applicable	Moderate
Urinary incontinence	0/65 (0%)	0/60 (0%)	Not estimable	Not estimable	
Blood transfusion	0/65 (0%)	8/60 (13.3%)	0.05 [0.00, 0.92]	126 fewer per 1000 [11 to 133 fewer]	Moderate
TUR syndrome	Not appropriate	0/60 (0%)	Not estimable	Not estimable	
Reoperation	3/65 (4.6%)	3/60 (5.0%)	RR: 0.92 [0.19, 4.40]	4 fewer per 1000 [40 fewer to 170 more]	Moderate
UTI	14/65 (21.5%)	16/60 (26.7%)	RR: 0.81 [0.43, 1.51]	51 fewer per 1000 [152 fewer to 136 more]	Moderate

8.4.3.2 Economic evidence

No economic studies were identified.

8.4.3.3 Evidence statement (s)

Clinical There is no statistically significant difference between laser vapourisation and OP in improving symptom scores at 3, 6, 12 or 18 months.

There is no statistically significant difference between laser vapourisation and OP in improving quality of life (IPSS question) at 3 months.

OP is more effective than laser vapourisation in improving quality of life (IPSS question) at 6, 12 and 18 months.

There is no statistically significant difference between laser vapourisation and OP in improving Qmax.

Fewer men treated with laser vapourisation than OP needed blood transfusions.

There is no statistically significant difference between laser vapourisation and OP in men experiencing urinary tract infections or reoperation.

Economic No economic studies were identified.

8.4.4 Laser vs. TUMT

See Evidence Table 29, Appendix D, Forest Plots in Figures E-133 to E-135, Appendix E and Economic Evidence Table 53, Appendix D.

8.4.4.1 Clinical evidence

Table 8-105: Laser coagulation vs. TUMT – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months[191]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 3, 12 months or more	0	RCT				
Qmax at 3 months	0	RCT				
Quality of life (IPSS question)						
Qmax at longest available follow up[191]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Complications[191]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a) *Study*[191] *did not report allocation concealment, blinding or method of randomisation.*
(b) *Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (symptom score and peak uriary flow). Complications outcomes were downgraded when the 95% confidence intervals around the estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.*

Table 8-106: Laser coagulation vs. TUMT - Clinical summary of findings

Outcome	Laser	TUMT	Relative risk	Absolute effect	Quality
Symptom score at 6 months	44	44	Not applicable	MD: 0.0 [-2.86, 2.86]	Low
Qmax at longest follow up	43	44	Not applicable	MD: 3.0 [-0.26, 6.26]	Low
Urinary retention	4/44 (9.1%)	3/46 (6.5%)	RR: 1.39 [0.33, 5.88]	25 more per 1000 [44 fewer to 317 more]	Low
Stricture	1/44 (2.3%)	0/46 (0%)	RR: 3.13 [0.13, 74.93]	0 more per 1000 [0 fewer to 0 more]	Low
UTI	27/44 (61.4%)	14/46 (30.4%)	RR: 2.02 [1.23, 3.31]	310 more per 1000 [70 more to 702 more]	Low
Urinary incontinence	0/44 (0%)	0/46 (0%)	Not applicable	Not applicable	
Reoperation	0/44 (0%)	1/46 (2.2%)	RR: 0.35 [0.01, 8.33]	14 fewer per 1000 [22 fewer to 161 more]	Low
Retrograde ejaculation	9/26 (34.6%)	6/27 (22.2%)	RR: 1.56 [0.65, 3.76]	124 more per 1000 [78 fewer to 613 more]	Low
All cause mortality	0/44 (0%)	0/46 (0%)	Not applicable	Not applicable	
Blood transfusion	0/44 (0%)	0/46 (0%)	Not applicable	Not applicable	

8.4.4.2 Economic evidence

We found three economic studies[140,190,245] comparing Laser with TUMT. The study by Norby et al. (2002)[190] was based on a RCT[191] included in our review of clinical evidence (8.4.4.1) where laser was Interstitial Laser Coagulation. In the HTA model[140] different types of lasers were included but in our analysis we will consider only HoLEP as it was the most cost-effective type. The study by Stovsky et al. (2006)[245] was eventually excluded because of worse quality and less applicable than the other two studies included. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-107: Laser coagulation vs. TUMT - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Norby2002[190]	Serious limitations (a)	Partially applicable (b)	Based on a RCT[191] included inour review of clinical evidence. Laser was Interstitial Laser Coagulation.
Lourenco2008 [140]	Minor limitations (c)	Directly applicable	HTA (model based on a systematic review). Laser was HoLEP (d)

(a) *Small sample size for economic analysis (costs collected in 20 patients). Short follow-up (6 months).*
(b) *Denmark study.*
(c) *Duration and cost of operations were equal in all the strategies. Training costs were not included.*
(d) *KTP was dominated by HoLEP in the study.*

Table 8-108: Laser coagulation vs. TUMT - Economic summary of findings

Study	Incremental cost per patient	Incremental effects	ICER	Uncertainty
Norby2002[190]	£311 (a)	0.08 IPSS score	£388 per point of reduction in IPSS	If TUMT catheters were reused once, ICER = £ 638 If ITT analysis is applied, ICER = £ 332
Lourenco2008 [140]	£5	0.006QALY	£833/QALY	NR (b)

(a) *GBP calculated using the PPP2007 1DKK = 0.08GBP*
(b) *Not reported for single treatment strategies but only for sequences of treatments.*

8.4.4.3 Evidence statement (s)

Clinical There is no statistically significant difference between TUMT and laser coagulation in improving symptom scores at 6 months postoperatively.

There is no statistically significant difference between TUMT and laser coagulation in improving the maximum urinary flow at longer follow-up postoperatively.

There is no statistically significant difference between laser coagulation and TUMT with number of patients experiencing urinary retention, strictures, reoperations and retrograde ejaculation.

More men treated with laser coagulation compared to TUMT experienced urinary tract infections.

Economic Laser (HoLEP) is cost-effective compared to TUMT. This evidence has minor limitations and direct applicability.

8.4.4.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.4.5 Laser vs. TUVP

See Evidence Table 30, Appendix D, Forest Plots in Figures E-136 to E-139, Appendix E and Economic Evidence Table 53, Appendix D.

8.4.5.1 Clinical evidence

Three studies were identified that compared laser to TUVP. Two of the studies[236,258] used laser vapourisation and one was a combination of coagulation and vapourisation methods[2].

Table 8-109: Laser vs. TUVP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 6 months[258]	1	RCT	Serious limitations (a)	No serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 12 months[2,258]	2	RCT	Serious limitations (a)	Very serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 2 years[2]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 3 years[2,258]	2	RCT	Serious limitations (a)	Very serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Symptom score at 4 years[2]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 5 years[258]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Quality of life (IPSS question) at 6 months[258]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 12 months [2,258]	2	RCT	Serious limitations (a)	Very serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 2 years[2]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life (IPSS question) at 3 years [2,258]	2	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	No serious imprecision
Quality of life (IPSS question) at 4 years[2]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 5 years[258]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at longest available follow up[2,258]	2	RCT	Serious limitations (a)	Serious inconsistency(b)	No serious indirectness	Serious imprecision (c)
All cause mortality[2,258]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Blood transfusion[258]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Urinary retention[2,236,258]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
UTI [258]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Strictures[2,236,258]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Reoperation[2,258]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No imprecision
Retrograde ejaculation[2]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No imprecision
Urinary incontinence[258]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
TUR syndrome	0					

(a) *All studies[2,236,258] did report masking the patients or outcomes investigators. Two studies[2,236] did not report randomisation sequence generation and allocation concealment methods. Two studies[2,236] have incomplete outcome data and do not report reasons for attrition. More than 50% of patients dropped out from the study after 1 year for IPSS and IPSS-QoL and Qmax at 1 year[258].*

(b) *Statistically significant heterogeneity was detected and random effects analyses were conducted. In outcomes with multiple duration of follow up, the consistency of the time trend was considered. Two studies [2,258] reported efficacy outomes and there were no overlap in their confidence intervals for IPSS and IPSS-QoL at 12 months, and there were very serious inconsistencies in other length of follow ups.*

(c) *Downgraded when sample sizes were not adequate to detect the MID or the 9%% CI crossed the MIDs*

Table 8-110: Laser vs. TUVP - Clinical summary of findings

Outcome	Laser	TUVP	Relative risk	Absolute effect	Quality
Symptom score at 6 months	33	37	Not applicable	MD 2.7 [0.63 to 4.77]	Very low
Symptom score at 12 months (a)	99	119	Not applicable	MD 3.61 [-4.43 to 11.64]	Very low
Symptom score at 2 years	62	78	Not applicable	MD 7 [5.43 to 8.57]	Very low
Symptom score at 3 years (a)	72	90	Not applicable	MD 5.17 [-2 to 12.33]	Very low
Symptom score at 4 years	62	78	Not applicable	MD 8.2 [6.65 to 9.75)	Very low
Symptom score at 5 years	17	12	Not applicable	MD 1.3 [-3.09 to 5.69]	Very low
Quality of life (IPSS question) at 6 months	33	37	Not applicable	MD -0.2 [-0.63 to 0.23]	Very low
Quality of life (IPSS question) at 12 months (a)	99	119	Not applicable	MD 0.81 [-1.54 to 3.16]	Very low
Quality of life (IPSS question) at 2 years	62	78	Not applicable	MD 1.8 [1.65 to 1.95]	Very low
Quality of life (IPSS question) at 3 years (a)	72	90	Not applicable	MD 1.57 [0.72 to 2.42]	Very low
Quality of life (IPSS question) at 4 years	62	78	Not applicable	MD 1.8 [1.53 to 2.07]	Very low
Quality of life (IPSS question) at 5 years	17	12	Not applicable	MD 0 [-0.73 to 0.73]	Very low
Qmax at longest available follow up(a)	79	90	Not applicable	MD -3.07 [-13.57 to 7.43]	Very low
Blood transfusion[258]	0/45 (0%)	0/46 (0%)	Not applicable	Not applicable	Very low
Urinary retention[2,236,258]	17/146 (11.6%)	3/156 (1.9%)	RR 5.75 [1.85 to 17.87]	90 more per 1000 [16 more to 321 more]	Very low
UTI [258]	5/45 (11.1%)	2/46 (4.3%)	RR 2.56 [0.52 to 12.5]	67 more per 1000 [21 fewer to 495 more]	Moderate
All cause mortality[2,258]	1/135 (0.7%)	2/136 (1.5%)	RR 0.5 [0.05 to 5.42]	7 fewer per 1000 [14 fewer to 66 more]	Very low
Strictures[2,236,258]	3/146 (2.1%)	3/156 (1.9%)	RR 1.15 [0.31 to 4.27]	3 more per 1000 [13 fewer to 62 more]	Very low
Reoperations[2,258]	36/135 (26.7%)	13/136 (9.6%)	RR 2.77 [1.56 to 4.94]	170 more per 1000 [54 more to 378 more]	Moderate
Retrograde ejaculation[2]	16/90 (17.8%)	57/90 (63.3%)	RR 0.28 [0.18 to 0.45]	456 fewer per 1000 [348 fewer to 519 fewer]	Moderate
Urinary incontinence[258]	14/45 (31.1%)	7/46 (15.2%)	RR 2.04 [0.91 to 4.59]	158 more per 1000 [14 fewer to 546 more]	Low

(a) Outcomes analysed using random effects analysis.

8.4.5.2 Economic evidence

We found one economic study[140] comparing Laser with TUVP. This HTA model was of good quality and directly applicable to the NHS setting. Different types of lasers were included but in our analysis we will consider only HoLEP as it was the most cost-effective type. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-111: Laser vs. TUVP - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Lourenco2008[140]	Minor limitations (a)	Directly applicable	HTA (model based on a systematic review) Laser was HoLEP (b)

(a) Capital cost of TUVP was not included. Duration and cost of operations were equal in all the strategies. Training costs were not included.

(b) HoLEP and not KTP was chosen to represent laser as KTP was dominated by HoLEP in the study.

Table 8-112: Laser vs. TUVP - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Lourenco2008[140]	£8 (a)	0.001QALY	£7,273/QALY	Not reported (b)

(a) Costs included were cost of procedure, equipment, short-term complications (acute urinary retention, bladder neck contracture or urethral stricture, blood transfusion, transurethral syndrome, urinary tract infections), long-term complications (incontinence: 95% oxybutinin, 5% artificial sphincter)

(b) Not reported for single treatment strategies but only for sequences of treatments.

8.4.5.3 Evidence statement (s)

Clinical TUVP is more effective than lasers in improving symptoms at 6 months, 2 years and 4 years post-operatively.

There is no statistically significant difference between TUVP and laser in improving symptom at 12 months, 3 years and 5 years postoperatively.

TUVP was more effective than lasers in improving quality of life at 2, 3, 4 and 5 years post-operatively.

There is no statistically significant difference between TUVP and laser in improving quality of life at 6 and 12 months postoperatively.

There is no statistically significant difference between laser and TUVP in improving the maximum urinary flow at longer follow-up postoperatively.

There is no statistically significant difference between laser and TUVP with number of patients who died or experienced strictures, urinary tract infections, retrograde ejaculation and incontinence.

More men treated with laser compared to TUVP experienced urinary retention or had reoperation.

Fewer men treated with laser compared to TUVP experienced retrograde ejaculation.

Economic Laser (HoLEP) is cost-effective compared to TUVP. This evidence has minor limitations and direct applicability.

8.4.5.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.4.6 Laser vs. laser

See Evidence Tables 31, 32 and 33, Appendix D, Forest Plots in Figures E-140 to E-147, Appendix E and Economic Evidence Table 53, Appendix D.

We found evidence for the following comparisons:

A. Laser vapourisation vs. Laser coagulation

Three studies which compared vapourisation with coagulation methods were identified[32,173,246].

B. HoLRP vs. VLAP

One study compared HOLRP against VLAP[86] was identified. However, only mean and range values for symptom scores (IPSS) and Qmax were reported[86].

C. HoLAP vs. Laser photoselective vapourisation.

One study compared HoLAP and laser photoselective vapourisation was identified

8.4.6.1 Clinical evidence

A. Laser coagulation vs. laser vapourisation

Table 8-113: Laser vapourisation vs. coagulation – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score : at 3 months [173,246]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Symptom score : at 6 months [32,173,246]	3	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Symptom score : at 12 months [173]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Symptom score : at 24 months [32]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Quality of life (IPSS question)	0					
Qmax at 3 months[173,246]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Qmax at longest available follow up [32,173,246]	3	RCT	Serious limitations(a)	Serious inconsistency (c)	No serious indirectness	No serious imprecision
Urinary retention[173]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Blood transfusions[32,173]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Developed Erectile dysfunction[32,173]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Reoperation[32,173]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Perioperative UTI[32,173]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
All cause mortality	0					
TUR syndrome	0					
Strictures	0					
Retrograde ejaculation	0					
Urinary incontinence	0					

(a) *All were open label studies*[32,173,246]*. Two studies did not report allocation randomisation and concealment*[32,246]*. One study did not report adverse events of the procedures*[246]*.*

(b) *The sample size was smaller than required to determine a minimal important difference. The 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm.*

(c) *Confidence intervals with minimal overlap, the p value for heterogeneity less than 0.05 and* $I^2 \geq 50\%$.

Table 8-114: Laser vapourisation vs. coagulation - Clinical summary of findings

Outcome	*Laser vapourisation*	*Laser Coagulation*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score: at 3 months (a)	42	42	Not applicable	MD -6.44 [-16.63, 3.76]	Very Low
Symptom score: at 6 months	62	58	Not applicable	MD -1.83 [-4.70 to 1.04]	Very Low
Symptom score: at 12 months	32	32	Not applicable	MD 0.10 [-7.94 to 8.14]	Very Low
Symptom score: at 24 months	21	17	Not applicable	MD 0.2 [-4.77 to 5.17]	Very Low
Qmax at 3 months	42	42	Not applicable	MD 1.32 [-3.40 to 6.04]	Very Low
Qmax at longest available follow up(a)	62	58	Not applicable	MD 0.66 [-2.43 to 3.74]	Low
Urinary retention	2/32 (6.3%)	8/32 (25%)	RR 0.25 [0.05 to 1.02]	188 fewer per 1000 [238 fewer to 5 more]	Very Low
Blood transfusions	1/53 (1.9%)	0/49 (0%)	RR 2.45 [0.11 to 56.68]	0 more per 1000 [0 fewer to 0 more]	Very Low
Developed Erectile dysfunction	1/53 (1.9%)	1/49 (2.0%)	RR 0.81 [0.05 to 12.01]	4 fewer per 1000 [19 fewer to 220 more]	Very Low
Reoperation	1/53 (1.9%)	7/49 (14.3%)	RR 0.18 [0.03 to 1.04]	117 fewer per 1000 [139 fewer to 6 more]	Very Low
Perioperative UTI	3/53 (5.7%)	3/49 (6.1%)	RR 0.9 [0.2 to 4.15]	6 fewer per 1000 [49 fewer to 192 more]	Very Low

(a) Random effects analysis was conducted

B. Holmium laser resection of the prostate (HoLRP) vs. laser coagulation

Table 8-115: HoLRP vs. Laser coagulation – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at any time points	0	RCT				
Quality of life (IPSS question) at any time points	0	RCT				
Qmax at any time points	0	RCT				
Urinary retention[86]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary tract infections[86]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
All cause mortality	0					
Reoperation	0					
TUR syndrome	0					
Acute urinary retention	0					
Blood transfusion	0					
Strictures	0					
Retrograde ejaculation	0					
Urinary incontinence	0					

(a) *Only one study was identified*[86]*. This was not a masked study, and randomisation allocation and concealment was not reported. Sample size was too small to detect a significant difference. The confidence interval includes no effect or crosses the minimal important difference (MID).*

Table 8-116: HoLRP vs. Laser coagulation – Clinical summary of findings

Outcome	*HoLRP*	*Laser Coagulation*	*Relative risk*	*Absolute effect*	*Quality*
Urinary retention	2/22 (9.1%)	8/22 (36.4%)	RR 0.25 [0.06 to 1.05]	273 fewer per 1000 [342 fewer to 18 more]	Very Low
Urinary tract infections	0/22 (0%)	3/22 (13.6%)	RR 0.14 [0.01 to 2.61]	117 fewer per 1000 [135 fewer to 219 more]	Very Low

8.4.6.2 Economic evidence

We found one economic study[140] comparing HoLEP with KTP. The HTA model was of good quality and directly applicable to the NHS setting. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-117: HoLEP vs. KTP - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Lourenco2008[140]	Minor limitations (a)	Directly applicable	HTA (model based on a systematic review)

(a) *Capital cost of HoLEP and KTP was not included. Duration and cost of operations were equal in all the strategies. Training costs were not included.*

Table 8-118: HoLEP vs. KTP - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects (QALYs)	ICER	Uncertainty
Lourenco2008[140]	Cost saving (a)	0.0048	HoLEP dominates KTP	Not reported (a)

(a) *Costs included were cost of procedure, equipment, short-term complications (acute urinary retention, bladder neck contracture or urethral stricture, blood transfusion, transurethral syndrome, urinary tract infections), long-term complications (incontinence: 95% oxybutinin, 5% artificial sphincter).*

(b) *Not reported for single treatment strategies but only for sequences of treatments.*

8.4.6.3 Evidence statement (s)

Clinical There is no statistically significant difference between laser coagulation and laser vapourisation in improving symptom at3, 6, 12 and 24 months post operatively.

There is no statistically significant difference between laser coagulation and laser vapourisation in improving symptom Qmax at 3 months or longest available follow up.

There is no statistically significant difference between laser vapourisation and coagulation in number of patients who experienced transfusion, urinary retention, urinary tract infections, reoperations or developed erectile dysfunction.

There is no statistically significant difference between HoLRP compared to laser coagulation in number of patients who experienced urinary tract infections or urinary retention.

Economic HoLEP is less costly and more effective than KTP. This evidence has minor limitations and direct applicability.

C. Holmium laser ablation of the prostate (HoLAP) vs. laser photoselective vapourisation:

Table 8-119: HoLAP vs. Laser vapourisation – Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptom score[66,66]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question)[66,66]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax[66,66]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Adverse events[66,66]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a)Limitations in study quality as allocation concealment unclear and reason for drop outs not reported.
(b)Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (symptom score and peak urinary flow). Complications outcomes were downgraded when the95% confidence intervals around the estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.

Table 8-120: HoLAP vs. Laser vapourisation – Clinical summary of findings

Outcome	HoLAP	Laser Vapourisation	Relative risk	Absolute effect	Quality
Symptom score at 3 months	44	39	Not applicable	MD: 2.60 [0.11, 5.09]	Low
Symptom score at 6 months	40	39	Not applicable	MD: 0.10 [-2.69, 2.89]	Low
Symptom score at 12 months	44	42	Not applicable	MD: -2.00 [-4.20, 0.20]	Low
Quality of life (IPSS question) at 3 months	44	39	Not applicable	MD: 0.30 [-0.24, 0.84]	Low
Quality of life (IPSS question) at 6 months	40	39	Not applicable	MD: 0.40 [-0.13, 0.93]	Low
Quality of life (IPSS question) at 12 months	44	42	Not applicable	MD: 0.10 [-0.45, 0.65]	Low
Qmax at 3 months	44	39	Not applicable	MD: -0.30 [-3.94, 3.34]	Low
Qmax at 6 months	40	39	Not applicable	MD: -2.00 [-5.23, 1.23]	Low
Qmax at 12 months	44	42	Not applicable	MD: -1.20 [-4.75, 2.35]	Low
Strictures	57	52	RR: 0.30 [0.03, 2.83]	41 fewer [56 fewer to 106 more]	Low
Urinary tract infections	57	52	RR: 1.37 [0.24, 7.87]	14 more [29 fewer to 261 more]	Low
Urinary incontinence (stress and urge)	57	52	RR: 0.91 [0.28, 2.97]	9 fewer per 1000 [from 69 fewer to 189 more]	Low
Re-catheterisation	57	52	RR: 1.06 [0.38, 2.96]	7 more [71 fewer to 225 more]	Low
Reoperation	57	52	RR: 1.82 [0.17, 19.53]	16 more [16 fewer to 352 more]	Low

8.4.6.4 Economic evidence

No economic studies were identified.

8.4.6.5 Evidence statement (s)

Clinical PVP laser vapourisation is more effective than HoLAP in improving symptom scores at 3 months.

There is no statistically significant difference between HoLAP and PVP laser vapourisation in improving symptom scores at 6 or 12 months.

There is no statistically significant difference between HoLAP and PVP laser vapourisation in improving quality of life IPSS symptom score at 3, 6 or 12 months.

There is no statistically significant difference between HoLAP and PVP laser vapourisation in improving Qmax at 3, 6 or 12 months.

There is no statistically significant difference between HoLAP and PVP laser vapourisation in men experiencing incontinence, re-catheterisation, reoperation, strictures or urinary tract infections.

Economic No economic studies were identified.

8.4.7 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.5 Transurethral microwave thermotherapy (TUMT)

8.5.1 TUMT vs. SHAM

See Evidence Table 34, Appendix D, Forest Plots in Figures E-148 to E-151, Appendix E and Economic Evidence Table 53, Appendix D.

8.5.1.1 Clinical evidence

Table 8-121: TUMT vs. SHAM – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[22,27,129]	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 6 months[129]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom scores at 12months plus	0	RCT				
Qmax at 3 months[22,27,55,129,198]	5	RCT (d)	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax at longest follow-up[55,129,185]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0	RCT				
Urinary retention[1,10,27,55,129,185,198,251]	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary tract infection[1,129,198,251]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation[129]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence[129,251]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Reoperation[22,30,55,129,198]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Strictures[10,129]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Transfusions	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Not estimable
All cause mortality[55,129]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
TUR syndrome	0					

(a) *8 studies [1 10 30 55 129 185 198 273] did not report allocation concealment. 8 studies [22 30 30 55 129,198 251 273] did not report method of randomisation. 6 studies [10 27 185 198 251 273] have incomplete outcome data and do not report reasons for attrition.*

(b) *Heterogeneity detected in outcome.*

(c) *Imprecision due to sample sizes being inadequate to detect MID for the primary outcomes or the 95% CI cross the MID therefore making estimate of effect uncertain. Complications outcomes were downgraded when the95% CI around the estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.*

(d) *One study[273] was excluded from Qmax outcome at 3 months as the baseline figures were significantly different.*

Table 8-122: TUMT vs. SHAM - Clinical summary of findings

Outcome	TUMT	SHAM	Relative risk	Absolute effect	Quality
Symptom score at 3 months	209	89	Not applicable	MD: -5.69 [-7.38, -3.99]	High
Symptom score at 6 months	120	35	Not applicable	MD: -3.80 [-6.27, -1.33]	Low
Qmax at 3 months	264	151	Not applicable	MD: 2.92 [2.03, 3.80]	Moderate
Qmax at longest follow-up	172	84	Not applicable	MD: 1.19 [0.17, 2.20]	Low
Urinary Retention	78/644 (12.1%)	2/354 (0.6%)	RR: 9.57 [3.91, 23.41]	51 more per 1000 [17 more to 134 more]	Moderate
Urinary Tract Infection	5/272 (1.8%)	0/117 (0%)	RR: 1.49 [0.84, 2.67]	38 more per 1000 [12 fewer to 129 more]	Low
Retrograde ejaculation	5/125 (4%)	0/44 (0%)	RR: 3.93 [0.22, 69.96]	Not estimable	Low
Urinary incontinence	5/272 (1.8%)	0/117 (0%)	RR: 3.93 [0.22, 69.96]	Not estimable	Low
Reoperation rate	14/232 (6.0%)	78/145 (53.8%)	RR: 0.16 [0.04, 0.56]	452 fewer per 1000 [37 fewer to 516 fewer]	Low
Blood transfusion	0/125 (0%)	0/144 (0%)	Not estimable	Not estimable	
Strictures	3/246 (1.2%)	0/106 (0%)	RR: 2.50 0.13, 47.46]	Not estimable	Low
All cause mortality	2/172 (1.2%)	0/90 (0%)	RR: 1.83 [0.21, 16.23]	Not estimable	Low

8.5.1.2 Economic evidence

We found one economic study[58] comparing high-energy TUMT with watchful waiting. In this decision model the clinical data for watchful waiting were estimated from AHCPR Guidelines[154] while data for the TUMT arm were estimated from a RCT[129] included in our review (8.5.1.1). Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-123: TUMT vs. SHAM- Economic study characteristics

Study	Limitations	Applicability	Other Comments
Moderate symptoms			
DiSantostefano2006[58]	Serious limitations (a)	Partially applicable (b)	
Severe symptoms			
DiSantostefano2006[58]	Serious limitations (a)	Partially applicable (b)	

(a) *The TUMT arm was modelled around a different RCT and potentially on a different population.*
(b) *USA study. The comparator was not sham but watchful waiting.*

Table 8-124: TUMT vs. SHAM - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects (QALYs)	ICER	Uncertainty
Moderate symptoms				
DiSantostefano2006[58]	£2,252 (a, b, c)	0.01 (c)	£225,200 (c)	Similar results if patients continue on initial treatment unless TURP is required. If patients are 55 or younger TUMT is cost-effective.
Severe symptoms				
DiSantostefano2006[58]	£2,262 (a, b, c)	0.51 (c)	£4,435 (c, d)	Similar results if patients continue on initial treatment unless TURP is required.

(a) *GBP calculated using the PPP 2004 1$ = 0.632GBP.*
(b) *Costs include only direct medical costs and were calculated using databases.*
(c) *Results reported for the scenario where patients can switch treatment.*
(d) *TURP is more cost-effective than TUMT in this group (8.5.2.2).*

8.5.1.3 Evidence statement (s)

Clinical

TUMT is more effective than SHAM in improving symptom scores at 3 months.

TUMT is more effective than SHAM in improving symptom scores at 6 months.

TUMT is more effective than SHAM in improving maximum urinary flow rate at 3 months and at longer follow-up.

TUMT is more effective than SHAM in improving maximum urinary flow rate at longer follow-up.

Fewer men treated with TUMT compared to SHAM experienced reoperations.

Fewer men treated with SHAM compared to TUMT experienced urinary retention.

There is no statistically significant difference between TUMT and SHAM treatment in number of men experiencing strictures, urinary tract infections, urinary incontinence, retrograde ejaculation and mortality.

Economic

TUMT is cost-effective compared to watchful waiting in men with severe symptoms. TUMT is not cost-effective in men with moderate symptoms. This evidence has serious limitations and partial applicability.

8.5.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.5.2 TUMT vs. TURP

See Evidence Table 35, Appendix D, Forest Plots in Figures E-152 to E-159, Appendix E and Economic Evidence Table 53, Appendix D.

8.5.2.1 Clinical evidence

Table 8-125: TUMT vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[50,53,259]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 6 months[7,50,259]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 12 months[50,53,259]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 24 months[53,259]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 36 months[53,259]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 48 months[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom scores at 60 months[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 3 months[50-52,259]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax at long term[7,50-53,259]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life score at 3 months (IPSS question)[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life score at 6 months[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life score at 12 months[53,259]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life score at 24 months[53,259]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life score at 36 months[53,259]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life score at 48 months[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life score at 60 month[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
All cause mortality[50,52,53,259]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Blood transfusion[7,50,52]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Infection[7,50-52,259]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Stricture[7,51-53]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence[51,53,259]	3	RCT	Serious limitations (a)	No serious inconsistency(a)	No serious indirectness	Serious imprecision (b)
Reoperation[50-53,259]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary retention[52,53,259]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
TUR syndrome[259]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation[7,53]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)

(a) *All the studies [7,50-53,259] have incomplete outcome data and do not report reasons for attrition or method of randomisation. One study [7] reported allocation concealment.*

(b) *Heterogeneity detected in outcome.*

(c) *Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (symptom score and peak urinary flow) or the confidence intervals are cross the MID therefore making estimate of effect uncertain. Complications outcomes were downgraded when the 95% confidence intervals around the estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.*

Table 8-126: TUMT vs. TURP - Clinical summary of findings

Outcome	TUMT	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	173	117	Not available	MD: 5.48 [0.94 to 10.01]	Very low
Symptom score at 6 months	153	93	Not available	MD: 1.25 [0.11 to 2.39]	Moderate
Symptom score at 12 months	178	108	Not available	MD: 2.26 [-0.38 to 4.91]	Very low
Symptom score at 24 months	123	76	Not available	MD: 3.65 [2.1 to 5.2]	Low
Symptom score at 36 months	103	68	Not available	MD: 6.03 [0.45 to 11.62]	Very low
Symptom score at 48 months	56	30	Not available	MD: 0.7 [-2.05 to 3.45]	Low
Symptom score at 60 months	63	34	Not available	MD: 1.4 [-0.88 to 3.68]	Low
Quality of life score at 3 months	84	41	Not applicable	MD: 0.4 [-0.17 to 0.97]	Low
Quality of life score at 6 months	93	42	Not applicable	MD: 0.3 [-0.24 to 0.84]	Low
Quality of life score at 12 months	151	91	Not applicable	MD: 0.62 [-0.76 to 1.99]	Very low
Quality of life score at 24 months	123	76	Not applicable	MD: 0.71 [0.12 to 1.30]	Low
Quality of life score at 36 months	103	68	Not applicable	MD: 1.01 [-0.37 to 2.38]	Very low
Quality of life score at 48 months	56	30	Not applicable	MD: 0.2 [-0.33 to 0.73]	Low
Quality of life score at 60 months	63	34	Not applicable	MD: 0.0 [-0.46 to 0.46]	Moderate
Qmax at 3 months	183	131	Not applicable	MD: -4.92 [-7.34, -2.49]	Moderate
Qmax at long term follow-up	197	158	Not applicable	MD: -5.40 [-7.29, -3.51]	Moderate
All cause mortality	3/246 (1.2%)	4/165 (2.4%)	RR: 0.60 [0.18, 2.01]	10 fewer per 1000 [20 fewer to 24 more]	Low
Infection	32/237 (13.5%)	18/169 (10.7%)	RR: 1.08 [0.64, 1.83]	9 more per 1000 [39 fewer to 89 more]	Low
Re-operation	31/285 (10.9%)	8/205 (3.9%)	RR: 2.81 [1.35, 5.86]	71 more per 1000 [14 to 190 more]	Moderate
TUR	0/100 (0%)	1/46 (2.2%)	RR: 0.16 [0.01, 3.74]	18 fewer per 1000 [22 fewer to 60 more]	Low
Urinary retention	28/215 (13%)	6/144 (4.2%)	RR: 2.22 [1.04, 4.73]	51 more per 1000 [2 to 157 more]	Low
Blood transfusion	0/98 (0%)	4/83 (4.8%)	RR: 0.11 [0.01, 1.98]	43 fewer per 1000 [48 fewer to 47 more]	Low
Stricture	1/184 (0.5%)	10/168 (6%)	RR: 0.20 [0.05, 0.78]	48 fewer per 1000 [13 to 57 fewer]	Low
Retrograde ejaculation	28/54 (51.9%)	17/61 (27.9%)	RR: 1.41 [0.09, 21.63]	114 more per 1000 [254 fewer to 1000 more]	Very low
Urinary incontinence(a)	11/217 (5.1%)	14/152 (9.2%)	RR: 0.52 [0.12, 2.21]	44 fewer per 1000 [81 fewer to 111 more]	Very Low

(a) *Outcomes analysed using random effects analysis.*

8.5.2.2 Economic evidence

We found eight economic studies[6,53,58,122,140,190,245,260] comparing TUMT with TURP. Most of them[53,122,190,245,260] were eventually excluded because of worse quality and less applicability than the other two studies [58,140]. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-127: TUMT vs. TURP- Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Moderate symptoms			
DiSantostefano2006[58]	Serious limitations (a)	Partially applicable (b)	
Severe symptoms			
DiSantostefano2006[58]	Serious limitations (a)	Partially applicable (b)	
Moderate and severe symptoms			
Lourenco2008 [140]	Minor limitations (c)	Directly applicable	

(a) *The TUMT arm was modeled around a different RCT and potentially on a different population than TURP.*
(b) *USA study. The comparator was not sham but watchful waiting.*
(c) *Capital cost of TUMT was not included. Duration and cost of operations were equal in all the strategies. Training costs were not included.*

Table 8-128: TUMT vs. TURP - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects (QALYs)*	*ICER*	*Uncertainty*
Moderate symptoms				
DiSantostefano2006[58]	Cost saving (a)	0.06 (a)	TUMT dominant (a, b)	Similar results if patients continue on initial treatment unless TURP is required.
Severe symptoms				
DiSantostefano2006[58]	-364 (a, c, d)	-0.17 (a)	TURP vs. TUMT £2141/QALY (a)	Similar results if patients continue on initial treatment unless TURP is required. Results do not change with the patient's age.
Moderate and severe symptoms				
Lourenco2008 [140]	19	0.0048	£3,958/QALY	Not reported (d)

(a) *Results reported for the scenario where patients can switch treatment.*
(b) *In this study TUMT was not cost-effective compared to watchful waiting (8.5.1.2)*
(c) *GBP calculated using the PPP 2007 1$ = 0.632GBP.*
(d) *Costs include only direct medical costs and were calculated using databases.*
(e) *Sensitivity analysis not reported for this comparison.*

8.5.2.3 Evidence statement (s)

Clinical TURP is more effective than TUMT in improving symptom scores at 3, 6, 24 and 36 months postoperatively.

There is no statistically significant difference between TURP and TUMT in improving symptom scores at 12, 48 or 60 months postoperatively.

TURP is more effective than TUMT in improving maximum urinary flow rates at 3 months and longest follow-up postoperatively.

TURP is more effective than TUMT in improving quality of life scores at 24 months post operatively.

There is no statistically significant difference between TURP and TUMT in

improving quality of life scores at 3, 6, 12, 36, 48 or 60 months.

There is no statistically significant difference between TUMT and TURP in number of patients experiencing infection, blood transfusion, TUR syndrome, incontinence or mortality.

There is no statistically significant difference between TUMT and TURP in number of men experiencing retrograde ejaculation.

Significantly fewer men treated with TURP experienced reoperations compared to TUMT.

Significantly fewer men treated with TURP experienced acute retention compared to TUMT.

Significantly fewer men treated with TUMT experienced strictures compared to TURP.

Economic TURP is more cost-effective than TUMT in men with severe symptoms. This evidence has minor limitations and direct applicability.

Neither TUMT nor TURP are cost-effective in men with moderate symptoms (see 8.5.1.2 and 8.14.1.2). This evidence has serious limitations and partial applicability.

8.5.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.5.3 TUMT vs. laser

The evidence for this can be found in section 0.

8.5.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.6 Transurethral vapourisation of prostate (TUVP)

8.6.1 TUVP vs. TURP

See Evidence Table 36, Appendix D, Forest Plots in Figures E-160 to E-166, Appendix E and Economic Evidence Table 53, Appendix D.

8.6.1.1 Clinical evidence

Table 8-129: TUVP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[83,113,175,194,237]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 6 months[79,83,113,237,257]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 1 year[64,83,92,113,237,257]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 2 years[79,92]	2	RCT	No serious limitations	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 3 years[92,257]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 5+ years[92,194,257]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[175]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Quality of life (IPSS question) at 6 months[79,257]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 1 year[64,92,257]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 2 years[79,92]	2	RCT	No serious limitations	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 years[92,257]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 5 years[92,257]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Qmax at 3 months [83,113,125,175,194,237,257]	7	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Qmax at longest follow up[64,83,92,113,194,194,257]	7	RCT	Serious limitations (a)	Serious Inconsistency (b)	No serious indirectness	Serious imprecision (c)
Blood transfusion[40,64,68,79,83,92,113,124,125,194,237,257]	13	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[64,83,92,124,125,194,257]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
UTI[68,92,113,124,175]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation[68,92,113,125,194]	5	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Urinary incontinence[83,92,113,124,175,261]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Reoperations[92,124,175,194,257]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
TUR syndrome [92,113,125,175,237,261]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Strictures[40,64,68,79,83,92,113,124,125,194,257,261]	12	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All cause mortality[64,92,257,261]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) *11 studies [40,68,83,113,125,175,194,201,237,257,261] do not report randomisation method. 11 studies [40,68,83,113,124,125,175,194,201,237,261] do not report allocation concealment. All studies except 1[92] do not report masked outcome assessment or it is unclear. 9 studies[40,68,79,124,175,201,237,257,261] have incomplete outcome data and do not report reasons for attrition. Standard deviations or p values for change from baseline at follow up are not reported in 2 studies[201,261]. 2 studies[175,257] have significant baseline differences in symptom score between groups and 1 study[175] also has significant baseline differences in Qmax between groups.*

(b) *Statistically significant heterogeneity is present which may be due to differences in treatment modality in terms of energy supplied for cutting and coagulation and differences in prostate size.*

(c) *Although sample sizes may be adequate to detect a minimally important difference (MID) for the primary outcomes (IPSS, Qmax & QoL), the confidence intervals are wide and cross or are close to the MID therefore making estimate of effect uncertain. Similarly although confidence intervals for some complication rates do not cross the MID and show appreciable benefit or harm, the sample sizes are not sufficient to meet the optimal information size criteria for these low event rates making the estimate of effect uncertain.*

Table 8-130: TUVP vs. TURP - Clinical summary of findings

Outcome	TUVP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	192	205	not applicable	MD -0.03 [-0.62 to 0.55]	Moderate
Symptom score at 6 months	276	292	not applicable	MD 0.34 [-0.14 to 0.82]	Moderate
Symptom score at 1 year	243	266	not applicable	MD 0.40 [-0.09 to 0.88]	Moderate
Symptom score at 2 years (a)	137	124	not applicable	MD -0.50 [-3.54 to -2.54]	Low
Symptom score at 3 years (a)	52	55	not applicable	MD -0.99 [-6.25 to 4.28]	Very Low
Symptom score at 5 years or longer	59	65	not applicable	MD -0.31 [-1.95 to 1.32]	Low
Quality of life (IPSS question) at 3 months	20	20	not applicable	MD -0.40 [-3.49 to 2.69]	Very Low
Quality of life (IPSS question) at 6 months	140	145	not applicable	MD 0.48 [0.14 to 0.82]	Low
Quality of life (IPSS question) at 1 year (a)	108	120	not applicable	MD 0.04 [-0.52 to 0.59]	Very Low
Quality of life (IPSS question) at 2 years (a)	136	127	not applicable	MD -0.25 [-0.94 to 0.43]	Low
Quality of life (IPSS question) at 3 years	52	55	not applicable	MD -0.48 [-0.93 to -0.03]	Low
Quality of life (IPSS question) at 5 years or longer	38	42	not applicable	MD -0.30 [-0.82 to 0.23]	Very Low
Qmax at 3 months	241	250	not applicable	MD -0.52 [-1.15 to 0.11]	Low
Qmax at long term follow-up	217	239	not applicable	MD -0.16 [-1.58 to 1.26]	Very low
Blood transfusion	2/536 (0.4%)	29/566 (5.1%)	RR: 0.19 [0.08 to 0.44]	41 fewer from 29 fewer to 47 fewer	Low
Urinary retention	26/291 (8.9%)	8/316 (2.5%)	RR: 3.10 [1.53 to 6.29]	52 more from 13 more to 132	Low
UTI	13/154 (8.4%)	14/160 (8.8%)	RR: 0.97 [0.48 to 1.98]	3 fewer from 46 fewer to 86 more	Low
Retrograde ejaculation (a)	68/171 (39.8%)	70/174 (40.2%)	RR: 0.97 [0.54 to 1.73]	12 fewer from 185 fewer to 294 more	Very Low
Urinary incontinence	10/301 (3.3%)	5/329 (1.5%)	RR: 2.29 [0.79 to 6.60]	19 more from 3 fewer to 84 more	Low
Reoperations	7/185 (3.8%)	7/198 (3.5%)	RR: 1.05 [0.41 to 2.72]	2 more from 21 fewer to 60 more	Low
TUR syndrome	3/266 (1.1%)	6/278 (2.2%)	RR: 0.59 [0.17 to 2.12]	9 fewer from 18 fewer to 25 more	Low
Strictures	80/578 (13.8%)	77/620 (12.4%)	RR: 1.09 [0.87 to 1.37]	11 more from 16 fewer to 46 more	Low
All cause mortality	6/221 (2.7%)	8/239 (3.3%)	RR: 0.82 [0.33 to 2.08]	6 fewer from 22 fewer to 36 more	Low

(a) *Outcomes analysed using random effects analysis.*

8.6.1.2 Economic evidence

We found three economic studies[79,140,175] comparing TUVP with TURP. One of those[79] was excluded because it did not report any cost figures. The study from Nathan and Wickham[175] is a UK cost-consequences analysis conducted alongside a RCT with some limitations while the decision model[140] was of good quality and directly applicable to the NHS setting. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-131: TUVP vs. TURP- Economic study characteristics

Study	Limitations	Applicability	Other Comments
NATHAN1996[175]	Serious limitations (a)	Directly applicable	
LOURENCO2008[140]	Minor limitations (b)	Directly applicable	

(a) *Cost components were only those that significantly differed between interventions. Short follow-up does not capture treatment failure.*

(b) *Capital cost of TUVP was not included. Duration and cost of operations were equal in all the strategies. Training costs were not included.*

Table 8-132: TUVP vs. TURP - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects	ICER	Uncertainty
NATHAN1996[175]	- 643 (a)	TUVP was more effective at improving IPSS, IPSS QoL, and Qmax (b)	Not applicable	Not reported
LOURENCO2008[140]	- 22 (c)	-0.0005 QALYs (c)	TURP vs. TUVP £44,000/QALY (c)	Not reported (d)

(a) *Costs included are cost of interventions and hospital stay.*

(b) *Statistical significance not reported.*

(c) *Results for single intervention strategies. TUVP followed by HoLEP in case of treatment failure is the most cost-effective strategy and dominates TURP.*

(d) *Sensitivity analysis not reported for this comparison. At the threshold of £20,000/QALY, TUVP followed by HoLEP has a probability of being cost-effective of about 80%.*

8.6.1.3 Evidence statement (s)

Clinical

There is no statistically significant difference between TUVP and TURP in improving symptonm score at any follow up interval.

TURP is more effective than TUVP in improving quality of life (IPSS question) at 6 months and 3 years follow up.

There is no statistically significant difference between TUVP and TURP in improving quality of life (IPSS question) at 3 months, 1 year, 2 years and 5 years or longer follow up.

There is no statistically significant difference between TUVP and TURP in improving Qmax.

Significantly more men treated with TUVP than TURP experience urinary retention.

Significantly more men treated with TURP than TUVP required blood transfusions.

There is no statistically significant difference between TUVP and TURP in number of men experiencing UTI, incontinence, retrograde ejaculation, TUR syndrome or strictures.

Economic

TUVP is more cost-effective than TURP. This evidence has minor limitations and direct applicability.

8.6.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.6.2 Bipolar TUVP vs. TURP

See Evidence Table 37, Appendix D, Forest Plots in Figures E-167 to E-169, Appendix E.

8.6.2.1 Clinical evidence

Table 8-133: Bipolar TUVP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Symptom score at 6 months[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Symptom score at 1 year[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Symptom score at 2 years[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Symptom score at 3 years[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Qmax at 3 months[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Qmax at 3 years[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Blood transfusion[102,116]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[63,102]	2	RCT	No serious limitations	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
UTI	0					
Retrograde ejaculation[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Urinary incontinence	0					
Complications: reoperations	0					
TUR[116]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Strictures[102,116]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All cause mortality	0					
Quality of life (IPSS question)	0					

(a) *One study [116] does not report randomisation method or allocation concealment. 2 studies [63,116] do not report masking of outcome assessment. 2 studies [102,116] do not report complete outcome data or it is unclear. Data*

(b) *Statistically significant heterogeneity is present which may be due to differences in treatment modality in terms of energy supplied, differences in prostate size or variations in perioperative practice in difference countries.*

(c) *Sample size is not adequate to detect a minimally important difference (MID) for the primary outcomes (IPSS, Qmax & QoL) and the confidence intervals are wide, crossing or close to the MID therefore making estimate of effect uncertain. Similarly although confidence intervals for some complication rates do not cross the MID and show appreciable benefit or harm, the sample sizes are not sufficient to meet the optimal information size criteria for these low event rates making the estimate of effect uncertain.*

Table 8-134: Bipolar TUVP vs. TURP - Clinical summary of findings

Outcome	Bipolar TUVP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	38	37	not applicable	MD -4.00 [-5.43 to -2.57]	Very Low
Symptom score at 6 months	38	37	not applicable	MD -4.00 [-5.20 to -2.80]	Very Low
Symptom score at 1 year	38	37	not applicable	MD -5.00 [-7.89 to -2.11]	Very Low
Symptom score at 2 years	25	15	not applicable	MD 1.90 [1.09 to 2.71]	Very Low
Symptom score at 3 years	25	15	not applicable	MD 1.90 [1.08 to 2.72]	Very Low
Qmax at 3 months	38	37	not applicable	MD -1.00 [-1.97 to -0.03]	Very Low
Qmax at 3 years	25	15	not applicable	MD -7.40 [-9.27 to -5.53]	Very Low
Blood transfusion	0/119 (0%)	6/116 (5.2%)	RR: 0.14 [0.02 to 1.11]	45 fewer from 51 fewer to 6 more	Low
Urinary retention	11/111 (9.9%)	3/100 (3.0%)	RR: 2.01 [0.14 to 28.04]	30 more from 26 fewer to 811 more	Low
Retrograde ejaculation	31/38 (81.6%)	32/37 (86.5%)	RR: 0.94 [0.77 to 1.15]	52 fewer from 199 fewer to 130 more	Very Low
TUR	0/38 (0%)	0/37 (0%)	not estimable	not estimable	Very Low
Strictures	3/119 (2.5%)	4/116 (3.4%)	RR: 0.73 [0.17 to 3.17]	9 fewer from 28 fewer to 74 more	Low
Catheterisation time (days)	38	37	not applicable	MD -1.30 [-1.68 to -0.92]	Very Low
Length of Stay (days)	119	116	not applicable	MD -0.84 [-1.73 to 0.04]	Very Low

8.6.2.2 Economic evidence

No economic studies were identified.

8.6.2.3 Evidence statement (s)

Clinical Bipolar TUVP is more effective than TURP in improving symptom score at 3 months, 6 months and 1 year follow up.

Bipolar TUVP is less effective than TURP in improving symptom score at 2 and 3 years follow up.

Bipolar TUVP is less effective than TURP in improving Qmax at 3 months and 3 years follow up.

There is no statistically significant difference between Bipolar TUVP and TURP in number of men requiring transfusion though the result is borderline in favour of Bipolar TUVP.

There is no statistically significant difference between Bipolar TUVP and TURP in the number of patients experiencing urinary retention, retrograde ejaculation, TUR syndrome or strictures.

Catheterisation time (days) is significantly shorter for those men treated with Bipolar TUVP compared to TURP.

There is no statistically significant difference between Bipolar TUVP and TURP in length of stay (days) though the result is borderline in favour of Bipolar TUVP.

Economic No economic studies were identified.

8.6.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15

8.6.3 TUVP vs. Laser

The evidence for this is in section 8.4.4.4.

8.6.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.7 Transurethral needle ablation (TUNA)

8.7.1 TUNA vs. TURP

See Evidence Table 38, Appendix D, Forest Plots in Figures E-170 to E-173, Appendix E and Economic Evidence Table 53, Appendix D.

Four RCTs comparing TUNA against TURP were found[46,97,99,119].

8.7.1.1 Clinical evidence

Table 8-135: TUNA vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months [46]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 6 months	0	RCT				
Symptom score at 12 months[97]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Symptom score at 18 months[46]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 2 years[97]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 3 years[97]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 4 years[97]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score at 5 years[97]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Quality of life (IPSS question) at 3 months [46]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life (IPSS question) at 18 months [46]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax- 3 months[46]	1	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax-Longest available follow up[46,97,99]	3	RCT	Very serious limitations(a)	No serious inconsistency	No serious indirectness	No serious imprecision
All cause mortality[99]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Blood transfusion[46,99,119]	3	RCT	Serious limitations(a)	Very serious inconsistency(c)	No serious indirectness	No serious imprecision
TUR syndrome	0	RCT				
Urinary retention (acute) [46,97,99]	3	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary tract infection[99,119]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary incontinence[46,97,99,119]	4	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Retrograde ejaculation[46,97,119]	3	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	No serious imprecision
Urinary stricture[97,119]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Reoperation[97,119]	2	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a) *One study described randomisation allocation but not concealment [97]. Some studies did not describe randomisation allocation [46,119] and concealment [46,97,119]. One study had unaccounted imbalance of sample size between the two comparison arms, i.e. no descriptions of drop outs or number randomised [46]. One study had high drop out rates after 1 year and not accounted for beyond 1 year [97].*

(b) *Sample size in study not powered to detect a minimally important difference (MID) in outcomes. Confidence interval included no difference between two arms, minimal important difference (MID) or relative risk of 0.75 to 1.25*

(c) *The number of blood transfusion in the TURP arm was 18.8% in a foreign language study where the criteria for blood transfusion is unknown[120] and 13.6% % in the other study included [99]. This is much higher than reported in the National Prostatectomy Audit reported a rate of 7.6% for two or more units of blood transfused after TURP [67].*

Table 8-136: TUNA vs. TURP - Clinical summary of findings

Outcome	TUNA	TURP	Relative risk	Absolute effect	Quality
Symptom Score at 3 months	26	33	Not applicable	MD 0.8 [-0.66 to 2.26]	Very Low
Symptom score at 6 months	0	0	Not applicable		No Data
Symptom score at 12 months	56	44	Not applicable	MD 3.9 [1.25 to 6.55]	Low
Symptom score at 18 months	26	33	Not applicable	MD -0.1 [-1.47 to 1.27]	Very Low
Symptom score at 2 years	43	35	Not applicable	MD 5.5 [2.17 to 8.83]	Low
Symptom score at 3 years	38	31	Not applicable	MD 5.1 [1.36 to 8.84]	Low
Symptom score at 4 years	24	21	Not applicable	MD 5.6 [1.3 to 9.9]	Very Low
Symptom score at 5 years	18	22	Not applicable	MD -0.1 [-4.25 to 4.05]	Very Low
Quality of life (IPSS question) at 3 months	26	33	Not applicable	0.20 [-0.06 to 0.46]	Very Low
Quality of life (IPSS question) at 18 months	26	33	Not applicable	0.10 [-0.11 to 0.31]	Very Low
Qmax- 3 months	26	33	Not applicable	MD -6.4 [-8.9 to -3.9]	Very Low
Qmax-Longest available follow up	58	67	Not applicable	MD -6.82 [-8.64 to -5]	
All cause mortality (follow-up 18 months)	0/25 (0%)	0/25 (0%)	Not estimable	Not estimable	Very Low
Blood transfusion	0/146 (0%)	22/156 (14.1%)	RR 0.05 [0.01 to 0.32]	134 fewer [96 to 140 fewer]	Very Low
Urinary retention (acute)	5/146 (3.4%)	4/156 (2.6%)	RR 1.25 [0.37 to 4.24]	6 more per 1000 [16 fewer to 84 more]	Low
Urinary tract infection	14/120 (11.7%)	11/123 (8.9%)	RR 1.32 [0.63 to 2.78]	28 more per 1000 [33 fewer to 158 more]	Low
Urinary incontinence	8/211 (3.8%)	19/212 (9%)	RR 0.42 [0.2 to 0.91]	52 fewer per 1000 [8 to 72 fewer]	Low
Retrograde ejaculation	5/191 (2.6%)	78/190 (41.1%)	RR 0.08 [0.03 to 0.17]	378 fewer per 1000 [341 to 399 fewer]	Moderate
Urinary stricture	1/165 (0.6%)	9/157 (5.7%)	RR 0.15 [0.03 to 0.82]	48 fewer per 1000 [10 to 55 fewer]	Very Low
Reoperation	9/165 (5.5%)	1/157 (0.6%)	RR 7.75 [1.01 to 59.33]	41 more per 1000 [0 to 350 more]	Very Low

8.7.1.2 Economic evidence

We found two economic studies[163,245] comparing TUNA with TURP. The decision model[163] of the report for the Australian Medicare Services Advisory Committee (MSAC) application was a cost-utility analysis of good quality, while the second study[245] was a cost-consequences analysis from the USA. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-137: TUNA vs. TURP- Economic study characteristics

Study	Limitations	Applicability	Other Comments
MSAC2002[163]	Minor limitations (a)	Partially applicable (b)	Report prepared from the University of Sydney for the MSAC
STOVSKY2006[245]	Minor limitations (c)	Partially applicable (d)	All the authors had financial interest and/or relationship with Laserscope.

(a) *Utilities were obtained from expert opinion and not elicited with recognised methods.*
(b) *Study conducted in Australia.*
(c) *Discount rate not reported; statistical significance not reported.*
(d) *USA Medicare perspective.*

Table 8-138: TUNA vs. TURP - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects	ICER	Uncertainty
MSAC2002[163]	£696 (a, b)	- 0.213 QALYs	TURP dominant	TUNA is cost-effective when either: - probability that TURP fails within 6 months ≥20%; - time horizon = 5 years; - annual failure rate of TUNA ≤ 2.4%; - probability of having TURP after TUNA fails is 100%
STOVSKY2006[245]	£807 (c, d)	TURP was more effective at improving IPSS, IPSS QoL, and Qmax (e, f)	TURP dominant	Not reported (g)

(a) *Includes the cost of procedures, side effects, treatment failure (GP visits, surgery, hospitalization, medical treatment)*
(b) *GBP calculated using the PPP 1AUD = 1.992 GBP*
(c) *Includes the cost of intervention, follow-up care, retreatment and adverse events (incontinence, UTI, impotence, dysuria/irritative voiding, bladder neck stenosis/stricture, urinary retention, hematuria)*
(d) *GBP calculated using the PPP 1USD = 1.550 GBP*
(e) *Statistical significance not reported*
(f) *Clinical outcomes obtained from the AUA Guidelines*[12]
(g) *Sensitivity analysis not reported for this comparison*

8.7.1.3 Evidence statement (s)

Clinical TUNA is less effective than TURP in improving symptoms scores at 12 months and 2, 3 and 4 years post-operatively.

There is no statistically significant difference between and TUNA and TURP in improving symptom scores at 3, 18 months and 5 years.

There is no statistically significant difference between TUNA and TURP in improving quality of life scores (IPSS question) at 3 and 18 months.

TUNA is less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up postoperatively.

There is no statistically significant difference between TUNA and TURP in all cause mortality or number of patients who experienced urinary retention or urinary tract infections.

Fewer men treated with TUNA compared to TURP experienced blood transfusion, strictures, retrograde ejaculation or urinary incontinence.

More men treated with TUNA compared to TURP had reoperations.

Economic TURP is more effective and less costly than TUNA. This evidence has minor limitations but it is partially applicable.

8.7.2 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.8 Transurethral incision of the prostate (TUIP)

8.8.1 TUIP vs. TURP

See Evidence Table 39, Appendix D, Forest Plots in Figures E-174 to E-178, Appendix E.

Eleven studies which compared the TUIP against TURP were indentified [62,95,106,128,133,188,215,217,228,242,250]. One of these studies was conducted solely in patients with acute urinary retention (AUR) and analysed separately[133].

8.8.1.1 Clinical evidence

Table 8-139: TUIP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom Score at 3 months [217]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Symptom Score at 6 months[217]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Symptom Score at 12 months	0	0				
Symptom Score at 24 months[250]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Quality of life (IPSS question) at 24 months[250]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Qmax- at 3 months[215,217]	2	RCT	Serious limitations (a),(b)	Serious inconsistency(c)	No serious indirectness	Serious imprecision (d)
Qmax at longest follow up[95,215,217,228,250]	5	RCT	Serious limitations (a),(b)	Serious inconsistency(c)	No serious indirectness	Serious imprecision (d)
All cause mortality[106,188,215,242]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(d)
Blood transfusion[62,95,106,188,217,242,250]	7	RCT	Serious limitations (a), (b)	No serious inconsistency	Serious indirectness (e)	No serious imprecision
TUR syndrome[242]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(d),
Urinary retention[95,106,188,242]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(d)
UTI [95,128]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Urinary incontinence[95,242]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(d)
Retrograde ejaculation[62,95,128,215,217,228,242,250]	8	RCT	Serious limitations (a),(b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision
Urinary stricture[62,95,188,242]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(d)
Reoperation[62,106,188,215,217,228]	6	RCT	Serious limitations (a),(b)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *All studies, except one [188], did not describe randomisation allocation methods. All studies did not describe allocation concealment methods, or masking the treatment to investigators, outcomes assessors or patients.*

(b) *The details of intervention methods are unknown for a foreign language study [217].*

(c) *There was serious unexplained heterogeneity in the pooled results*

(d) *Downgraded when sample size of pooled outcomes were smaller than required to detect a minimal important difference(ie smaller than OIS)or confidence interval cross minimal important difference (MID).*

(e) *Some studies reported blood transfusion rates which did not reflect the rates in usual practice. One study reported 80% [188], and another study reported 38/110(34%)[242]. This is much higher than reported in the National Prostatectomy Audit reported a rate of 7.6% for two or more units of blood transfused after TURP [67].*

Table 8-140: TUIP vs. TURP - Clinical summary of findings

Outcome	TUIP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	20	21	Not applicable	MD -0.5 [-3.35 to 2.35]	Low
Symptom score at 6 months	20	21	Not applicable	MD 2 [-1.17 to 5.17]	Low
Symptom score at 24 months	50	50	Not applicable	MD -1 [-1.73 to -0.27]	Low
Quality of life (IPSS question) at 24 months	50	50	Not applicable	MD 0.2 [0.01 to 0.39]	Low
Qmax at 3 months	62	65	Not applicable	MD -1.39 [-9.54 to 6.76]	Low
Qmax at longest available follow up	130	134	Not applicable	MD -2.25 [-4.68 to 0.17]	Low
All cause mortality	16/238 (6.7%)	12/233 (52.0%)	RR 1.24 [0.62 to 2.46]	12 more per 1000 [20 fewer to 76 more]	Low
Blood transfusion	1/287 (0.3%)	65/292 (22.3%)	RR 0.05 [0.02 to 0.15]	212 fewer per 1000 [190 to 219 fewer]	Moderate
TUR syndrome	0/110 (0%)	7/110 (6.4%)	RR 0.07 [0 to 1.15]	60 fewer per 1000 [64 fewer to 10 more]	Low
Urinary retention (acute)	12/188 (6.4%)	5/190 (2.6%)	RR 2.28 [0.86 to 6.08]	33 more per 1000 [4 fewer to 132 more]	Low
Urinary tract infection	2/30 (6.7%)	3/31 (9.7%)	RR 0.63 [0.12 to 3.35]	36 fewer per 1000 [85 fewer to 228 more]	Low
Urinary incontinence	2/134 (1.5%)	5/135 (3.8%)	RR 0.46 [0.1 to 2.01]	20 fewer per 1000 [33 fewer to 37 more]	Low
Retrograde ejaculation	48/209 (23%)	96/198 (67.4%)	RR 0.42 [0.24 to 0.75]	281 fewer per 1000 [121 to 369 fewer]	Low
Urinary stricture	6/174 (3.4%)	8/179 (4.5%)	RR 0.82 [0.32 to 2.1]	8 fewer per 1000 [31 fewer to 49 more]	Low
Reoperation	39/197 (19.8%)	16/195 (8.2%)	RR 2.37 [1.38 to 4.07]	112 more per 1000 [31 to 252 more]	Moderate

8.8.1.2 Economic evidence

No economic studies were identified.

8.8.1.3 Evidence statement (s)

Clinical

There is no statistically significant difference between TUIP and TURP in improving symptom scores at 3 and 6 months post operatively.

TUIP is significantly more effective than TURP in improving symptom scores at 24 months post operatively.

There is no data for TUIP compared TURP at 12 months, or beyond 24 months post operatively in improving symptom scores.

TUIP is less effective than TURP in improving quality of life scores at 24 months post operatively.

There is no data for TUIP compared to TURP in improving quality of life scores at 3, 6, 12, 36, 48 or 60 months post operatively.

There is no significant difference between TUIP and TURP in

improving flow rate (Qmax) at 3 months post operatively.

There is no significant difference between TUIP and TURP in improving peak flow rate (Qmax) at the longest available follow up period reported.

There is no statistically significant difference between TUIP and TURP in all cause mortality, number of patients experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

Significantly fewer men treated with TUIP compared to TURP required blood transfusions or experienced retrograde ejaculations.

More men treated with TUIP compared to TURP had reoperations.

Economic No economic studies were identified.

8.8.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.8.2 TUIP vs. TURP for AUR patients

8.8.2.1 Clinical evidence

Table 8-141: TUIP vs. TURP for AUR patients – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
All cause mortality[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Blood transfusion[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(b)
TUR syndrome[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary retention (acute)[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary tract infection[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary incontinence[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Retrograde ejaculation	0	RCT				
Urinary stricture[133]	1	RCT	Serious Limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Reoperation	0					
Symptom score	0					
Quality of life (IPSS question)	0					
Qmax	0					

(a) No masking of investigators, patients, or outcomes assessors were reported.

(b) Sample size was too small to detect significance for rarer side-effects. Confidence interval crossed line of no effect or 0.75 to 1.25, making any conclusions of benefits or arms uncertain.

Table 8-142: TUIP vs. TURP for AUR patients - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
All cause mortality	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Blood transfusion	2/29 (6.9%)	13/30 (43.3%)	RR 0.16 [0.04 to 0.64]	364 fewer per 1000 [156 to 416 fewer]	Low
TUR syndrome	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Urinary retention (acute)	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Urinary tract infection	5/29 (17.2%)	13/30 (43.3%)	RR 0.4 [0.16 to 0.97]	260 fewer per 1000 [13 to 364 fewer]	Very Low
Urinary incontinence	1/29 (3.4%)	2/30 (6.7%)	RR 0.52 [0.05 to 5.4]	32 fewer per 1000 [64 fewer to 295 more]	Very Low
Urinary stricture	0/29 (0%)	1/30 (3.3%)	RR 0.34 [0.01 to 8.13]	22 fewer per 1000 [33 fewer to 235 more]	Very Low

8.8.2.2 Economic evidence

No economic studies were identified.

8.8.2.3 Evidence statement (s)

Clinical In men with AUR, there is no statistically significant difference between TUIP and TURP in all cause mortality, number of men experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

In men with AUR, significantly fewer men treated with TUIP compared to TURP required blood transfusions.

Economic No economic studies were identified.

8.8.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.8.3 TUIP vs. HoLEP

The evidence for this can be found in section 8.3.2.4.

8.8.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.9 Botulinum toxin in the prostate

8.9.1 Botulinum toxin in prostate vs. placebo

See Evidence Table 40, Appendix D, Forest Plots in Figures E180 to E-182, Appendix E.

8.9.1.1 Clinical evidence

Table 8-143: Botulinum toxin vs. placebo – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score - 1-month follow up [148]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Symptom score - 2-month follow up [148]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Qmax - 2- month follow up [148]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary incontinence[148]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
All cause mortality	0					
Blood transfusion	0					
Urinary retention (acute)	0					
Urinary tract infection	0					
Retrograde ejaculation	0					
Urinary stricture	0					
TUR syndrome	0					
Reoperation	0					

(a) *Only one very small RCT wqs found. It was a short term follow up (less than three months) and it was unclear whether all relevant adverse outcomes had been reported in this study.*

(b) *Very small sample size – 15 patients in each arm. Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (symptom score and peak urinary flow).*

Table 8-144: Botulinum vs. placebo - Clinical summary of findings

Outcome	*Botulinum toxin*	*Placebo*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score – 1-month follow up	15	15	Not applicable	MD -12.8 [-14.77 to -10.8]	Very Low
Symptom score – 2-month follow up	15	15	Not applicable	MD -15.3 [-17.16 to -13.44]	Very Low
Qmax - 2- month follow up	15	15	Not applicable	MD 6.7 [5.25 to 8.15]	Very Low
Urinary incontinence	0/15 (0%)	0/15 (0%)	Not applicable	No events	Very Low

8.9.1.2 Economic evidence

One economic study[111] was identified but it was then excluded because non-comparative.

8.9.1.3 Evidence statement (s)

Clinical Botulinum toxin injection is more effective than placebo in improving symptom scores at 1 and 2 months post injection.

Botulinum toxin injection is more effective than placebo in improving peak flow at the longest available follow up (2 months) post injection.

There is no data for botulinum toxin compared to placebo in improving symptom scores at 3, 6, 12, 18 or 24 months and beyond in improving peak flow rates (Qmax).

There are no events in urinary incontinence for botulinum toxin compared placebo.

Economic No economic studies were included.

8.9.2 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.10 Transurethral vaporesection of the prostate (TUVRP)

8.10.1 TUVRP vs. TURP

See Evidence Table 41, Appendix D, Forest Plots in Figures E-183 to E-188, Appendix E.

8.10.1.1 Clinical evidence

Table 8-145: TUVRP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[89,136]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 6 months[91,247]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Symptom score at 1 year[91,94]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 2 years[136]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[136]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 2 years[136]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 3 months[89,136]	2	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 2 years[136]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Blood transfusion[89,91,94,126,136,247]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[91,126,136,247]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
UTI[89]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Retrograde ejaculation[126,136,186]	3	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Urinary incontinence[89,91,94,126,136]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Reoperations[94,136]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
TUR[89,91,126,136,186,247]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Strictures[89,91,94,126,136,186,247]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All cause mortality[91]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

(a) *Only 1 study [89] reports randomisation method. None of the studies report allocation concealment or it is unclear. None of the studies report masking of outcome assessment or it is unclear. Only 2 studies [89,94] have complete follow up data. 2 studies [186,247] have significant baseline differences in symptom score, and 4 studies [89,94,126,247] have significant baseline differences in Qmax. 1 study [136] has unbalanced baseline patient numbers suggesting a problem with randomisation method and allocation procedure and there is also a high attrition rate for QoL and Qmax outcome measures.*

(b) *Statistically significant heterogeneity is present which may be due to differences in treatment modality in terms of energy supplied for cutting and coagulation and differences in prostate size.*

(c) *Although sample sizes may be adequate to detect a minimally important difference (MID) for the primary outcomes (IPSS, Qmax & QoL), the confidence intervals are wide and cross or are close to the MID therefore making estimate of effect uncertain. Similarly although confidence intervals for some complication rates do not cross the MID and show appreciable benefit or harm, the sample sizes are not sufficient to meet the optimal information size criteria for these low event rates making the estimate of effect uncertain.*

Table 8-146: TUVRP vs. TURP - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Symptom score at 3 months	65	58	not applicable	MD 0.17 [-0.59 to 0.92]	Very Low
Symptom score at 6 months (a)	84	84	not applicable	MD -0.68 [-1.98 to 0.62]	Low
Symptom score at 1 year	129	119	not applicable	MD -0.20 [-0.32 to -0.08]	Moderate
Symptom score at 2 years	42	30	not applicable	MD 0.60 [-0.72 to 1.92]	Very Low
Quality of life (IPSS question) at 3 months	36	26	not applicable	MD 0.20 [-0.11 to 0.51]	Very Low
Quality of life (IPSS question) at 2 years	36	26	not applicable	MD 0.20 [-0.13 to 0.53]	Very Low
Qmax at 3 months	52	49	not applicable	MD -0.77 [-2.08 to 0.53]	Very Low
Qmax at 2 years	29	21	not applicable	MD -1.60 [-3.37 to -0.17]	Very Low
Blood transfusion	7/296 (2.4%)	12/283 (4.2%)	RR: 0.57 [0.24 to 1.36]	18 fewer [32 fewer to 15 more]	Low
Urinary retention	6/178 (3.4%)	7/166 (4.2%)	RR: 0.72 [0.26 to 2.05]	12 fewer [31 fewer to 44 more]	Low
UTI	0/25 (0%)	0/25 (0%)	not estimable	not estimable	Low
Retrograde ejaculation	2/262 (0.8%)	2/249 (0.8%)	RR: 1.28 [0.78 to 2.08]	127 more [100 fewer to 491 more]	Very Low
Urinary incontinence	62/107 (57.9%)	46/101 (45.5%)	RR: 0.82 [0.14 to 4.88]	1 fewer [7 fewer to 31 more]	Low
Reoperations	11/137 (8.0%)	8/124 (6.5%)	RR: 1.12 [0.33 to 3.80]	8 more [44 fewer to 182 more]	Very Low
TUR	1/243 (0.4%)	3/229 (1.3%)	RR: 0.37 [0.06 to 2.29]	8 fewer [12 fewer to 17 more]	Low
Strictures	12/336 (3.6%)	15/321 (4.7%)	RR: 0.75 [0.36 to 1.57]	12 fewer [30 fewer to 27 more]	Low
All cause mortality	1/50 (2%)	0/50 (0%)	not estimable	not estimable	Low

(a) *Outcomes analysed using random effects analysis*

8.10.1.2 Economic evidence

One economic study [136] was identified but excluded because of poor quality and non-applicability.

8.10.1.3 Evidence statement (s)

Economic No economic studies were included.

8.10.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.10.2 Bipolar TUVRP vs. TURP

See Evidence Table 42, Appendix D, Forest Plots in Figures E-189 to E-192, Appendix E.

8.10.2.1 Clinical evidence

Table 8-147: B-TUVRP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life (IPSS question) at 3 months[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax at 3 months[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Blood transfusion	0					
Urinary retention[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
UTI[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
TUR syndrome[82]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Retrograde ejaculation	0					
Urinary incontinence	0					
Reoperations	0					
Strictures	0					
All cause mortality	0					

(a) *Allocation concealment is not reported and there is a serious lack of data in the Bipolar TUVRP arm where 8 patients did not receive their operation because of machine failure.*

(b) *Sample size is not adequate to detect a minimally important difference (MID) for the primary outcomes (IPSS, Qmax & QoL) and the confidence intervals are wide, crossing or close to the MID therefore making estimate of effect uncertain. Similarly although confidence intervals for some complication rates do not cross the MID and show appreciable benefit or harm, the sample sizes are not sufficient to meet the optimal information size criteria for these low event rates making the estimate of effect uncertain.*

Table 8-148: B-TUVRP vs. TURP - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score at 3 months	21	30	not applicable	MD -0.82 [10.02 to 8.38]	Very Low
Quality of life (IPSS question) at 3 months	21	30	not applicable	MD -0.99 [-2.38 to 0.40]	Very Low
Qmax at 3 months	21	30	not applicable	MD 1.86 [-8.91 to 12.63]	Very Low
Urinary retention	4/21 (19.0%)	3/30 (10.0%)	RR: 1.90 [0.47 to 7.64]	90 more [53 fewer to 664 more]	Very Low
UTI	4/21 (19.0%)	4/30 (13.3%)	RR: 1.43 [0.40 to 5.08]	57 more [80 fewer to 543 more]	Very Low
TUR syndrome	0/21 (0%)	0/30 (0%)	not applicable	MD -0.07 [-0.33 to 0.19]	Very Low

8.10.2.2 Economic evidence

No economic studies were identified.

8.10.2.3 Evidence statement (s)

Clinical There is no statistically significant difference between Bipolar TUVRP and TURP in improving symptom score from baseline at 3 months.

There is no statistically significant difference between Bipolar TUVRP and TURP in improving IPSS QoL score from baseline at 3 months.

There is no statistically significant difference between Bipolar TUVRP and TURP in improving Qmax from baseline at 3 months.

There is no statistically significant difference between Bipolar TUVRP and TURP in the number of men experiencing urinary retention, UTI and TUR syndrome.

Economic No economic studies were identified.

8.10.3 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.11 High intensity focused ultrasound (HIFU)

8.11.1.1 Clinical evidence

There were no studies retrieved.

8.11.1.2 Economic evidence

There were no studies retrieved.

8.11.2 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.12 Transurethral ethanol ablation of the prostate (TEAP)

8.12.1 TEAP vs. TURP

See Evidence Table 43, Appendix D, Forest Plot in Figure E-193, Appendix E.

8.12.1.1 Clinical evidence

Table 8-149: TEAP vs. TURP– Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score	0	RCT				
Quality of life (IPSS question)	0	RCT				
Qmax	0	RCT				
Blood transfusions[120]	1	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	No serious imprecision
Urinary retention[120]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary tract infection[120]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Stricture[120]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence[120]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All cause mortality	0					
TUR syndrome	0					
Reoperation	0					
Retrograde ejaculation	0					

(a) *This was a foreign language study [120] included in the HTA report [140]. Randomisation allocation, concealment and blinding were rated as "unclear". At baseline, it was likely that patients in the TURP group have significantly more severe conditions than the TEAP group: larger prostate size, higher IPSS score and lower peak flow rate. No standard deviations or standard errors were reported for the baseline and follow up values for these outcomes values. See Evidence Table 43, Appendix D.*

(b) *The blood transfusion rate reported in this study, 19% was noted to be different from the usual rates observed in the UK practice. No criteria for initiating blood transfusion in were reported in this study.*

(c) *Sample size was too small to detect rarer side-effects. The confidence interval of effect size crossed both benefits and harms, or minimal important difference (MID).*

Table 8-150: TEAP vs. TURP - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Blood transfusions	0/94 (0%)	19/101 (18.8%)	RR 0.03 [0 to 0.45]	182 fewer per 1000 [103 to 188 fewer]	Low
Urinary retention	2/94 (2.1%)	4/101 (4%)	RR 0.54 [0.1 to 2.87]	18 fewer per 1000 [36 fewer to 75 more]	Low
Urinary tract infection	5/94 (5.3%)	7/101 (6.9%)	RR 0.77 [0.25 to 2.34]	16 fewer per 1000 [2 fewer to 92 more]	Low
Urinary Stricture	0/94 (0%)	5/101 (5%)	RR0.1 [0.01 to 1.74]	45 fewer per 1000 [50 fewer to 37 more]	Low
Urinary incontinence	0/94 (0%)	4/101 (4%)	RR 0.12 [0.01 to 2.19]	35 fewer per 1000 [40 fewer to 48 more]	Low

8.12.1.2 Economic evidence

No economic studies were identified.

8.12.1.3 Evidence statement (s)

Clinical No studies report symptom score, quality of life or peak flow (Qmax) for TEAP compared to TURP at any time point of follow up.

Significantly fewer men had blood transfusions for TEAP compared to TURP.

There is no statistically significant difference between TEAP and TURP in number of men who experienced urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

Economic No economic studies were identified.

8.12.2 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.13 Open prostatectomy

8.13.1 Open prostatectomy vs. HoLEP

The evidence for this can be found in section 8.3.3.4.

8.13.1.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.13.2 Open prostatectomy vs. laser vapourisation

The evidence for this can be found in section 8.4.2.4.

8.13.2.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.13.3 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14 Transurethral resection of the prostate (TURP)

8.14.1 TURP vs. watchful waiting (WW)

See Evidence Table 44, Appendix D, Forest Plots in Figures E-194 to E-195, Appendix E and Economic Evidence Table 53, Appendix D.

8.14.1.1 Clinical evidence

Table 8-151: TURP vs. WW– Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score	0	RCT				
Quality of life (IPSS question)	0	RCT				
Qmax at 3 years[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
All cause mortality[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Blood transfusion[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
TUR syndrome	0	RCT				
Urinary retention (acute)[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary tract infection[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Urinary incontinence -at 3 years follow up[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Retrograde ejaculation	0	RCT				
Urinary stricture	0	RCT				
Reoperation/received surgery in watchful waiting group (3 years)[262]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *No randomisation allocation and concealment methods reported.*
(b) *Uncertainty in effect size estimate due to small sample size for relatively rare events. The confidence interval included both benefits and harms, relative risk of 0.75 to 1.25 or minimal important difference.*

Table 8-152: TURP vs. WW - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Qmax at longest available follow up(3 years)	280	276	Not applicable	MD 5.1 [3.71 to 6.49]	Moderate
All cause mortality	13/280 (4.6%)	10/276 (3.6%)	RR 1.28 [0.57 to 2.87]	10 more per 1,000 [15 fewer to 67 more]	Low
Blood transfusion	3/280 (1.1%)	0/276 (0%)	RR 6.9 [0.36 to 132.97]	0 more per 1000 [0 fewer to 0 more]	Low
TUR syndrome					No data
Re-catheterisation	9/280 (3.2%)	0/276 (0%)	RR 18.73 [1.1 to 320.24]	0 more per 1000 [0 more to 0 more]	Low
Urinary tract infection	2/280 (0.7%)	0/276 (0%)	RR 4.93 [0.24 to 102.2]	0 more per 1000 [0 fewer to 0 more]	Low
Urinary incontinence - at 3 years follow up	4/280 (1.4%)	4/276 (1.4%)	RR 0.99 [0.25 to 3.9]	0 fewer per 1000 [10 fewer to 41 more]	Low
Reoperation/received surgery in watchful waiting group (3 years)	26/280 (9.3%)	65/276 (23.6%)	RR 0.39 [0.26 to 0.6]	144 fewer per 1000 [94 to 175 fewer]	Moderate

8.14.1.2 Economic evidence

We found four economic studies[18,58,109,189] comparing TURP with watchful waiting. One study[18] was excluded because non-comparative, one study[109] because TURP and Open Prostatectomy were lumped together, and another study[189] because patients in the watchful waiting arm had actually received some conservative treatment. In the decision model by DiSantostefano et al. (2006)[58], the clinical data for both interventions were estimated from AHCPR Guidelines[154]. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 8-153: TURP vs. WW - Economic study characteristics

Study	Limitations	Applicability	Other Comments
DISANTOSTEFANO2006[58]	Minor limitations	Partially applicable (a)	

(a) *USA study*

Table 8-154: TURP vs. WW - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects	ICER (£/QALY)	Uncertainty
Moderate symptoms				
DISANTOSTEFANO2006[58]	2,642 (a, b, c)	-0.05 QALY (c)	WW is dominant (c)	Not reported (d)
Severe symptoms				
DISANTOSTEFANO2006[58]	2,626 (a, b, c)	0.68 QALY (c)	£3,862/QALY (c)	For a WTP=$50,000 TURP has 90% probability of being cost-effective.

(a) *GBP calculated using the PPP 1USD = 0.632GBP*
(b) *Costs include only direct medical costs and were calculated using databases.*
(c) *Results reported for the scenario where patients can switch treatment*
(d) *Sensitivity analysis not reported for this comparison.*

8.14.1.3 Evidence statement (s)

Clinical TURP is more effective than watchful waiting in improving Qmax at 3 years follow up.

Significantly more men were re-catheterised perioperatively for the TURP group compared to watchful waiting.

3.2% of men following TURP were re-catheterised.

Significantly fewer men had reoperation or received surgery for the TURP group compared to the watchful waiting group during the follow up period.

There is no significant difference between TURP and watchful waiting in the number of all cause mortality or number of men who experienced blood transfusions, urinary tract infections and urinary incontinence.

Economic TURP is not cost-effective in men with moderate symptoms but it is cost-effective in men with severe symptoms. This evidence has minor limitations and partial applicability.

8.14.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.2 Bipolar TURP vs. TURP

See Evidence Table 45, Appendix D, Forest Plots in Figures E-196 to E-199b, Appendix E.

8.14.2.1 Clinical evidence

Table 8-155: Bipolar TURP vs. TURP – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score at 3 months[230]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 6 months[119,230]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 1 year[17,69,105,195,230]	5	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Symptom score at 2 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 3 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptoms score at 4 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[230]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 6 months[230]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 1 year[17,69,105,230]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecsion
Quality of life (IPSS question) at 2 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 3 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question) at 4 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 3 months[26,230]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Qmax at 4 years[17]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Blood transfusion [54,69,101,105,165,195,200]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[54,69,101,105,165,195]	6	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
UTI[101,119,200,238]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Retrograde ejaculation	0					
Urinary incontinence[69,119,195]	3	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Reoperations[17,69,165,195]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
TUR syndrome [54,69,101,105,119,165,195,238]	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Strictures[17,26,69,101,119,195,230,238]	8	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All cause mortality[69]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

(a) *3 studies [69,119,195] do not report randomisation method. 8 studies [54,69,101,119,165,195,230,238] do not report allocation concealment. 6 studies [54,69,101,119,165,195] do not report masking of outcome assessment. 2 studies [119,238] have incomplete or unclear follow up data. Standard deviations or p values for change from baseline at follow up are not reported in 3 studies[54,101,238], and 2 studies[165,200] have a very short follow up of ≤ 1 month and have no primary outcome data.*

(b) *Statistically significant heterogeneity is present which may be due to differences in treatment modality in terms of energy supplied for cutting and coagulation and differences in prostate size.*

(c) *The confidence intervals are wide and cross the MID therefore making estimate of effect uncertain. Similarly although the 95% CI for some complication rates do not cross the MI, the sample sizes were less than OISor these low event rates making the estimate of effect uncertain.*

Table 8-156: Bipolar TURP vs. TURP - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Symptom score at 3 months	24	24	not applicable	MD -1.30 [-4.26 to 1.66]	Low
Symptom score at 6 months	49	48	not applicable	MD 0.45 [-0.20 to 1.11]	Low
Symptom score at 1 year	227	228	not applicable	MD 0.06 [-0.38 to 0.50]	Moderate
Symptom score at 2 year	33	34	not applicable	MD -0.30 [-2.14, 1.54]	Low
Symptom score at 3 year	33	33	not applicable	MD 0.60 [-1.90, 3.10]	Low
Symptom score at 4 year	32	31	not applicable	MD 0.50 [-1.26, 2.26]	Low
Quality of life (IPSS question) at 3 months	24	24	not applicable	MD -0.30 [-0.92 to 0.32]	Low
Quality of life (IPSS question) at 6 months	24	23	not applicable	MD 0.00 [-0.60 to 0.60]	Low
Quality of life (IPSS question) at 1 year	203	202	not applicable	MD -0.03 [-0.23 to 0.17]	Moderate
Quality of life (IPSS question) at 2 years	33	34	not applicable	MD -0.10 [-1.29 to 1.09]	Low
Quality of life (IPSS question) at 3 years	33	33	not applicable	MD -0.10 [-0.71 to 0.51]	Low
Quality of life (IPSS question) at 4 years	32	31	not applicable	MD -0.10 [-0.96 to 0.76]	Low
Qmax at 3 months	58	57	not applicable	MD 0.38 [-6.05 to 4.25]	Low
Qmax at 4 years	32	31	not applicable	MD -1.40 [-4.93 to 2.13]	Low
Blood transfusion	8/426 (1.9%)	12/399 (3.0%)	RR: 0.62 [0.25 to 1.50]	11 fewer from 22 fewer to 15 more	Low
Urinary retention	12/373 (3.2%)	14/383 (3.7%)	RR: 0.90 [0.44 to 1.86]	4 fewer from 21 fewer to 32 more	Low
UTI	12/156 (7.7%)	13/158 (8.2%)	RR: 0.91 [0.44 to 1.92]	7 fewer from 46 fewer to 75 more	Low
Urinary incontinence	1/172 (0.6%)	3/175 (1.7%)	RR: 0.45 [0.07 to 3.02]	9 fewer from 16 fewer to 34 more	Low
Reoperations	2/297 (0.7%)	12/301 (4.0%)	RR: 0.32 [0.09 to 1.07]	27 fewer from 36 fewer to 3 more	Low
TUR	0/428 (0%)	7/438 (1.6%)	RR: 0.23 [0.05 to 1.07]	12 fewer from 15 fewer to 1 more	Low
Strictures	20/340 (5.9%)	14/345 (4.1%)	RR: 1.42 [0.74 to 2.71]	17 more from 11 fewer to 70 more	Low
All cause mortality	0/120 (0%)	0/120 (0%)	not estimable	not estimable	Very Low
Catheterisation time (days)	397	401	not applicable	MD -0.82 [-1.20 to -0.45]	Very Low
Length of Stay (days)	200	201	not applicable	MD -0.91 [-1.87 to -0.04]	Very Low

8.14.2.2 Economic evidence

No economic studies were identified.

8.14.2.3 Evidence statement (s)

Clinical There is no statistically significant difference between Bipolar TURP and TURP in improving symptom score at any follow up interval.

There is no statistically significant difference between Bipolar TURP and TURP in improving IPSS QoL score at any follow up interval.

There is no statistically significant difference between Bipolar TURP and TURP in improving Qmax at 3 months or 1 year follow up.

There is no statistically significant difference between Bipolar TURP and TURP in number of men requiring transfusion.

There is no statistically significant difference between Bipolar TURP and TURP in number of men experiencing urinary retention, UTI, incontinence or strictures.

There is no statistically significant difference between Bipolar TURP and TURP in number of men experiencing TUR syndrome though the result is borderline in favour of Bipolar TURP.

There is no statistically significant difference between Bipolar TURP and TURP in reoperation rate or mortality rate.

Economic No economic studies were identified.

8.14.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.3 TURP vs. TUVP

The evidence for this can be found in section 8.6.1.

8.14.3.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.4 TURP vs. TUNA

The evidence for this can be found in section 8.7.1.

8.14.4.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.5 LASER (coagulation and vapourisation) vs. TURP

The evidence for this can be found in section 8.4.1 and 8.4.2.

8.14.5.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.6 TURP vs. TUMT

The evidence for this can be found in section 8.5.1.4.

8.14.6.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.7 TURP vs. TUIP

The evidence for this can be found in section 8.8.1.

8.14.7.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.8 TURP vs. HoLEP

The evidence for this can be found in section 8.3.1.

8.14.8.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.9 TURP vs. TUVP

The evidence for this can be found in section 8.6.1.

8.14.9.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.10 TURP vs. Bipolar TUVP

The evidence for this can be found in section 8.6.1.4.

8.14.10.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.11 TURP vs. TUVRP

The evidence for this can be found in section 8.10.1.

8.14.11.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.12 TURP vs. Bipolar TUVRP

The evidence for this can be found in section 8.10.1.4.

8.14.12.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.14.13 TURP vs. TEAP

The evidence for this can be found in section 8.12.1.

8.14.13.1 Recommendations and link to evidence

See recommendations and link to evidence in section 8.15.

8.15 Recommendations and link to evidence

Recommendation	**If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a centre specialising in the technique.**
Relative values of different outcomes	IPSS, quality of life, flow and complications of transfusion and reoperation were considered the most important outcomes. Length of stay and catheterisation were also considered to be important outcomes for this comparison. Length of stay was considered an important outcome to reflect on recent improvements in surgery times.
Trade off between clinical benefits and harms	Effectiveness of HoLEP is equal to TURP but short-term adverse events and length of stay favor laser. TUVP has efficacy which is equivalent to TURP though the incidence of retention postoperatively may be higher.
Economic considerations	Our original economic model shows that the cost-effectiveness of TURP and HoLEP is similar as the sensitivity analysis shows that the results are very sensitive to small changes in parameters. Other economic evidence has shown that TUVP is more cost-effective than TURP and less cost-effective than HoLEP. However the cost-effectiveness of one over the other cannot be established with certainty and depends on factors that are likely to change from surgeon to surgeon (e.g operating time).
Quality of evidence	Studies included were on patients having a first surgery and without prior catheterisation, therefore not totally generalisable. The economic evidence has minor limitations and is directly applicable.
Other considerations	Feasibility of implementation would be a big issue for HoLEP. It was felt that patient preference could lean toward HoLEP as it is considered less invasive. Men with religious concerns or on anticoagulants should be offered HoLEP due to lower rates of blood transfusions compared to TURP. Few centres in the UK are currently able to offer HoLEP routinely and it is a difficult technique to learn. It involves learning to coagulate and resect tissue using the HoLEP laser – both techniques which are NOT recommended routinely by this guideline, and there is a learning curve associated with this. This is the reason for recommending that HoLEP should be performed only in centres which specialise in the technique. There are limited centres offering HoLEP in the UK. National organisations should investigate ways of facilitating expansion of this service with the appropriate training and mentoring process in place. This recommendation should be linked to patient information:

patients should be provided with appropriate information before making a decision.

TUVP is more directly comparable to TURP in terms of learning the surgical technique and requires no change in equipment other than different electrodes for the surgeon to be able to perform.

Recommendation	**Offer transurethral incision of the prostate (TUIP) as an alternative to TURP, TUVP or HoLEP to men with a prostate estimated to be smaller than 30 g.**
Relative values of different outcomes	IPSS, quality of life, flow and complications of transfusion and reoperation were considered the most important outcomes. Length of stay and catheterisation were also considered to be important outcomes for this comparison.
Trade off between clinical benefits and harms	The higher reoperation rates of TUIP may be justified if similar efficacy can be achieved in smaller glands with an operation that causes lower morbidity than TURP.
Economic considerations	The GDG did not expect the cost of TUIP to be any higher than the cost of TURP. Possibly the shorter length of stay and the lower likelihood of transfusions would make TUIP less costly. Therefore in men where this intervention is effective it is also cost-effective.
Quality of evidence	There is a high degree of uncertainty with the evidence reviewed (low to very low quality – further impact is very likely to have an important impact on our confidence of the estimate, or may change the estimate). Only a very small RCT with important study limitations was found. Holmium laser, instead of the usual TUIP procedures were used. No economic evidence was identified.
Other considerations	The majority of studies had an inclusion criterion of prostate size between 20 and 40 grams (only one was up to 60). We selected the mid point of 30 grams as a guide. However this is based on clinical expertise and the GDG appreciated that in clinical practice it will be based on experience.

Recommendation	**Offer open prostatectomy as an alternative to TURP, TUVP or HoLEP to men with prostates estimated to be larger than 80 g.**
Relative values of different outcomes	IPSS, quality of life, flow and complications of transfusion and reoperation were considered the most important outcomes. Length of stay and catheterisation were also considered to be important outcomes for this comparison.
Trade off between clinical benefits and harms	In men with very large prostates, standard TURP and other tissue ablative techniques take a long time to perform. The

	former may be complicated by increased blood loss and a higher risk of complications. In these circumstances the potential morbidity and longer hospital stay associated with open prostatectomy is felt to be justified by the improved efficacy.
Economic considerations	In men with very large prostate, open prostatectomy can reduce the operating time but increase the hospital length of stay.
Quality of evidence	One small study found OP to be more effective at improving quality of life than HoLEP at three months but this was not seen at later follow up periods. The GDG were uncertain about these results as patients following OP usually still have pain and continence problems at 3 months. As the group was uncertain about these results they recommended OP as an alternative surgery to HoLEP for men with larger prostates. No economic evidence was identified.
Other considerations	The studies had an inclusion criterion of prostate size more than 70 grams or more than 100grams. We selected the mid point of 80 grams as a guide. However this is based on clinical expertise and the GDG appreciated that in clinical practice it will be based on experience.

1

2

1

Recommendation	**If offering surgery for managing voiding LUTS presumed to be secondary to BPE, do not offer minimally invasive treatments (including transurethral needle ablation [TUNA], transurethral microwave thermotherapy [TUMT], high-intensity focused ultrasound [HIFU], transurethral ethanol ablation of the prostate [TEAP] and laser coagulation) as an alternative to TURP, TUVP or HoLEP.**
Relative values of different outcomes	IPSS, quality of life, flow and complications of transfusion and reoperation were considered the most important outcomes. Length of stay and catheterisation were also considered to be important outcomes for this comparison.
Trade off between clinical benefits and harms	Whilst these minimally invasive techniques offer potentially lower morbidity and shorter lengths of stay than conventional TURP or HoLEP, the current evidence suggests they are less effective and there is little evidence regarding long term outcomes, side effects or the economic evidence suggests that they are not cost effective.
Economic considerations	Both TUNA and TUMT are less cost-effective than TURP.
Quality of evidence	Almost all the studies in these procedures are not blinded, and did not report methods for randomisation allocation and concealment. These are important study limitations, especially when patient reported or subjective outcomes were considered. There are uncertainties in our confidence of the evidence – the quality of ranged from moderate to very low. The economic evidence on TURP compared to TUMT has minor limitations and direct applicability; while the economic evidence on TURP compared to TUNA has minor limitations and partial applicability.
Other considerations	None.

2

Recommendation	**If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer botulinum toxin as part of a clinical trial.**
Relative values of different outcomes	IPSS and quality of life were considered the most important outcomes. Urinary retention was thought to be an important complication.
Trade off between clinical benefits and harms	There is a simple trade off between improvement in symptoms and the risk of urinary retention but it is also important that patients are made aware of the still experimental nature of treatment with Botulinum Toxin and the remaining uncertainty about its long term effects.
Economic considerations	There is not enough evidence or cost data to comment on the cost-effectiveness of this intervention.
Quality of evidence	There is high degree of uncertainty with the evidence (low to

	very low quality – further impact is very likely to have an important impact on our confidence of the estimate, or may change the estimate). Only one very small RCT with a short-term follow up was found and it was unclear whether all relevant adverse outcomes had been reported in this study. No economic evidence was found.
Other considerations	There is a need for further research into the efficacy and safety of botulinum toxin in the treatment of male LUTS.

1

Recommendation	**If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer laser vapourisation[a], bipolar TUVP or monopolar or bipolar transurethral vapourisation resection of the prostate (TURVP) as part of a clinical trial.**
Relative values of different outcomes	IPSS, quality of life, flow and complications of transfusion and reoperation were considered the most important outcomes. Length of stay and catheterisation were also considered to be important outcomes for this comparison
Trade off between clinical benefits and harms	Although there are benefits to laser vapourisation in terms of shorter length of stay, the measures of effectiveness demonstrate lower effectiveness than for TURP. However, some men may be prepared to accept lower efficacy in return for reduced perioperative morbidity and shorter hospital stays.
Economic considerations	Laser vapourisation is not cost-effective compared to TURP.
Quality of evidence	One small study comparing laser vapourisation to OP found similar results but was conducted in men with larger prostates. The economic evidence has minor limitations and direct applicability.
Other considerations	The GDG felt that they could not recommend these procedures outside of research. NICE Interventional procedure (120) considered potassium-titanyl-phosphate (KTP) laser vapourisation to be a safe and efficacious procedure but research is necessary to understand its role compared with other treatments. There is uncertainty surrounding the effectiveness of laser vapourisation and GDG felt it was appropriate to recommend research on KTP laser vapourisation as one small study showed similar benefit to OP. Laser vapourisation had significantly

[a] Current evidence on the safety and short-term efficacy of potassium-titanyl-phophate (KTP) laser vaporisation of the prostate for benign prostatic obstruction appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance. (NICE interventional procedure guidance120). However, research is necessary to understand its role compared with other treatments.

longer operation time but shorter hospital stay and time to catheter removal than OP.

8.16 Supporting recommendations

Recommendation	**Offer surgery only to men with severe voiding symptoms, or men with voiding symptoms for whom drug treatment and conservative management options have been unsuccessful or are not appropriate. Discuss the alternatives to and outcomes from surgery.**
Trade off between clinical benefits and harms	The benefits of surgery are an improvement of symptoms and the harms are the complications associated with the procedure. The benefits outweigh the harms for men with severe symptoms or when medical treatment has not worked. Men with mild or moderate symptoms should try other options before surgical intervention.
Economic considerations	Surgical interventions are associated with high costs and should be offered only if other treatments have failed.
Other considerations	None.

8.17 Summary of recommendations

- Offer surgery only to men with severe voiding symptoms, or men with voiding symptoms for whom drug treatment and conservative management options have been unsuccessful or are not appropriate. Discuss the alternatives to and outcomes from surgery.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vapourisation of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a centre specialising in the technique.

- Offer transurethral incision of the prostate (TUIP) as an alternative to TURP, TUVP or HoLEP to men with a prostate estimated to be smaller than 30g.

- Offer open prostatectomy as an alternative to TURP, TUVP or HoLEP to men with prostates estimated to be larger than 80g.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, do not offer minimally invasive treatments (including transurethral needle ablation [TUNA], transurethral microwave thermotherapy [TUMT], high-intensity focused ultrasound [HIFU], transurethral ethanol ablation of the prostate [TEAP] and laser coagulation) as an alternative to TURP, TUVP or HoLEP.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer botulinum toxin as part of a clinical trial.

- If offering surgery for managing voiding LUTS presumed secondary to BPE, only offer laser vapourisation[b], bipolar TUVP or monopolar or bipolar transurethral vapourisation resection of the prostate (TURVP) as part of a clinical trial.

8.18 Research recommendations

8.18.1 Green light laser prostatectomy

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of green light laser prostatectomy compared to transurethral resection of the prostate (TURP) in men with moderate to severe bothersome LUTS considering surgery for bladder outlet obstruction?

Why this is important

The evidence base is inadequate to give clear guidance. This research would help plan future guidance on the use of green light laser prostatectomy for men with LUTS who are having surgery. The potential advantages of reduced blood loss, shorter hospital stay and earlier return to normal activities make Green Light Laser prostatectomy attractive to patients and healthcare providers although there is uncertainty around degree of symptom improvement and improvement in quality of life in the short and longer term. The study design should be a randomised controlled trial.

[b] Current evidence on the safety and short-term efficacy of potassium-titanyl-phophate (KTP) laser vaporisation of the prostate for benign prostatic obstruction appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance. (NICE Interventional Procedure 120). However, research is necessary to understand its role compared with other treatments.

9 Surgery for men with storage symptoms

9.1 Introduction

If conservative or pharmacological therapies have failed to control the storage symptoms suggestive of detrusor overactivity, currently often called 'overactive bladder', men who wish to pursue further action to relieve their symptoms may wish to be considered for surgical intervention. Surgery is performed with the aim of returning bladder storage and voiding function to as close to normal as possible. The reality of such surgery is that, in attempting to restore normality, it will frequently expose the patient both to perioperative risk and to new symptoms, and sometimes also to long term consequences. Surgeons and patients face the additional problem that, whilst there are several surgical options, the evidence base for most of them is, at best, very meagre.

Some of the procedures require only day-case admission, whilst others may require major surgery, with long hospital stays, risk of morbidity, and measureable mortality.

There is also a need for counselling of patients, where the pros and cons of each procedure are carefully reviewed and patients can discuss why further treatment is being considered and what it entails. In this occasion, patients are told of the lack of evidence relating to surgery, and about the uncertainties regarding long term outcomes and risks. In particular, in discussion with patients, surgeons should be able to provide information about outcomes in their own hands of the various options.

Procedures for Detrusor Overactivity

Where conservative therapy (with lifestyle change, bladder training or drugs) has been unsuccessful, there is a range of surgical interventions with different postulated mechanisms of action. The aims of such surgery may be to increase the capacity of the bladder, to alter or modulate its nerve supply and contractility, or to bypass the lower urinary tract completely. It is an inevitable consequence of all operations which aim to reduce bladder contractility or to increase bladder outlet resistance, that voiding difficulty may occur following surgery. For this reason, it is important to advise men before surgery about the possible need to do intermittent self catheterisation after their operation.

Cystoplasty

The aim of augmentation cystoplasty is to disrupt the ability of the overactive bladder to generate synchronous contractions (that allow the rises in detrusor pressure characteristic of detrusor overactivity). This is done by bivalving the overactive bladder wall, and then incorporating into it a segment of vascularised bowel, removed from continuity with the rest of the bowel. This also increases the capacity of the bladder. Many configurations of bowel segment have been used to achieve this, best known in the UK being the detubularised enterocystoplasty or "Clam" cystoplasty.

Intravesical botulinum toxin

Botulinum toxin is a potent neurotoxin derived from the bacterium *Clostridium botulinum*. Two strains are available for clinical use, types A and B. In striated muscle, botulinum toxin is known to block the release of acetylcholine and it will temporarily paralyse any muscle into which it is injected. The toxin may also significantly alter sensory neurotransmitter function. However, the precise mechanism of action when injected into the detrusor muscle is unknown. It can be injected directly into the bladder wall and this procedure can be performed on a day-case basis, under local anaesthesia, using a flexible cystoscope. There are currently two commonly used preparations of Botulinum Toxin A available in the UK, BOTOX® [Allergan Ltd] and Dysport® [Ipsen Ltd]. These have different formulations, and molecular structures; and safety and efficacy may also not be the same for both products. All the evidence in this guideline refers to BOTOX® [Allergan Ltd].

Neuromodulation

The term neuromodulation can apply to any method of electrical modulation of the sacral nerve root pathway involved in bladder function. This can be done by the application of external electrodes to appropriate dermatomes, temporary implantation of electrodes e.g. posterior tibial nerve stimulation, or by permanent implantation. Chronic stimulation of the S3 nerve roots directly has been achieved with permanently implantable sacral root stimulators. Patients first undergo a percutaneous nerve evaluation (PNE) in which a needle is inserted through the sacral foramina under local anaesthetic. This is connected

to an external stimulation source and left in place for a few days. Those who show satisfactory response to the PNE, may then proceed to a permanent implant.

Guidance on sacral nerve stimulation (SNS) for urgency incontinence and urgency-frequency was issued by the Interventional Procedures Programme of NICE, in 2004[180]. It states that: 'Current evidence on the safety and efficacy of sacral nerve stimulation for urge(ncy) incontinence and urgency-frequency appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance'.

Myectomy

The whole of the overactive detrusor muscle above the bladder "equator" is stripped from the underlying urothelium. The resulting bladder defect can be covered by application of a pedicle of greater omentum. In principle, the operation is expected to remove the overactive muscle which causes increased pressure and incontinence, replacing it with compliant tissue. It is a smaller operation than cystoplasty, because it does not require mobilization of a bowel segment and its incorporation into the bladder.

Procedures for Stress Incontinence

Stress incontinence in men most commonly occurs following radical prostatectomy for localised prostate cancer, but can also occur after surgical intervention for benign prostate disease, radiotherapy, pelvic injury and in neurological conditions. Surgical treatment with the artificial urinary sphincter is well established in clinical practice, but other techniques have been introduced recently. These with possibly the exception of injectables are currently undergoing evaluation and should be considered in light of this.

Male sling

The principle of male slings, as described by their innovators, varies from product to product. There are three main types:

- Polypropylene or silicone tapes which aim to compress the bulbar urethra gently, and are inserted through either a retropubic or transobturator route. Their effect is assumed to be a result of gentle compression and the creation of very modest degrees of urethral obstruction.

- Retrobulbar polypropylene tapes, inserted via a transobturator route, which aim to elevate retrobulbar tissues and "realign" the posterior component of the external sphincter mechanism.

- Broader meshes which are inserted through a perineal approach, but fixed to the pubic rami, purporting to provide support to the bulbar urethra.

This wide range of techniques, concepts and materials make comparison difficult and renders the evaluation of "slings" as a group potentially misleading. Some devices allow for adjustment of the sling tension after implantation

Injectables

There is a wide range of semifluid materials available for injection into tissue spaces where the materials provide a bulking effect. They have been extensively used in female stress incontinence and can also be applied in men with stress incontinence. Unfortunately, men who have undergone radical prostate surgery usually have significant scarring of tissues at the bladder neck. This makes it difficult for injected materials to achieve the same bulking effect that is possible in "virgin" tissues.

Implantable silicone balloons

Implantable silicone balloons have been developed which can be deployed into tissue spaces under radiological or ultrasound screening, and placed accurately close to the bladder neck. The inflated volume of the balloons can then be adjusted by means of injection of contrast material into a separate injection port located under the scrotal skin. Thus, in theory the amount of fluid can be either increased or decreased to achieve continence without voiding difficulty.

Artificial sphincter

The artificial urinary sphincter consists of an implanted inflatable cuff which is placed around the urethra, usually at the bulb and sometimes around the prostatic apex. This cuff is connected to a pressure regulating balloon and to an implanted pump. With the pump, the man can deflate the cuff to allow voiding to take place. The device is made from silicone and constructed in separate units which must be filled with contrast fluid and connected during surgery. Whilst the device provides a constant closure pressure in the urethra, it is unable to respond to changes in abdominal pressure, so transient high pressures will still result in leakage of urine. Recent modifications and alternative products may allow for conditional adjustment of the device and better response to transient pressure rises.

Procedures for intractable bladder symptoms

Some men with intractable bladder symptoms may wish to consider urinary diversion as an alternative to other forms of surgery.

In its simplest form, urinary diversion is achieved by the passage of a urethral or suprapubic catheter. Simple catheterisation carries relatively low risks, however in men with severe detrusor overactivity there may be continued feelings of urgency and even of leakage around an indwelling catheter.

The ileal conduit procedure uses an isolated, vascularised segment of distal ileum to create a conduit joined at one end to the ureters and at the other to create a permanent cutaneous stoma. Urine is collected in a stoma appliance worn on the abdominal wall. Other bowel segments can be used, including jejunum and colonic segments, but these are seldom done, and jejunum should not be used because of the hazards of metabolic derangement that its use causes. Like a cystoplasty, this is a major operation and requires incision of both the urinary and intestinal tracts. There are significant long term consequences, including parastomal hernia, stomal prolapse and fistula, infection and stone formation, and renal deterioration.

An alternative to an ileal conduit is continent urinary diversion. There are many different surgical techniques described to achieve the goal of a continent intra-corporeal storage reservoir, either by means of bladder augmentation or formation of a reservoir from intestine, together with a catheterisable channel through which the subject can empty the augmented bladder or reservoir.

9.2 Surgical treatments for men with storage symptoms

We searched for RCT evidence investigating the effectiveness of interventions compared to other interventions or to no treatment in men with lower urinary tract symptoms. The interventions we included in our search were cystoplasty, intravesical botulinium toxin, neuromodulation, sacral root stimulation, myectomy, male slings, injectables, diversion, artificial sphincter, adjustable compression devices and suprapubic catheters. We looked for any studies that compared the effectiveness of two or more of these interventions (or no treatment). We would include studies with mixed male and female populations if the results were reported separately.

9.2.1 What is the effectiveness and comparative effectiveness of surgery in reducing storage symptoms?

9.2.1.1 Clinical evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified.

9.2.1.2 Economic evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified.

9.2.1.3 Evidence statement (s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

9.3 Recommendations and link to evidence

Recommendation	**Consider offering cystoplasty to manage detrusor overactivity only to men whose symptoms have not responded to conservative management or drug treatment and are willing to self-catheterise. Before offering cystoplasty, discuss serious complications (that is, bowel disturbance, metabolic acidosis, mucus production and/or mucus retention in the bladder, urinary tract infection and urinary retention).**
Relative values of different outcomes	Symptom score, relief of incontinence, quality of life and serious adverse events (death, sepsis, retention, UTI, bowel dysfunction, mucus, metabolic problems small malignant risk) were considered primary outcomes.
Trade off between clinical benefits and harms	Cystoplasty is a major operation. Informed consent is essential. There is a high risk of both perioperative and long term complications. Whilst the primary problem of urgency incontinence may be relieved successfully, there is often a trade off with the development of new symptoms such as poor bladder emptying, recurrent infections, mucus production etc.
Economic considerations	This intervention is associated with high costs and should be offered only if other treatments have failed.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	Surgery of this magnitude requires clearly informed consent. It is essential that the patient understands the potential for development of serious complications and the significant change in quality of life that may occur.

Recommendation	**Consider offering bladder wall injection with botulinum toxin[a] only to men with detrusor overactivity whose symptoms have not responded to conservative management and drug treatment and who are willing to self-catheterise.**
Relative values of different outcomes	Symptom score, relief of incontinence, adverse events (pain, muscle weakness, transient UTI) and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	This is an apparently low risk day case procedure that can be performed under local anaesthetic. However the long term

[a] At the time of publication (July 2009), botulinum toxin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

	outcomes are unknown.
Economic considerations	This intervention is associated with high costs and should be offered only if other treatments have failed.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	Despite the lack of evidence this intervention is already in widespread unlicensed use because the alternatives for patients with intractable symptoms all include the risks of more major and complex surgery and unpredictable outcomes.

1

Recommendation	**Consider offering implanted sacral nerve root stimulation to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.**
Relative values of different outcomes	Symptom score, relief of incontinence, adverse events and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	The implantation involves surgery and it is inevitable that the batteries will fail and require further surgery to replace, even without any other complications occurring. The long term consequences of implantation remain unknown.
Economic considerations	This intervention is associated with high costs and should be offered only if other treatments have failed.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	Initial percutaneous skin testing helps to identify those patients who are most likely to benefit. This reversible prediction of outcome is very unusual in surgery and is a major advantage of the technique.

2

Recommendation	**Do not offer myectomy to men to manage detrusor overactivity.**
Relative values of different outcomes	Symptom score, relief of incontinence, adverse events and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	Myectomy involves major abdominal surgery and yet the outcomes are very poorly documented. It was felt by the GDG that this form of abdominal surgery could not be justified without robust evidence of there being a positive improvement in symptoms and quality of life, which does not currently exist.
Economic considerations	This intervention is associated with high costs. Considering the possible adverse events and the poor evidence on clinical outcomes, there are many doubts as to its cost-effectiveness.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	None.

3

Recommendation	**Consider offering intramural injectables, implanted adjustable compression devices and male slings[b] to manage stress urinary incontinence only as part of a clinical trial.**
Relative values of different outcomes	Symptom score, relief of incontinence, adverse events and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	The clinical benefits are that the stress urinary incontinence may be reduced or relieved, without recourse to the more major procedure of an artificial urinary sphincter operation. The possible harm is that this surgery might be ineffective and so the risks and delay entailed by ineffective surgery would be added to the risks of subsequent artificial urinary sphincter surgery
Economic considerations	This intervention is associated with high costs. Considering the poor evidence on clinical outcomes, there are many doubts as to its cost-effectiveness.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	NICE Interventional procedure (256) considered suburethral synthetic sling insertion to be a safe and efficacious procedure. However, research is necessary to understand its role compared with other treatments.

1

Recommendation	**Consider offering urinary diversion to manage intractable urinary tract symptoms only to men who symptoms have not responded to conservative management and drug treatments, and if cystoplasty or sacral root stimulation are not appropriate or unacceptable.**
Relative values of different outcomes	Symptom score, adverse events and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	Urinary diversion is major abdominal surgery with the potential for both serious perioperative and long term complications. The creation of a well functioning stoma reliably eliminates the problem of urinary incontinence though stoma and bag problems can be common and distressing.
Economic considerations	This intervention is associated with high costs and should be

[b] Current evidence on the safety and efficacy of suburethral synthetic sling[183] insertion for stress urinary incontinence in men appears adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance (NICE interventional procedure guidance 256). However, research is necessary to understand its role compared with other treatments.

	offered only if other treatments have failed.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	None

1

Recommendation	**Consider offering implantation of an artificial sphincter to manage stress urinary incontinence only to men whose symptoms have not responded to conservative management and drug treatments.**
Relative values of different outcomes	Symptom score, adverse events and quality of life were considered primary outcomes.
Trade off between clinical benefits and harms	Whilst the artificial sphincter is effective in men with stress incontinence it should only be offered to men who have not responded to conservative and pharmacological treatments, it requires surgery both for implantation and for any subsequent adjustment of the device. This is inevitable for most patients over time because of mechanical failure, infection or gradual return of incontinence.
Economic considerations	This intervention is associated with high costs and should be offered only if other treatments have failed.
Quality of evidence	No clinical or economic evidence was identified.
Other considerations	Operation of the device requires dexterity.

2

3

4 ## 9.4 Supporting recommendations

Recommendation	**Consider offering surgery only to men whose storage symptoms have not responded to conservative management and drug treatment. Discuss the alternatives of containment or surgery. Inform men being offered surgery that effectiveness, side effects and long-term risk are uncertain.**
Trade off between clinical benefits and harms	The effectiveness of surgical interventions should be balanced against their potential harm. Patients need to have realistic expectation about the uncertainty of benefits from surgery for storage symptoms and the risk of these invasive procedures. On the other hand patients may lose hope and feel that there are no other alternatives to improve their condition, or they may delay surgery.
Economic considerations	Surgical interventions are associated with high costs and should be offered only if other treatments have failed.
Other considerations	Reports of surgery have been almost exclusively for patients with urodynamically-proven detrusor overactivity so the GDG

therefore felt that surgery could only be recommended for this specific group of men with intractable overactive bladder symptoms. Most of these surgical techniques are performed quite rarely and, for this reason, the GDG would recommend that this type of surgery is only carried out in centres where adequate support facilities exist and where urologists have specialised and are experienced in surgery for these problems.

Recommendation	**If considering offering surgery for storage LUTS, refer men to a urologist to discuss:** • **the surgical and non-surgical options appropriate for their circumstances and** • **the potential benefits and limitations of each option, particularly long-term results**
Trade off between clinical benefits and harms	The benefits from a methodical approach to patient counselling as suggested are that unnecessary surgery will be much less likely, and so less harm will result from unnecessary surgery.
Economic considerations	Referring patients to a urologist has an opportunity cost but this is offset by the unnecessary interventions averted.
Other considerations	Surgery for storage symptoms requires very careful patient assessment and detailed counselling which must be based on individual experience rather than evidence reported from the literature in non randomised trials. Only those surgeons who have taken a particular interest in these patients and procedures are likely to have the range of experience necessary to meet these criteria. It is recommended that surgeons should participate in national audit of complex incontinence procedures.

9.5 Summary of recommendations on surgery for patients with storage symptoms

- Consider offering surgery only to men whose storage symptoms have not responded to conservative managementt and drug treatment. Discuss the alternatives of containment or surgery. Inform men being offered surgery that effectiveness, side effects and long-term risks are uncertain.

- If considering offering surgery for storage LUTS, refer men to a urologist to discuss:
  - the surgical and non-surgical options appropriate for their circumstances and
  - the potential benefits and limitations of each option, particularly long-term results.

- Consider offering cystoplasty to manage detrusor overactivity only to men whose symptoms have not responded to conservative management or drug treatment and are willing to self-catheterise. Before offering cystoplasty, disucss

serious complications (that is, bowel disturbance, metabolic acidosis, mucus production and/or mucus retention in the bladder, urinary tract infection and urinary retention).

- Consider offering bladder wall injection with botulinum toxin[c] only to men with detrusor overactivity whose symptoms have not responded to conservative management and drug treatments and who are willing to self-catheterise.
- Consider offering implanted sacral nerve root stimulation to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.
- Do not offer myectomy to men to manage detrusor overactivity.
- Consider offering intramural injectables, implanted adjustable compression devices and male slings[d] to manage stress urinary incontinence only as part of a clinical trial.
- Consider offering urinary diversion to manage intractable urinary tract symptoms only to men whose symptoms have not responded to conservative management and drug treatments, and if cystoplasty or sacral root stimulation are not appropriate or unacceptable.
- Consider offering implantation of an artificial sphincter to manage stress urinary incontinence only to men whose symptoms have not responded to conservative management and drug treatments.

9.6 Research recommendation

9.6.1 Male Slings

The GDG recommended the following research question:

- In men with mild to moderate post prostatectomy urinary incontinence, what is the clinical and cost effectiveness of a male sling or an extraurethral non circumferential compression device, when assessed by symptom severity, quality of life, changes in measured leakage, and occurrence of adverse events?

Why this is important?

Guidance is needed on the most suitable surgical options for this growing group of men who, until recently, have had no acceptable treatment option other than insertion

[c] At the time of publication (July 2009), botulinum toxin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[d] Current evidence on the safety and efficacy of suburethral synthetic sling[183] insertion for stress urinary incontinence in men appears adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance (NICE Interventional Procedure 256). However, research is necessary to understand its role compared with other treatments.

of an artificial urinary sphincter. However many men consider this treatment to be too invasive and too prone to complication or failure, and therefore depend on containment alone for control of their urinary incontinence. A number of new interventions have been devised but it is uncertain which of these offers the best outcomes. This research could lead to clear recommendations and effective treatment for the majority of these men. A randomised controlled trial comparing up to three current interventions; retrobulbar “non compressive” male sling, adjustable compression sling, and extraurethral non circumferential compression device is recommended.

10 Drug treatment versus conservative management

10.1 Introduction

The management options for male LUTS include conservative therapies, medical (pharmaceutical) therapies and surgery. The decision to opt for a particular type of therapy is dependent on informed patient choice, patients' perceptions and aspirations and clinical considerations, such as severity of symptoms, degree of prostatic enlargement and the response to any preceding treatment. It also takes into account the risk/benefit balance of each therapy.

In general terms, conservative management carry the lowest risk but may have a lower chance of success and a higher chance of symptom recurrence. Drug treatments with drugs such as alpha blockers, 5 alpha-reductase inhibitors and anti-muscarinics carry a greater risk of interactions and adverse effects, but may produce better subjective and objective improvement.

Evidence comparing different drug treatments to each other or to no treatment and comparative evidence on conservative managment are considered in chapters 5 and 6. In this chapter we consider evidence comparing medical and conservative strategies and make recommendations on their use.

10.1.1 What is the effectiveness of medications compared to conservative therapies in managing LUTS?

No clinical or economic studies were identified.

10.1.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

10.1.2 Recommendations and link to evidence

Recommendation	Offer men with bothersome LUTS drug treatment only when conservative management options have been unsuccessful or are not appropriate.
Relative values of different outcomes	Improved quality of life from reduction of LUTS symptoms as measured by IPSS or improved continence were considered to be the most important benefits. Side-effects of treatments were also important.
Trade off between clinical benefits and harms	Medical therapy may be effective in reducing LUTS symptoms where conservative measures have failed. This is balanced against the associated side-effects, which differ depending on class of medications used.
Economic considerations	Not addressed
Quality of evidence	No clinical or economic evidence was retrieved.
Other considerations	Patient preference, the severity of symptoms and prior experience with conservative treatments are some of the considerations.

10.2 Summary of recommendations

- Offer men with bothersome LUTS drug treatment only when conservative management options have been unsuccessful or are not appropriate.

11 Conservative management versus surgery

11.1 Introduction

The management options for male LUTS include conservative management, drug (pharmaceutical) treatment and surgery. The decision to opt for a particular type of therapy is dependent on both clinical consideration and informed patient choice.

Surgical options are invasive but may produce better subjective and objective improvement than conservative options. This option is usually considered when conservative and medical options have failed or are not appropriate.

Evidence comparing different surgical options to each other or to no treatment and comparative evidence on conservative interventions are considered in chapters 5 and 8. In this chapter we consider evidence comparing surgical and conservative strategies and make recommendations on their use.

Although all conservative and surgical interventions are considered, evidence was only found for catheters or bladder training vs. TURP.

11.1.1 What is the effectiveness of conservative compared to surgical therapies in managing lower urinary tract symptoms?

11.1.1.1 Bladder training vs. transurethral resection of the prostate (TURP)

Bladder retraining is thought to be useful in managing the symptoms of urinary urgency and frequency. This is an educational and behavioural approach to re-establish bladder control and restore a normal bladder pattern and may be a preferable option for some patients with mild or moderate symptoms before more invasive options such as surgery is considered.

11.1.1.2 Clinical evidence

Only one RCT[61] comparing TURP against bladder training was found.

See Evidence Table 46, Appendix D, Forest Plots in Figures E-200 to E-202, Appendix E and Economic Evidence Table 53, Appendix D.

Table 11-157: Bladder training vs. TURP - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in symptom score at 6 months follow up[61]	1	RCT	No serious limitations (a) Further notes (b)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in quality of life (IPSS question) at 6 months follow up[61]	1	RCT	No serious limitations (a) Further notes (b)	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax at 6 months follow up[61,110]	2	RCT	No serious limitations (a) Further notes (b)	No serious inconsistency	No serious indirectness	No serious imprecision
Adverse events	0	RCT				

(a) *Both studies report adequate randomisation methods, evidence of allocation concealment and complete outcome data but neither study reports masked outcome assessment. One study*[61] *reports change from baseline and the other study*[110] *reports outcomes at follow up. Both outcome measures are combined where possible in a single meta-analysis following methods described in the Cochrane handbook.*

(b) *There is variation between studies in how bladder training is delivered and followed up. In one study*[61] *men receive only general advice on bladder training whereas in the other study*[110] *men are followed up at weekly visits for the first month with analysis of frequency/volume charts to assess progress.*

Table 11-158: Bladder training vs. TURP - Clinical summary of findings

Quality	Bladder training	TURP	Relative risk	Absolute effect	Quality
Change in symptom score at 6 months follow up	85	89	Not applicable	MD 11.00 [-9.10 to -12.90]	High
Change in quality of life (IPSS question) at 6 months follow up	85	85	Not applicable	MD 1.80 [-1.35 to- 2.25]	High
Qmax at 6 months follow up	109	119	Not applicable	MD -8.79 [-10.33 to -7.25]	High

11.1.1.3 Economic evidence

We found one economic study[189] comparing bladder training with TURP. This is a cost-utility analysis[189] based on a RCT[61] included in our clinical review.

Please see Economic Evidence Table 53 in Appendix D for further details.

Table 11-159: Bladder training vs. TURP - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NOBLE2002[189]	Serious limitations (a)	Directly applicable	Bard UK provided the laser fibres used in the study.

(a) *The study did not report an incremental analysis. Resource use data were available only for 30% of the patient population. The conclusions of the study were incorrect. Short follow-up (7.5 months).*

Table 11-160: Bladder training vs. TURP - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
NOBLE2002[189]	- 883 (a)	- 0.017 QALYs	£51,941/QALY (b)	Results not sensitive to cost of equipment.

(a) *Costs include investigations, staff time, equipment, medication, hospital stay, rehospitalisation for catheter-free trial, outpatient visits, GP and nursing visits, consumables (catheter bags, pads and other aids).*

(b) *ICER of TURP vs. Bladder training.*

11.1.1.4 Evidence statement (s)

Clinical TURP is more effective than bladder training in improving symptom score at 6 months follow up.

TURP is more effective than bladder training in improving IPSS QoL at 6 months follow up.

TURP is more effective than bladder training in improving Qmax at 6 months follow up.

Comparison of adverse events from TURP against bladder training was not reported.

Economic TURP is more effective but more costly than bladder training. In the short-term it is not cost-effective. This evidence has serious limitations and direct applicability.

11.1.2 Recommendations and link to evidence

Recommendation	**Inform men with LUTS and proven bladder outlet obstruction that bladder training is less effective than surgery.**
Relative values of different outcomes	Symptom score, quality of life (IPSS question) and maximum urinary flow rate were considered the primary outcomes.
Trade off between clinical benefits and harms	Bladder training is less effective than surgical intervention in improving quality of life, symptom score and urinary flow rate. However, TURP is an invasive procedure and maybe have important complications such as blood loss and strictures.
Economic considerations	Bladder training is more cost-effective than surgery in the short term. However being less effective, it may only delay the surgical intervention.
Quality of evidence	Only two very small RCTs which compared bladder training against TURP were found. The economic evidence has serious limitations and direct applicability.
Other considerations	Patient preference is an important consideration in deciding the appropriate treatment. Some patients (e.g. those with cognitive problems) may not be able to perform bladder training.

11.1.3 Catheters vs. TURP

Men may require or opt for catheterisation rather than prostatic resection for a number of reasons including physical or cognitive impairment, the relative risks of surgery or patient choice. This group of patient included those with acute or chronic retention.

11.1.3.1 Clinical evidence

One RCT which compared intermittent self-catheterisation against TURP was found in patients with chronic urinary retention [84]. We identified no studies which considered indwelling catheterisation vs. TURP or in other LUTS patients.

See Evidence Table 46, Appendix D, and Forest Plots in Figures E-203 to E-204, Appendix E.

Table 11-161: Intermittent (self) catheterisation vs. TURP - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Change in symptom score at 6 months follow up[84]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Change in quality of life (IPSS question) at 6 months follow up[84]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax	0	RCT				
Quality of life	0	RCT				
Adverse events	0	RCT				

(a) *The study does not report randomisation method, allocations concealment or masking of outcome assessment but outcome data is complete. Complications are reported but not divided by group.*
(b) *Imprecision due to wide confidence intervals around effect size crossing minimally important difference or small sample size.*

Table 11-162: Intermittent catheterisation vs. TURP - Clinical summary of findings

Outcome	*Intermittent catheterisation*	*TURP*	*Relative risk*	*Absolute effect*	*Quality*
Change in symptom score at 6 months follow up	24	17	Not applicable	MD 8.04 [2.81 to 13.27]	Very Low
Change in quality of life (IPSS question) at 6 months follow up	24	17	Not applicable	MD 0.46 [-0.42 to 1.34]	Very Low

11.1.3.2 Economic evidence

No economic studies were identified.

11.1.3.3 Evidence statement (s)

Clinical TURP is more effective than intermittent (self-) catheterisation in improving symptom score at 6 months follow up for patients with chronic retention.

There is no statistically significant difference between intermittent (self-) catheterisation and TURP in improving IPSS QoL for patients with chronic retention.

Economic No economic studies were identified.

11.1.4 Recommendations and link to evidence

See recommendations and link to evidence in the Urinary Retention chapter 13.4.

11.2 Summary of recommendations

- Inform men with LUTS and proven bladder outlet obstruction that bladder training is less effective than surgery.

12 Drug treatment versus surgery

12.1 Introduction

The management options for male LUTS include conservative managment, drug (pharmaceutical) therapies and surgery. The decision to opt for a particular type of therapy is dependent on patient choice and clinical considerations, such as severity of symptoms, degree of prostatic enlargement and the response to any preceding treatment. It also takes into account the risk/benefit balance of each therapy.

In general terms the conservative treatments carry the lowest risk but have a lower chance of success and a higher chance of symptom recurrence. Medical therapies with drugs such as alpha blockers and 5 alpha-reductase inhibitors carry a greater risk of interactions and adverse effects but may produce better subjective and objective improvement. Surgical intervention carries the greatest possibility of improvement, particularly in those with severe symptoms but this must be weighed against the risks of surgery, anaesthesia and hospitalisation.

Evidence comparing different medical therapies to each other or to no treatment and comparative evidence on surgical options are considered in chapters 6 and 8. In this chapter we consider evidence comparing medical and surgical strategies and make recommendations on their use.

12.1.1 What is the effectiveness of medications compared to surgical therapies in managing LUTS?

12.1.1.1 Clinical evidence

No studies were identified.

12.1.1.2 Economic evidence

Few economic studies were identified comparing medical with surgical interventions. Four studies[6,141,208,254] were excluded because poorly conducted; a further study[108] was excluded because based on the assumption that the risk of AUR and TURP in the medical arm was equal to the risk in the placebo arm. In conclusion, only one study[58] was included in the evidence. In this study a subgroup analysis based on symptoms severity was performed. Please see Economic Evidence Table 53 in Appendix D for further details.

Table 12-163: Surgical vs. medical interventions - Economic study characteristics

Study	Limitations	Applicability	Other Comments
DiSantostefano2006	Minor limitations (a)	Partially applicable (b)	Financially supported by the Institute of Aging and Agency for Healthcare Research and Quality.

(a) Study conducted in the USA.

Table 12-164: Surgical vs. medical interventions - Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
Moderate symptoms (a)				
DiSantostefano2006	1,222 (b,c)	- 0.13	Medical intervention dominates	If switching between treatments was not permitted, TURP would be cost-effective with an ICER=£ 19,090/QALY. PSA: 70% probability of medical treatment being cost-effective if willingness to pay is $50,000.
Severe symptoms (a)				
DiSantostefano2006	1,197	0.59	2,029	PSA: 90% probability of surgical treatment being cost-effective if willingness to pay is $50,000.

(a) Only TURP arm was considered for the surgical interventions. Data for the TUMT arm were based on expert opinion. Alpha blockers were chosen to represent the medical intervention as they were the dominant drug treatment in the study.
(b) Cost of visits, tests, drugs, operations, complications (strictures, and artificial urinary sphincter)
(c) Costs converted from 2004 US$ using the Purchasing Power Parities $1=£0.632.

12.1.1.3 Evidence statement (s)

Clinical No clinical studies were identified.

Economic Medical interventions are cost-effective in patients with moderate symptoms. Surgical interventions are cost-effective in patients with severe symptoms. This evidence has minor limitations and partial applicability.

12.1.2 Recommendations and link to evidence

These recommendations can be found in the previous chapters on surgery at sections 8.16 and 9.4.

13 Treating men with urinary retention

13.1 Introduction

Urinary retention has a very major impact on patients' quality of life. It is classified into three forms:

- **Acute retention:** This is the abrupt (over a period of hours) development of the inability to pass urine, associated with increasing pain and the presence of a distended bladder, which can be palpated when the patient is examined. The pain can be excruciating and can be described as similar to that caused by passage of a kidney stone. The bladder may contain between 500ml and one litre when the patient is seen, and the rapid stretching of the bladder results in pain. Acute retention may be precipitated by some other event (such as excessive fluid intake or constipation) or it may be apparently spontaneous.

- **Chronic retention:** This is the gradual (over months or years) development of the inability to empty the bladder completely, associated with the presence of a distended bladder, which can be palpated when the patient is examined. The insidious nature of onset of the condition means that the bladder stretches slowly enough for there to be no pain. The bladder may contain up to and sometimes more than a litre when the patient is seen. There may be lower urinary tract symptoms, sometimes leakage at night, but there may be no symptoms at all. Sometimes the bladder is distended at high pressure, and this result in back-pressure on the kidneys, with kidney failure to a varying degree.

- **Acute-on-chronic retention:** This is the abrupt development of acute retention in a patient who previously had chronic retention, either knowingly or more often unknowingly.

13.2 Management of men in acute retention

13.2.1 What is the effectiveness of alpha blockers in treating men after acute urinary retention?

Acute urinary retention due to benign prostatic enlargement (BPE) may be associated with an increase in alpha-adrenergic activity. Inhibition of these receptors by alpha blockers may decrease bladder outlet resistance thereby facilitating normal micturition and increasing the chances of a successful trial without catheter (TWOC).

See Evidence Table 47, Appendix D, Forest Plots in Figures E-205 to E-206, Appendix E and Economic Evidence Table 53, Appendix D.

13.2.1.1 Clinical evidence

Table 13-165: Alpha blocker vs. placebo – Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Able to void[142,158,159,232]	4	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Re-catheterisation[142,232]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(d) *One study [232] did not report method of randomisation or allocation concealment.*
(e) *Imprecision due to small sample size and confidence intervals cross MID (0.75 or 1.25).*

Table 13-166: Alpha blocker vs. placebo - Clinical summary of findings

Outcome	Alpha-blocker	Placebo	Relative risk	Absolute effect	Quality
Able to void	211/402 (52.5%)	106/282 (37.6%)	1.30 [1.10, 1.55]	113 more per 1000 [8 to 207 more]	Moderate
Re-catheterisation	54/105 (51.4%)	64/98 (65.3%)	0.79 [0.63, 1.01]	137 fewer per 1000 [42 fewer to 7 more]	Low

13.2.1.2 Economic evidence

We found a cost-effectiveness analysis[15] comparing alpha blockers to placebo and immediate prostatectomy in patients hospitalized for acute urinary retention. Patients in the alpha blockers group were treated with Alfuzosin 10mg once daily for 3 days during the initial hospitalisation followed by TWOC. After a successful TWOC this group was treated again with Alfuzosin for 6 months. We report here only the comparison between alpha blockers and placebo.

Please see Economic Evidence Table 53 in Appendix D for further details.

Table 13-167: Alpha blocker vs. placebo - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Annemans2005[15]	Minor limitations (a)	Partial applicability (b)	Based on the ALFAUR study[160]

(a) *Not a full economic evaluation*
(b) *Short follow-up (6 months) after which treated patients are very likely to need surgery.*

Table 13-168: Alpha blocker vs. placebo - Economic summary of findings

Study	Incremental cost (£) per patient	Incremental effects	ICER	Uncertainty
Annemans2005[15]	349 (a)	Not reported	Not applicable	(95% CI £64-£624)

(a) *Costs include hospitalisation, drugs, unsuccessful TWOC followed by prostatectomy and tests, over 6 months.*

13.2.1.3 Evidence statement(s)

Clinical

In men with acute urinary retention, an alpha blocker is more effective than placebo in increasing their chance of voiding after catheter removal.

In men with acute urinary retention, there was no significant difference between alpha blockers and placebo in the number of men who required

recatheterisation after catheter removal.

Economic In men with acute urinary retention, alpha blockers are cost-saving over a 6-month period. This evidence has minor limitations bur partial applicability.

13.2.2 Recommendations and link of evidence

See recommendations and link of evidence in section 13.4.

13.3 Management of men with chronic retention

Catheters may be used as a long term solution where persistent urinary retention is causing incontinence, infection or renal dysfunction and an operative solution is not feasible. Their use is associated with an increased risk of adverse events including recurrent urinary infections, trauma to the urethra, pain and stone formation. Intermittent catherisation releases a patient from having a continuous indwelling catheter which in many patients is better tolerated with an improvement in QOL and reduced morbidity.

The evidence for this section is reviewed and presented in the relevant chapters on the type of treatment. Please see the following chapters:

- Conservative Chapter 5 (comparison of different types of catheters) and Evidence Table X, Appendix D.
- Conservative vs. Surgery Chapter 11(comparison of catheterisation vs. TURP) and Evidence Table X, Appendix D.

13.4 Recommendations and link to evidence

Recommendation	**Immediately catheterise men with acute retention.**
Relative values of different outcomes	The GDG considered the alleviation of pain to be the primary outcome of interest.
Trade off between clinical benefits and harms	Immediate catheterisation is required to alleviate the acute retention and pain. The potential harm of inserting a catheter includes, urinary tract infections, haematuria, trauma to the urethra, pain and stone formation. The greatly outweighs the small risk of adverse events.
Economic considerations	Not addressed as no other strategy can be considered.
Quality of evidence	No evidence was found.
Other considerations	None.

Recommendation	**Offer an alpha blocker to men for managing acute urinary retention before removal of the catheter.**
Relative values of different outcomes	The most important outcomes are to restore normal voiding and increase the chance of a successful trial without catheter without the need for re-catheterisation.
Trade off between clinical benefits and harms	The group considered that men's ability to void and not being re-catheterised outweighed potential adverse events of the treatment, which includes dizziness, somnolence, postural hypotension, syncope, rhinitis, asthenia (fatigue), headache, erectile dysfunction, abnormal ejaculation.
Economic considerations	Alpha blockers can be cost-saving compared to placebo. Although the GDG considers the economic evidence to have drawbacks due to its short follow-up, it is their opinion that alpha blockers could still be cost-effective.
Quality of evidence	All the studies were imprecise as they crossed the minimally important difference confidence intervals. The re-catheterisation outcome was low quality as there were also limitations in the study design of one of the two studies retrieved. The economic evidence has minor limitations but partial applicability as the follow-up is very short.
Other considerations	There is no clear evidence for how long this treatment should continue before TWOC, but it seems likely that this should be at least two days treatment before TWOC.

1

Recommendation	**Consider offering intermittent or indwelling catheterisation before surgery in men with chronic urinary retention.**
Relative values of different outcomes	Renal failure is most important outcome. Other important outcomes include failure to void, enuresis, urinary infections.
Trade off between clinical benefits and harms	Risk of renal dysfunction outweighs any disadvantages for catheterisation.
Economic considerations	The GDG considered that the cost of catheterisation is justified when the patient is judged to be at risk of renal dysfunction.
Other considerations	The principal problem is impaired bladder function to a variable degree. Any form of treatment needs to bear this in mind. The decision to catheterise for chronic retention is a value judgement, where the risks of catheterisation may outweigh the benefits in a fit patient planned for early prostate surgery.

2

Recommendation	**Consider offering self- or carer-administered intermittent urethral catheterisation as an alternative to indwelling catheterisation for men with chronic or acute urinary retention.**
Relative values of different outcomes	Alleviation of retention and prevention of incontinence, infection or renal dysfunction from persistent retention is important. Recurrent urinary tract infections, haematuria, trauma to the urethra, pain and stone formation are important adverse events to be considered.
Trade off between clinical benefits and harms	The benefits of alleviating retention and preventing incontinence, urinary tract infections and renal dysfunction from persistent catheterisation outweigh the harms. Harms include incorrect use of catheter, and complications such as recurrent urinary tract infections, trauma to the urethra, accidental removal, recurrent blockage and stone formation. Patients may also be in pain or discomfort.
Economic considerations	It is unlikely that there is much cost difference between the alternative strategies.
Quality of evidence	No clinical or economic studies were found.
Other considerations	The ability of patients to self-catheterise and availability of support from carers are important considerations.

1

Recommendation	**Consider intermittent self catheterisation as an alternative to TURP in men with chronic retention if there is evidence of poor bladder function.**
Relative values of different outcomes	Change in symptom scoring was the only outcome reported but QOL would be more helpful as IPSS score is not a useful measure in men self catheterising. In chronic retention patients there is often little in the way of LUTS and hence undue reliance on scoring of LUTS may be misleading.
Trade off between clinical benefits and harms	The GDG considered the avoidance of surgery and surgical morbidity vs. the benefit of a definitive solution and the inconvenience and discomfort of self- catheterisation over a potentially long period. Ultimately this will depend on an assessment of whether the bladder has sufficient function to result in adequate bladder emptying after surgical intervention. Discussion between the patient and clinician should take account of mode of presentation -high (associated renal failure) or low pressure chronic retention and evidence from assessment of post void residuals/catherisation volumes and urodynamic assessment with pressure flow studies.
Economic considerations	In men with poor bladder function TURP might fail to solve the problem, generating unnecessary costs.
Quality of evidence	There was only one small study found in patients with chronic retention; the level of uncertainty with the evidence is very high.

	No economic studies were identified.
Other considerations	Patient preference, fitness for surgery and the likelihood of success following a surgical intervention vs. continued catherisation are factors in helping men to decide on the relative benefits of each option.

Recommendation	**Provide active surveillance (imaging and creatinine) to men with non-bothersome LUTS secondary to chronic retention who have not had their bladder drained.**
Relative values of different outcomes	Preservation of renal function and relief of symptoms are considered to be the most important outcomes
Trade off between clinical benefits and harms	Ensuring there is no deterioration of renal function or any other complications as a consequence of non intervention is worth the effort of recalling patients for monitoring.
Economic considerations	Follow-up is associated with costs but these could be offset by the timely identification of complication.
Quality of evidence	No clinical studies were identified. No economic studies were identified.
Other considerations	Regular follow up with serum creatinine and renal ultrasound should be provided.

13.5 Supporting recommendations

Recommendation	**Carry out a serum creatinine test and imaging of upper urinary tract in men with chronic urinary retention.**
Trade off between clinical benefits and harms	This is to differentiate between high pressure chronic retention with impaired renal function and low pressure retention with normal renal function. In the presence of abnormal renal function and renal dilatation, patients require early catheterisation and often hospital admission to monitor renal function until it stabilises. The benefits of preventing further deterioration of renal function outweigh any risks of catheterisation.
Economic considerations	There are costs associated with additional specialised tests. However, misdiagnosis of underlying conditions is associated with costs and health detriment that are likely to outweigh the costs of these tests.
Other considerations	None.

Recommendation	**Consider offering surgery without catheterisation to men who have chronic urinary retention and other bothersome LUTS but no impairment of renal function or upper renal tract abnormality.**
Trade off between clinical benefits and harms	Quality of life of the patient is the most important outcome. Trauma to the urethra, discomfort, urinary infection, haematuria are also important outcomes. The benefits of catheterisation need to be considered against the complications of inserting a catheter. Quality of life of patients may be better without catheterisation. Duration between presentation and surgical intervention may influence the decision whether to catheterise or not.
Economic considerations	In this group of men the benefits of catheterisation are unlikely to outweigh the complications and costs.
Other considerations	TURP may be safer (less blood loss) and more effective for patients who have previously not been catheterised.

1

Recommendation	**Catheterise men who have impaired renal function or hydronephrosis secondary to chronic urinary retention.**
Trade off between clinical benefits and harms	Improved renal function outweighs all other considerations such as complication from catheters.
Economic considerations	In this group of men the benefits of catheterisation outweigh its risks and costs.
Other considerations	Post obstructive diuresis needs to be carefully monitored and may be an indication for hospital admission.

2

Recommendation	**Continue or start long-term catheterisation in men with chronic retention for whom surgery is unsuitable.**
Trade off between clinical benefits and harms	The benefits of catheterisation to reduce the risk of potential renal dysfunction and symptoms outweigh the complications of catheterisation.
Economic considerations	In this group of men the benefits of catheterisation outweigh its risks and costs.
Other considerations	The type of catheterisation is important in determining quality of life (intermittent or indwelling urethral or suprapubic). Reassess for potential surgical intervention in the future.

3

4 ## 13.6 Summary of recommendations

5 ➢ Immediately catheterise men with acute retention.

6 ➢ Consider offering self- or carer-administered intermittent urethral
7 catheterisation as an alternative to indwelling catheterisation for men with
8 chronic or acute urinary retention.

- Offer an alpha blocker to men for managing acute urinary retention before removal of the catheter.
- Carry out a serum creatinine test and imaging of upper urinary tract in men with chronic urinary retention.
- Catheterise men who have impaired renal function or hydronephrosis secondary to chronic urinary retention.
- Consider offering intermittent or indwelling catheterisation before surgery in men with chronic urinary retention.
- Consider offering surgery without catheterisation to men who have chronic urinary retention and other bothersome LUTS but no impairment of renal function or upper renal tract abnormality.
- Consider intermittent self-catheterisation as an alternative to TURP in men with chronic retention if there is evidence of poor bladder function.
- Continue or start long-term catheterisation in men with chronic retention for whom surgery is unsuitable.
- Provide active surveillance (imaging and creatinine) to men with non-bothersome LUTS secondary to chronic retention who have not had their bladder drained.

14 Complementary and alternative treatment for men with lower urinary tract symptoms

14.1 What is the effectiveness of complementary and alternative therapies in managing LUTS?

14.2 Phytotherapy

Most of these are herbal extracts (phytotherapy) and none are licensed medications. Phytotherapies have not been subject to the degree of efficacy and safety research that would be required of a conventional treatment, but are perceived by some as a 'natural' alternative to pharmaceutical preparations. There are data comparing the efficacy of phytotherapies against placebo and some conventional treatments, but side effect and safety data is often incomplete or missing.

The following complementary and alternative therapies were considered in this review:

- Saw palmetto (Serenoa repens) is an extract of the fruit serenoa replens. It has high levels of phytosterols and fatty acids and has been used to treat benign prostatic hyperplasia.
- Pygeum is an extract from the bark of Prunus africana and is used to reduce symptoms of LUTS.
- Urtica diocia is an extract of the root of the common stinging nettle that has been used to treat benign prostatic hyperplasia.
- Beta sitosterols are phytosterols found in a number of plants including saw palmetto and pygeum africanum. They are chemically similar to cholesterol and have been used to treat LUTS.
- Cernilton® is an extract prepared from the rye grass pollen (secale cereale) and has been used to treat benign prostatic hyperplasia.

14.2.1 Phytotherapy vs. placebo

See Evidence Table 48, Appendix D, Forest Plots in Figures E-207 to E-215, Appendix E.

14.2.1.1 Clinical evidence

Table 14-169: Phytotherapy vs. placebo – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Beta-sitosterols						
Symptom score[270]	2	RCT (a)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax[270]	4	RCT (a)	No serious limitations	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Quality of life (IPSS question)	0					
Urinary incontinence	0					
Progression	0					
Serenoa repens						
Symptom score[25,234,268]	3	RCT (b)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax[234,268]	11	RCT (b)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Quality of life (IPSS question)[266]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Urinary incontinence	0					
Progression	0					
Urtica diocia						
Symptom score[225]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Qmax[225]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Quality of life(IPSS question)	0					
Urinary incontinence	0					
Progression	0					
Pygeum						
Symptom score	0					
Qmax[269]	4	RCT (a)	No serious limitations	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Urinary incontinence	0					
Progression	0					
Cernilton						
Symptom score	0					
Qmax[271]	1	RCT (a)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Urinary incontinence	0					
Progression	0					

a) *Study quality and outcome effect sizes taken from Cochrane Systematic Reviews by Wilt et al., 1998*[269,271]*, 1999*[270]*, 2002*[268]
b) *Study quality and outcome effect sizes taken from Cochrane Systematic Review by Wilt 2002*[268] *and RCTs referenced.*
c) *Statistically significant heterogeneity present*
d) *Imprecision due to wide confidence intervals around effect size crossing minimally important difference or small sample size.*

Table 14-170: Phytotherapy vs. placebo - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Beta-sitosterols: symptom score	173	169	Not applicable	Mean Difference (MD): -4.91 [-6.29 to -3.53]	High
Beta-sitosterols: Qmax	237	237	Not applicable	MD: 3.91 [0.91to 6.90]	Low
Serenoa repens: symptom score	197	199	Not applicable	MD: -0.12 [-0.96 to 0.72]	High
Serenoa repens: Qmax	519	521	Not applicable	MD: 1.56 [1.02 to 2.10]	Moderate
Serenoa repens: quality of life (IPSS question)	46	47	Not applicable	MD: -0.14 [-0.74, 0.46]	Moderate
Urtica diocia: symptom score	287	271	Not applicable	MD: -5.90 [-6.49 to -5.31]	High
Urtica diocia: Qmax	287	271	Not applicable	MD: 4.70 [4.00 to 5.40]	High
Pygeum: Qmax	183	180	Not applicable	MD: 2.50 [0.29 to 4.71]	Low
Cernilton: Qmax	26	24	Not applicable	MD: -1.60 [-5.79 to 2.59]	Moderate

14.2.1.2 Economic evidence

No economic studies were identified

14.2.1.3 Evidence statement (s)

Clinical Beta-sitosterol is more effective than placebo in improving symptoms scores.

Beta-sitosterol is more effective than placebo in improving flow rates.

There is no statistically significant difference between saw palmetto and placebo in improving symptom scores or quality of life (IPSS question).

Serenoa repens is more effective than placebo in improving flow rates.

Urtica dioica is more effective than placebo in improving symptom scores.

Urtica dioica is more effective than placebo in improving flow rates.

Pygeum is more effective than placebo in improving flow rate.

There is no statistically significant difference between Cernilton and placebo in improving flow rate.

Economic No economic studies were identified.

14.2.2 Phytotherapy combinations vs. placebo

See Evidence Table 49, Appendix D, Forest Plots in Figures E-216 to E-222, Appendix E.

14.2.2.1 Clinical evidence

Table 14-171: Phytotherapy combinations vs. placebo – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Serenoa repens and urtica diocia: symptom score[139,268]	2	RCT (a)	No serious limitations	Serious inconsistency	No serious indirectness	Serious imprecision (d)
Serenoa repens and urtica diocia: Qmax[139,268]	2	RCT (a)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Serenoa repens and urtica diocia: quality of life (IPSS question)	0					
Progression	0					
Urinary incontinence	0					
Pygeum and urtica: symptom score[164]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Pygeum and urtica: Qmax[164]	1	RCT	No serious limitations	No serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Pygeum and urtica: quality of life (IPSS question)[164]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Progression	0					
Urinary incontinence	0					
Cernitin, Serenoa repens phytostero and Vitamin E: symptom score[207]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Cernitin, Serenoa repens, phytostero and Vitamin E: Qmax[207]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Progression	0					
Urinary incontinence	0					

(a) Study quality and outcome effect sizes taken from Cochrane Systematic Reviews by Wilt et al., 2002[268]
(b) Statistically significant heterogeneity present
(c) Imprecision due to effect size crossing minimally important difference

Table 14-172: Phytotherapy combinations vs. placebo - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Serenoa repens and urtica diocia: symptom score	147	146	Not applicable	MD: 1.76 [-4.02, -0.49]	Low
Serenoa repens and urtica diocia: Qmax	147	146	Not applicable	MD: -1.76 [-4.02, 0.49]	Moderate
Pygeum and urtica: symptom score	27	22	Not applicable	MD: -1.00 [-5.30, 3.30]	Moderate
Pygeum and urtica: Qmax	27	22	Not applicable	MD: 1.10 [-1.70, 3.90]	Moderate
Pygeum and urtica: quality of life (IPSS question)	27	22	Not applicable	MD: -0.40 [-1.20, 0.40]	Moderate
Cernitin, serenoa repens, phytosterol and Vitamin E: change in symptom score	70	57	Not applicable	MD: -2.93 [-5.06, -0.80]	Moderate
Cernitin, serenoa repens, phytosterol and Vitamin E: Qmax	70	57	Not applicable	MD: -1.30 [-3.69, 1.09]	Moderate

14.2.2.2 Economic evidence

No economic studies were identified

14.2.2.3 Evidence statement (s)

Clinical Serenoa repens/urtica combination is more effective than placebo in improving symptoms scores.

There is no statistically significant difference between serenoa repens urtica combination and placebo in the change in symptom scores.

There is no statistically significant difference between serenoa repens /urtica combination and placebo in improving maximum urinary flow rate.

There is no statistically significant difference between Pygeum/urtica combination and placebo in improving symptoms scores.

There is no statistically significant difference between Pygeum/urtica combination and placebo in improving quality of life scores.

There is no statistically significant difference between Pygeum/urtica combination and placebo in improving maximum urinary flow.

Cernitin/serenoa repens /phytosterol/Vitamin E combination is more effective than placebo in improving change in symptoms scores.

There is no statistically significant difference between Cernitin/serenoa repens /phytosterol/Vitamin E combination and placebo in improving maximum urinary flow rate.

Economic No economic studies were identified.

14.2.3 Phytotherapy vs. alpha blockers

See Evidence Table 50, Appendix D, Forest Plots in Figures E-223 to E-226, Appendix E.

14.2.3.1 Clinical evidence

Table 14-173: Phytotherapy vs. alpha blockers – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Change in symptom score at 6 months[100]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 12 months[56]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Change in quality of life (IPSS question) at 6 months follow up[100]	1	RCT	Very Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Change in Qmax at 6 month[100]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Q max at 12 months[56]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[56]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence	0					

(a) *The study by Hizli 2007*[100] *was open label and its outcomes have been downgraded with very serious limitations. Neither study reports randomisation method, allocation concealment but follow up data was clearly reported and patients were masked to treatment allocation in one study*[56] *Neither study was placebo controlled.*
(b) *Statistical heterogeneity observed*
(c) *Imprecision resulting from wide confidence intervals crossing minimally important difference or small sample size.*

Table 14-174: Phytotherapy (serenoa repens) vs. alpha blockers - Clinical summary of findings

Outcome	*Serenoa repens**	*Alpha blocker**	*Relative risk*	*Absolute effect*	*Quality*
Change in symptom score at 6 months	20	20	Not applicable	MD 1.50 [-0.37 to 3.37]	Very low
Symptom score at 12 months	269	273	Not applicable	MD -0.20 [-1.17 to 0.77]	Low
Change in quality of life (IPSS question) score at 6 months	20	20	Not applicable	MD 0.50 [-0.03 to 1.03]	Very low
Change in Qmax at 6 months	20	20	Not applicable	MD -0.50 [-1.99 to 0.99]	Very low
Q max at 12 months	267	265	Not applicable	MD -0.30 [-1.16 to 0.56]	Low
Adverse events: urinary retention	3/349 (0.9%)	3/354 (0.8%)	Relative Risk (RR): 1.01 [0.21 to 4.99]	0 more per 1000 [6 fewer to 32 more]	Low

* *Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

14.2.3.2 Economic evidence

No economic studies were identified.

14.2.3.3 Evidence statement (s)

Clinical There is no statistically significant difference between serenoa repens and alpha blockers in change in symptom score at 6 months follow up.

There is no statistically significant difference between serenoa repens

and alpha blockers in improving symptom score at 1 year follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in change in IPSS QoL score at 6 months follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in change in Qmax at 6 months follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in improving Qmax at 1 year follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients withdrawing from study due to adverse events.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing urinary retention.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing decreased libido though the effect is borderline in favour of phytotherapy.

Fewer patients treated with serenoa repens compared to alpha blockers experienced ejaculation disorders.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing asthenia, fatigue or rhinitis.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing dizziness, postural hypotension, headache or dry mouth.

Economic No economic studies were identified.

14.2.4 Phytotherapy vs. 5-Alpha reductase

See Evidence Table 51, Appendix D, Forest Plots in Figures E-227 to E-232, Appendix E.

14.2.4.1 Clinical evidence

Table 14-175: Phytotherapy vs. 5-alpha reductase – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Serenoa repens: Symptom score at 6 months[37]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: Quality of life (IPSS question) at 6 months[37]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: Qmax at longest follow-up[37]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: Urinary Retention[37]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence	0					
Serenoa repens and uritica diocia: Symptom score at 6 months[240]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Symptom score at 12 months[240]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Qmax at 3 months[240]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Qmax at longest follow-up[240]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0					
Urinary retention	0					
Urinary incontinence	0					

(a) *Both studies reported adequate randomisation method but one study*[37] *did not report allocation concealment and one study*[240] *did not report follow up data for all patients. In both studies patients were masked to treatment but masking of outcome assessment was not clear. Neither study was placebo controlled.*
(b) *Statistical heterogeneity observed*
(c) *Imprecision resulting from wide confidence intervals crossing minimally important difference or small sample size.*

Table 14-176: Phytotherapy vs. 5-alpha reductase inhibitors (5ARI) - Clinical summary of findings

Outcome	*Serenoa repens**	*5ARI**	*Relative risk*	*Absolute effect*	*Quality*
Serenoa repens: Symptom score at 6 months	476	484	Not applicable	MD: 0.40 [-0.29 to 1.09]	Moderate
Serenoa repens: Quality of life (IPSS question) at 6 months	464	484	Not applicable	MD: 0.10 [-0.06 to 0.26]	Moderate
Serenoa repens: Qmax at longest follow-up	467	484	Not applicable	MD: 0.70 [-1.60 to 0.20]	Moderate
Serenoa repens: Urinary Retention	7/553 (1.3%)	3/545 (0.6%)	RR: 2.3 [0.60 to 8.85]	8 more per 1000 [2 more to 47 more]	Low
Serenoa repens and uritica diocia: Symptom score at 6 months	233	230	Not applicable	MD: 0.20 [-0.85 to 1.25]	Moderate
Serenoa repens and uritica diocia: Symptom score at 12 months	230	223	Not applicable	MD: 0.30 [-0.71 to 1.31]	Moderate
Serenoa repens and uritica diocia: Qmax at 3 months	240	242	Not applicable	MD: -0.40 [-1.53 to 0.73]	Moderate
Serenoa repens and uritica diocia: Qmax at longest follow-up	233	232	Not applicable	MD: -0.80 [-2.00 to -0.40]	Low

14.2.4.2 Economic evidence

No economic studies were identified.

14.2.4.3 Evidence statement (s)

Clinical There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in improving symptom score at 6 months follow up.

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in improving quality of life (IPSS score) at 6 months follow up.

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in improving Qmax at longest follow up.

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in number of patients experiencing urinary retention.

There is no statistically significant difference between serenoa repens/uritica diocia combination and 5-alpha reductase inhibitors in improving symptom score at 6 and 12 months follow up.

There is no statistically significant difference between serenoa

repens/uritica diocia combination and 5-alpha reductase inhibitors in improving Qmax at 3 months and longest follow up.

Economic No economic studies were identified.

14.2.5 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5

14.3 Acupuncture

Acupuncture is a complementary therapy that involves puncturing the skin with needles in defined points to relieve pain and reduce the symptoms of certain conditions. It has been a major therapy in Traditional Chinese Medicine (TCM) for several thousand years but has only recently been used to a limited extent by practitioners of western medicine. There seems to have been little serious research to compare its efficacy with traditional medicine.

14.3.1 In men who report LUTS, what is the effect of acupuncture vs. no acupuncture or other conservative therapy on patient related and biometric outcomes and adverse events?

No clinical or economic studies were identified.

14.3.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

14.3.2 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5

14.4 Homeopathy

Homeopathy is a form of alternative medicine that is based on the concept that substances that produce symptoms of sickness in healthy people can be given in very dilute quantities to sick people with the same symptoms. The idea is that these homeopathic remedies will stimulate the body's own healing processes.

14.4.1 What is the effectiveness and comparative effectiveness of homeopathy in reducing symptoms for managing LUTS?

No clinical or economic studies were identified.

14.4.1.1 Evidence statement(s)

Clinical No clinical studies were identified.

Economic No economic studies were identified.

14.4.2 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5

14.5 Recommendations and link to evidence

Recommendation	**Do not offer homeopathy, phytotherapy or acupuncture for treating LUTS in men.**
Relative values of different outcomes	The group considered that an improvement in symptom scores (including the IPSS quality of life question), maximum urinary flow rate and adverse events were the primary outcomes.
Trade off between clinical benefits and harms	There was weak evidence for a benefit in using phytotherapy but the GDG was concerned about side-effects arising from potential interactions with other drugs as these are less rigorously investigated than the clinical trials designed for licensing of other pharmaceutical medications. There is also a lack of standardisation in formulation, source or quantity of active components and doses provided by different suppliers. It is uncertain whether similar benefits can be gained when a different formulation or brand is used. The absence of data from studies makes it impossible to determine either benefits or harms from acupuncture or homeopathy.
Economic considerations	Due to the lack of placebo controlled data associated with the use of phytotherapy, the GDG felt that this intervention could generate unnecessary costs to treat side effects. Since the clinical effectiveness of acupuncture and homeopathy is unknown, the cost-effectiveness cannot be assessed.
Quality of evidence	One of the studies comparing alpha blockers to phytotherapy was open label without any blinding of the participants and investigators. This study has been included but the outcomes reported have been downgraded with very serious limitations. The results should be interpreted with caution from this study especially when considering subjective and patient-reported outcomes. The trials comparing alpha blockers and 5-alpha reductase to phytotherapy did not have a placebo arm. No economic evidence was found on homeopathy, phytotherapy or acupuncture.
Other considerations	For the comparison of 5-alpha reductase to phytotherapy (Serenoa repens) both prostate volume and serum PSA were significantly decreased by 5-alpha reductase compared to phytotherapy.

14.6 Summary of recommendations:

- Do not offer homeopathy, phytotherapy or acupuncture for treating LUTS in men.

15 Provision of information to, and support of, patients

15.1 Introduction

The term "lower urinary tract symptoms (LUTS)" covers symptoms that may be caused by a wide range of lower urinary tract conditions in men. Identifying what underlying conditions are present may not be straightforward, and may involve a stepwise approach to successive management options. It is therefore important to ensure that men are properly informed and adequately supported when decisions are made; this may be complex, and information and support may be difficult to maintain over extended periods of time.

Men with LUTS will often need the support of their family and carers, where they are involved. LUTS may be under-reported or reported at a late stage by men from some cultural or religious backgrounds. LUTS may have an impact on partners similar to that of the patient. Because of the multi-faceted nature of LUTS, the wide variety of public sources of information may confuse rather than illuminate, so support and guidance to the best sources is essential.

LUTS can affect men with special needs that influence the course of their diagnosis, treatment and management. Typical special needs include; age related physical or cognitive impairment, learning difficulties, language barriers, restricted manual dexterity and visual impairment.

15.2 What information is needed?

Men with LUTS need different specific information and support at each point in the process of diagnosis and treatment. Their partners and carers may also need to understand the condition in order to help to make treatment effective and management acceptable and effective.

15.2.1 Towards Diagnosis

If patients have a good understanding of their lower urinary tract anatomy and its normal way of working, they may better communicate their symptoms to the clinician and better understand the diagnostic process.

LUTS may affect sexual performance and self-confidence. Men can present primarily because their partner has persuaded them to do so, perhaps because of sexual dysfunction, hygiene problems or social disruption. Opportunities to discuss self-confidence, feelings of masculinity, self-respect and sexual performance, with a healthcare professional in the context of LUTS should be created throughout the assessment and management process.

The diagnostic process in LUTS may involve intrusive examination, and potentially unpleasant tests (such as multichannel cystometry or cystoscopy). Men who are made aware of the structure and function of their lower urinary tracts may be better able to give truly informed consent, and to co-operate and engage throughout this process. They should also understand what is being done, why, and what the expected outcome is, including the possible adverse outcomes.

Many men seek treatment for LUTS because they are worried about possible cancer. In such patients referral to the NICE clinical guideline on Prostate Cancer[a] may be helpful.

15.2.2 Management

The options available for management of the LUTS should be specifically described to the patient; including benefits and risks of each choice and the risks of doing nothing or deferring treatment, in both the short and long-term.

Drug effectiveness may critically depend on concordance and accurate titration. Choice and type of preparation may influence the level of concordance. Men should be counseled, offered appropriate drug presentations and followed up to encourage concordance.

Until treatment has been successful, and in cases where long-term management of incontinence is necessary, patients may need specialist support close to their homes.

15.3 Does provision of information about management of LUTS improve patient outcomes?

See evidence Table 52, Appendix D, Forest Plots in Figures E-233 to E-235, Appendix E and Economic Evidence Table 53, Appendix D.

15.3.1 Interactive video based learning

These include computer and interactive video-based shared decision making programme designed to educate men about their condition and its treatments.

[a] See the NICE clinical guideline on prostate cancer (www.nice.org.uk/CG58)

15.3.1.1 Clinical evidence

Table 15-177: Educational interventions vs. no intervention – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Median change in symptom score[171]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Mean change in symptom score[20]	1	RCT	No serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Qmax	0					
Quality of Life (IPSS question)	0					

(a) *Imprecision as outcomes from only one study.*
(b) *This study had two phases of recruitment (pre-consent and post consent randomisation phase). The video based learning intervention was compared to the control group who were provided with a brochure containing basic information about the prostate gland and disease that can affect it.*

Table 15-178: Educational interventions vs. no intervention - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Symptom score (12 months)	104	123	Not applicable	MD: 0.57 [-1.27, 2.41]; p=0.54	Moderate
Median change in symptom score (9 months)	*57*	*55*	Not applicable	Int: -1 Cont: -2; p=0.8	Moderate

15.3.1.2 Economic evidence

We identify only one economic study on provision of information. Murray et al. (2001)[171] conducted a cost-consequences analysis together with their clinical study, included in the review of clinical evidence (15.3.1.1). Please see Economic Evidence Table 53 in Appendix D for details.

Table 15-179: Educational interventions vs. no intervention - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Murray2001[171]	Minor limitations (a)	Partially applicable (b)	

(a) *Not a full economic evaluation.*
(b) *The intervention does not reflect the clinical practice.*

Table 15-180: Educational interventions vs. no intervention - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Murray2001[171]	406 (a)	Not applicable (b, c)	Not applicable	Not reported

(a) *1999GBP. Cost of intervention (equipment, staff time) and following care (consultations with GPs, referrals, drugs, tests, diagnostic and surgical procedures).*
(b) *Many outcomes are reported with none given more relevance.*
(c) *No difference in health utility scores (EQ-5D) or anxiety scores but data were not provided.*

15.3.1.3 Evidence statement (s)

Clinical There is no statistically significant difference between interactive video

based programmes and normal care/no intervention in improving symptom scores.

Economic The interactive multimedia programme is more costly considering the cost of the intervention and the cost of subsequent care, and it did not generate better quality of life as measure by EQ-5D.

15.3.2 Self Management

Self management comprised of small group sessions facilitated by Urology Nurses trained to enhance self management skills and provided support. The aim was to modify conservative interventions to improve patient outcomes compared to standard care.

15.3.2.1 Clinical evidence

Table 15-181: Self management and standard care vs. standard care – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Mean IPSS[31]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Quality of life[31]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)
Qmax	0					

a) *Imprecision due to sample sizes being inadequate to detect a minimally important difference for the primary outcomes (IPSS and quality of life) or the confidence intervals are wide and cross or are close to the MID therefore making estimate of effect uncertain.*

Table 15-182: Self management and standard care vs. standard care - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean symptom score (12m)	53	51	Not applicable	MD 5.1 [2.7 to 7.6]	Moderate
Quality of life (IPSS question) (12m)	54	52	Not applicable	MD 0.5 [0 to 1.0]	Moderate

15.3.2.2 Economic evidence

No studies were identified.

15.3.2.3 Evidence statement (s)

Clinical Self management is more effective than standard care in improving symptoms scores.

Self management is more effective than standard care in improving quality of life symptom scores.

Economic No economic studies were identified.

15.3.3 Recommendations and link to evidence

	The GDG felt that it was important that men with LUTS should be given information on their condition and management options. A specific recommendation was not formulated as this topic is adequately covered in the introduction of the NICE guideline.
Relative values of different outcomes	The group considered an improvement in their symptoms and quality of life to be the primary outcomes. The quality of life reported was from the IPSS symptom score questionnaire. However, incontinence is one important quality of life factor that is not recorded by IPSS.
Trade off between clinical benefits and harms	The GDG considered it important that patients are fully aware of their condition and its management. The harm associated with lack of information and subsequent understanding could be increased anxiety and low compliance of medications.
Economic considerations	A study showed that providing interactive multimedia programmes increases costs with no significantly different outcome. However, this intervention does not reflect the clinical practice where other means of provision of information are adopted, which can improve outcomes or patient satisfaction without increasing costs to the NHS.
Quality of evidence	All three clinical studies were of moderate quality due to a lack of precision. The economic evidence has minor limitations but partial applicability as the intervention considered does not reflect the clinical practice.
Other considerations	The interactive programmes did not result in a significant improvement in symptoms and the group felt it was more appropriate to recommend general provision of information rather than specific techniques.

15.3.4 Supporting recommendations

Recommendation	**Ensure that, if appropriate, men's carers are informed and involved in managing their LUTS and can give feedback on treatments.**
Trade off between clinical benefits and harms	Many treatments for lower urinary tract symptoms, particularly drug therapies, are critically dependent upon dose titration and patient behaviour (e.g. lifestyle changes, eating and drinking). It is often helpful to have a continuing record (bladder diary) of symptoms, treatment and lifestyle modalities. Those men who need the support of a carer are unlikely to be able to maintain a bladder diary without help, but the potential value of this record justifies the involvement of the carer in this exercise.
Economic considerations	Not addressed.

Other considerations	The trade-off between involving a carer so closely in the man's treatment, and managing matters of patient confidentiality and consent may be complex. Where family members, for instance are able to act as carers, then appropriate training and support should be considered.
Recommendation	**Ensure men with LUTS have access to care that can help with:** • **their emotional and physical conditions and** • **relevant physical, emotional, psychological, sexual and social issues.** **Provide men with LUTS maintenance products at point of need and access to relevant support groups.**
Trade off between clinical benefits and harms	LUTS tend still to be a social taboo. Their impact covers many areas of lifestyle that are hard to discuss. However, management and recovery must include coping with that impact and many men may need help to do so.
Economic considerations	Not addressed.
Other considerations	Incontinence is a symptom that can destroy quality of life: it reduces freedom to travel and to socialise, self-respect and sexual function. The sooner that continence can be improved, the sooner the patient's quality of life will begin to improve. At present many PCTs will not provide such continence management until a diagnosis and treatment plan is in place. Though delay in providing access to specialist local expert continence advice and support services is economically understandable, distress may be avoided by giving access to continence advice and management services at an early stage.

15.4 Summary of recommendations

- Ensure that, if appropriate, men's carers are informed and involved in managing their LUTS and can give feedback on treatments.

- Ensure men with LUTS have access to care that can help with:
  - their emotional and physical conditions
  - relevant physical, emotional, psychological, sexual and social issues.

- Provide men with LUTS maintenance products at point of need and access to relevant support groups.

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