High-energy transurethral microwave thermotherapy for benign prostatic hyperplasia

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Nathan Walters and Mr Koji Makino from M-TAG Pty Ltd, a unit of IMS Health. Ms Alison Hillman of M-TAG Pty Ltd, a unit of IMS Health, edited the report. The report was endorsed by the Minister for Health and Ageing on 28 November 2005.

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Executive summary

The procedure

High-energy transurethral microwave thermotherapy (HE-TUMT) is a minimally invasive technology for the treatment of benign prostatic hyperplasia (BPH). The procedure involves a microwave antenna being positioned within the prostatic fossa, which then produces microwave energy to destroy obstructive prostatic tissue.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision-making when funding is sought under Medicare. A team from the Medical Technology Assessment Group (M-TAG) Pty Ltd, a unit of IMS Health, was engaged to conduct a systematic review and economic evaluation of HE-TUMT for the treatment of benign prostatic hyperplasia. An advisory panel with appropriate expertise then evaluated this evidence and provided advice to MSAC.

MSAC's assessment of high-energy transurethral microwave thermotherapy

The evidence for the efficacy and safety of HE-TUMT is based on a total of 10 studies comparing the procedure with one or more of the following: transurethral resection of the prostate (TURP), medication, interstitial laser coagulation of the prostate (ILCP) and transurethral needle ablation (TUNA).

There is a reasonable amount of evidence comparing HE-TUMT with TURP, consisting of five level II studies, one level III-1 study and three level III-2 studies. These studies varied in duration from three months to 36 months. Six studies used cooled HE-TUMT (five with the Prostatron® v2.5 system and one with the Dornier UroWave® system) and three studies used non-cooled HE-TUMT (ProstaLund®).

There is limited evidence comparing HE-TUMT with pharmacotherapy, consisting of an 18-month level III-1 study using the Targis® system versus terazosin and a six-month level III-2 study comparing the Prostatron® v2.5 system with terazosin. There are no studies comparing HE-TUMT with either prazosin or tamsulosin.

The evidence for HE-TUMT versus ILCP and/or TUNA is even more limited, based on one six-month level II study using the Prostatron® v2.5 system and two level III-2 studies (a six-month study using the Prostatron® v2.5 system and a three-month study using the Dornier UroWave® system).

In addition to the 10 comparative studies, the safety analysis includes secondary evidence from a number of single-arm studies of HE-TUMT, derived either from

non-comparative studies, or from other comparative studies in which the comparator is not one of the above (eg, sham or placebo).

Clinical need

BPH is one of the most common medical conditions in middle-aged and older men, with international studies estimating its prevalence at 14–21 per cent in men aged 40–59 years, increasing to 27–51 per cent in men over 60 years. Many patients with BPH complain of bothersome lower urinary tract symptoms, typified by urinary frequency, urgency, nocturia, decreased and intermittent force of stream and the sensation of incomplete bladder emptying. Left untreated, BPH can occasionally result in acute urinary retention, recurrent bladder infections and renal failure.

There are several treatment options available for managing the lower urinary tract symptoms associated with BPH. Pharmacotherapy is typically the 'first-line' therapy offered, and includes alpha-blockers such as tamsulosin, prazosin and terazosin, and the alpha-reductase inhibitor finasteride. However, more invasive surgical options are often necessary, particularly in patients who do not respond to pharmacological treatment. TURP is the gold standard for the surgical treatment of BPH, but there are also several 'minimally' invasive procedures available, such as TUNA (which recently received interim funding) and ILCP. HE-TUMT falls into this class of minimally invasive therapies.

Safety

Based on the available evidence, HE-TUMT is safer than TURP, resulting in a lower incidence of postoperative adverse events including serious haematuria (1.9% versus 6.5% respectively), transfusions (0% versus 8–13% respectively), incontinence (1.0% versus 2.2% respectively), urethral strictures and bladder neck stenosis (0.5% versus 6.8% respectively), and the potentially serious TUR syndrome (0% versus 2–4% respectively). Urinary tract infections are reported in a similar proportion of patients following both HE-TUMT and TURP (16% versus 14% respectively). Mortality associated with HE-TUMT and TURP is low (1.1% and 1.6%, respectively), and probably driven by co-morbid conditions in this population. No cases of fistulae formation were reported with HE-TUMT in the 10 comparative studies, although three cases resulting from operator error were identified in the secondary evidence.

The impact of these procedures on sexual function is an important consideration when choosing the appropriate therapy to treat the urinary symptoms associated with BPH. Although the evidence is limited due to poor reporting and follow-up, and a high degree of sexual dysfunction at baseline, it appears that, consistent with the existing literature, HE-TUMT results in much lower rates of ejaculatory and erectile dysfunction, compared with TURP. Three recent reviews found a lower rate of erectile dysfunction and ejaculatory dysfunction associated with HE-TUMT (4.4% and 19.8% respectively) compared with TURP (9.3–15.7% and 63.0–74.4% respectively) (de la Rosette et al 2003b; NHMRC uncomplicated LUTS management, 1996; Kirby et al 1994).

HE-TUMT has a slightly worse side effect profile compared with terazosin. Typical adverse events associated with terazosin are dizziness (13.5%), asthenia (7.7%), headache (5.8%), hypotension (1.9%), nausea (1.9%) and postural dizziness (1.9%).

The evidence, although limited, suggests HE-TUMT has a similar or better safety profile than ILCP/TUNA. The main differences include a higher incidence of urinary tract infection (61%) and bladder neck stenosis (2.1%) with ILCP.

Effectiveness

In patients with moderate-to-severe symptoms at baseline, HE-TUMT leads to significant and sustained improvements in subjective measures such as lower urinary tract symptoms and quality of life, as well as in objective measures such as maximum urinary flow rate and post-void residual volume. As shown in the safety assessment, HE-TUMT has a minimal impact on sexual function.

However, improvements following TURP tend to be both more rapid initially and significantly greater in the long-term, compared with HE-TUMT, for all objective and subjective measures except sexual function. For example, symptom scores (as assessed by the IPSS index), improve from a common baseline mean of 17–21 (moderate-to-severe), to a mean of 5–8 (mild) with HE-TUMT, and a mean of 3–7 (mild) with TURP at 12 months. After three years follow-up, HE-TUMT scores worsen slightly to a mean of 8–12 (moderate) in contrast to TURP scores that remain relatively stable at a mean of 3–6 (mild). Maximum urinary flow rates show a similar trend, improving from 8–9 mL/s at baseline in both groups, to 13–17 mL/s with HE-TUMT and 15–24 mL/s with TURP at 12 months, followed by a slow decline to 12–15 mL/s with HE-TUMT compared to a relatively stable 14–23 mL/s with TURP at three years.

HE-TUMT also results in a higher rate of treatment failure necessitating further treatment, compared with TURP (6.5–12.2% versus 4.8–9.6% at 12 months respectively; 19.5–25.8% versus 4.8–11.0% at three years respectively). Treatment failure with HE-TUMT is usually a result of a lack of, or decline in, effectiveness while complications, such as urethral strictures and bladder neck stenosis, are the typical reasons for further treatment in patients treated with TURP.

Although terazosin initially provides a more rapid improvement in symptoms, quality of life and uroflowmetry, it is significantly less effective than HE-TUMT in the long term on all measures. For example, symptom scores at 18 months improve to only 11.5 (moderate) with terazosin, compared with 7.5 (mild) with HE-TUMT. Furthermore, terazosin is associated with a very high rate of treatment failure due to lack of efficacy (41% at 18 months).

Compared with other minimally invasive therapies such as ILCP and TUNA, the limited evidence available indicates that HE-TUMT probably has a similar degree of efficacy.

Cost-effectiveness

The treatment pathway starting with HE-TUMT is associated with higher costs than the pathway starting with TURP ($5959 versus $5444 respectively), but lower costs than the pathway starting with pharmacotherapy ($7088) over the 10-year simulation period. The number of quality adjusted life years (QALYs) during the simulation period is greatest with TURP (6.72) followed by HE-TUMT (6.52) and then pharmacotherapy (6.35). All estimates are discounted at 5 per cent per annum.

These results indicate that the treatment pathway starting with HE-TUMT represents a dominant treatment strategy compared with the pathway starting with pharmacotherapy, generating superior effectiveness at lower economic costs. However, the pathway starting with HE-TUMT is dominated by that starting with TURP.

A series of sensitivity analyses have been performed to assess the robustness of the results. The results of these analyses indicate that the health outcomes in the HE-TUMT arm remain inferior to those in the TURP arm even under the most favourable scenario

for the HE-TUMT arm. However, the cost difference between the HE-TUMT and TURP arms are seen to diminish with even a slight change in the cost assumptions. For example, when a slightly higher procedural cost estimate for TURP is used, the resulting overall costs were lower with HE-TUMT ($6358) compared with TURP ($6443). This may indicate that the treatment costs can be considered largely comparable between the two treatment pathways. The sensitivity analyses also show that, compared with the pharmacotherapy arm, HE-TUMT is consistently a dominant treatment option.

Recommendation

MSAC recommended that on the strength of evidence pertaining to high-energy transurethral microwave therapy (HE-TUMT) for patients with moderate to severe symptoms of benign prostatic hypertrophy public funding should be supported for this procedure.

– The Minister for Health and Ageing accepted this recommendation on 28 November 2005. –

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of high-energy cooled transurethral microwave thermotherapy (HE-TUMT) which is a therapeutic technology for benign prostatic hyperplasia (BPH). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for HE-TUMT for BPH.

Background

High-energy transurethral microwave thermotherapy

The procedure

High-energy transurethral microwave therapy (TUMT) is minimally invasive in that no cutting or incision is involved, and only local or regional anaesthesia is employed. This means the procedure can be undertaken on an outpatient or day surgery basis. Expert opinion within the Advisory Panel indicated that 50–75 per cent of patients in Australia would undergo the procedure as day surgery with analgesia and/or sedation in addition to local or regional anaesthesia. Microwave energy is delivered to the prostatic tissue via the transurethral route using a flexible applicator. The goal of thermotherapy is to destroy intraprostatic tissue by heating it to temperatures in excess of 45°C, the cytotoxic thermal threshold in prostatic adenomatous tissue (Devonec et al 1991). Early application of the procedure utilised 'lower-energy' protocols, in which the intraprostatic temperature did not exceed this threshold and caused little or no tissue destruction. As a result, 'higher-energy' protocols were introduced in which the intraprostatic temperature ranges between 45°C and 80°C, which leads to coagulative necrosis and creation of a prostatic cavity. The procedure was previously delivered in a 60–70 minute session although more recent developments have reduced this to a 30-minute session.

There has been some confusion over the use of the term 'high-energy', which has been used to refer to both the power output of the device (> 60 W) and also the intraprostatic temperature (> 45°C). However, as it is the intraprostatic temperature that is the critical determinant of TUMT effects, in the context of this assessment report, 'high-energy' will refer to those devices that result in intraprostatic temperatures in excess of 45°C. Where the intraprostatic temperature has not been reported in a publication, the power output will be used as a secondary indicator for determining whether to include a study (ie, power output of > 60 W will also be included as 'high-energy'). All other devices have been grouped as 'low-energy' and will not be discussed further in this assessment report.

The Targis®, Prostatron® (v2.5 and v3.5) and Dornier UroWave® TUMT systems are designed to protect and spare the urethra from injury. This is achieved by the circulation of cooled water through channels within the dedicated microwave catheter and around the enclosed microwave antenna. By cooling the urethral surface and maintaining its temperature at no more than 45°C, the urethra is preserved whilst deeper coagulative necrosis can be achieved at the peak temperature location 6–7 mm from the urethral mucosa. As the thermal pain threshold is also 45°C, urethral cooling also allows the procedure to be relatively painless, requiring minimal anaesthesia or sedation and shortens recovery time, with no need for extended hospitalisation beyond the immediate recovery period following the procedure. Furthermore, post-procedural discomfort resulting from the irritative symptoms associated with the sloughing of urethral tissue can be avoided.

Non-cooled systems such as the ProstaLund® use lower power outputs to reach similar high intraprostatic temperatures, however, the urethral mucosa is not spared as with the cooled HE-TUMT systems (Albala et al 2002).

This report will assess the evidence from both cooled and non-cooled HE-TUMT systems.

Intended purpose

HE-TUMT is intended to treat symptomatic benign prostatic hyperplasia (BPH) to relieve lower urinary tract symptoms (LUTS).

Clinical need/burden of disease

Benign prostatic hyperplasia is one of the most common medical conditions in middle aged and older men. The clinical symptoms of BPH, which include loss of bladder control, urgency, weak stream, painful urination, and nocturia, profoundly affect a person's quality of life. Occasionally, BPH leads to serious health conditions, including acute urinary retention, recurrent bladder infections, and renal failure.

Treatment statistics for benign prostatic hyperplasia

The number of patients requiring treatment for BPH in Australia can be estimated through hospital morbidity and HIC data. Using the ICD-10-AM code for primary diagnosis there were 21,449 hospitalisations for prostate hyperplasia between 2002 and 2003 (AIHW hospital separation data, 2005; see **Table 1**). There has been no major change in hospitalisations for prostate hyperplasia in the period from 2000 to 2003.

Table 1 Separations for principal diagnosis of BPH 2002–2003

ICD-10-AM code	Condition	2000–2001	2001–2002	2002–2003
N40	Hyperplasia of the prostate	21,476	21,552	21,449

Source: AIHW National Hospital Morbidity Database
http://www.aihw.gov.au/cognos/cgibin/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0203

Correspondingly, over 20,000 occurrences for principal procedures used to treat BPH were recorded for 2002 to 2003 (AIHW hospital separation data, 2005; see **Table 2**).

Table 2 Occurrences for principal procedures to treat BPH 2002–2003

ICD-10-AM code	Procedure	2002–2003
37203-00	Transurethral resection of the prostate (TURP)	20,146
37203-01	Transurethral needle ablation of the prostate (TUNA)	37
37203-01	Transurethral vaporisation of the prostate	40
37200-03	Suprapubic prostatectomy	106
37200-04	Retropubic prostatectomy	77
37200-05	Other open prostatectomy	169
Total		**20,575**

Source: AIHW National Hospital Morbidity Database (accessed April 2005)
http://www.aihw.gov.au/cognos/cgi–bin/ppdscgi.exe?DC=Q&E=/AHS/procedures_0203

However, not all patients diagnosed with BPH undergo surgery. In some patients symptoms of BPH can be significantly improved with pharmacological treatments. Drugs such as the alpha-adrenergic blockers terazosin (Hytrin®) and tamsulosin (Flomax®) and the alpha reductase inhibitor finasteride (Proscar®) can be used for the medical management of BPH. Currently these drugs are reimbursed on the Repatriation Pharmaceutical Benefit Scheme (RPBS) for men with BPH where other drug therapy is contra-indicated or has failed and surgery is not appropriate. They are also available on private prescription. In the period between July 2003 and June 2004, a total of 32,424 claims for terazosin, tamsulosin and finasteride were processed (HIC claims statistics, 2005; **Table 3**).

The Advisory Panel also indicated that a significant number of people with BPH are treated with prazosin. As prazosin is also prescribed for hypertension, it is not possible to determine the number of scripts written for the treatment of BPH.

In 1997, 1.4 million US men opted for drug therapy (Feldman, 1997). Extrapolating mathematically from this population-based figure, based on 2001 Australian census data identifying the numbers of men in the 'at risk' age groups for developing LUTS, approximately 90,000 Australian men would be using medications to control their urinary symptoms. In the report prepared by Vos and Mathers (1999), some estimates of medical management are included, credited to Associate Professor Mark Frydenberg (Urologist, Head of Unit, Monash Medical Centre), based upon his own clinical experience with BPH patients. Using this information, it was estimated that approximately one third of men will have a poor response to medication and will require further treatment. This translates to around 30,000 men at any one time.

Table 3 Pharmaceutical agents used to treat BPH where surgery is inappropriate

RPBS item number	Pack sizes	Number of claims (July 2003 to June 2004)
Alpha adrenergic blocking agents		
Terazosin hydrochloride		
Authority required. Treatment of benign prostatic hyperplasia where surgery is inappropriate, or where other drug treatment has failed or is contraindicated		
4396J	Starter pack containing 7 tablets 1 mg and 7 tablets 2 mg	14
4397K	Tablet 2 mg	802
4398L	Tablet 5 mg	1086
4399M	Tablet 10 mg	220
Tamsulosin hydrochloride		
Authority required. Treatment of benign prostatic hyperplasia where surgery is inappropriate, or where other drug treatment has failed or is contraindicated		
4464Y	Capsule 400 µg (modified release)	18,638
Alpha reductase inhibitor		
Finasteride		
Authority required. Treatment of benign prostatic hyperplasia where surgery is inappropriate, or where other drug treatment has failed or is contraindicated		
4233T	Tablet 5 mg	11,664

Source: HIC claims data (accessed April 2005) http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml

Prevalence of benign prostatic hyperplasia

The prevalence of BPH in Australian men can be estimated from a number of international epidemiology studies. In men aged 40–59 years the prevalence of BPH in Scotland (Garraway et al 1991), the United Kingdom (Trueman et al 1999) and the United States (Jacobsen et al 1995) ranged from 14–21 per cent. In men over 60 years, the prevalence of BPH increases to between 27–51 per cent.

Existing procedures

Pharmacological treatments options are generally the 'first-line' therapy offered to most men following the initial assessment of their lower urinary tract symptoms. These include type II 5-alpha-reductase inhibitors such as finasteride (Proscar®) and alpha-1 adrenergic antagonists such as tamsulosin (Flomax®) and terazosin (Hytrin®). Type II 5-alpha reductase inhibitors prevent the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT), on which the enlargement of the prostate in BPH in dependent, thereby reducing prostate volume. Binding of alpha-1 adrenergic antagonists to the prostate results in relaxation of the prostate smooth muscle, increasing urinary flow by reducing smooth muscle tension in the prostate and urethra (Lepor et al 1996; Lieber 1998; McConnell et al 1998).

Patients who do not respond to pharmacological treatment will be considered for more invasive procedures. The gold standard for the surgical treatment of BPH is transurethral resection of the prostate (TURP), which involves the use of electrocauterisation to remove tissue from within the prostate gland. A satisfactory outcome is achieved with TURP in 90–95 per cent of patients over a 5–6-year follow-up period (Mebust 1998). Consequently, TURP is the 'reference standard' for comparison with the HE-TUMT procedure.

Other surgical options include open prostatectomy, which is generally recommended for patients with enlarged prostates, and transurethral incision of the prostate (TUIP). TUIP involves the use of a knife, electrode or laser to make one or more incisions, usually from the bladder neck to the verumontanum. These incisions are then deepened until the capsule of the prostate is reached, thereby relieving the obstruction around the urethra. Symptom improvement is reported in 98 per cent of patients (Jepsen & Bruskewitz 1998) undergoing open prostatectomy, with a treatment failure rate of approximately 2 per cent (Jepsen & Bruskewitz 1998; Roos et al 1989). The treatment failure rate for TUIP is reported as similar to TURP (Baine et al 1998; Jepsen & Bruskewitz 1998).

Additionally, interim funding is being provided for the use of transurethral needle ablation (TUNA) of the prostate for patients with moderate to severe lower urinary tract symptoms who are not medically fit for TURP. Patients not medically fit for TURP include those with a high risk of developing a serious complication from the surgery and patients with a co-morbidity, which may substantially increase the risk of TURP or the risk of the anaesthetic necessary for TURP. TUNA belongs to the group of less invasive procedures, which also includes transurethral vaporisation of the prostate (TVP), visually assisted laser prostatectomy (VLAP), interstitial laser coagulation of the prostate (ILCP), TUMT and high-intensity focused ultrasound (HIFU) (Baine et al 1998; Blute et al 1996; Jepsen & Bruskewitz 1998). TUNA involves the delivery of radiofrequency energy directly into the hyperplastic prostatic tissue, resulting in selective thermal ablation.

Comparator

The Advisory Panel indicated that TURP is the gold standard for treatment of BPH and is thus an appropriate comparator for HE-TUMT.

The Advisory Panel also indicated that pharmacotherapy is almost universally used as first line therapy in patients with bothersome BPH in the Australian setting before pursuing one of the minimally invasive (eg, TUNA) or surgical (eg, TURP) options. However, determining the appropriateness of pharmacotherapy as a comparator to HE-TUMT, the Advisory Panel did note that it is possible that some patients, given the choice, may elect HE-TUMT over medication as a first line therapy for BPH. Therefore, this assessment report will consider the evidence for pharmacotherapy as a comparator to HE-TUMT. However, it was the expert opinion of the Advisory Panel that in clinical practice, HE-TUMT would not be used as a first line therapy. Most doctors would recommend (and most patients would choose) medication as a first line treatment for BPH. The most likely place for HE-TUMT would be as a second line therapy in those patients in whom medication had failed. As such, the comparator would then be TURP.

The aim of the literature search conducted for this review was to find all reports comparing HE-TUMT to TURP (the gold standard for treatment of BPH), and pharmacotherapy as well as any of the other newer, less invasive procedures detailed above.

Marketing status of the device/technology

A search of the Therapeutic Goods Administration website using the terms 'Prostatron', 'Targis', 'UroWave', 'Prostcare', 'TUMT', and 'transurethral microwave thermotherapy', found that only the Prostatron® brand of TUMT is registered (**Table 4**).

Table 4 TGA registered TUMT devices

ARTG number	59395
Sponsor name	Urology Solutions Pty Ltd
ADG	Thermal Control Equipment
Product ID	117312
Product name	PROSTATRON®
UMDNS code and description	17905 Prostatic Hypertrophy Treatment Systems, Microwave

Current reimbursement arrangement

Currently there is no specific Medicare Benefits Schedule item number for the TUMT procedure.

Approach to assessment

Research question

To what extent is high-energy transurethral microwave thermotherapy (HE-TUMT), safe, effective and cost-effective in the treatment of the lower urinary tract symptoms (LUTS) associated with the condition of BPH, relative to the listed comparators?

Review of literature

The medical literature was searched to identify all relevant studies and reviews published up to 2005. Searches were conducted via in the primary databases indicated in **Table 5**.

Search strategy

Primary databases

Table 5 Electronic databases searched for the review of the use of HE-TUMT for treating LUTS in patients with benign prostatic hyperplasia

Database	Period covered/date searched
Medline	1966 to May Week 3 2005
EMBASE	1980 to 2005 Week 21
Cochrane Library	Issue 2, 2005 (26 May 2005)

The search terms included the following:

- Microwave diathermy, microwave induced hyperthermia, transurethral microwave thermotherapy, high energy microwave thermotherapy
- Prostatron®, Prostasoft, ProstaLund®, Targis®, Coretherm®
- Prostatic hyperplasia, lower urinary tract symptoms, bladder obstruction.

A manual search of bibliographies from the relevant included studies was also conducted. Complete details of the literature searches performed using the Medline and EMBASE databases are presented in **Appendix F**.

Inclusion criteria

- Original publications reporting the results of one or more clinical trials (ie, non-systematic reviews, editorials, opinion pieces and letters will be excluded)
- Use of HE-TUMT as currently approved by the Therapeutic Goods Administration (TGA)
- Publications reporting studies in patients with diagnosed benign prostatic hyperplasia (or hypertrophy) or LUTS
- Publication in English

- Comparison of HE-TUMT with the appropriate comparator
- Reporting of an appropriate outcome (eg patient symptom scores).

Exclusion criteria

- Non-human or *in vitro* studies
- Foreign language publications
- Trials with 20 or fewer patients will be excluded from the efficacy evaluation. However, adverse events and safety outcome data from such trials will be included for completeness
- Non-comparative trials will be excluded from the efficacy evaluation. However, adverse events and safety outcome data from such trials will be included for completeness.

Search results

The flow chart in **Figure 1** summarises the exclusion of studies from the safety and effectiveness review of high-energy TUMT. A total of 583 references were identified by the search, of which 20 were included in the effectiveness review. Of these 583, 115 met the criteria to be considered as evidence in the safety review of which 81 reported safety outcomes.

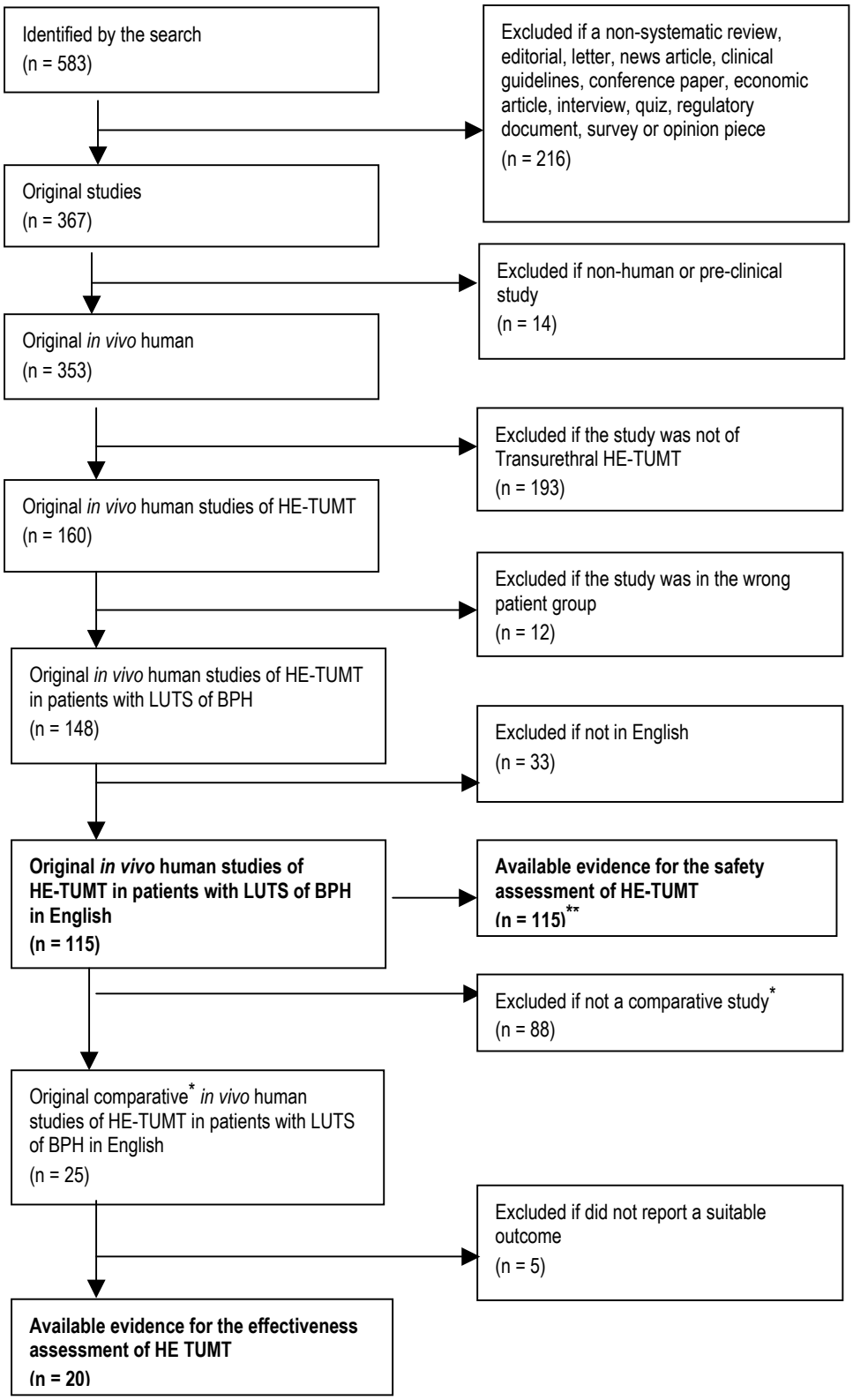

Figure 1 Reasons for exclusion of published reports of HE-TUMT identified by the literature search

Abbreviations: HE TUMT, high-energy transurethral microwave thermotherapy; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia

**77 reported safety outcomes and were included in the safety review*

***This group includes comparative trials in which the comparator is not TURP, TUNA, ILCP or medication as well as single-arm non-comparative trials*

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000).

These dimensions (**Table 6**) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 6 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design*
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

**See Table 7*

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in **Table 7**.

Table 7 Designations of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Modified from NHMRC 2000

Expert advice

An Advisory Panel with expertise in the management of benign prostatic hyperplasia (BPH) was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided in **Appendix B**.

Evidence

Evidence for safety has been divided into primary and secondary evidence. The primary evidence contains only comparative trials of HE-TUMT versus TURP, medication, ILCP or TUNA. These constitute the trials also included in the efficacy review (**Table 8**). The secondary evidence contains single-arm studies of HE-TUMT, derived either from non-comparative studies, or from other comparative studies in which the comparator is not one of the above (eg, sham or placebo). For a complete listing of both primary and secondary studies included in the safety analyses, see **Appendix C**.

Results from duplicate studies, or studies containing overlapping patient populations (ie, recruited from the same cohort) are not presented in the safety section. In these cases, the largest inclusive cohort or the study presenting the most complete outcomes have been used. Duplicate publications providing further information at different time points have, however, been presented. They have been grouped in tables with the main publication, indented and separated by a broken line. Studies with incomplete or poorly reported outcomes are not presented in the main body of this document, but are presented in **Appendix C**. Treatment failure rates are calculated based on numbers entered into the study rather than number used in the analysis.

Table 8 Relevant published and unpublished studies of HE-TUMT identified for the efficacy analysis (and primary safety analysis)

Study	Publication status	Study design
Hoffman et al 2004	Published	Systematic review of randomised controlled trials
Ahmed et al 1997	Published	Prospective, open, randomised controlled trial
Arai et al 2000	Published	Prospective controlled before-and-after study
D'Ancona et al 1997b	Published	Prospective, open, randomised controlled trial
D'Ancona et al 1998	Published	Study duplicate (d'Ancona et al 1997b)
De la Rosette 2003a	Published	Prospective, open, randomised controlled trial
Djavan et al 1999e	Published	Prospective, open. Pseudo-randomised controlled trial
Djavan et al 2001	Published	Study duplicate (Djavan et al 1999e)
Floratos et al 2001a	Published	Study duplicate (de la Rosette 2003a)
Francisca et al 1999c	Published	Study duplicate (de la Rosette 2003a)[a]
Francisca et al 2000	Published	Study duplicate (de la Rosette 2003a)[a]
Hansen et al 1997	Published	Prospective controlled before-and-after study
Kobelt et al 2004	Published	Study duplicate (Wagrell et al 2002)
Norby et al 2002a	Published	Prospective, open, randomised controlled trial
Norby et al 2002b	Published	Study duplicate (Norby et al 2002a)
"Study B"[b]	Published	Prospective, open, randomised controlled trial
Wagrell et al 2002	Published	Prospective, open, randomised controlled trial
Wagrell et al 2003	Abstract	Study duplicate (Wagrell et al 2002)
Wagrell et al 2004	Published	Study duplicate (Wagrell et al 2002)
Witjes et al 1997	Published	Prospective controlled before-and-after study

[a]*Hoffman reports this as a duplicate of Floratos et al 2001a*
[b]*Identified from FDA website: http://www.fda.gov/cdrh/pdf/p010055.html*

Systematic reviews

One systematic review of TUMT versus TURP was identified (Hoffman et al 2004). Inclusion criteria, assessment of quality and applicability of the review are summarised in **Table 69 (Appendix D)**. The review, whilst of high quality, was of limited applicability as it only assessed comparative efficacy and safety of TUMT versus TURP, and not other comparators such as alpha-blockers, ILCP or TUNA. Furthermore, only randomised trials were included: non-randomised comparative studies were excluded from the search. Finally, low-energy and high-energy TUMT studies were included, whereas this evaluation will only be assessing the efficacy and safety of the high-energy TUMT devices. Nevertheless, the conclusions of the review were that TUMT was safe and effective in the short term as an alternative to TURP for treating BPH. However, the degree of symptom relief and urinary flow improvements were greater with TURP. Furthermore, the treatment failure rates were lower with TURP compared to TUMT.

Comparative studies included in the efficacy and primary safety analyses

The literature search identified 10 studies comparing cooled or non-cooled HE-TUMT against either TURP, alpha-blockers (terazosin), ILCP or TUNA. Study design, patient characteristics and an assessment of NHMRC level of evidence, study quality and applicability are presented in **Appendix D**.

Five of the studies were randomised controlled level II studies comparing HE-TUMT to TURP (d'Ancona et al 1998; Floratos et al 2001a; Norby et al 2002a; Witjes et al 1997; Wagrell et al 2004; Study B in 2002 submission to FDA, PMA P010055 SSED). One of the studies had an additional treatment arm in which patients were randomised to ILCP (Norby et al 2002a). Two additional pseudo-randomised trials (level III-1) were identified, one comparing HE-TUMT with TURP (Ahmed et al 1997) and the other comparing HE-TUMT with an alpha-blocker (Djavan et al 1999e, 2001). All the randomised trials were open label.

In terms of the initial randomisation process in which treatment was allocated, some studies reported that the method of randomisation involved sealed envelopes. However, treatment allocation was explicitly reported as double-blinded in only two of the trials (Wagrell et al 2004; Study B in 2002 submission to FDA, PMA P010055 SSED). In the remainder, the adequacy of treatment allocation could not be determined due to a lack of sufficient detail. Analyses were most commonly performed on evaluable patients at each time point rather than intention-to-treat (ITT). In most cases, this corresponded to more than 80 per cent of patients at up to 12 months, although this dropped to less than 70 per cent and sometimes under 60 per cent over longer follow-up periods (up to three years). Exclusion of patients from the analyses was often due to loss to follow-up (refusal, non-contactable, death) treatment failure or incomplete reporting of outcomes.

Three prospective controlled before-and-after studies (level III-2) were also included which compared HE-TUMT to TURP, ILCP, alpha-blockers and/or TUNA (Arai et al 2000; Witjes et al 1997; Hansen et al 1997). Selection bias was a significant issue with these trials as treatment allocation was based on doctors' advice, the severity of symptoms or patients' views of the benefits including symptom improvements versus risks. Therefore baseline patient demographics are typically not well matched. Finally, patient characteristics and outcomes were generally poorly reported. In the study by Witjes et al (1997) patients undergoing TURP were selected from and assessed at a different hospital using different criteria to the cooled HE-TUMT, terazosin and ILCP patients. Consequently, this study was of limited use in interpreting the comparative efficacy of cooled HE-TUMT versus TURP.

Seven of the included studies used cooled HE-TUMT systems: five used the Prostatron® v2.5 device (d'Ancona et al 1998; de la Rosette et al 2003a; Floratos et al 2001a; Norby et al 2002a; Witjes et al 1997; Ahmed et al 1997) one used the Targis® device (Djavan et al 1999e, 2001) and one used the Dornier UroWave® device (Arai et al 2000). The three remaining non-cooled HE-TUMT studies all used the ProstaLund® device (Wagrell et al 2004; Study B in 2002 submission to FDA, PMA P010055 SSED; Hansen et al 1997).

Patient characteristics and baseline variables are presented in **Table 9**. The average age of patients included in the studies was similar (mean approximately 68). In general, patients with moderate-to-severe symptoms were included (the mean baseline IPSS were

approximately 20, indicating severe BPH[1]). It is worth noting that in the study by Djavan et al (1999e, 2001), medication was used to treat patients with moderate-to-severe baseline symptoms.

The average prostate volume was approximately 44 mL. Three trials specified inclusion criteria for patients of prostate volumes from 30–100 mL (d'Ancona et al 1998; Wagrell et al 2004; Study B in 2002 submission to FDA, PMA P010055 SSED). Two other studies had similar criteria, one including patients with prostate volumes 25–100 mL (Ahmed et al 1997) and another with prostate volumes > 30 mL (de la Rosette et al 2003a; Floratos et al 2001a). Five other trials did not have inclusion/exclusion criteria regarding prostate volume (Norby et al 2002a; Arai et al 2000; Witjes et al 1997; Hansen et al 1997; Djavan et al 1999e, 2001).

Norby et al (2002a) differed from the others in that it specified that patients in the TUMT group with prostate volumes less than 30 mL were treated with low-energy TUMT (prostatron v2.0), whilst for larger prostates, high-energy protocols were used (Prostatron® v2.5). In the TUMT group, 8/46 (17.4%) received LE-TUMT, and 37/46 (80.4%) received HE-TUMT. One patient (2.2%) received a TURP instead of TUMT because the surgeon believed a median prostatic lobe was an exclusion criteria: although the presence of a large median lobe is an indication not to use TUMT, strictly speaking, this patient did not receive the treatment to which they were randomised, although they were included with the TUMT group on an ITT basis. Furthermore, TURP and TUIP were grouped together in Norby et al (2002a) because TUIP was considered comparable with TURP when treating patients with small prostates. Of the 24 randomised to TURP/TUIP, one refused surgery whilst 23 were treated as per randomisation: 18 patients received TURP, three received TUIP and two were not specified as they were excluded from analyses (pathology revealed T1 prostate cancer).

Wagrell et al (2002) reported outcomes at three, six and 12 months follow-up, whilst Wagrell et al (2004) provided 12-month results plus further results at 24 and 36 months follow-up. As 12-month results were identical in both publications, short-term results for this study (less than 12 months) were extracted from Wagrell et al (2002), whilst long-term results (at least 12 months) were extracted from Wagrell et al (2004). Safety results from 'Study B' (in 2002 submission to FDA, PMA P010055 SSED) were reported as a combined result with Wagrell et al (2002) and a non-comparative study by Gravas et al (2003) for most outcomes, limiting the information that could be extracted from this study.

De la Rosette et al (2003a) and Floratos et al (2001a) reported three-year follow-up data for cooled HE-TUMT versus TURP. Efficacy results were reported in greater detail in de la Rosette (2003a) in contrast to safety that was reported in greater detail in Floratos et al (2001a). Francisca et al (1999c) and Francisca et al (2000) were study duplicates of de la Rosette et al (2003a), although the number randomised differed, as did the number of patients evaluated. Where possible, results presented were from de la Rosette et al

[1] An IPSS score of 0–8 indicates mild symptoms, 8–19 indicates moderate symptoms and 20–35 indicates severe symptoms.

(2003a) and Floratos et al (2001a). However, for some outcomes that were poorly reported, such as quality of life and sexual function, the duplicate references were used.

Hansen et al (1997) was of low quality and limited use, as it did not report patient characteristics.

Table 9 Patient characteristics in the included studies for efficacy

Study	Study design	NHMRC level of evidence	Treatment group	Age (years)	Prostate volume (mL)	Mean IPSS/ AUA	Q_{max} (mL/s)
D'Ancona et al 1998	Prospective, open, randomised controlled trial	II	HE-TUMT	69.3	43.4	18.3	9.3
			TURP	69.6	44.9	16.7	9.3
De la Rosette 2003a	Prospective, open, randomised controlled trial	II	HE-TUMT	67	51	20	9.2
			TURP	66	52	20	8.0
Norby et al 2002a	Prospective, open, randomised controlled trial	II	LE/HE-TUMT	66	43	20.5	9.1
			ILCP	65	44	21.4	10.2
			TURP/TUIP	68	44	21.3	9.6
Wagrell et al 2004	Prospective, open, randomised controlled trial	II	HE-TUMT	67	49	21.0	7.6
			TURP	69	53	20.4	7.9
'Study B'[b]	Prospective, open, randomised controlled trial	II	HE-TUMT	67.5	51.9	20.0	7.0
			TURP	67.7	56.0	19.2	7.0
Ahmed et al 1997	Prospective, open, randomised controlled trial	III–1	HE-TUMT	69.36	36.6	18.5	10.1
			TURP	69.45	46.1	18.4	9.5
Djavan et al 1999e, 2001	Prospective, open. Pseudo-randomised controlled trial	III–1	HE-TUMT	66.2	39.6	19.4	8.3
			Terazosin	64.0	39.1	18.9	8.9
Arai et al 2000	Prospective controlled before-and-after study	III–2	HE-TUMT	66.4	39.0	18.4	7.7
			TURP	68.8	38.6	19.0	7.7
			Laser	69.7	47.4	19.3	7.6
			TUNA	68.5	47.0	19.8	8.2
Hansen et al 1997	Prospective controlled before-and-after study	III–2	HE-TUMT	–	–	–	–
			TURP	–	–	–	–
			Degree of BOO[a,b]:	**N, M, S**	**N, M, S**	**N, M, S**	**N, M, S**
Witjes et al 1997	Prospective controlled before-and-after study	III–2	HE-TUMT	65, 66, 68	47, 52, 70	15, 19, 17	9.5, 10.4, 8.7
			TURP	70, 69, 68	28, 28, 34	5, 9, 9[c]	10.5, 9.9, 8.8
			Terazosin	63, 64, 65	34, 41, 46	20, 17, 23	14.2, 8.9, 8.3
			Laser	60, 66, 64	38, 42, 50	19, 21, 21	9.8, 8.1, 7.8
			Watchful waiting	66, 62, 64	37, 37, 45	12, 14, 13	14.2, 13.4, 10.0

Abbreviations: *BOO, bladder outlet obstruction, N, none; M, moderate; S, severe; LPURR, linear passive urethral resistance ratio*

[a]*Severity based on LPURR obstruction category: none = 0 or 1; moderate = 2 or 3; severe = 4 or more*

[b]*Median scores reported*

[c]*Symptom score in TURP group was that described by Frimodt-Moller et al (1984)*

Results of assessment

Is it safe?

Evidence for safety has been divided into primary and secondary evidence. The primary evidence contains only comparative studies of HE-TUMT versus TURP, medication, ILCP or TUNA and constitute the trials also included in the efficacy review (**Table 8**). However, only seven of these primary studies (five level II, two level III-1), varying from three to 36 months in duration, reported safety outcomes. Four level II studies and one level III-1 study examined the comparative safety of HE-TUMT versus TURP. There was limited evidence for HE-TUMT versus terazosin (one level III-1 study) and HE-TUMT versus ILCP/TUNA (one level III-1 study). Study quality and design for these primary studies are described in the section titled '**Evidence**' in **Appendix D**.

The secondary evidence contains single-arm studies of HE-TUMT, derived either from non-comparative studies, or from other comparative studies in which the comparator is not one of the above (such as sham or placebo). For a complete listing of both primary and secondary studies included in the safety analyses, see **Appendix C**.

Expert opinion indicates that most patients will experience urinary retention following HE-TUMT in the immediate post treatment period and that patients will typically be catheterised as a result up to 10 days. Thus transient urinary retention or catheterisation has not been extracted, although accompanying tables may make some comment where appropriate. Re-retention, persistent retention and re-catheterisation after the initial post treatment period, however, have been recorded.

Primary evidence

Most of the comparative studies noted that the majority of patients experienced transient dysuria (often reported together with urgency as irritative symptoms) and haematuria as a result of the HE-TUMT procedure. Typically, these resolved within a few days to weeks in almost all patients.

In **Table 10**, the numbers in the column showing the incidence of haematuria refer only to serious haematuria (often requiring hospitalisation) as opposed to transient haematuria associated with the procedure. For example, Wagrell et al (2002, 2004) reported haematuria as a serious adverse event usually requiring hospitalisation due to clot retention. These authors also reported non-serious haematuria, probably of a transient nature; these cases are not included in the column showing the incidence of haematuria in **Table 10** (though they are included in the comments column).

The rate of serious haematuria in HE-TUMT treated patients was estimated at 3/161 (1.9%) (**Table 10;** Ahmed et al 1997; d'Ancona et al 1997b; Wagrell et al 2002 and 2004). The comparative rate in patients treated with TURP was 7/107 (6.5%). Haematuria was not reported with either terazosin (Djavan et al 1999e; 2001) or ILCP (Norby et al 2002a) treated patients.

Urinary tract infections were fairly common in patients treated with both HE-TUMT (42/258; 16%) and TURP (17/121; 14%), although much less common than in patients treated with ILCP (27/48; 61%) (**Table 10**). There were no urinary tract infections reported with terazosin in the study by Djavan et al (1999e, 2001). It was not always clear whether a diagnosis of UTI was confirmed by bacterial culture.

In the studies by Djavan et al (2001e) and Ahmed et al (1997), the diagnosis of UTI appeared to be confirmed by bacterial culture. The study by Norby et al (2002a) reported that patients diagnosed in an outpatient setting were confirmed by culture, whereas no such information was available for those diagnosed by a general practitioner. D'Ancona et al (1997b) and Wagrell et al (2002, 2004) did not report whether UTI was diagnosed symptomatically (ie, extrapolated from symptoms of frequency, urgency and dysuria) or by culture.

Less commonly occurring adverse events were haemospermia and epididymitis with HE-TUMT (and the latter with TURP) and persistent urinary retention with HE-TUMT, TURP and ILCP (**Table 10**). The most common adverse events with terazosin treated patients were dizziness (15%), asthenia (8%), headache (6%) and hypotension (2%) (**Table 10**). None of these were reported with HE-TUMT.

Transfusions were required in 4/30 (13%) of TURP patients in the study by Ahmed et al (1997) and 2/24 (8%) of TURP patients in the study by Norby et al (2002a). No patient treated with HE-TUMT required a transfusion.

The TUR syndrome is an uncommon but potentially serious complication associated with TURP attributed to the absorption of irrigating fluid during the operation and in the immediate postoperative period. Symptoms include confusion, hypotension, bradycardia, nausea and vomiting and collapse. TUR syndrome occurred in 1/24 (4%) of TURP patients in the study by Norby et al (2002a), and 1/46 (2%) of TURP patients in the study by Wagrell et al (2002; 2003) (**Table 10**). No incidents of TUR syndrome were noted with HE-TUMT.

Incontinence occurred in 2/208 (1.0%) of HE-TUMT patients and 3/136 (2.2%) of TURP patients (Floratos et al 2001a; Wagrell et al 2004; Norby et al 2002a). Transient incontinence was also reported in 3 per cent of HE-TUMT patients and 13 per cent of TURP patients at 12 months in the study by Wagrell et al (2002).

Table 10 Common adverse events in the comparative trials of HE-TUMT versus TURP/ medication/ILCP/TUNA

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
HE-TUMT							
Ahmed 1997	6	Prostatron v2.5	30	1/30 (3.3)	1/30 (3.3)	–	All patients reported temporary dysuria; constipation and haematuria reported in all patients for up to 24 hours. Patient with the UTI also had epididymo-orchitis and haematuria (hospitalised). Two patients had catheters for 10 days, and one for 6 weeks
D'Ancona 1997b	12	Prostatron v2.5	31	5/31 (16.0)	0/31 (0)	–	Irritative voiding symptoms (n = 9). No patient required a transfusion
Floratos 2001a	36	Prostatron v2.5	82	–	–	1/82 (1.2)	Treatment failures resulting in further treatment were as a consequence of stress incontinence (n = 1), severe storage symptoms (n = 1), urinary retention (n = 2)
Djavan 1999e[a]	6	Targis	51	3/51 (5.6)	–	–	Haemospermia (n = 1), epididymitis (n = 1), urinary retention ≥ 1 week (n = 1). No dizziness, asthenia, headache, hypotension, nausea or postural dizziness was observed
Djavan 2001	18	Targis	51	4/51 (7.8)	–	–	Haemospermia (n = 2), Epididymitis (n = 2), urinary retention > 1 week (n = 1). No dizziness, asthenia, headache, hypotension, nausea, postural dizziness was observed
Norby 2002a	6	Prostatron v2.0/2.5	46	14/46 (30.0)	–	0/46 (0.0)	Bleeding (n = 1), urinary retention (n = 4), No transfusion was necessary for these patients, no patient suffered from TUR syndrome, no penile oedema were noted, no patients reported incontinence
Wagrell 2002, 2003[b]	12	ProstaLund	100	18/100 (18)	1/100 (1)	3/100 (3.0)	**Serious events:** urine retention (n = 1). **Non-serious events:** micturition urgency (37%), urinary retention (19%), transient incontinence (3%), haematuria (13%)
Wagrell 2004[b]	12–36	ProstaLund	80	0/80 (0.0)	1/80 (1.3)	1/80 (1.3)	**NB: These results are for 12–36 months: Serious events:** bladder calculus (n = 1); prostatic disorder (n = 1); **Non-serious events:** urgency (n = 2), urinary retention (n = 2), urethral disorder (n = 1), haematuria (3.8%). No epididymitis, back pain or myelitis was noted in these patients

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
TURP							
Ahmed 1997	6	TURP	30	3/30 (10.0)	0/30 (0.0)	–	Blood transfusion (n = 4), one of the patients with a UTI developed septicaemia. Two patients had catheters in for four weeks
D'Ancona 1997b	12	TURP	21	1/21 (4.8)	3/21 (14.3)	–	Irritative voiding symptoms (n = 4) No patient required a transfusion
Floratos 2001a	36	TURP	73	–	–	0/73 (0.0)	–
Norby 2002a	6	TURP	24	3/24 (14.0)	–	1/24 (4.2)	Transfusion (n = 2), TUR syndrome (n = 1) (this patient was one who required transfusion and who also developed stricture). Retention (n = 1), mild stress incontinence not requiring further treatment (n = 1), No bladder evacuation was necessary for these patients, no persistent retention was noted, there were no reports of penile oedema
Wagrell 2002, 2003[b]	12	TURP	46	9/46 (20)	4/46 (8.7)	6/46 (13.0)	Other serious events: TUR syndrome (n = 1), urosepsis (n = 1), clot retention (n = 1). Non-serious events: Micturition urgency (13%), urinary retention (13%), transient incontinence (13%), haematuria (39%)
Wagrell 2004[b]	12–36	TURP	39	1/39 (2.6)	0/39 (0.0)	2/39 (5.1)	NB: These results are for 12–36 months: Serious events: no additional events. Non-serious events: Urgency (n = 5), urethral disorder (n = 3), epididymitis (n = 1), back pain (n = 1), myelitis (n = 1). No increase in prostate-specific antigen or urinary retention was noted in these patients
Terazosin							
Djavan 1999e[a]	6	Terazosin	52	0/52 (0.0)	–	–	Dizziness (n = 7), asthenia (n = 4), headache (n = 3), hypotension (n = 1), nausea (n = 1), postural dizziness (n = 1). No epididymitis, haemospermia or urinary retention $\geq$ 1 week was observed
Djavan 2001	18	Terazosin	52	0/52 (0.0)	–	–	Dizziness (n = 9), asthenia (n = 5), headache (n = 4), hypotension (n = 2), nausea (n = 2), postural dizziness (n = 1). No epididymitis, haemospermia, or urinary retention > 1 week was observed
ILCP							
Norby 2002a	6	ILCP	48	27/48 (61.0)	–	0/48 (0.0)	Urinary retention (n = 4), penile oedema (n = 1); no transfusion or bladder evacuation was necessary for these patients, no patient suffered from TUR syndrome, no persistent retention was noted, no patient reported incontinence

[a]*Values not included in total as quoted in text: Djavan et al 2001 used as cumulative incidences*
[b]*Values from Wagrell et al 2004 were only for period of 12–36 months: values added to Wagrell et al 2002 for calculating the total in the text*

Urethral strictures and bladder neck stenosis

Urethral strictures and bladder neck stenosis or contractures occurred in 6.8 per cent of TURP patients compared with only 0.5 per cent of HE-TUMT patients (pooled estimate, **Table 11**). The corresponding rate in ILCP patients was 2.1 per cent (Norby et al 2002a). Urethral strictures and bladder neck stenosis or contractures were not reported in the primary studies comparing HE-TUMT to terazosin (Djavan et al 1999e; 2001) or TUNA (Arai et al 2000). These side effects in most cases required further treatment: urethrotomy for urethral strictures and bladder neck incisions for bladder neck stenosis or contractures.

Table 11 Urethral strictures and bladder neck stenosis or contractures in primary studies of HE-TUMT versus TURP/medication/ILCP/TUNA

Paper	Duration months	Treatment device	N	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Comment
HE-TUMT					
Ahmed 1997	6	Prostatron® v2.5	30	0/30 0.0)	
D'Ancona 1997b[a]	12	Prostatron® v2.5	31	0/31 (0.0)	
D'Ancona 1998	30	Prostatron® v2.5	31	0/31 (0.0)	
Floratos 2001a	36	Prostatron® v2.5	82	1/82 (1.2)	Urethral strictures treated with internal optical urethrotomy
Francisca 1999[c], 2000[a]	12	Prostatron® v2.5	74	1/74 (1.4)	Urethral strictures treated with internal optical urethrotomy
Norby 2002a	6	Prostatron® v2.0/2.5	46	0/46 (0.0)	
Total				1/189 (0.5)	
TURP					
Ahmed 1997	6	TURP	30	3/30 (10.0)	
D'Ancona 1997b[a]	12	TURP	21	1/21 (4.8)	
D'Ancona 1998	30	TURP	21	1/21 (4.8)	
Floratos 2001a	36	TURP	73	5/73 (6.9)	Complications were managed in the following way: bladder neck incision for bladder neck stenosis (n = 3), internal optical urethrotomy for urethral strictures (n = 2)
Francisca 1999c, 2000[a]	12	TURP	73	2/73 (2.7)	Urethral strictures treated with internal optical urethrotomy
Norby 2002a	6	TURP	24	1/24 (4.2)	Patient with stricture also had TUR syndrome and required a transfusion
Total				10/148 (6.8)	
ILCP					
Norby 2002a	6	ILCP	48	1/48 (2.1)	
Total				**1/48 (2.1)**	

[a]*Not included in total: publication with longest cumulative rate included in total*

Ejaculatory and erectile dysfunction

Ejaculatory dysfunction (absence of or retrograde ejaculation) and erectile dysfunction were not well reported across the primary studies, particularly for terazosin, ILCP and TUNA. Furthermore, a large proportion of patients did not answer the questions and the estimates are often only based on a small subgroup of the recruited patients. Consequently, few conclusions can be drawn from these results.

Expert opinion from the Advisory Panel indicated that erectile dysfunction very much depends on the pre-operative (or pre-intervention) state of the patient, which various significantly between age groups.

Coagulative necrosis in the prostate can cause enough obstruction to prostatic tubules to result in an absence of ejaculation. This is in contrast to retrograde ejaculation, where ejaculation does occur, however, it is emitted backwards into the bladder. Unless formally investigated are undertaken, retrograde ejaculation can be mistaken for an absence of ejaculation. Thus, in many of the trials, there may be some overlap between these two conditions.

In Wagrell et al (2002, 2004) 80 per cent of HE-TUMT and 85 per cent of TURP patients were evaluated for 36 months. The incidence of impotence during the first 12 months follow-up was 6 per cent, versus 11 per cent for HE-TUMT and TURP patients respectively. At 36 months follow-up, the corresponding rates were 6/80 (7.5%) and 6/39 (15.4%) respectively. The results were not significantly different.

In the study by Francisca et al (1999c), the response rates for questions relating to ejaculatory dysfunction or erectile dysfunction were often less than 50 per cent, and patients were not consistent between baseline and endpoint in whether they responded to specific questions. These limitations should be kept in mind when interpreting the data. Of those responding at baseline, 12 per cent of HE-TUMT patients and 7 per cent of TURP patients reported lack of ejaculation. At three months, the corresponding figures were 24 per cent and 68 per cent, respectively. Problems with erection were reported in 29 per cent versus 33 per cent of HE-TUMT and TURP patients at baseline, and 20 per cent versus 17 per cent, respectively, at three months.

The proportion of patients responding to questions on sexual function in the study by Norby et al (2002a) was also relatively poor (58–60%). In the 27 patients in the LE/ HE-TUMT group answering the question, all had antegrade ejaculation at baseline, and six (22%) developed retrograde ejaculation by six months. Similarly, all 14 patients in the TURP/TUIP group answering the question had antegrade ejaculation at baseline, whilst seven (50%) had developed retrograde ejaculation at six months. In the ILCP group, 26 of 29 men answering the question had antegrade ejaculation at baseline, while a further nine (35%) developed retrograde ejaculation at six months

In the LE/HE-TUMT group, 22 of 28 patients answering the question on erectile function reported normal or slightly reduced erectile function at baseline, two of whom developed erectile dysfunction at six months. In the TURP/TUIP group, seven patients of 14 reported normal erectile function at baseline, with one developing erectile dysfunction at six months. Eighteen of 29 patients in the ILCP group reported normal erectile function at baseline; and four developed erectile dysfunction at six months.

Ahmed et al (1997) reported a failure of antegrade ejaculation at six months in four of 18 (22%) sexually active men in the HE-TUMT group compared with 12 of 19 (63%)

sexually active men in the TURP group. HE-TUMT caused no effect on erectile dysfunction whilst four of 19 (21%) sexually active men in the TURP group reported a failure of erection at six months.

In Arai et al (2000), 155/173 (89.6%) of patients completed a questionnaire in which six patients (19.4%) in the HE-TUMT group reported no ejaculate at three months, compared with 12 (30.8%) in the TURP group, two (5.3%) in the ILCP group, and seven (18.9%) in the TUNA group.

In Djavan et al (2001), one patient (2%) reported loss of ejaculation in the first six months in the HE-TUMT group. Between 6- and 18-month follow-up, a further two patients (4%) in the HE-TUMT group reported loss of ejaculation. No patients in the terazosin group reported loss of ejaculation. Erectile dysfunction was not reported in the study comparing HE-TUMT with terazosin (Djavan et al 1999e; 2001) or the study comparing HE-TUMT with TUNA (Arai et al 2000).

Fistula formation

The FDA released a Public Health Notification in October 200 due to several cases of serious thermal injury to the penis and/or urethrorectal fistula formation following treatment with HE-TUMT (see **Appendix G**: FDA Public Health Notification: Serious injuries from microwave thermotherapy for benign prostatic hyperplasia). However, no such events were reported in the primary comparative studies.

Mortality

The sample size and relative short duration of most of the trials prevents accurate measures of mortality associated with HE-TUMT and the various comparators from the comparative trials (**Table 12**). The pooled estimate of mortality across all available primary studies for HE-TUMT was 1.1 per cent compared with 1.6 per cent in TURP. In the two longest trials of approximately three years duration, the mortality associated with HE-TUMT was 2.4–3.2 per cent compared with 0–2.7 per cent (d'Ancona et al 1998; Floratos et al 2001a). Deaths were generally stated as not related to treatment.

The reported mortality is not unexpected given that both HE-TUMT and TURP are undertaken in populations that may have significant comorbidities. Deaths are therefore recorded during the follow-up period, but these appear to be due principally to the comorbid conditions.

No deaths were reported in trials associated with terazosin, ILCP or TUNA.

Table 12 Mortality in the primary studies of HE-TUMT versus TURP/medication/ILCP/TUNA

Paper	Duration months	Treatment device	N	Deaths n/N (%)	Comment
HE-TUMT					
Ahmed 1997	6	Prostatron® v2.5	30	0/30 (0.0)	
D'Ancona 1998	30	Prostatron® v2.5	31	1/31 (3.2)	Death non-treatment related
Floratos 2001a	36	Prostatron® v2.5	82	2/82 (2.4)	Deaths unrelated to treatment. (One death before treatment but not stated to which treatment group was randomised)
Francisca 1999c	12	Prostatron® v2.5	74	0/74 (0.0)	
Study B, ProstaLund® submission to FDA, PMA P010055 SSED	6	ProstaLund®	42	0/42 (0.0)	
Wagrell 2004	36	ProstaLund®	80	0/80 (0.0)	
Wagrell 2002, 2003	12	ProstaLund®	100	0/100 (0.0)	
Total				3/285 (1.1)	
TURP					
Ahmed 1997	6	TURP	30	0/30 (0.0)	
D'Ancona 1998	30	TURP	21	0/21 (0.0)	
Floratos 2001a	36	TURP	73	2/73 (2.7)	Deaths unrelated to treatment. (One death before treatment but not stated to which treatment group was randomised)
Francisca 1999c	12	TURP	73	2/73 (2.7)	
Study B, ProstaLund® submission to FDA, PMA P010055 SSED	6	TURP	20	0/20 (0.0)	
Wagrell 2004	36	TURP	39	1/46 (2.2)	NB No additional deaths during the 12–36 month period: this death related to first 12 months reported in Wagrell et al 2002
Wagrell 2002, 2003	12	TURP	46	1/46 (2.2)	
Total				**3/190 (1.6)**	

Secondary evidence: single-arm studies of HE-TUMT

Table 13 presents the common adverse events in the single-arm studies of HE-TUMT. Compared with results from the primary evidence, a lower incidence of urinary tract infections (9.7%) but higher incidence of haematuria (41.1%) was evident from the these studies (pooled estimates, **Table 13**). The differences can be partly attributed to heterogeneity in the patient populations arising from methodological issues (such as selection bias) associated with uncontrolled studies. Additionally, due to poor reporting, the estimated incidence of haematuria is an overestimate as it includes transient and minor occurrences resulting from the procedure itself that resolved within a few weeks.

As in the primary evidence, urinary retention and irritative symptoms (urgency, dysuria etc) occurred in the post treatment period, but were mostly transient in nature and resolved within a few weeks. Bladder spasm was associated with catheterisation during this period. Re-catheterisation due to persistent urinary retention or re-retention was noted in some studies.

Incontinence was uncommon (pooled estimate, 1.9%), with several trials reporting no cases and those that did generally stating that it was either minor or of a transient nature. Incidents of epididymitis and haematospermia were noted but were relatively uncommon.

Urethral strictures and bladder neck stenoses or contractures were uncommon with HE-TUMT, with only 15/1534 (1.0%) incidents occurring across the single-arm studies (**Table 14**). As in the primary evidence, these adverse events typically required the patient to undergo an urethrotomy or bladder neck incision respectively.

Ejaculatory and erectile dysfunctions were poorly reported across the single-arm studies (**Table 15**) and the reported data showed much variation. Pooled estimates were calculated, indicating that there was absence of ejaculation in approximately 4 per cent of patients, retrograde ejaculation in 6 per cent of patients and erectile dysfunction in 2 per cent of patients (**Table 15**).

Only three of the single-arm studies reported serious thermal injury to the penis or urethrorectal fistula formation following treatment. Two of these occurred with LE-TUMT and would therefore be normally excluded from the assessment. However, due to the serious nature and concern over these events, they are reported in **Appendix G:** FDA Public Health Notification: Serious injuries from Microwave Thermotherapy for Benign Prostatic Hyperplasia. Lee et al (1995) analysed results from 100 consecutive cases treated by TUMT between 1991 and 1992 with the Prostatron® device. Although the version was not reported, it was specified that the prostate be heated to between 45° C and 60° C; hence this is classed as a high-energy study. A bulbo-cutaneous fistula developed in one patient (1%) although it was not certain whether this was a result of HE-TUMT, or to a prolonged indwelling catheter which the patient had had for six weeks prior to fistula formation Norby et al (2000) reported the development of a urethrorectal fistula following treatment with a LE-TUMT. Excessive heating caused the movement of the rectal probe monitoring rectal temperature (resulting in fewer interruptions of treatment if the rectal threshold temperature was exceeded). Eliasson et al (1998b) and Sjodin et al (1997) reported a single case of a thermal injury in a patient treated with a low-energy protocol. In addition to a deep skin injury, the patient developed a urethral stricture and complete and lasting erectile dysfunction. None of the remaining single-arm studies reported similar events:

Albala et al (2000) specifically noted that there were no cases of rectal fistulae in 130 patients treated with HE-TUMT.

Mortality associated with HE-TUMT the single-arm studies varied (**Table 16**). Francisca et al (1999c) recorded 5/357 (1.4%) deaths during 48 months follow-up after HE-TUMT treatment. In the study by Miller et al (2003), 10/150 (6.7%) patients had died over a 60-month period, whilst in Thalmann et al (2002), 15/200 (7.5%) had died after 24 months follow-up. Lee et al (1995) reported 10/100 (10.0%) deaths during follow-up that were stated as unrelated to the procedure. It must be noted that the average age of these patients is generally mid 60s, with patients up to 85 included, so these rates are not unexpected for the population in question The mortality rate in Australian men aged 65 to 85 year old age group ranges from 1.4 per cent to 11.2 per cent, as shown in **Figure 2**.

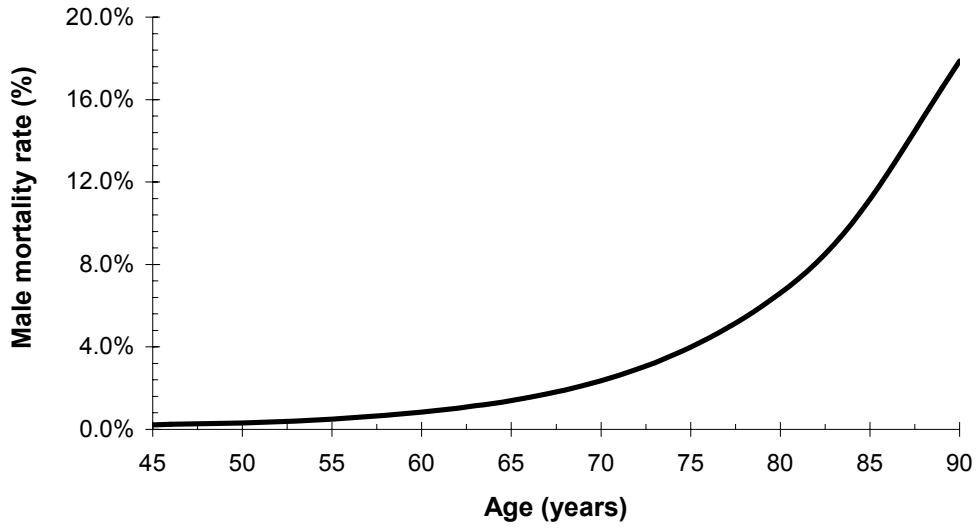

Figure 2 Mortality rates for Australian males aged 45–90 years (2000–2002)
Source: Australian Bureau of Statistics Cat. No. 3302.0 released 2003. Deaths 2002

As stated in the primary safety evidence, these procedures are undertaken in populations with quite significant comorbidities. Given the results of the studies presented here, together with the mortality data for the general male population aged 65–85 years, it appears likely that the deaths reported in the literature were not related to the procedures.

Table 13 Common adverse events in the single-arm studies of HE-TUMT

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
Albala 2002	12	TherMatrx®	121	–	11/121 (9.1)	–	Bladder spasm (4.1%). No patient suffered from urgency. Re-catheterisation (16.8%). Dysuria (n = 8)
Alivizatos 2005	12	ProstaLund®	38	3/33 (9.1)	15/33 (45.5)	–	Haematuria did not require any intervention; 5/33 (15.2%) patients had bladder stones; 19/33 (57.6%) patients had irritative symptoms eg, frequency, urgency, nocturia, pain during micturition; 1/33(3.0%) patients required suprapubic catheterisation
Berger 2003	24	Targis®	78	14/78 (18.0)	19/78 (24.4)	–	Urinary retention (n = 15): 5 patients re-developed urinary retention while in another 10 patients urinary retention persisted after TUMT treatment. Epididymitis (n = 2). Prolonged catheterisation was noted in 6 patients, haematuria was resolved within 3 weeks of treatment, irritative urinary symptoms occurred in all patients but resolved within 2 weeks
Blute 1996	12	Prostatron®	78	–	54/78 (69.2)	–	Urethral bleeding (n = 16), urethral discharge (n = 2), urinary retention (n = 20), other urinary tract problems (n = 11), reproductive (n=8), rectal (n=4), systemic (n = 2), gastro-intestinal (n = 3), renal (n = 1), and neurological adverse events (n = 2). No adverse events were reported affecting the cardiovascular, respiratory, musculoskeletal, dermatological or oral/ophthalmic systems
De la Rosette 2000	12	Prostatron® v3.5	108	10/108 (9.3)	–	–	Epididymitis (n = 1), bladder spasms (n = 25). Several patients had minimal haematuria, which resolved in 3 weeks, at the 3 month evaluation all treatment related complaints were resolved
Dicuio 2002	1	Prostatron® + Medication	89	14/89 (16.0)	23/89 (26.0)	–	Urinary retention (15%), bladder spasms (81%), perineal discomfort (65%). All complications resolved within the first 4 weeks. Bladder spasms associated with catheter
Djavan 1998	3	Targis® + Sedoanalgesia	22	0/22 (0.0)	–	–	No urinary retention $\geq$ 2 weeks, no patient reported blood loss, UTI or re-catheterisation
		Targis® + Topical Anaesthesia	23	0/23 (0.0)	–	–	No urinary retention > 2 weeks, no patient reported blood loss, UTI or re-catheterisation
Djavan 1999d	1	Targis® + Prostatic Bridge	54	2/54 (3.7)	–	–	Early catheter removal (n = 6), No cases of epididymitis or haematospermia was recorded in these patients. Second treatment arm (TUMT + standard catheterisation) was the cohort from Djavan et al 1999e)

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
Djavan 1999f	3	Targis® + Tamsulosin	41	1/41 (2.4)	–	–	Urinary retention ≥ 1 week (n = 1), haematospermia (n = 2). Micturition status represented dysuria, haematuria, incontinence, subjective discomfort, subjective urine flow
		Targis® – Tamsulosin	40	2/40 (5.0)	–	–	Urinary retention ≥ 1 week (n = 5), haematospermia (n = 1). Micturition status represented dysuria, haematuria, incontinence, subjective discomfort, subjective urine flow
Djavan 2000a	4	Targis®	29	2/29 (6.9)	–	–	Epididymitis (n = 1). Acute urinary retention inclusion
Eliasson 1995	12	Prostcare	172	4/172 (2.3)	106/172 (61.6)	–	Urine retention (n = 10), bladder spasms (n = 8), haematospermia (n = 2), rectal bleeding (n = 2), epididymitis (n = 1). Most cases of haematuria were resolved in the first 3 days and there were no complications due to this bleeding. No re-catheterisation
Eliasson 1998b	6	Low Effect Prostcare	98	0/98 (0.0)	66/98 (67.4)	–	Urinary retention (n = 5) occurred within first 24 hours post treatment. All haematuria was transient. Epididymitis (n = 2), no prostatitis was observed in patients, no patient experienced haematospermia
		High Effect Prostcare	98	1/98 (1.0)	67/98 (68.4)	–	Urinary retention (n = 11) occurred within first 24 hours post treatment. Haematospermia (n = 4), and haematuria were transient. Prostatitis (n = 1) no cases of epididymitis
		High Effect Base Prostcare	31	1/31 (3.2)	25/31 (80.7)	–	Urinary retention (n = 12) occurred within first 24 hours post treatment. Haematospermia (n = 3) and haematuria were transient. No patient in this group experienced epididymitis or prostatitis
Eliasson 1998a	12	Prostcare	32	0/32 (0.0)	–	1/12 (8.3)	Urinary retention (n = 28) after treatment, minor urge incontinence (n = 1), transient haematospermia (n = 5). Majority of patients had haematuria or urethral bleeding, some patients suffered sloughing, several patients experienced detrusor instability for a few weeks. No stress incontinence
Goldfarb 1995	12	UroWave®	62	0/62 (0.0)	50/62 (80.0)	0/62 (0.0)	Gross haematuria was intermittent in nature and stopped in all patients within 6 weeks. No patient required a transfusion. No patient suffered from incontinence. Re-catheterisation (n = 3)

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
Gravas 2003	12	ProstaLund®	41	15/41 (36.6)	2/41 (5.0)	2/41 (5.0)	Epididymitis (n = 1), urosepsis (n = 1), bladder spasms (n = 17), urgency (n = 7), pain (n = 5), frequency (n = 5), urinary retention (n = 3), dysuria (n = 10)
Jakubczyk 2002	6	Targis®	61	4/61(6.6)	–	–	Epididymitis (n = 1)
Javle 1996	12	Targis®	50	8/50 (16.0)	39/50 (78.0)	–	Acute urinary retention (6%), carcinoma (2%). Haematuria was self-limiting
Kellner 2004	18	Targis®	39	4/39 (10.3)	–	–	Epididymitis (n = 1)
Krogh 1998	6	ProstaLund®	28	6/28 (21.4)	–	0/28 (0.0)	Urinary retention (n = 3) immediately following treatment. Most of the patients had immediate haematuria which subsided spontaneously, no patient developed incontinence
Kurita 1996	30	Prostcare	43	0/43 (0.0)	–	–	No urinary retention or major complications, all patients experience urge to urinate and haematuria during treatment
Larson 1998a	6	Targis®	125	8/125 (6.0)	–	5/125 (4.0)	Peri-procedural blood loss (n = 1), epididymitis (n = 3), urinary retention $\geq$ 1 week (n = 10), haematuria and incontinence were transient
Lee et al 1995	12	Prostatron®	100	7/100 (7.0)	7/100 (7.0)	–	Haematuria (gross) did not require further intervention. 28/100 of the patients were in urinary retention at the start of the trial. The remainder were treated for symptoms of bladder obstruction. **Non-retention group:** temporary urinary retention (17/72; 24%); UTI (3/72; 4%); gross haematuria (6/72; 8%) **Retention group:** UTI (4/28; 14%); gross haematuria (1/28; 3.6%); bulbo-cutaneous fistula (1/28; 3.6%). NB: patient with fistula was in retention group and had an indwelling catheter for previous 6 weeks, which may have been the cause
Ramsey 1998	36	Targis®	155	17/155 (11.0)	–	3/155 (1.9)	Epididymitis (n = 4), temporary acute incontinence (n = 3), Re-catheterisation due to urinary retention (n = 19)
Ramsey[a] 1997	12	Targis®	154	19/154 (13.0)	–	3/154 (1.9)	Hospitalisation for irritative symptoms with urinary retention (n = 3) and evaluation of voiding function (n = 4). Temporary acute urinary incontinence (n = 3), urinary retention >1 week (n = 17), epididymitis (n = 5). Most urinary retention and UTIs were transient

Paper	Duration months	Treatment device	N	UTI n/N (%)	Haematuria n/N (%)	Incontinence n/N (%)	Other/comments
Naqvi 2000	24	Prostatron® v2.5	200	–	80/200 (40.0)	–	Epididymo-orchitis (n = 3). Transient dysuria occurred in 80 per cent of patients and lasted for 2–4 weeks. Haematuria was transient lasting 1–3 days
Pace 2001	6	Prostatron®	61	13/61 (21.3)	–	1/61 (1.6)	Urgency/bladder spasms (n = 9), urge incontinence (n = 1), bowel urge (n = 1), epididymitis (n = 2)
Roehrborn 1998	6	UroWave®	147	11/147 (7.5)	20/147 (13.6)	0/147 (0.0)	Irritative voiding symptoms mainly dysuria and urgency (n = 32), pain (n = 13), gastro-intestinal disturbances (n = 10), urinary retention (n = 8), miscellaneous (n = 17). No incontinence. Within the first 3 days of treatment patients experienced pain (n = 129), haematuria (n = 55), bladder spasms (n = 32), dysuria and urgency (n = 29), rectal disorders (n = 5), hypertension (n = 2), apnoea (n = 1), syncope (n = 1), nausea (n = 1), haemoptysis (n = 1)
Schelin 2001	12	ProstaLund®	24	7/24 (29.2)	1/24 (4.2)	–	Temporary catheter care (n = 1), catheter retained (n = 5)
Thalmann 2002	24	Targis®	200	47/200 (24.0)	–	–	Blood pressure (n = 1), epididymitis (n = 1). Temporary therapy discomfort was experienced by 171 patients
Thalmann 1999	12	Targis®	134	27/134 (20.0)	0/134 (0.0)	–	Blood pressure (n = 1), epididymitis (n = 1). 3 patients had severe coagulopathy and 24 were receiving oral anticoagulants. Temporary therapy discomfort experienced by 101 patients
Total				**203/2083 (9.7)**	**585/1422 (41.1)**	**12/631 (1.9)**	

[a]Values from Ramsey et al 1998 not included in total: Ramsey et al 1997 used as quoted higher figure
[b]Values from Thalmann et al 1999 not included in total: Thalmann et al 2002 used as quoted higher figure

Table 14 Urethral structures and bladder neck stenosis or contractures in single-arm studies

Paper	Duration months	Treatment device	Total patients	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Comment
D'Ancona 1997	24	Prostatron® v2.5	301	3/301 (1.0)	3 patients had bladder neck incisions (assumption: cause was bladder neck stenosis)
De la Rosette 1996[a]	12	Prostatron® v2.5	116	0/116 (0.0)	–
Albala 2000	12	TherMatrx®	130	0/130 (0.0)	–
De la Rosette 2000	12	Prostatron® v3.5	108	1/108 (0.93)	Urethral strictures treated with urethrotomy
Eliasson 1998[b]	6	Low Effect Prostcare	98	1/98 (1.0)	Thermal injury caused urethral stricture / complete and lasting erectile dysfunction/deep skin injury
		High Effect Prostcare	98	0/98 (0.0)	
		High Effect Base Prostcare	31	0/31 (0.0)	
Jakubczyk 2002	6	Targis®	61	1/61 (1.6)	Acute urinary retention associated with urethral stricture treated with urethrotomy
Krogh 1998	6	ProstaLund®	28	0/28 (0.0)	–
Larson 1998a	6	Targis®	125	3/125 (2.4)	–
Ramsey 1998	36	Targis®	155	1/155 (0.7)	–
Ramsey 1997[b]	12	Targis®	154	1/154 (0.7)	–
Osman 2003	12	Targis®®	40	2/40 (5.0)	Bladder neck incision carried out on patients with bladder neck contracture (n = 2)
Trachtenberg 1998	6	UroWave®	147	1/147 (0.7)	–
Yokoyama 2004	12	Targis® (60 min)	27	2/27 (7.4)	–
		Targis® (30 min)	31	0/31 (0.0)	
Total				**15/1534 (1.0)**	

[a]Not included in total. Patients in d'Ancona et al (1997b) were recruited from the Netherlands. De la Rosette et al (1996) was a multi-centre and multinational trial but it included patients from the Netherlands which overlap with d'Ancona et al (1998)

[b]Values from duplicate Ramsey et al 1998 not included in total

Table 15 Ejaculatory and erectile dysfunction in the single-arm studies of HE-TUMT

Paper	Duration months	Treatment device	N	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence n/N (%)	Other
Albala 2000	12	TherMatrx®	130	–	0/130 (0.0)	–	–
Blute 1996	12	Prostatron®	78	–	–	–	There were no reports of sexual dysfunction
De Wildt 1996	12	Prostatron® v2.5	85	–	18/85 (21.2)	0/85 (0.0)	Diminished ejaculatory volume (n = 6)
De la Rosette 1996	12	Prostatron® v2.5	116	–	See comment	–	A third of patients with antegrade ejaculation at the start of the study had retrograde ejaculation at the end of the study
Djavan 1999d	1	Targis® + Prostatic Bridge	54	0/54 (0.0)	16/54 (29.6)	4/54 (7.4)	Ejaculatory and erectile dysfunction calculated as new cases at 1 month compared to baseline: 3 patients at baseline had no ejaculation compared with 2 at 1 month. Retrograde ejaculation was seen in 4 patients at baseline and 29 at 1 month. Severe erectile dysfunction in 4 at baseline and 8 at 1 month (by score)
Djavan 1999f	3	Targis® + Tamsulosin	41	2/41 (4.9)	25/54 (46.3)	–	–
		Targis® – Tamsulosin	40	1/40 (2.5)	–	–	–
Eliasson 1998b	6	Low Effect Prostcare	98	–	0/98 (0.0)	1/98 (1.0)	The urethral stricture was a result of thermal injury and also resulted in complete and lasting erectile dysfunction and a deep skin injury (see Sjodin 1997)
		High Effect Prostcare	98	–	0/98 (0.0)	–	
		High Effect Base Prostcare	31	–	0/31 (0.0)	–	
Eliasson 1995	12	Prostcare	172	–	0/172 (0.0)	–	

Paper	Duration months	Treatment device	N	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence n/N (%)	Other
Eliasson 1998a	12	Prostcare	32	–	–	–	8 patients with lack of ejaculation had it before treatment: 3 probably had retrograde ejaculation (sperm cells in urine). Decrease in erectile function in 6/23 with normal function before treatment; improvement in 5/9 with severely reduced or no erection before treatment; reduced ejaculation in 13/23 with normal ejaculation prior to therapy; improvement in 2/9 with reduced or no ejaculation prior to therapy
Goldfarb 1995	12	UroWave®	62	2/62 (3.2)		–	No patient noticed a change in potency
Gravas 2003	12	ProstaLund®	41	7/41 (17.1)	–	–	Lack of ejaculation calculated as change from baseline (n = 7) to 1 year (n = 14)
Javle 1996	12	Targis®	50	–	1/50 (2.0)	–	–
Krogh 1998	6	ProstaLund®	28	0/28 (0.0)	0/28 (0.0)	0/28 (0.0)	–
Lancaster 1997	12	UroWave®	93	13/93 (14.0)	–	4/93 (4.3)	Decreased or lack of ejaculation grouped together (n = 13)
Larson 1998a	6	Targis®	125	5/125 (4.0)	–	–	
Lee 1995	12	Prostatron®	100	–	0/100 (0.0)	2/100 (2.0)	28/100 of the patients were in urinary retention at the start of the trial. The remainder were treated for symptoms of bladder obstruction. Impotence (2/100; 2%) (both in the non-retention group) although one patient claimed increased sexual libido
Ramsey 1997	12	Targis®	154	0/154 (0.0)	–	0/154 (0.0)	–
Naqvi 2000	24	Prostatron® v2.5	200	–	2/200 (1.0)	–	–
Roehrborn 1998	6	UroWave®	147	See comments	See comments	See comments	Sexual dysfunction including haematospermia and ejaculatory (n = 44)
Thalmann 1999	12	Targis®	134	3/134 (2.2)	–	–	–
Total				**33/772 (4.3)**	**62/1100 (5.6)**	**11/612 (1.8)**	–

Table 16 Mortality in the single-arm studies of HE-TUMT

Paper	Duration months	Treatment device	N	Deaths n/N (%)	Comment
Francisca 1999c	48	Prostatron® v2.5	357	5/357 (1.4)	
Dicuio 2002	1	Prostatron® + Medication	89	1/89 (1.1)	Death due to cardiac infarction the day after treatment: cardiologist judged this unrelated to treatment
Djavan 1998	3	Targis® + Sedoanalgesia	22	0/22 (0.0)	
		Targis® + Topical Anaesthesia	23	0/23 (0.0)	
Djavan 2000a	4	Targis®	29	0/29 (0.0)	
Gravas 2003	12	ProstaLund®	41	0/41 (0.0)	
Larson 1998a	6	Targis®	125	1/125 (0.8)	Death unrelated to treatment
Lee 1995	12	Prostatron®	100	10/100 (10.0)	Death unrelated to treatment
Miller 2003	60	Targis®	150	10/150 (6.7)	
Ramsey 1997	12	Targis®	154	1/154 (0.6)	Death judged unrelated to treatment
Osman 2003	12	Targis®	40	0/40 (0.0)	
Thalmann 2002	24	Targis®	200	15/200 (7.5)	Deaths were non-treatment related
Thalmann 1999	12	Targis®	134	7/134 (5.2)	Deaths due to non-treatment related cardiovascular disease, all had failed HE-TUMT initially and received HE-TUMT treatment failure

Summary

Primary evidence

Table 17 summarises the adverse events occurring with HE-TUMT, TURP, ILCP and terazosin based on seven primary studies (five level II, two level III-1), which varied from three to 36 months in duration. The comparative safety of HE-TUMT versus TURP was based on four level II studies and one level III-1 study. Limited evidence was available for HE-TUMT versus terazosin (one level III-1 study) and HE-TUMT versus ILCP/TUNA (1 level III-1 study).

Table 17 Summary of adverse events associated with HE-TUMT, TURP, ILCP and terazosin from the primary studies

Adverse event	HE-TUMT %	TURP %	ILCP %	Terazosin %
Serious haematuria[a]	1.9	6.5	–	–
UTI[b]	16	14	61	0
Incontinence	1.0	2.2	–	–
Urethral stricture and bladder neck stenosis[c]	0.5	6.8	2.1	–
TUR syndrome	0	2–4	–	–
Transfusions	0	8–13	–	–
Fistula formation	0	–	–	–
Deaths	1.1	1.6	0	0
Other less common events	Haemospermia, epididymitis, persistent urinary retention	Epididymitis, persistent urinary retention	Persistent urinary retention	Dizziness, asthenia, headache and hypotension with terazosin

[a]*Requiring hospitalisation*
[b]*Usually but not always diagnosed by bacterial culture*
[c]*Requiring urethrotomy bladder neck incisions respectively*

Mild and transient dysuria and haematuria were experienced by the majority of patients following these procedures, and are thus not presented in **Table 17**.

HE-TUMT was found to have a lower incidence of most adverse events including serious haematuria, incontinence, urethral strictures and bladder neck stenosis compared with TURP patients (**Table 17**). In addition, 2–4 per cent of TURP patients developed TUR syndrome and 8–13 per cent required transfusions, whilst neither of these events occurred in HE-TUMT patients. UTIs were relatively common after both procedures and occurred in a similar proportion of patients. No cases of fistula formation were reported after HE-TUMT in the primary studies.

From the available evidence, it appears that HE-TUMT has little impact on ejaculatory and erectile dysfunction. The comparative rates after TURP tended to be higher. However, these events were poorly reported in the primary studies, and the results based on only a small numbers of patients who answered the questions (often less then 60 per cent of the enrolled patients), therefore, it is difficult to draw too many conclusions (and no values are reported in **Table 17**). Expert opinion indicates that erectile dysfunction very much depends on the pre-operative (or pre-intervention) state of the patient, which various significantly between age groups. In the included studies, many of the patients had existing erectile problems prior to the procedure.

A pooled mortality estimate for HE-TUMT was 1.1 per cent compared with 1.6 per cent in TURP. In the two longest trials of approximately three years duration, the mortality associated with HE-TUMT was 2.4–3.2 per cent compared with 0–2.7 per cent (d'Ancona et al 1998; Floratos et al 2001a). No deaths were reported in trials associated with terazosin, ILCP or TUNA. Deaths were generally stated as not related to treatment and are probably principally driven by co-morbid conditions, which are common in this population.

Secondary evidence

Table 18 summarises the adverse observed in the secondary studies for HE-TUMT. These pooled estimates must be interpreted with caution, as the rates from individual trials tended to vary widely, reflecting differences in methodology, patient population and poor reporting (particularly for ejaculatory and erectile dysfunction). Trial duration varied between one month and 60 months.

Table 18 Summary of adverse events associated with HE-TUMT from the secondary studies

Adverse event	HE-TUMT
	%
Haematuria (transient and serious)	41.1
UTI	9.7
Incontinence	1.9
Retrograde ejaculation	5.6
Absence of ejaculation	4.3
Erectile dysfunction	1.8
Urethral stricture and bladder neck stenosis[a]	1.0
Fistula formation / thermal injury	3 cases
Deaths	0–10
Other less common events	Haemospermia, epididymitis

[a]*Requiring urethrotomy and bladder neck incisions respectively*

Similar to the primary studies, mild and transient dysuria and haematuria was common following the procedure. However, due to poor reporting, it was not possible to separate transient from serious events in many of the studies, hence the much higher estimated rate of haematuria compared to the primary studies is an overestimate. The incidence of other adverse events such as incontinence, urethral strictures and bladder neck stenosis were comparable to that observed in the primary trials.

A single case of serious thermal injury was reported in one of the secondary studies following LE-TUMT, which resulted in a deep skin injury, a urethral stricture and complete and lasting erectile dysfunction. Two cases of fistula formation were reported in the secondary studies: a bulbo-cutaneous fistula after HE-TUMT and an urethrorectal fistula following after LE-TUMT. It appears that these injuries were a result of operator error, however, the serious nature of these incidents prompted a FDA Public Health Notification: Serious injuries from Microwave Thermotherapy for Benign Prostatic Hyperplasia (**Appendix G**).

Mortality associated with HE-TUMT in the single-arm studies ranged between 0 and 10 per cent. As stated in the primary evidence, these deaths are probably principally driven by co-morbid conditions, which are common in this population.

Is it effective?

The efficacy evidence for HE-TUMT has been divided into subsections according to comparator: TURP, medication (terazosin) and other minimally invasive procedures (ILCP/TUNA).

The three primary outcomes assessed in this report were symptom scores (IPSS, AUA scores), maximum urinary flow rates (Q_{max}) and post-void residual volume (PVR). Symptom scores are considered the most important indication of treatment success, as stated by the American Urological Association (AUA) guidelines (2003):

> "… symptoms score changes and the degree of each patient's bother due to the symptoms should be the primary determinants of treatment response or disease progression in the follow-up period …".

The IPSS questionnaire is included in **Appendix I**. This scoring system assesses symptoms including incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. An additional question assesses quality of life due to urinary symptoms.

Other important outcomes presented are treatment failure rates, changes in quality of life and changes in sexual function.

In the context of this assessment report, treatment failure is defined as:

- lack of efficacy requiring further management (eg, a TURP or HE-TUMT, or pharmacotherapy)
- complications of the procedure requiring further management (eg, urethral strictures requiring a urethrotomy).

HE-TUMT versus TURP

Nine trials were identified that compared HE-TUMT with TURP: five level II studies, one level III-1 study, and three level III-2 studies. Trials varied in duration from three months to 36 months. Study quality and design are described in the section titled '**Evidence**' and in Table 69 of **Appendix D**.

Six studies compared cooled HE-TUMT with TURP: Five used the Prostatron® v2.5 device (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a; Norby et al 2002a; Witjes et al 1997; Ahmed et al 1997), and one used the Dornier UroWave® device (Arai et al 2000). Three studies compared non-cooled HE-TUMT with TURP: all used the ProstaLund® device (Wagrell et al 2004; Study B in 2002 submission to FDA, PMA P010055 SSED; Hansen et al 1997).

Symptoms scores: IPSS/AUS

IPSS/AUS symptom scores were reported in six studies of cooled HE-TUMT versus TURP (d'Ancona et al 1999; de la Rosette et al (2003a)/Floratos et al 2001a; Norby et al 2002a; Ahmed et al 1997; Arai et al 2000; Witjes et al 1997) and in two studies of non-cooled HE-TUMT versus TURP (Wagrell et al 2004; Study B (FDA)). The IPSS and AUA scoring systems are identical except for an additional quality of life question added at the end of the IPSS questionnaire (reported separately). Madsen scores were also reported in d'Ancona et al (1999) and Floratos et al (2001a), however, are not presented

here, as results were similar to the IPSS/AUS scores. One study of non-cooled HE-TUMT versus TURP by Hansen et al (1997) did not assess symptoms using any of these scales, instead using a scale based on the questionnaire of Boyarsky et al (1977).

Cooled HE-TUMT

In the RCT (level II) by d'Ancona et al (1998), symptom scores had improved significantly in the cooled HE-TUMT group by six months, and were stable out to 2.4 years (**Table 19**) The TURP group also showed significant improvements, with a larger improvement by three months than in the cooled HE-TUMT group. The differences, however, were not significant at any time point, although the authors note the analyses included a small number of patients.

De la Rosette et al (2003a)/Floratos et al (2001a) reported symptom scores out to three years in an RCT (level II), with significant improvements observed in both treatment groups compared to baseline. The improvement was significantly greater in the TURP group compared to cooled HE-TUMT group ($p = 0.000$), although it is not clear from the publication whether this refers to one, two and/or three years. Although three month data were not reported in this publication, an earlier duplicate publication (Francisca et al 2000) demonstrated a significantly greater improvement at three months in the TURP group (from 20.8 ± 6.2 down to 5.3 ± 5.2) than in the cooled HE-TUMT group (from 20.1 ± 6.5 down to 10.5 ± 7.9; $p < 0.01$), although the number randomised (n = 147) differed from de la Rosette et al (2003a) and Floratos et al (2001a) (n = 155) as did the number of patients analysed.

The randomised trial (level II) by Norby et al (2002a) differed from the other included trials in that both low and high-energy cooled TUMT systems were used. The choice of low or high-energy protocols depended on the size of the patient's prostate. Patients with prostate volumes less than 30 mL were treated with low-energy (Prostatron® v2.0) whilst for larger prostates; the high-energy protocol (Prostatron® v2.5) was used. Of the 45 patients who received cooled TUMT treatment, 37 received cooled HE-TUMT whilst only eight received cooled LE-TUMT. Overall, IPSS had decreased significantly within one month compared with baseline in both the TURP/TUIP group and cooled LE/HE-TUMT group ($p < 0.01$), although the difference was significantly greater in the TURP/TUIP group ($p < 0.002$). Further reductions had occurred in both groups by three months, with a significant difference still observed between the TURP/TUIP group and cooled LE/HE-TUMT group ($p < 0.002$). However, by six months the improvement in symptom scores was no longer significantly different between the two groups, although both were significantly better than baseline ($p < 0.001$). A *post hoc* analysis of patients treated with low-energy compared with high-energy cooled TUMT was conducted, although no conclusions could be drawn because of the small number involved. Nevertheless, the decrease in IPSS at six months was 11.3 points with cooled HE-TUMT compared with 8.9 points in the cooled LE-TUMT group. The difference was not significant (RD 2.4 [95%CI: –9.5, 14.4]).

Additionally, patients in the study by Norby et al (2002a) estimated the average time at which they first noted a reduction in symptoms as 29 days in the cooled LE/HE-TUMT group and 12 days in the TURP/TUIP group. Although not presented in , DANPSS-1 (Danish Prostatic Symptom Score) results were also reported; this scoring system includes three questions about sexual function. Median total scores were similar at baseline for the cooled LE/HE-TUMT and TURP/TUIP groups (25 and 27

respectively), but decreased significantly more in the TURP/TUIP group at six months (seven and one for cooled LE/HE-TUMT and TUPR/TUIP respectively; $p = 0.009$).

A pseudo-randomised trial (level III-1) by Ahmed et al (1997) found significant improvements in symptom scores relative to baseline in both treatment groups at six months, but no significant difference between the improvements seen in the two groups (**Table 19**).

The prospective controlled before-and-after study by Arai et al (2000) was the only one using the Dornier UroWave® device. Results from this and a similarly designed trial (level III-2) (Witjes et al 1997) must be interpreted with caution because of bias in the selection of patients: therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference. Consequently, treatment groups are not well matched for baseline characteristics. Nevertheless, significant improvements in symptom scores were observed in both the cooled HE-TUMT and TURP groups relative to baseline at three months in Arai et al (2000), although the improvement was significantly greater with TURP than cooled HE-TUMT (**Table 19**).

In Witjes et al (1997), only baseline median and median changes were presented for symptom scores (**Table 19**). Furthermore, patients undergoing TURP were assessed using a different symptom index (based on that described by Frimodt-Moller et al 1984) and were selected from a different hospital using different criteria to the cooled HE-TUMT patients. Consequently, the comparative efficacy of cooled HE-TUMT and TURP cannot be evaluated in this study. Nevertheless symptom scores, stratified by severity of bladder outlet obstruction (BOO), decreased significantly compared to baseline in both the TURP and cooled HE-TUMT groups.

Non-cooled HE-TUMT

Results from two RCTs comparing non-cooled HE-TUMT (ProstaLund®) with TURP (Wagrell et al 2002; Study B in 2002 submission to FDA, PMA P010055 SSED) indicated that both treatments resulted in similar significant improvements in symptom scores at three, six and 12 months (**Table 20**). However, long-term follow-up at 24 and 36 months (Wagrell et al 2004) indicated that symptom scores in the TURP group continued to improve whilst HE-TUMT scores remained stable. Consequently, at two and three years follow-up, the improvements in the TURP group were significantly greater than in the non-cooled HE-TUMT group ($p = 0.014$ and 0.024, respectively).

Hansen et al (1997) reported symptom scores based on the questionnaire of Boyarsky et al (1977), and were therefore not presented in **Table 20**. However, on this scale, a significant improvement in symptoms was seen in both treatment groups at three months versus baseline ($p < 0.001$). Although the magnitude of improvement was greater with TURP, the difference was not significant. It is difficult to interpret the results of this study in the context of the other included studies as no details on patient demographics were reported and therefore the applicability of these results is limited.

Table 19 Cooled HE-TUMT versus TURP: IPSS/AUA Index

Trial/ publication	Treatment arm	Mean age yrs ± SD	N	IPSS/AUA index mean ± SD / [95%CI] (n)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36[a] months	
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	18.3 ± 6.3 (31)	15.1 ± 8.2 (31)	6.7 ± 5.5 (28)	5.0 ± 2.7 (27)	–	7.9 ± 6.3 (17)	**Level II:** Follow-up > 80 per cent at 12 months but ~55 per cent by 3 years. Significance of changes compared to baseline difficult to interpret, although both groups showed significant changes in symptom scores
	TURP	69.6 ± 8.5	21	16.7 ± 5.6 (21)	5.1 ± 3.1 (21)	4.0 ± 2.1 (20)	3.4 ± 2.2 (17)	–	6.3 ±4.8 (12)	
	p value			NR	> 0.05	> 0.05	> 0.05	–	> 0.05	
De la Rosette et al 2003a / Floratos et al 2001a	**HE-TUMT**	67 ± 8.3	82	20 ± 6.7 (82)	–	–	8.1 ± 6.0 (58)[b]	9.3 ± 7.3 (46)[b]	11.5 ± 6.4 (35)[b]	**Level II:** Values from de la Rosette (2003): outcomes poorly reported in Floratos et al (2001a). Significant loss to follow-up at each time point (<70 per cent at 1 year and < 50 per cent by 3 years). Significance of results between HE-TUMT and TURP from Floratos et al (2001a): not clear if applies to 1, 2 and/or 3 years
	TURP	66 ± 8.2	73	20 ± 6.3 (73)	–	–	3.2 ± 3.0 (48)[b]	3.7 ± 4.9 (38)[b]	2.6 ± 2.2 (33)[b]	
	p value			NR	–	–			0.000	
Norby et al 2002[a]	**LE/HE-TUMT**	66 ± 7	46	20.5 ± 5.7 (46)	–	9.5 ± 7.1 (44)[c]	–	–	–	**Level II:** LE- and HE-TUMT not reported separately. Former used in patients with prostate volume < 30 mL, latter used in larger prostates. TURP and TUIP reported together
	TURP/TUIP	68 ± 7	24	21.3 ± 6.6 (22)	–	6.8 ± 5.7 (22)[c]	–	–	–	
	p value			0.640	–	0.128				
Ahmed et al 1997	**HE-TUMT**	69.36	30	18.5 [17.1–20.1] (30)[c]	–	5.3 [3.9–6.4] (30)[b,c]	–	–	–	**Level III-1:** Patients who discontinued were replaced
	TURP	69.45	30	18.4 [16.7–20.1] (30)[c]	–	5.2 [3.9–6.5] (30)[b,c]	–	–	–	
	p value			–	–	NR	–	–	–	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	18.4 ± 6.2 (34)	13.2 ± 6.8 (34)[b]	–	–	–	–	**Level III-2:** Selection bias because selection was primarily on patients views of the benefits including symptom improvements versus risks
	TURP	68.8 ± 7.9	65	19.0 ± 7.2 (55)	7.6 ± 4.9 (55)[b]	–	–	–	–	
	p value			0.862	< 0.001	–	–	–	–	

				IPSS/AUA index Baseline median		IPSS/AUA index 6 month median change				
Witjes et al 1997	**HE-TUMT**				–		–	–	–	**Level III-2**: Only median and median changes reported. Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients at each time point. Selection bias because therapy was recommended based on severity of symptoms, grade of bladder outlet obstruction or patient preference. TURP patients were from a different hospital; were selected using different criteria and a different symptom score system was used – therefore results cannot be compared with HE-TUMT
	Without BOO[d]	65 ± 7	21	15		–8[e]				
	Moderate BOO[d]	66 ± 9	57	19		–9[e]				
	Severe BOO[d]	68 ± 8	58	17		–10[e]				
	p value			NR	–	0.40	–	–	–	
	TURP[f]				–		–	–	–	
	Without BOO[d]	70 ± 9	7	5		–3[e]				
	Moderate BOO[d]	69 ± 8	36	9		–6[e]				
	Severe BOO[d]	68 ± 8	44	9		–7[e]				
	p value			NR	–	0.11	–	–	–	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TUIP, transurethral incision of the prostate; TURP, transurethral resection of the prostate; IPSS, international prostate symptom score; ITT, intention-to-treat; AUA, American urological association; NR, not reported

[a] *Follow-up was 30 months for d'Ancona et al (1998) b p<0.001 versus baseline*

[b] *p<0.001 versus baseline*

[c] *Patient dropouts were substituted; AUA symptom scores rather than IPSS*

[d] *severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[e] *p < 0.05 versus baseline*

[f] *Symptom score in TURP group was that described by Frimodt-Moller et al (1984)*

Table 20 Non-cooled HE-TUMT versus TURP: IPSS Index

Trial/ publication	Treatment arm	Mean age yrs ± SD	N	IPSS index Mean ± SD (n)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36 months	
Wagrell et al 2004	HE-TUMT	67 ± 8	103	21.0 ± 5.4 (99)	8.4 ± 5.5 (85)	7.4 ± 6.2 (95)	7.2 ± 6.2 (93)	7.2 ± 5.9 (77)	8.2 ± 6.9 (68)	Level II: 1 year data were the primary endpoint, however, study was extended thereafter and patients asked to return yearly for up to 5 years. Follow-up at 1 year > 80%, however, this decreased to ~75% by 2nd year and <70% by third year. 3, 6 and 12-month data taken from Wagrell et al 2002. 24 and 36-month data taken from Wagrell et al 2004 (12 month data matched earlier publication)
	TURP	69 ± 8	51	20.4 ± 5.9 (46)	6.7 ± 4.3 (41)	5.9 ± 5.0 (43)	7.1 ± 6.6 (43)	4.6 ± 4.4 (38)	5.0 ± 3.9 (35)	
	p value			–	NS	NS	0.578	0.014	0.024	
Study B (FDA)	HE-TUMT	67.5	42	20.0 (42)	~7.0a	~4.5a	~4.0a	–	–	Level II: Endpoint data read from graph. 95% CIs were graphed but not extracted
	TURP	67.7	19	19.2 (19)	~8.0a	~5.5a	~7.0a	–	–	
	p value			–	NR	NR	NR	–	–	

Abbreviations: BOO, bladder outlet obstruction; FDA, Food and Drug Administration; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, international prostate symptom score; ITT, intention-to-treat; NR, not reported; NS, not significant

[a]*Approximated values (~) reported mean endpoint scores as these were read from a graph*

Maximum urinary flow rate (Q_{max})

Cooled HE-TUMT

Three randomised studies (level II: d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a; Norby et al 2002a) and one prospective before-and-after study (level III-2: Witjes et al 1997) reported significant improvements in maximum urinary flow rate (Q_{max}) at six months relative to baseline following treatment with both cooled HE-TUMT and TURP (**Table 21**). Improvements at six months were significantly greater with TURP compared with cooled HE-TUMT in one of the randomised studies (Norby et al 2002a) but no different in the third (d'Ancona et al 1998).

Long-term data from two of the randomised studies (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a) indicated that improvements in Q_{max} were maintained for up to three years with both cooled HE-TUMT and TURP. In the study by d'Ancona et al (1998), improvements at 30 months was 62 per cent and 105 per cent in the cooled HE-TUMT and TURP groups, respectively, although the difference was not significant (possibly because of the small number of patients analysed). In contrast, de la Rosette et al (2003a)/Floratos et al (2001a) reported the improvement in Q_{max} was significantly greater with TURP compared to cooled HE-TUMT at one, two and three years follow-up.

Norby et al (2002a) also present results from a *post hoc* analysis comparing patients treated with low-energy and high-energy cooled TUMT protocols. The small numbers involved prevent any conclusions being made, although the mean increases (improvement) in Q_{max} was 1.3 mL/s and 4.4 mL/s for the low-energy and high-energy protocols respectively (RD 3.1 [95%CI: –6, 8.7]).

One pseudo-randomised trial (level III-1: Ahmed et al 1997) and another prospective before-and-after study (level III-2: Arai et al 2000) demonstrated no improvement at six and three months respectively with cooled HE-TUMT, compared to significant improvement with TURP.

Non-cooled HE-TUMT

Large and sustained improvements in Q_{max} were observed from three months out to 36 months post treatment with both non-cooled HE-TUMT and TURP in one randomised study (level II: Wagrell et al 2002, 2004; **Table 22**). Improvements in the TURP groups were significantly better than non-cooled HE-TUMT only at 24 months follow-up. Results from a second 12-month randomised study supported these results (Level II: Study B in 2002 submission to FDA, PMA P010055 SSED; **Table 22**).

A prospective controlled before-and-after study by Hansen et al (1997) noted significant increases in Q_{max} at three months for the TURP group but not the non-cooled HE-TUMT group; however, the applicability of this study is limited due to a lack of reporting of patient characteristics (**Table 22**).

Table 21 Cooled HE-TUMT versus TURP: Q_{max}

Trial/ publication	Treatment arm	Mean age yrs ± SD	N	Q_{max} (mL/s): Mean ± SD / [95%CI] (n)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36[a] months	
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	9.3 ± 3.9 (31)	15.5 ± 8.0 (31)	17.0 ± 7.5 (28)	17.1 ± 7.8 (27)	–	15.1 ± 9.6 (17)	**Level II:** Follow-up > 80% at 12 months but drops to ~55% by 3 years. Significance of changes compared to baseline difficult to interpreter from the publication
	TURP	69.6 ± 8.5	21	9.3 ± 3.4 (21)	19.6 ± 11.2 (21)	15.3 ± 5.9 (20)	19.3 ± 10.7 (17)	–	19.1 ± 8.2 (12)	
	p value			NR	> 0.05	> 0.05	> 0.05		> 0.05	
De la Rosette et al 2003a / Floratos et al 2001a	**HE-TUMT**	67 ± 8.3	82	9.2 ± 3.1 (82)	–	–	14.9 ± 7.2 (58)[b]	13.7 ± 6.4 (46)[b]	11.7 ± 5.8 (35)[c]	Values obtained from de la Rosette (2003) as these were poorly reported in Floratos et al (2001a). Significant loss to follow-up at each time point (< 70 and < 50% at 1 and 3 years respectively). Significance between HE-TUMT and TURP from Floratos et al (2001a): not clear if applies to 1 and 2 years as well as 3
	TURP	66 ± 8.2	73	8.0 ± 2.9 (73)	–	–	23.8 ± 10.4 (48)[b]	22.5 ± 11.4 (38)[b]	22.8 ± 11.6 (33)[b]	
	p value			NR	–	–	0.000	0.000	0.000	
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	9.1 ± 4.2 (46)	–	13.2 ± 6.9 (44)[d]	–	–	–	**Level II:** LE- and HE-TUMT not reported separately. Former used on patients with prostate volume < 30mL whereas latter used in larger prostates. TURP and TUIP reported together
	TURP/TUIP	68 ± 7	24	9.6 ± 3.2 (22)	–	20.6 ± 12.8 (22)[d]	–	–	–	
	p value			0.639	–	0.019	–	–	–	
Ahmed et al 1997	**HE-TUMT**	69.36	30	10.1 [9.2, 10.9] (30)[e]	–	9.1 [8.0, 10.2] (30)[e,f]	–	–	–	**Level III-1:** Patients who discontinued were replaced
	TURP	69.45	30	9.5 [8.9, 10.1] (30)[e]	–	14.6 [13.4, 15.8] (30)[e,g]	–	–	–	
	p value			NR	–	NR	–	–	–	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	7.7 ± 4.3 (34)	8.6 ± 4.9 (34)[h]	–	–	–	–	**Level III-2:** Selection bias: selection was primarily on patients views of the benefits including symptom improvements versus risks
	TURP	68.8 ± 7.9	65	7.7 ± 4.6 (55)	14.4 ± 7.8 (55)[f]	–	–	–	–	
	p value			0.92	< 0.001	–	–	–	–	

				Baseline Q_{max} (mL/s)		**Mean change in Q_{max} at 6 months (mL/s)**				
Witjes et al 1997	**HE-TUMT**									**Level III–2**: Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point. Selection bias because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference. Furthermore, TURP patients were from a different hospital and were selected using different criteria so results cannot be compared with HE-TUMT
	Without BOO[i]	65 ± 7	21	9.5 ± 2.8	–	+ 3.9 ± 5.4[j]	–	–	–	
	Moderate BOO[i]	66 ± 9	57	10.4 ± 2.8	–	+ 2.3 ± 4.9[j]	–	–	–	
	Severe BOO[i]	68 ± 8	58	8.7 ± 3.3	–	+ 6.6 ± 7.0[j]	–	–	–	
	p value across severity groups			NR	–	< 0.001	–	–	–	
	TURP									
	Without BOO[i]	70 ± 9	7	10.5 ± 5.3	–	3.0 ± 2.9	–	–	–	
	Moderate BOO[i]	69 ± 8	36	9.9 ± 5.7	–	8.8 ± 9.9[j]	–	–	–	
	Severe BOO[i]	68 ± 8	44	8.8 ± 6.4	–	9.4 ± 10.8[j]	–	–	–	
	p value across severity groups			NR	–	0.38	–	–	–	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TUIP, transurethral incision of the prostate; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association Symptom Score; NR, not reported

[a]*Follow-up was 30 months for d'Ancona et al (1998)*

[b]*p < 0.001 versus baseline*

[c]*p = 0.013 versus baseline*

[d]*p < 0.01 versus baseline*

[e]*Patient dropouts were substituted*

[f]*HE-TUMT versus baseline not significant*

[g]*p < 0.001 for TURP versus baseline*

[h]*p = 0.0844 for HE-TUMT versus baseline*

[i]*Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[j]*p < 0.05 versus baseline*

Table 22 Non-cooled HE-TUMT versus TURP: Q_{max}

Trial/ publication	Treatment arm	Mean age yrs ± SD	N	Mean ± SD (n)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36 months	
Wagrell et al 2004	**HE-TUMT**	67 ± 8	103	7.6 ± 2.7 (79)	12.8 ± 6.1 (81)	13.5 ± 6.1 (91)	13.3 ± 6.0 (73)	12.4 ± 5.3 (77)	11.9 ± 4.9 (66)	**Level II:** 1-year data were primary endpoint, however, study was extended thereafter and patients asked to return yearly for up to 5 years. Follow-up at 1 year > 80%, however, this decreased to ~ 75% by second year and < 70% by third year. 3, 6 and 12-month data taken from Wagrell et al 2002. 24 and 36 month data taken from Wagrell et al 2004 (12 month data matched earlier publication)
	TURP	69 ± 8	51	7.9 ± 2.7 (35)	14.6 ± 9.0 (41)	13.8 ± 6.8 (43)	15.2 ± 7.8 (31)	15.6 ± 9.6 (37)	13.5 ± 7.4 (34)	
	p value			NR	NS	NS	0.565	0.020	0.584	
Study B (FDA)	**HE-TUMT**	67.5	42	7.0 (42)	–	–	19.9	–	–	**Level II:** No SDs provided. Baseline TURP value from table: text reported a different figure of 7.9 mL/s but unclear whether this was an error or whether it was calculated for a different number of patients (eg, per-protocol?)
	TURP	67.7	19	7.0 (19)	–	–	25.2	–	–	
	p value			NR	–	–	NS[a]	–	–	
Hansen et al 1997)	**HE-TUMT[b]**	NR	62	9.0	11.0[c]	–	–	–	–	**Level III-2:** Decisions to perform HE-TUMT or TURP based on diagnostic work-up. Patient characteristics and follow-up not reported. Results are estimated from graphical results
	TURP[b]	NR	110	7.5	17.5[d]	–	–	–	–	
	p value			NR	NR	–	–	–	–	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, international prostate symptom score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported; NS not significant

[a]*Ratio of HE-TUMT/TURP for Q_{max} was 69.9% with a one-sided 95% CI of 54.6% which was within the statistical target of = 80%; baseline adjusted Q_{max} results in accordance with these results*

[b]*Approximated values read from a graph*

[c]*Not significant versus baseline*

[d]*p < 0.001 versus baseline*

Post-void residual volume (PVR)

Cooled HE-TUMT

De la Rosette et al (2003a) reported a significant reduction in PVR compared to baseline for patients treated with TURP. In contrast, there was no improvement after cooled HE-TUMT (there is an increase in PVR by year 2 and 3, although Floratos et al (2001a) noted that at each of these time points, the mean PVR showed no statistically or clinically relevant difference from baseline).

The difference in the reduction in PVR for TURP compared with cooled HE-TUMT was reported as significant ($p < 0.05$) in Floratos et al (2001a). In the duplicate publication by Francisca et al (2000), although the number of patients analysed at each time point differed, as did the magnitude of the changes observed, the overall trend of the results was the same (ie, cooled HE-TUMT showed no significant changes in PVR at 12 weeks or one year compared with baseline, whilst there was a significant decrease in PVR in the TURP group at both time points compared to baseline and compared with cooled HE-TUMT). Similarly, in the duplicate reference by Francisca et al (1999c), although the number analysed differed from both other publications – the baseline and one year mean PVR values for the TURP group were nevertheless similar to those reported in de la Rosette et al (2003a) with a large improvement for TURP from 96 mL down to 19 mL. There was no change at one year in the cooled HE-TUMT group (57 mL and 56 mL for baseline and one year, respectively).

Results from d'Ancona et al (1998) revealed a general decrease in PVR following treatment with both cooled HE-TUMT and TURP that was sustained for up to 30 months (**Table 23**). The significance of the changes relative to baseline and between treatments could not be interpreted from the publication; however, the magnitude of decrease in PVR was greater with TURP compared with cooled HE-TUMT.

In Norby et al (2002a), median PVR decreased significantly by six months in the cooled LE/HE-TUMT and the TURP/TUIP groups compared to baseline. However, PVR decreased significantly more in the TURP/TUIP group compared with the cooled LE/HE-TUMT group ($p = 0.013$).

In two further studies, PVR did not improve significantly relative to baseline at three months (Arai et al 2000) and six months (Ahmed et al 1997), in the cooled HE-TUMT group, in contrast to significant improvements observed with TURP in both studies. The study by Witjes et al (1997) demonstrated significant decreases in PVR across all severities of BOO at six months in the cooled HE-TUMT group, and in the moderate-to-severe subgroups receiving TURP.

Non-cooled HE-TUMT

In the study by Wagrell et al (2002, 2004), large decreases in PVR were observed in both the non-cooled HE-TUMT group and TURP group at 12 months, which were sustained at 24 and 36 months (**Table 24**). There was no significant difference between the groups.

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean ± SD / [95%CI] (n) (mL)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36[a] months	
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	49.5 ± 69.9 (31)	25.5 ± 58.1 (31)	30.6 ± 41.0 (28)	70.4 ± 81.3 (27)	–	27.4 ± 49.1 (17)	**Level II:** Follow-up > 80% at 12 months but drops to ~55% by 3 years. Significance of changes could not be interpreted from the publication
	TURP	69.6 ± 8.5	21	91.1 ± 104.7 (21)	10.5 ± 24.5 (21)	52.7 ± 70.7 (20)	23.6 ± 29.8 (17)	–	9.3 ± 14.6 (12)	
	p value			NR	–[b]	–[b]	–[b]	–	–[b]	
De la Rosette et al 2003a / Floratos et al 2001a	**HE-TUMT**	67 ± 8.3	82	65 ± 84 (82)	–	–	55 ± 69 (58)	91 ± 116 (46)	94 ± 114 (35)	**Level II:** Values obtained from de la Rosette (2003) as these were poorly reported in Floratos et al (2001a)
	TURP	66 ± 8.2	73	91 ± 98 (73)	–	–	20 ± 49 (48)[c]	29 ± 39 (38)[c]	35 ± 56 (33)[c]	
	p value						NR	NR	NR	
Ahmed et al 1997	**HE-TUMT**	69.36	30	94.4 [70.0, 112.8] (30)[d]	–	104.9 [78.9, 130.9] (30)[d]	–	–	–	**Level III-1:** Patients who discontinued were replaced
	TURP	69.45	30	109.1 [88.2, 130.0] (30)[d]	–	32.5 [22.5, 40.5] (30)[c,d]	–	–	–	
	p value			NR	–	NR	–	–	–	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	58.1 ± 65.7 (34)	63.6 ± 80.6 (34)[e]	–	–	–	–	**Level III-2:** Selection bias because selection was primarily on patients views of the benefits including symptom improvements versus risks
	TURP	68.8 ± 7.9	65	133.3 ± 211.4 (55)	39.2 ± 58.8 (55)[f]	–	–	–	–	
	p value			< 0.05	NS	–	–	–	–	

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean ± SD / [95%CI] (n) (mL)						NHMRC level / comment
				Baseline	3 months	6 months	12 months	24 months	36[a] months	
Witjes et al 1997	**HE-TUMT**									**Level III-2**: Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point. Selection bias because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference. Furthermore, TURP patients were from a different hospital and were selected using different criteria so results cannot be compared with HE-TUMT
	Without BOO[g]	65 ± 7	21	53 ± 82	–	–47 ± 74[h]	–	–	–	
	Moderate BOO[g]	66 ± 9	57	65 ± 72	–	–32 ± 108[h]	–	–	–	
	Severe BOO[g]	68 ± 8	58	86 ± 94	–	–43 ± 125[h]	–	–	–	
	p value across severity groups			NR	–	0.86	–	–	–	
	TURP									
	Without BOO[g]	70 ± 9	7	71 ± 76	–	–42 ± 47	–	–	–	
	Moderate BOO[g]	69 ± 8	36	93 ± 152	–	–61 ± 101[h]	–	–	–	
	Severe BOO[g]	68 ± 8	44	138 ± 157	–	–121 ± 150[h]	–	–	–	
	p value across severity groups			NR	–	0.07	–	–	–	
				Median PVR (mL) baseline: [IQR] (n)		**Median PVR (mL) 6 months: [IQR] (n)**				
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	110 [50–210] (46)	–	48 [24–129] (44)	–	–	–	**Level II:** LE- and HE-TUMT not reported separately. Former used on patients with prostate volume < 30 mL whereas latter used in larger prostates. TURP and TUIP reported together
	TURP/TUIP	68 ± 7	24	75 [17–193] (22)	–	23 [3–48] (22)	–	–	–	
	p value			0.273	–	0.013	–	–	–	

Abbreviations: BOO, Bladder outlet obstruction; HE-TUMT, high energy transurethral microwave thermotherapy; IQR, inter-quartile range; PVR: Post-void residual volume; TUIP, Transurethral incision of the prostate; TURP, transurethral resection of the prostate; ITT, intention to treat; NR, not reported; NS, not significant

[a]30 months for d'Ancona et al (1998)

[b]Significance could not be interpreted from the publication

[c]p < 0.001 for TURP versus baseline

[d]Patient dropouts were substituted

[e]p = 0.624 versus baseline

[f]p < 0.014 versus baseline

[g]severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more

[h]p < 0.05 versus baseline

Table 24 Non-cooled HE-TUMT versus TURP: PVR

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean ± SD (n)				NHMRC level / comment
				Baseline	12 months	24 months	36 months	
Wagrell et al 2004	**HE-TUMT**	67 ± 8	103	106 ± 77 (99)	49 ± 70 (86)	55 ± 63 (75)	47 ± 62 (68)	**Level II:** 1-year data were primary endpoint, however, study was extended thereafter and patients asked to return yearly for up to 5 years. Follow-up at 1 year > 80%, however, this decreased to ~ 75% by second year and < 70% by third year. 3 and 6 month data available in document from FDA website but not included here as are graphed only and results were similar to 12 months
	TURP	69 ± 8	51	94 ± 82 (45)	54 ± 77 (38)	40 ± 48 (38)	54 ± 118 (34)	
	p value			NR	0.680	0.380	0.760	

Abbreviations: BOO, Bladder outlet obstruction; HE-TUMT, high energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, international prostate symptom score; ITT, intention to treat; AUA, American urological association symptom score; NR, not reported; NS not significant

Treatment failure

Three randomised studies of cooled HE-TUMT versus TURP reported treatment failure rates (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a; Norby et al 2002a) (**Table 25**). Treatment failures with HE-TUMT were usually due to a lack of effectiveness. The majority of these patients were re-treated with a TURP. In contrast, treatment failures with TURP were usually a result of a complication (8/9 cases; 89%), typically a urethral stricture (requiring a urethrotomy) or bladder neck stenosis (requiring a bladder neck incision) (**Table 25**). Only one of nine (11%) treatment failures with TURP was due to a lack of effectiveness.

In most of the studies, there were a number of patients who refused to participate any further or who were lost to follow-up. It is possible that patients who were dissatisfied with their results sought further treatment elsewhere, thus affecting the estimate of treatment failure. **Table 25** includes two sets of estimates for each study, where relevant: the first includes patients specifically reported as receiving further management for treatment failure; the second includes all patients who refused to participate any further, or who were lost to follow-up.

The 12 months cumulative treatment failure rates in d'Ancona et al (1998) were similar in the cooled HE-TUMT and TURP groups (6.5% and 4.8% respectively). However, at 30 months, 25.8 per cent of patients in the cooled HE-TUMT group had received further treatment (either TURP or an alpha-blocker) compared with only 4.8 per cent of TURP patients (bladder neck incision). A *post hoc* analysis indicates the difference was significant at 30 months only ($p = 0.049$). Including loss to follow-up and those who refused to participate further, the upper estimate for treatment failures at 12 months was 3/31 (9.8%) for cooled HE-TUMT and 2/21 (9.5%) for TURP. The treatment failure rates for cooled HE-TUMT and TURP at 30 months were 13/31 (41.9%) and 5/21 (23.8%) respectively ($p = 0.18$).

De la Rosette et al (2003a) reported a higher 12-month cumulative treatment failure rate for the cooled HE-TUMT group (12.2%) compared with the TURP group (9.6%). The cumulative treatment failure rate at 24 and 36 months remained higher in the cooled HE-TUMT group (14.6% and 19.5% respectively) compared with the TURP group (11.0% at both time points). The difference was not significant at either time point. Including patients lost to follow-up and those who refused to participate further, the upper estimate for the treatment failure rates at 36 months for cooled HE-TUMT and TURP were 21/82 (25.6%) and 19/73 (26.0%) respectively.

Norby et al (2002a) conducted a six-month study, during which 2.2 per cent of cooled HE-TUMT patients underwent further management for treatment failure. There were no treatment failures in the TURP group.

Only one randomised study of non-cooled HE-TUMT versus TURP reported treatment failure rates (Wagrell et al 2004) (**Table 25**) and there were no treatment failure data for the initial 12 months (primary endpoint) of the study. At the end of 12 months follow-up, 11/103 (10.8%) of non-cooled HE-TUMT patients and 3/51 (5.9%) of TURP patients withdrew from the study. At the end of the 36 months follow-up, the number of patients evaluated had fallen to 80/103 (77.8%) in the non-cooled HE-TUMT group and 39/51 (60.8%) in the TURP group. The treatment failure rates within this cohort of patients who continued on from 12 months to 36 months was 5.0 per cent in the non-cooled HE-TUMT patients compared with 2.6 per cent in TURP patients.

However, the applicability of this result is limited by the lack of reporting during the initial 12-month period, and significant loss to follow-up. For example, if all those lost to follow-up were assumed to be treatment failures, the corresponding treatment failure rates over the entire 36-month follow-up would be 27/103 (26.2%) in the non-cooled HE-TUMT group and 13/51 (25.5%) in the TURP group.

Table 25 Cumulative treatment failure rates for cooled and non-cooled HE-TUMT versus TURP

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Cumulative treatment failure rate n/N (%)				NHMRC level / comment
				6 months	12 months	24 months	36 months[a]	
Cooled HE-TUMT								
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	2/31 (6.5)	2/31 (6.5)	–	8/31 (25.8)	**Level II: HE-TUMT:** The 2 patients at 6 months and 4 at 30 months were re-treated with TURP. The remaining 2 received alpha-blockers at 30 months. **TURP:** The TURP patient received a bladder neck incision *This is a lower estimate of treatment failure: it does not include patients lost to follow-up or who refused to participate further*
	TURP	69.6 ± 8.5	21	0/21 (0.0)	1/21 (4.8)	–	1/21 (4.8)	
	HE-TUMT + LTF	69.3 ± 5.9	31	2/31 (6.5)	3/31 (9.7)	–	13/31 (41.9)	*This is an upper estimate of treatment failure assuming all patients who refused to participate further, or who were lost to follow-up, were re-treated*
	TURP + LTF	69.6 ± 8.5	21	1/21 (4.8)	2/21 (9.5)	–	5/21 (23.8)	
De la Rosette et al 2003a / Floratos et al 2001a[b]	**HE-TUMT**	67 ± 8.3	82	NR	10/82 (12.2)	12/82 (14.6)	16/82 (19.5)	**Level II:** HE-TUMT: treatment failures were managed in the following way: TURP (8). Laser prostatectomy (1), cystolithotripsy (2), internal optical urethrotomy (1), HE-TUMT (1) and alpha-blockers (3). TURP: management of treatment failures due to complications: bladder neck incisions for bladder neck stenosis (4), internal optical urethrotomy for urethral stricture (2), physiotherapy for stress urinary incontinence (1), α-blockers for UTI (1), anticholinergics for severe storage symptoms (1) *This is a lower estimate of treatment failure: it does not include patients lost to follow-up or who refused to participate further*
	TURP	66 ± 8.2	73	NR	7/73 (9.6)	8/73 (11.0)	8/73 (11.0)	
	HE-TUMT + LTF	67 ± 8.3	82	NR	–	–	21/82 (25.6)	*This is an upper estimate of treatment failure assuming all patients who refused to participate further, or who were lost to follow-up, were re-treated. It was only possible to estimate treatment failure at 36 months since lost to follow-up was not reported according to earlier time points*
	TURP + LTF	66 ± 8.2	73	NR	–	–	19/73 (26.0)	
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	1/46 (2.2)	–	–	–	**Level II:** HE-TUMT: treatment failure due to persistent UTI (1) requiring further treatment with TURP
	TURP/TUIP	68 ± 7	24	0/24 (0)	–	–	–	

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Cumulative treatment failure rate n/N (%)				NHMRC level / comment
				6 months	12 months	24 months	36 months[a]	
Non-cooled HE-TUMT								
Wagrell et al 2004	**HE-TUMT**	67 ± 8	103		NR	–	4/80 (5)	**Level II:** Treatment failures: not reported for the initial 12 months of the study in Wagrell et al (2002). Treatment failure rates at 36 months were for the group who continued from 12 months up to 36 months as reported in Wagrell et al (2004) *This is a lower estimate of treatment failure: it does not include patients lost to follow-up or who refused to participate further*
	TURP	69 ± 8	51		NR	–	1/39 (2.6)	
	HE-TUMT + LTF	67 ± 8	103	–	–	–	27/103 (26.2)	*This is an upper estimate of treatment failure over the entire 36 months follow-up assuming all patients who refused to participate further, or who were lost to follow-up, were re-treated*
	TURP + LTF	69 ± 8	51	–	–	–	13/51 (25.5)	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high energy transurethral microwave thermotherapy; LTF, lost to follow-up; TUIP, transurethral incision of the prostate; TURP, transurethral resection of the prostate; NR, not reported; NS not significant, n, number experiencing event; N, number randomised

[a]*Follow-up was 30 months for d'Ancona et al (1998)*

[b]*Results from de la Rosette et al (2003a); Floratos et al (2001a) reported fewer treatment failures in the HE-TUMT group (n = 14)*

Quality of life

Quality of life (QoL) was reported in three studies using cooled HE-TUMT devices (de la Rosette et al 2003a/Floratos et al 2001a; Norby et al 2002a; Arai et al 2000).

Arai et al (2000) assessed QoL using two scales, the IPSS QoL and BPH impact index scores (Mebust et al 1993) (**Table 26**). IPSS QoL scores significantly improved by three months in both the cooled HE-TUMT and TURP groups. The improvement was reported as significantly greater in the TURP group, although the p value of < 0.07 is not the standard threshold for significance. BPH impact index scores also significantly improved from baseline to three months in the cooled HE-TUMT group (6.1 ± 2.8 to 3.6 ± 2.9 respectively; $p < 0.001$) and the TURP group (6.2 ± 3.1 to 2.3 ± 2.7 respectively; $p < 0.001$). However, the improvement was significantly greater in the TURP group ($p < 0.05$).

Table 26 Cooled HE-TUMT versus TURP: Quality of life reported in Arai et al (2000)

QoL scale (possible range)	Treatment arm	Mean age yrs ± SD	N	Mean ± SD		NHMRC level / comment
				Baseline	3 months	
IPSS QoL (0–6)	**HE-TUMT**	66.4 ± 8.0	40	4.4 ± 1.2	2.7 ± 1.4[a]	Number evaluated not specified, although it was noted that data were not available for some patients
	TURP	68.8 ± 7.9	65	4.5 ± 1.1	1.9 ± 1.3[a]	
	p value				< 0.07[b]	
BPH impact index (0–13)	**HE-TUMT**	66.4 ± 8.0	40	6.1 ± 2.8	3.6 ± 2.9[a]	
	TURP	68.8 ± 7.9	65	6.2 ± 3.1	2.3 ± 2.7[a]	
	p value				< 0.01	

[a] *p < 0.001 versus baseline*
[b] *Reported as significant, even though actual value was stated as < 0.07, and usual threshold is < 0.05*

A self-reported questionnaire was completed at three months follow-up by patients in the study by Arai et al (2000). This questionnaire addressed patient satisfaction with treatment (**Table 27**) and impact on sexual activity (reported in the sexual function section below; **Table 33**). All 173 patients in the study were asked to complete the questionnaire, of who 169 responded. Significantly more patients in the TURP group were delighted, pleased or mostly satisfied with treatment (46/52, 88.5%) compared with the cooled HE-TUMT group (20/33, 60.6%; $p < 0.001$ versus TURP).

Table 27 Cooled HE-TUMT versus TURP: Patient satisfaction with treatment at three months in Arai et al (2000)

Response	HE-TUMT n/N (%)	TURP n/N (%)
Delighted	0/33 (0)	13/52 (25.0)
Pleased	8/33 (24.2)	16/52 (30.8)
Mostly satisfied	12/33 (36.4)	17/52 (32.7)
Mixed	8/33 (18.2)	3/52 (5.8)
Mostly dissatisfied	4/33 (12.1)	2/52 (3.8)
Dissatisfied	3/33 (9.1)	1/52 (1.9)
Greatly dissatisfied	0/33 (0)	0/52 (0)

n, number of patients; N, number evaluated

In Norby et al (2002a), QoL scores were reported, although the scale used was not. Median scores were similar at baseline for the cooled LE/HE-TUMT and TURP/TUIP groups (median [inter-quartile distance]: 4[4–4] and 4[4–5] respectively) and improved at six months, although the difference between the groups was not significant (median [inter-quartile distance]: 2[1–3] and 1[1–2] respectively; $p = 0.055$). Patients' rating of overall satisfaction with treatment was significantly greater in the TURP/TUIP group compared with the cooled LE/HE-TUMT group ($p = 0.004$). In a *post hoc* analysis, median QoL scores at six months in patients treated with low-energy TUMT was 2.5 compared with 2.0 in patients treated with high-energy cooled TUMT. Subjective evaluation showed that 3/8 (38%) of low-energy patients compared with only 4/37 (11%) of high-energy patients rated themselves as unimproved.

De la Rosette et al (2003a) reported significant improvements in quality of life at one, two and three years follow-up as assessed by the IPSS QoL scale for both the cooled HE-TUMT and TURP (**Table 28**). Quality of life was reported as being significantly more improved in the TURP group compared with the cooled HE-TUMT group, although the exact time point(s) at which these were compared, whilst probably one, two and three years, was not specified (Floratos et al 2001a). In the duplicate reference by Francisca et al (1999c), similar baseline and 12 months results for the IPSS quality of life were presented, although the number of patients analysed differed. Three-month data from this publication demonstrated a similar improvement as seen in Arai et al (2000) at three months.

In addition to the IPSS QoL scores reported in de la Rosette et al (2003a)/Floratos et al (2001a), quality of life was examined in more detail in the duplicate reference by Francisca et al (2000). A self-administered questionnaire designed specifically to assess QoL for patients with BPH currently undergoing treatment was used (**Table 29**). Of 147 patients randomised, 23 patients were excluded from the analysis, leaving 66 and 56 in the cooled HE-TUMT and TURP groups respectively. In addition, questionnaire sections that were inadequately completed were also excluded from the analysis, such that the number analysed on each question differed. The instrument itself was a 41-item questionnaire that assessed general and specific perception of urinary symptoms, sexual function, daily activities, psychological well-being, social activities and improvement experience. On all questions, a lower score indicated better QoL. There was no significant difference on any of the items between the groups at baseline. However, at three months, both groups experienced improvements in general and specific perception of urinary difficulties and daily activities. Improvements in these areas were sustained at one year, with further improvements seen on the general and specific perception of urinary difficulties item. Comparing between the two groups, significantly greater improvements were seen in the TURP group on the specific perception of urinary difficulties and daily activities items at three months and one year, and the general perception of urinary difficulties at one year. However, there was no difference in the improvement for all scales following treatment between both groups at three months or one year.

Table 28 Cooled HE-TUMT versus TURP: IPSS quality of life reported in the study by de la Rosette et al (2003a)/Floratos et al (2001a)

Trial/ publication	Treatment arm	Mean age years ± SD	Mean ± SD (n)[a]						NHMRC level / comment
			N	Baseline	3 months	12 months	24 months	36 months	
De la Rosette et al 2003a / Floratos et al 2001a	**HE-TUMT**	67 ± 8.3	82	4 ± 0.9 (82)	–	1.9 ± 1.3 (58)[b]	1.9 ± 1.0 (4.6)[b]	2.3 ± 1.2 (35)[b]	**Level II:** Values obtained from de la Rosette (2003a) as these were poorly reported in Floratos et al (2001a). Significant loss to follow-up at each time point (< 70% at 1 year and < 50% by 3 years). Significance between HE-TUMT and TURP from Floratos et al (2001a): not clear if applies to years 1 and 2 as well as 3
	TURP	66 ± 8.2	73	4 ± 1.1 (73)	–	0.6 ± 0.7 (48)[b]	0.9 ± 1.1 (38)[b]	0.6 ± 0.8 (33)[b]	
	p value			NR	–	0.000			
Francisca et al 1999c	**HE-TUMT**	66.2	74	4.2	2.1	1.9	–	–	Duplicate of Floratos et al (2001a), although number randomised differs. Number analysed at each time point was not reported, although it was stated that the number of patients included in the analysis was 66 and 56 in the HE-TUMT and TURP groups respectively
	TURP	64.6	73	4.2	1.3	0.6	–	–	
	p value			NR	NR	NR	–	–	

[a] *Scores can range from 0 to 6, with lower scores indicating better QoL*

[b] *p < 0.001 versus baseline*

Table 29 Cooled HE-TUMT versus TURP (Francisca et al 2000): Quality of life scales as assessed by a self-administered questionnaire

Questionnaire item (possible range of scores)	Treatment arm	Mean ± SD (n)			NHMRC level / comment
		Baseline	3 months	12 months	
General perception of urinary difficulties (5–25)	HE-TUMT	10.7 ± 3.0 (59)	8.2 ± 3.2 (57)	7.4 ± 2,7 (32)	**Level II:** Duplicate reference to Floratos et al 2001a, however, the number randomised differs, and large number of patients excluded from analysis Number randomised HE-TUMT = 74 TURP = 73
	TURP	11.1 ± 3.6 (56)	8.1 ± 3.5 (53)	5.6 ± 1.0 (43)	
	p value	0.47	0.30	< 0.01	
Specific perception of urinary difficulties (5–20)	HE-TUMT	11.3 ± 4.4 (59)	8.3 ± 3.6 (57)	7.0 ± 2.8 (43)	
	TURP	12.4 ± 4.8 (56)	7.1 ± 3.0 (50)	5.8 ± 1.3 (32)	
	p value	0.20	0.02	< 0.01	
Sexual functions (7–21)	HE-TUMT	14.2 ± 6.0 (56)	14.5 ± 5.6 (53)	14.3 ± 5.9 (38)	
	TURP	14.9 ± 4.7 (56)	14.4 ± 4.3 (51)	15.4 ± 3.6 (31)	
	p value	0.49	0.15	0.19	
Daily activities (8–36)	HE-TUMT	12.4 ± 4.0 (58)	10.4 ± 3.1 (56)	9.8 ± 2.8 (42)	
	TURP	13.8 ± 3.9 (56)	9.8 ± 3.1 (53)	8.9 ± 2.1 (32)	
	p value	0.07	0.01	< 0.01	
Psychological well being (7–30)	HE-TUMT	26.4 ± 4.4 (57)	27.9 ± 4.0 (56)	27.3 ± 3.7 (43)	
	TURP	27.3 ± 5.3 (56)	27.9 ± 4.6 (52)	29.4 ± 2.6 (32)	
	p value	0.36	0.63	0.95	
Social well being (4–23)	HE-TUMT	13.4 ± 3.8 (55)	13.6 ± 4.4 (53)	14.4 ± 3.3 (42)	
	TURP	12.5 ± 3.4 (54)	12.0 ± 3.9 (50)	12.8 ± 3.9 (32)	
	p value	0.19	0.69	0.66	
Improvement experienced (4–20)	HE-TUMT	NA	12.2 ± 5.9 (70)	8.8 ± 6.3 (69)	
	TURP	NA	11.5 ± 6.7 (69)	6.7 ± 6.4 (70)	
	p value	NA	0.58	0.07	

Sexual function

Absences of ejaculation, retrograde ejaculation and impotence have been discussed in the safety section. Further to this, this section presents results from two of the comparative studies, which specifically examined the impact of cooled HE-TUMT and TURP on sexual function (Francisca et al 1999c: a duplicate of de la Rosette et al 2003a/Floratos et al 2001a; and Arai et al 2000).

There were a number of limitations with this evidence. First, the studies used different questionnaires, making it impossible to directly compare results, a common problem with studies examining sexual dysfunction. Second, there was a poor response to questions on sexual function in both studies (often less than 60% of those randomised). Finally, the response varied from question to question and also between baseline and endpoint. These issues are a significant source of bias and thus the results are of limited value and must be interpreted with caution.

The reference by Francisca et al (1999c) (a duplicate of Floratos et al 2001a) specifically examined the changes in sexual function associated with cooled HE-TUMT and TURP. These results were from a self- administered questionnaire evaluating sexual function before and three and 12 months after treatment, although only the three-month results were reported (**Table 30**).

Of the 147 randomised, the analysis was performed on 122 who completed the questionnaire at baseline.

Table 30 Cooled HE-TUMT versus TURP (Francisca et al 2000): Sexual function as assessed by a self-administered questionnaire

Questionnaire item	Treatment arm	n (%)		NHMRC level / comment
		Baseline	3 months	
Morning erection	**HE-TUMT**	39 (65)	35 (63)	**Level II:** Duplicate reference to Floratos et al 2001a, however, the number randomised differs, and large number of patients excluded from analysis
	TURP	33 (66)	38 (78)	
Sexual activities (intercourse or masturbation)	**HE-TUMT**	45 (78)	46 (82)	
	TURP	39 (78)	42 (86)	
Premature loss of erection	**HE-TUMT**	18 (35)	14 (28)	Number randomised HE-TUMT = 74 TURP = 73 Number reported as included in analyses HE-TUMT = 66 TURP = 56 Number analysed for each question does differ, however, exact number not reported
	TURP	11 (24)	10 (21)	
Orgasm	**HE-TUMT**	43 (84)	41 (80)	
	TURP	39 (83)	36 (78)	
Orgasm associated with ejaculation[a]	**HE-TUMT**	42 (88)	37 (76)	
	TURP	36 (93)	12 (31)	
Change in function	**HE-TUMT**	12 (23)	8 (17)	
	TURP	8 (17)	17 (36)	
Problem with erection	**HE-TUMT**	14 (29)	13 (33)	
	TURP	7 (20)	9 (17)	

Abbreviation: n number with event

*[a]Includes those answering yes or sometimes – see **Table 31** for breakdown*

More patients reported no ejaculation associated with orgasm at three months compared with baseline in both the cooled HE-TUMT group ($p = 0.04$ versus baseline for those answering 'yes'; **Table 31**) and the TURP group ($p < 0.001$ versus baseline for those answering 'yes'; **Table 31**). Significantly more patients reported absence of ejaculation in the TURP group compared to the cooled HE-TUMT group ($p < 0.0005$): at three months and one year, 74 per cent and 67 per cent, respectively, of cooled HE-TUMT patients still had ejaculation compared with only 27 per cent and 37 per cent, respectively, in the TURP group.

No other statistical difference was seen for any parameter in the cooled HE-TUMT group at three months versus baseline. In the TURP group, more patients reported morning erections at three months compared with baseline ($p = 0.025$; **Table 30**).

Although the change in sexual function at three months was not significant in either treatment group compared to baseline, it was reported that significantly more patients in the TURP group had a change in sexual function at three months (36%) versus the cooled HE-TUMT group (17%; $p = 0.038$; **Table 30**).

Table 31 Response to question about orgasm associated with an ejaculation (Francisca et al 2000)

Response	HE-TUMT n (%)		TURP n (%)		NHMRC level / comment
	Baseline	3 months	Baseline	3 months	
Yes	42 (82)	37 (74)	36 (80)	12 (27)	Number analysed for each question does differ, however, exact number not reported. Significant number of patients not completing question or not included in analyses at baseline and 3 months post treatment
Sometimes	3 (6)	1 (2)	6 (13)	2 (5)	
No	6 (12)	12 (24)	3 (7)	30 (68)	

Furthermore, more patients in the cooled HE-TUMT group were very satisfied or satisfied (55% and 26% respectively) with their sexual functioning at three months compared with the TURP group (21% and 64% respectively; $p = 0.014$) (**Table 32**).

Table 32 Response to question about satisfaction with sexual relationship (Francisca et al 2000)

Response	HE-TUMT n (%)		TURP n (%)		NHMRC level / comment
	Baseline	3 months	Baseline	3 months	
Very satisfied	24 (49)	17 (55)	15 (37)	6 (21)	Number analysed for each question does differ, however, exact number not reported. Significant number of patients not completing question or not included in analyses at baseline and 3 months post treatment
Satisfied	13 (27)	8 (26)	13 (32)	18 (64)	
Unsatisfied	4 (8)	3 (10)	7 (17)	3 (11)	
Very unsatisfied	8 (12)	3 (10)	6 (14)	1 (4)	

Sexual function was evaluated in 155 of 173 patients in the prospective controlled before-and-after study by Arai et al (2000), using the Sapporo Medical University Sexual Function Questionnaire, validated previously in more than 5000 Japanese men (Kumamoto et al 1992; Arai et al 1999; Kato et al 1999). In addition, a self-reported questionnaire assessed ejaculatory function and impact on sexual activity. Results from both questionnaires are presented in **Table 33**. No changes were reported in sexual desire or erectile function six months post treatment compared to baseline in either treatment group as assessed using the Sapporo Medical University Sexual Function Questionnaire. However, erectile function scores were significantly higher in the cooled HE-TUMT group compared with the TURP group at baseline and also at six months post treatment, suggesting that more sexually active patients may have selected cooled HE-TUMT over TURP.

In the self-reported questionnaire, 145 of 173 patients responded to the question relating to the volume of ejaculate and 153 of 173 patients responded to the question relating to impact on sex life (**Table 33**). In the cooled HE-TUMT group, 29 per cent of patients reported no ejaculate or severe decrease in ejaculate volume compared with 49 per cent of TURP patients. The proportion of patients reporting that their sex life was slightly better, to much better, was 28 per cent and 22 per cent in the cooled HE-TUMT and TURP groups respectively; while 19 per cent and 31 per cent, respectively, reported their sex life was slightly worse to much worse.

Table 33 Cooled HE-TUMT versus TURP: Sexual function in Arai et al (2000)

Questionnaire	Outcome	HE-TUMT	TURP
Sapporo Medical University Sexual Function Questionnaire	Sexual desire score (0–10)		
	Mean baseline ± SD	3.2 ± 1.7	2.7 ± 1.8
	Mean 3 months ± SD	3.3 ± 1.8	2.7 ± 1.9
	p value	0.913	0.921
	Number reporting change in sexual desire score at 3 months: n/N (%)		
	Decreased by 2 or more	3 (9.1)	7 (13.7)
	Changed by 1 or less	27 (81.8)	38 (74.5)
	Increased by 2 or more	3 (9.1)	6 (11.8)
	Erectile function score (0–10)		
	Mean baseline ± SD	4.2 ± 2.5	3.1 ± 2.4[a]
	Mean 3 months ± SD	4.1 ± 2.3	3.0 ± 2.5[a]
	p value	0.919	0.831
	Number reporting change in erectile function score at 3 months relative to baseline: n/N (%)		
	Decreased by 2 or more	6 (18.2)	13 (26.5)
	Changed by 1 or less	22 (66.7)	26 (53.1)
	Increased by 2 or more	5 (15.2)	10 (20.4)
Self-reported questionnaire	Number reporting amount of ejaculate at 3 months relative to baseline: n/N (%)		
	None	6/31 (19.4)	12/39 (30.8)
	Severely decreased	3/31 (9.7)	7/39 (18.0)
	Moderately decreased	7/31 (22.6)	8/39 (20.5)
	Somewhat decreased	3/31 (9.7)	5/39 (12.8)
	Same	12/31 (38.7)	7/39 (17.9)
	Number reporting an impact on sex life: n/N (%)		
	Much better	1/32 (3.1)	0/45 (0)
	Better	2/32 (6.3)	8/45 (17.8)
	Slightly better	6/32 (18.8)	2/45 (4.4)
	Same	17/32 (53.1)	21/45 (46.7)
	Slightly worse	3/32 (9.4)	5/45 (11.1)
	Worse	2/32 (6.3)	6/45 (13.3)
	Much worse	1/32 (3.1)	3/45 (6.7)

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; n, number of patients in this category; N, number evaluated; NHMRC, National Health and Medical Research Council; TURP, transurethral resection of the prostate
[a] p < 0.05 for HE-TUMT versus TURP at both time points

HE-TUMT versus terazosin

Even though the most commonly used medication prescribed for BPH in Australia is prazosin (a non-specific alpha-blocker) followed by tamsulosin (a prostate specific alpha-blocker), the literature search only identified two comparative studies of HE-TUMT, both of which compared this procedure to terazosin (an alpha-blocker).

This limited evidence was made up of one level III-1 study with 18 months follow-up (Djavan et al 1999e, 2001) and one level III-2 study with six months follow-up (Witjes et al 1997). Both these studies used cooled HE-TUMT systems (Targis® and Prostatron® v2.5 respectively). Study quality and design are described in the section titled '**Evidence**' and in **Table 69** of **Appendix D**.

Symptoms scores: IPSS

In the study by Djavan et al (1999e, 2001) (level III-1), IPSS index decreased (improved) significantly by six months in both the terazosin and cooled HE-TUMT treatment groups ($p < 0.0005$ relative to baseline; **Table 34**). Terazosin symptom scores decreased faster initially ($p < 0.01$ at week 2), however, by week 12 symptom scores in the cooled HE-TUMT were significantly lower than in the terazosin group ($p < 0.0005$;). By six months, both groups experienced a significant improvement in symptoms compared with baseline, which was sustained to 18 months. However, the mean symptom scores were 38 per cent and 35 per cent lower at six months and 18 months respectively in the cooled HE-TUMT group compared to the terazosin group ($p < 0.0005$ at both time points; **Table 34**). Additionally, the proportion of patients achieving at least a 50 per cent improvement in IPSS at six months was significantly greater in the cooled HE-TUMT group (78%) compared to the terazosin group (33%; $p < 0.0005$) (**Table 34**).

The 18-month results were based on a follow-up of only 56 per cent in the terazosin group compared with 92 per cent in the cooled HE-TUMT group (Djavan et al 2001). The large difference in follow-up is attributed to treatment failure (see the Safety section for more detail: 21/52 discontinued medication of which 19 subsequently underwent cooled HE-TUMT and two underwent TURP).

In the level III-2 study by Witjes et al (1997), significant decreases in the IPSS index were observed in all groups stratified by severity of bladder outlet obstruction (BOO) in both the terazosin and cooled HE-TUMT groups at six months compared with baseline (**Table 34**). The magnitude of change was comparable in both treatment groups; however, selection bias is likely to significantly affect these results. Choice of therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference. Therefore, treatment groups are not well matched for baseline characteristics (eg, baseline symptoms scores were generally higher for terazosin).

Table 34 Cooled HE-TUMT versus terazosin : IPSS Index

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean [95%CI] (n)			NHMRC level / comment
				Baseline	6 months	18 months	
Djavan et al 1999e, 2001	**HE-TUMT**	66.2 ± 8.0	51	19.4 [18.5–20.3] (51)	6.8 [6.2, 7.5] (50)[a]	7.5 (47)[b]	**Level III-1:** Baseline values were taken from Djavan et al 1999a, as these were only graphed in Djavan et al 1999b. Six-month results were reported in both publications and matched. Results for week 2, 6 and 12 were also available in graph form from Djavan et al 1999a but were not extracted here. Follow-up at 18 months was much lower in the terazosin group (56%) compared with the HE-TUMT group (92%)
	Terazosin	64.0 ± 11.4	52	18.9 [18.0–19.9] (52)	11.0 [10.2, 11.9] (43)[a]	11.5 (29)[b]	
	p value (between group comparison)			0.46	< 0.005	< 0.0005	
				Median baseline	Median change at 6 months		
Witjes et al 1997	**HE-TUMT**					–	**Level III-2**: only median and median changes reported. Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time–point. Selection bias is likely to affect these results significantly, because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[c]	65 ± 7	21	15	–8[d]		
	Moderate BOO[c]	66 ± 9	57	19	–9[d]		
	Severe BOO[c]	68 ± 8	58	17	–10[d]		
	p value across severity groups			NR	0.40	–	
	Terazosin					–	
	Without BOO[c]	63 ± 7	13	20	–8[d]		
	Moderate BOO[c]	64 ± 8	30	17	–9[d]		
	Severe BOO[c]	65 ± 9	17	23	–12[d]		
	p value across severity groups			NR	0.72	–	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported

[a] *p < 0.0005 versus baseline*

[b] *18-month data had to be read from a graph although significances stated*

[c] *Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[d] *p < 0.05 versus baseline*

Maximum urinary flow rate (Q_{max})

In the study by Djavan et al (1999e, 2001) (level III-1), peak urinary flow improved more rapidly in the terazosin group initially (ie, by week two), with a significant difference compared with cooled HE-TUMT (Djavan et al 1999e; **Table 35**). However, by six weeks there was no difference between the groups, with both showing a significant improvement compared with baseline ($p < 0.0005$). Thereafter, Q_{max} was significantly higher in the cooled HE-TUMT group compared with the terazosin group at week 12 ($p < 0.0005$), six months (by 19.8%; $p < 0.0005$) and 18 months (by 22%; $p < 0.0005$). The proportion of patients achieving 50 per cent or greater increase in Q_{max} was significantly higher in the cooled HE-TUMT group versus terazosin group at six months (65% versus 10% respectively; $p < 0.0005$) (**Table 35**).

In the level III-2 study by Witjes et al (1997), although Q_{max} improved significantly at six months compared with baseline in the cooled HE-TUMT group across all grades of BOO severity, the improvement was greatest in patients with the most severe obstruction. In contrast, only terazosin patients with mild to moderately severe BOO experienced an improvement in Q_{max} relative to baseline (**Table 35**).

Table 35 Cooled HE-TUMT versus terazosin: Q_{max}

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean [95%CI] (n) mL/s			NHMRC level / comment
				Baseline	6 months	18 months	
Djavan et al 1999e, 2001	**HE-TUMT**	66.2 (8.0)	51	8.3 [7.9. 8.8] (51)	13.9 [13.2, 14.6] (50)[a]	13.8 [13.2, 14.5] (47)	**Level III–1:** Baseline values were taken from Djavan et al 1999a, as these were only graphed in Djavan et al 2001. Six-month results were reported in both publications and matched. Eighteen months were taken from Djavan et al 2001. Results for weeks 2, 6 and 12 were also available in graph form from Djavan et al 1999a but were not extracted. Follow-up at 18 months was much lower in the terazosin group (56%) compared with the HE-TUMT group (92%)
	Terazosin	64.0 (11.4)	52	8.9 [8.4, 9.3] (52)	11.6 [11.2, 12.1] (43)[a]	11.3 [10.9, 11.7] (29)	
	p value (between group comparison)			0.10	< 0.0005	< 0.0005	
					Mean change at 6 months		
Witjes et al 1997	**HE-TUMT**						**Level III-2:** Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point. Selection bias is likely to affect these results significantly, because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[b]	65 ± 7	21	9.5 ± 2.8	+ 3.9 ± 5.4[c]	–	
	Moderate BOO[b]	66 ± 9	57	10.4 ± 2.8	+ 2.3 ± 4.9[c]	–	
	Severe BOO[b]	68 ± 8	58	8.7 ± 3.3	+ 6.6 ± 7.0[c]	–	
	p value across severity groups			NR	< 0.001	–	
	Terazosin						
	Without BOO[b]	63 ± 7	13	10.5 ± 5.3	+ 4.1 ± 3.7[c]	–	
	Moderate BOO[b]	64 ± 8	30	9.9 ± 5.7	+ 4.1 ± 4.8[c]	–	
	Severe BOO[b]	65 ± 9	17	8.8 ± 6.4	+ 0.3 ± 2.3	–	
	p value across severity groups			NR	< 0.01	–	

Abbreviations: BOO, Bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported

[a] p < 0.0005 versus baseline

[b] Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more

[c] p < 0.05 versus baseline

Post-void residual volume (PVR)

Only the level III-2 study by Witjes et al (1997) presented mean changes in PVR for cooled HE-TUMT versus terazosin (**Table 36**). Significant improvements were observed at six months relative to baseline across all degrees of obstruction severity in the cooled HE-TUMT group. In contrast, a significant improvement in PVR was observed only in the moderate severity group treated with terazosin.

Table 36 Cooled HE-TUMT versus terazosin: PVR

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Baseline mean ± SD	6 months mean change ± SD	NHMRC level / comment
Witjes et al 1997	**HE-TUMT**					**Level III-2**: Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point. Selection bias is likely to affect these results significantly, because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[a]	65 ± 7	21	53 ± 82	–47 ± 74[b]	
	Moderate BOO[a]	66 ± 9	57	65 ± 72	–32 ± 108[b]	
	Severe BOO[a]	68 ± 8	58	86 ± 94	–43 ± 125[b]	
	p value across severity groups			NR	0.86	
	Terazosin					
	Without BOO[a]	63 ± 7	13	70 ± 141	0 ± 75	
	Moderate BOO[a]	64 ± 8	30	90 ± 180	–58 ± 173[b]	
	Severe BOO[a]	65 ± 9	17	85 ± 57	–12 ± 65	
	p value across severity groups			NR	0.88	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported

[a]*Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[b]*$p < 0.05$ versus baseline*

Treatment failure

In the study by Djavan et al (2001), the 18-month cumulative treatment failure rate for the cooled HE-TUMT group (5.8%) was significantly lower than that for the terazosin group (41.2%; $p < 0.0005$). Retreated patients in the HE-TUMT group underwent surgery (TURP), whilst the majority of patients who received further treatment in the terazosin group received cooled HE-TUMT (**Table 37**).

Table 37 Cooled HE-TUMT versus terazosin: cumulative treatment failure rates

Trial/publication	Treatment arm	Mean age yrs ± SD	N	18 month treatment failure rate n/N (%)	NHMRC level / comment
Djavan et al 1999e, 2001	**HE-TUMT**	66.2 (8.0)	51	3/52 (5.8)	**Level III-1:** HE-TUMT: Treatment failure requiring further surgery, most probably TURP Terazosin: Treatment failure required further treatment with HE-TUMT (19) and TURP (2)
	Terazosin	64.0 (11.4)	52	21/51 (41.2)	
	p value			< 0.0005	

Quality of life

In the study by Djavan et al (1999e, 2001), the IPSS self-administered questionnaire included a question for determining the quality of life (QoL) score by the World Health Organization method (**Table 38**). Quality of life improved more rapidly in the terazosin group compared with the cooled HE-TUMT group, with a significant difference between the groups at two weeks (Djavan et al 1999e). However, from 12 weeks to six months, the QoL scores were significantly lower (more improved) in the cooled HE-TUMT group compared with the terazosin group ($p < 0.0005$). At six months, the QoL scores were 38.1 per cent lower in the cooled HE-TUMT group. Furthermore, 84.3 per cent of patients in the cooled HE-TUMT group experienced a 50 per cent or greater improvement in QoL scores at six months compared with only 40.4 per cent in the terazosin group (Djavan et al 1999e). These improvements were maintained at 18 months (Djavan et al 2001), with the cooled HE-TUMT group demonstrating a 43 per cent lower score compared with terazosin group ($p < 0.0005$).

Table 38 Cooled HE-TUMT versus terazosin: IPSS quality of life

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean [95%CI] (n)				NHMRC level / comment
				Baseline	2 weeks	6 months	18 months	
Djavan et al 1999e, 2001	**HE-TUMT**	66.2 (8.0)	51	3.9 [3.7, 4.2] (51)	3.2 [2.5, 3.1](52)	1.3 [1.0, 1.5] (50)	1.3 [1.0, 1.9] (47)	**Level III-1:** Baseline values were taken from Djavan et al 1999a, as these were only graphed in Djavan et al 2001. Six-month results were reported in both publications and matched. 18 months were taken from Djavan et al 2001. Results for week 2, 6 and 12 were also available in graph form from Djavan et al 1999a but were not extracted here. Follow-up at 18 months was much lower in the terazosin group (56%) compared with the HE-TUMT group (92%)
	Terazosin	64.0 (11.4)	52	3.8 [3.5, 40.0] (52)	2.8 [2.5, 3.1] (51)	2.1 [1.9, 2.4] (43)	2.3 [2.1, 2.5] (29)	
	p value			NR	0.033	< 0.0005	< 0.0005	

HE-TUMT versus ILCP/TUNA

One level II and two level III-2 studies compared HE-TUMT with ILCP and/or TUNA (Norby et al 2002a; Witjes et al 1997; Arai et al 2000) (**Table 39**). All three studies used cooled HE-TUMT systems (Prostatron® v2.5 in the former two and the Dornier UroWave® in the latter). Trial duration was three months in one, and six months in the other two. Study quality and design are described in the section titled '**Evidence**' and in **Table 69** of **Appendix D**.

Symptoms scores: IPSS

In the study by Norby et al (2002a), the mean IPSS index decreased to a similar degree in both the cooled LE/HE-TUMT and ILCP groups at one, three and six months (**Table 39**). The improvement compared to baseline was significant ($p < 0.001$) in both groups at all time points.

Arai et al (2000) reported significant decreases in IPSS at three months in patients treated with cooled HE-TUMT, ILCP and TUNA (**Table 39**). The magnitude of change was similar between the cooled HE-TUMT and TUNA groups; however, the ILCP group experienced a significantly greater improvement ($p < 0.001$) relative to the cooled HE-TUMT group.

Results from Witjes et al (1997) (of limited applicability due to differences in reporting), indicated that median changes in the IPSS index were significant at six months compared with baseline in the cooled HE-TUMT and ILCP groups in the study by Witjes et al (1997). Although the magnitude was greater in the ILCP group, the baseline symptoms scores were also greater with ILCP (**Table 39**).

Table 39 Cooled HE-TUMT versus ILCP/TUNA: IPSS Index

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean [95%CI] (n)			NHMRC level / comment
				Baseline	3 months	6 months	
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	20.5 ± 5.7 (46)	–	9.5 ± 7.1 (44)[a]	**Level II:** LE- and HE-TUMT not reported separately. 1 and 3 month results also available but only presented graphically in the publication
	ILCP	65 ± 8	48	21.4 ± 5.8 (44)	–	9.5 ± 6.6 (44)[a]	
	p value (between group comparison)			NR	–	NR	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	18.4 ± 6.2 (34)	13.2 ± 6.8 (34)[s]	–	**Level III-2:** Selection bias because selection was primarily on patients views of the benefits including symptom improvements versus risks
	Laser coagulation	69.7 ± 6.9	48	19.3 ± 8.4 (42)	6.9 ± 4.9 (42)[a]	–	
	TUNA	68.5 ± 7.0	51	19.9 ± 5.9 (42)	10.5 ± 6.5 (42)[a]	–	
	p value (between group comparison)			0.862	< 0.001 versus laser	–	
				Median baseline		Median change at 6 months	
Witjes et al 1997	**HE-TUMT**				–		**Level III-2**: only median and median changes reported. Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point except for patients with moderate BOO in the laser therapy treatment group. Selection bias is likely to affect these results significantly, because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[b]		21	15		-8[c]	
	Moderate BOO[b]		57	19		-9[c]	
	Severe BOO[b]		58	17		-10[c]	
	p value across BOO groups			NR	–	0.40	
	Laser therapy				–		
	Without BOO[b]		2	19 (1)		-16 (1)[c]	
	Moderate BOO[b]		34	21		-15[c]	
	Severe BOO[b]		47	21		-17[c]	
	p value across BOO groups			NR	–	0.89	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; ILCP, interstitial laser coagulation of the prostate; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported

[a]*p < 0.001 versus baseline*

[b]*Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[c]*p < 0.05 versus baseline*

Maximum urinary flow rate (Q_{max})

In Norby et al (2002a), Q_{max} was significantly higher at six months compared with baseline in both the cooled LE/HE-TUMT and ILCP treatment groups. No comparison between the groups in terms of significance was reported (**Table 40**).

In the study by Witjes et al (1997), Q_{max} increased significantly by six months compared with baseline by in all the cooled HE-TUMT groups stratified by obstruction severity, whereas significant improvements were only seen in the moderate-to-severe obstruction groups treated with ILCP.

In the study by Arai et al (2000), Q_{max} did not improve in either the cooled HE-TUMT group or TUNA group by three months, whereas there was a significant improvement in the ILCP group. Furthermore, the difference between the cooled HE-TUMT group and ILCP group was significant in favour of the latter ($p < 0.01$).

Table 40 Cooled HE-TUMT versus ILCP/TUNA: Q_{max}

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Mean [95%CI] (n) mL/s			NHMRC level / comment
				Baseline	3 months	6 months	
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	9.1 ± 4.2 (46)	–	13.2 ± 6.9 (44)[a]	**Level II:** LE- and HE-TUMT not reported separately. 1 and 3 month results also available but only presented graphically in the publication
	ILCP	65 ± 8	48	10.2 ± 4.0 (44)	–	16.2 ± 8.5 (44)[a]	
	p value (between group comparison)			NR	–	NR	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	7.7 ± 4.3 (34)	8.6 ± 4.9 (34)[b]	–	**Level III-2:** Selection bias is likely to affect these results significantly because selection was primarily on patients views of the benefits including symptom improvements versus risks
	Laser coagulation	69.7 ± 6.9	48	7.6 ± 3.5 (42)	12.6 ± 4.7 (42)[c]	–	
	TUNA	68.5 ± 7.0	51	8.2 ± 4.1 (42)	9.2 ± 4.2 (42)[d]	–	
	p value (between group comparison)			NR	< 0.01 HE-TUMT versus laser	–	
						Mean change at 6 months	
Witjes et al 1997	**HE-TUMT**						**Level III-2**: Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point except for patients with moderate BOO in the laser therapy treatment group. Selection bias is likely to affect these results significantly because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[e]	65 ± 7	21	9.5 ± 2.8	–	+ 3.9 ± 5.4[f]	
	Moderate BOO[e]	66 ± 9	57	10.4 ± 2.8	–	+ 2.3 ± 4.9[f]	
	Severe BOO[e]	68 ± 8	58	8.7 ± 3.3	–	+ 6.6 ± 7.0[f]	
	p value across BOO groups			NR	–	< 0.001	
	Laser therapy						
	Without BOO[e]	60 ± 6	2	9.8 ± 1.1	–	+ 12.6 ± 2.0	
	Moderate BOO[e]	66 ± 7	34	8.1 ± 1.1	–	+ 12.1 ± 5.4[f]	
	Severe BOO[e]	64 ± 7	47	7.8 ± 3.2	–	+ 12.9 ± 6.3[f]	
	p value across BOO groups			NR	–	0.90	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; ILCP, interstitial laser coagulation of the prostate; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported; TUNA, transurethral needle ablation

[b]*p 0.0844 versus baseline*

[c]*p < 0.001 versus baseline*

[d]*p < 0.187 versus baseline*

[e]*Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[f]*p < 0.05 versus baseline*

Post-void residual volume (PVR)

In Norby et al (2002a), median PVR decreased significantly in the cooled LE/HE-TUMT and ILCP groups compared to baseline. The magnitude of change was similar in the two groups (the significance of the difference between the two groups was not reported) (**Table 41**).

Similar to the results for Q_{max} there was a significant improvement in PVR by six months compared with baseline in the study by Witjes et al (1997) for patients treated with cooled HE-TUMT groups across all degrees of obstruction, whereas significant improvements were only seen in the moderate-to-severe obstruction groups treated with ILCP.

In the study by Arai et al (2000), only the ILCP group experienced a significant decrease in PVR at three months relative to baseline. Furthermore, the difference between the cooled HE-TUMT group and ILCP group was significant in favour of the latter ($p < 0.05$).

Table 41 Cooled HE-TUMT versus ILCP/TUNA: PVR

Trial/publication	Treatment arm	Mean age yrs ± SD	N	Median [IQR] (n) (mL)			NHMRC level / comment
				Baseline	3 months	6 months	
Norby et al 2002a	**LE/HE-TUMT**	66 ± 7	46	110 [50–210] (46)	–	48 [24–129] (44)	**Level II:** LE- and HE-TUMT not reported separately. One and three month results also available but only presented graphically in the publication
	ILCP	65 ± 8	48	117 [50–180] (44)	–	58 [24–129] (43)	
	p value (between group comparison)			NR	–	NR	
				Mean [95%CI] (n)			
				Baseline	3 months	6 months	
Arai et al 2000	**HE-TUMT**	66.4 ± 8.0	40	58.1 ± 65.7 (34)	63.6 ± 80.6 (34)[a]	–	**Level III-2:** Selection bias is likely to affect these results significantly because selection was primarily on patients views of the benefits including symptom improvements versus risks
	Laser coagulation	69.7 ± 6.9	48	102.3 ± 86.1 (42)	30.4 ± 35.9 (42)[b]	–	
	TUNA	68.5 ± 7.0	51	81.5 ± 90.5 (42)	59.4 ± 54.0 (42)[c]	–	
	p value (between group comparison)			NR	< 0.05 HE-TUMT vs. laser	–	
				Baseline	Mean change at 6 months		
Witjes et al 1997	**HE-TUMT**						**Level III-2**: Results were presented stratified by degree of bladder outlet obstruction. Could not determine number of patients analysed at each time point except for patients with moderate BOO in the laser therapy treatment group. Selection bias is likely to affect these results significantly because therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference
	Without BOO[d]	65 ± 7	21	53 ± 82	–	–47 ± 74[e]	
	Moderate BOO[d]	66 ± 9	57	65 ± 72	–	–32 ± 108[e]	
	Severe BOO[d]	68 ± 8	58	86 ± 94	–	–43 ± 125[e]	
	p value across BOO groups			NR	–	0.86	
	Laser therapy						
	Without BOO[d]	60 ± 6	2	45 ± 38	–	–45 ± 38	
	Moderate BOO[d]	66 ± 7	34	68 ± 84	–	42 ± 71[e]	
	Severe BOO[d]	64 ± 7	47	107 ± 88	–	100 ± 88[e]	
	p value across BOO groups			NR	–	< 0.01	

Abbreviations: BOO, bladder outlet obstruction; HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate; IPSS, International Prostate Symptom Score; ITT, intention to treat; AUA, American Urological Association symptom score; NR, not reported; TUNA, transurethral needle ablation

[a] *p = 0.624 versus baseline*

[b] *p < 0.001 versus baseline*

[c] *p = 0.052 versus baseline*

[d] *Severity based on linear passive urethral resistance ratio (LPURR) obstruction category: moderate = 2 or 3; severe = 4 or more*

[e] *p < 0.05 versus baseline*

Treatment failure

In the randomised study by Norby et al (2002a), 1/46 (2.2%) of patients in the cooled HE-TUMT group were retreated in the six-month period (with TURP). None of the 48 patients randomised to ILCP were re-treated.

Quality of life

Two studies reported QoL outcomes for cooled HE-TUMT compared to ILCP and/or TUNA (Norby et al 2002a; Arai et al 2000).

In Norby et al (2002a), the scale used was not reported. Median scores improved from four (inter-quartile range: 4–4) at baseline to one (inter-quartile range: 1–2) at six months in the ILCP group. The corresponding values in the cooled LE/HE-TUMT group were four (4–4) and two (1–3) respectively.

In the study by Arai et al (2000), significant improvements in the IPSS QoL index were observed in the cooled HE-TUMT, ILCP and TUNA groups at three months compared with baseline (**Table 42**). The improvement in the ILCP was reported as significantly better compared to HE-TUMT, although the value of < 0.07 is not the standard threshold for testing significance. BPH impact index scores also indicated significant improvements in all three groups relative to baseline, although the improvement in the cooled HE-TUMT was not as great as in the ILCP group.

Table 42 Cooled HE-TUMT versus ILCP/TUNA: Arai et al 2000

QoL scale (possible range)	Treatment arm	Mean age yrs ± SD	N	Mean ± SD (n)		NHMRC level / comment
				Baseline	3 months	
IPSS QoL (0–6)	**HE-TUMT**	66.4 ± 8.0	40	4.4 ± 1.2	2.7 ± 1.4[c]	Number evaluated not specified, although it was noted that data was not available for some patients
	ILCP	69.7 ± 6.9	48	4.3 ± 1.5	1.8 ± 1.3[c]	
	TUNA	68.5 ± 7.0	51	4.7 ± 0.6	2.4 ± 1.4[c]	
	p value				< 0.07[d] ILCP versus HE-TUMT	
BPH impact index (0–13)	**HE-TUMT**	66.4 ± 8.0	40	6.1 ± 2.8	3.6 ± 2.9[c]	
	ILCP	69.7 ± 6.9	48	5.8 ± 3.9	1.7 ± 2.3[c]	
	TUNA	68.5 ± 7.0	51	6.3 ± 2.5	3.3 ± 3.2[c]	
	p value				< 0.01 ILCP versus HE-TUMT	

[a]*Number evaluated determined from graph referred to in text, although this reported median values, not mean values*
[b]*As reported in text; median vales graphed but not presented here*
[c]*p < 0.001 versus baseline*
[d]*Reported as significant, even though actual value was stated as < 0.07, and usual threshold is < 0.05*

In a separate self-reported questionnaire completed by 169/173 patients in the study by Arai et al (2000), patient satisfaction with treatment (delighted, pleased, or mostly satisfied) was significantly higher in the ILCP (39/42, 92.9%) and TUNA (32/42, 76.2%) groups compared with the cooled HE-TUMT group (20/33, 60.6%; $p < 0.05$ versus both other groups) (**Table 43**).

Table 43 Cooled HE-TUMT versus ILCP/TUNA: Patient satisfaction with treatment at three months in Arai et al (2000)

Response	HE-TUMT n/N (%)	ILCP n/N (%)	TUNA n/N (%)
Delighted	0/33 (0)	11/42 (26.2)	7/42 (16.7)
Pleased	8/33 (24.2)	20/42 (47.6)	16/42 (38.1)
Mostly satisfied	12/33 (36.4)	9/42 (47.6)	9/42 (21.4)
Mixed	8/33 (18.2)	1/42 (2.4)	4/42 (9.5)
Mostly dissatisfied	4/33 (12.1)	0/42 (0)	3/42 (7.1)
Dissatisfied	3/33 (9.1)	1/42 (2.4)	3/42 (7.1)
Greatly dissatisfied	0/33 (0)	0/42 (0)	0/42 (0)

Abbreviations: n, Number of patients; N, number evaluated

Sexual function

Arai et al (2000) examined the impact of cooled HE-TUMT, ILCP and TUNA on sexual function (**Table 44**).

No changes were reported in sexual desire or erectile function six months post-treatment compared with baseline or to each other in the cooled HE-TUMT, ILCP or TUNA treatment groups as assessed using the Sapporo Medical University Sexual Function Questionnaire (**Table 44**).

In the self-reported questionnaire, 145 of 173 patients responded to the question relating to the volume of ejaculate and 153 of 173 patients responded to the question relating to impact on sex life (**Table 44**). No difference was observed in the proportion of patients reporting a severe decrease or absence of ejaculate between the cooled HE-TUMT, ILCP and TUNA groups (29%, 24% and 29% respectively). A similar proportion of patients reported a slightly better to much better sex life n the cooled HE-TUMT, ILCP and TUNA groups (28%, 28% and 27% respectively). Similarly, the proportion of patients reporting a slightly worse to much worse, sex life was comparable between the groups (19%, 13% and 19% in the cooled HE-TUMT, ILCP and TUNA groups respectively).

Table 44 Cooled HE-TUMT versus ILCP/TUNA: Sexual function in Arai et al (2000)

Questionnaire	Outcome	HE-TUMT	ILCP	TUNA
Sapporo Medical University sexual function questionnaire	Sexual desire score (0–10)			
	Mean baseline ± SD	3.2 ± 1.7	3.3 ± 2.0	2.9 ± 1.9
	Mean 3 months ± SD	3.3 ± 1.8	3.1 ± 1.8	3.0 ± 1.7
	p value	0.913	0.368	0.923
	Number reporting change in sexual desire score at 3 months: n/N (%)			
	Decreased by 2 or more	3 (9.1)	7 (18.4)	6 (17.1)
	Changed by 1 or less	27 (81.8)	28 (73.7)	21 (60.0)
	Increased by 2 or more	3 (9.1)	3 (7.9)	8 (22.9)
	Erectile function score (0–10)			
	Mean baseline ± SD	4.2 ± 2.5	4.0 ± 2.4	3.5 ± 2.4
	Mean 3 months ± SD	4.1 ± 2.3	3.7 ± 2.5	3.2 ± 2.2
	p value	0.919	0.48	0.363
	Number reporting change in erectile function score at 3 months: n/N (%)			
	Decreased by 2 or more	6 (18.2)	7 (18.4)	7 (20.0)
	Changed by 1 or less	22 (66.7)	28 (73.7)	22 (62.9)
	Increased by 2 or more	5 (15.2)	3 (7.9)	6 (17.1)
Self-reported questionnaire	Number reporting amount of ejaculate at 3 months: n/N (%)			
	None	6/31 (19.4)	2/38 (5.3)	7/31 (18.9)
	Severely decreased	3/31 (9.7)	7/38 (18.4)	2/31 (5.4)
	Moderately decreased	7/31 (22.6)	6/38 (15.8)	8/31 (21.6)
	Somewhat decreased	3/31 (9.7)	3/38 (7.9)	3/31 (8.1)
	Same	12/31 (38.7)	20/38 (52.6)	17/31 (45.9)
	Number reporting an impact on sex life: n/N (%)			
	Much better	1/32 (3.1)	3/39 (7.7)	0/37 (0)
	Better	2/32 (6.3)	6/39 (15.4)	7/37 (18.9)
	Slightly better	6/32 (18.8)	2/39 (5.1)	3/37 (8.1)
	Same	17/32 (53.1)	23/39 (59.0)	20/37 (54.1)
	Slightly worse	3/32 (9.4)	5/39 (12.8)	4/37 (10.8)
	Worse	2/32 (6.3)	0/39 (0)	3/37 (8.1)
	Much worse	1/32 (3.1)	0/39 (0)	0/37 (0)

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; ILCP, interstitial laser coagulation; n, number of patients in that category; N, number evaluated; TUNA, transurethral needle ablation

Summary

The three primary outcomes assessed in this report were symptom scores (IPSS, AUA score), maximum urinary flow rates (Q_{max}) and post-void residual volume (PVR). Changes in symptom scores are considered the most important indication of treatment success. Other important outcomes considered were treatment failure rates, quality of life and sexual function.

HE-TUMT versus TURP

The evidence for the comparative efficacy of HE-TUMT versus TURP was based on five level II studies, one level III-1 study, and three level III-2 studies. Trials varied in duration from three months to 36 months. Six studies used cooled HE-TUMT (five with the Prostatron® v2.5 system and one with the Dornier UroWave® system) and three studies used non-cooled HE-TUMT (ProstaLund®).

Symptom scores

The included comparative studies of cooled and non-cooled HE-TUMT and TURP indicate that both groups experience significant improvements in symptoms compared to baseline for up to three years, as assessed by the IPSS index and AUA score index. Improvements tended to occur more rapidly in the TURP group compared with the HE-TUMT group (ie, at three months), although by six months, both groups experienced a similar degree of improvement.

In three long-term studies (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a; Wagrell et al 2004) symptoms scores fell from mean baseline values of 17–21 (moderate-to-severe), to a mean of 5–8 (mild) with HE-TUMT and 3–7 (mild) with TURP at 12 months (**Figure 3**). The difference between the two treatments was not significantly different in two studies (d'Ancona et al 1998; Wagrell et al 2004) but was significantly better with TURP in a third (de la Rosette et al 2003a/Floratos et al 2001a). There was not enough evidence to establish whether there was any difference between cooled and non-cooled HE-TUMT techniques.

A slow decline in effectiveness was observed with HE-TUMT after three years follow-up, with scores increasing to a mean of 8–12 (moderate) (**Figure 3**). In contrast, TURP scores remained relatively stable, with a mean of 3–6 (mild) (**Figure 3**). The difference was significant (in favour of TURP) in two long-term studies (de la Rosette et al 2003a/Floratos et al 2001a; Wagrell et al 2004), but was no different in a third (d'Ancona et al 1998).

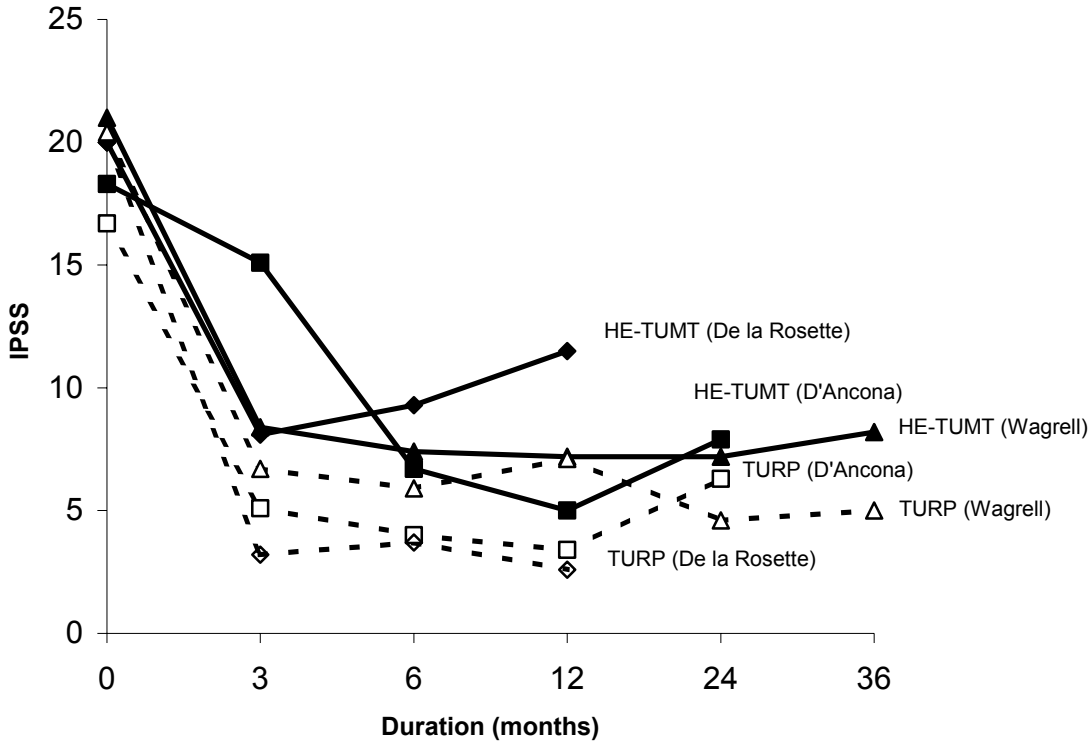

Figure 3 **Changes in symptom scores (IPSS) for the three long-term studies of HE-TUMT versus TURP**

Legend: TURP: broken lines, open symbols; HE-TUMT: solid lines, filled symbols; d'Ancona et al (1998): squares; de la Rosette et al (2003a): diamonds; and Wagrell et al (2004): triangles

Uroflowmetry

TURP patients demonstrated significant improvements (relative to baseline) in Q_{max} within six months. These improvements were maintained for up to three years in three long-term studies (**Figure 4**). In contrast, improvements following HE-TUMT were slower to develop: some studies indicated a significant improvement within six months, whilst others did not. However, HE-TUMT did demonstrate significant improvements at 12 months relative to baseline. Although these improvements remained significant for up to three years, there was a steady decline in Q_{max} values over this period (**Figure 4**).

Comparing between treatments, TURP was significantly better than HE-TUMT at 12, 24 and 36 months in one study (de la Rosette et al 2003a/Floratos et al 2001a), but only at 24 months in another (Wagrell et al 2004), and at no time point in a third (d'Ancona et al 1998). There was not enough evidence to establish whether there was any difference between cooled and non-cooled HE-TUMT techniques.

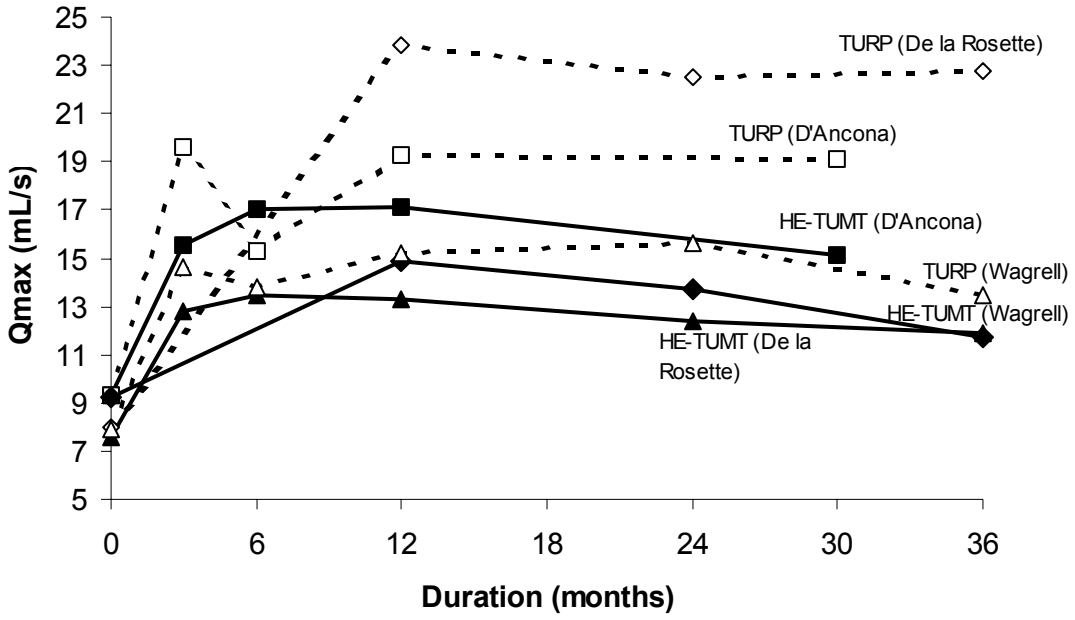

Figure 4 Changes in Q_{max} for the three long-term trials of HE-TUMT versus TURP

Legend: TURP: dotted lines, open symbols; HE-TUMT: solid lines, filled symbols; d'Ancona et al (1998): squares; de la Rosette et al (2003a): diamonds; and Wagrell et al (2004): triangles

Following TURP, significant improvements in post-void residual volume (PVR) were observed within three to six months, which were sustained for up to three years. Improvements with HE-TUMT were mixed: several studies demonstrated no improvement, whilst some long-term studies did, although to a significantly lesser degree than compared with TURP.

Treatment failure

Cumulative treatment failure rates from three randomised studies of cooled HE-TUMT versus TURP are summarised in **Table 45** (d'Ancona et al 1998; de la Rosette et al 2003a/ Floratos et al 2001a; Norby et al 2002a). In the two trials with duration greater than 12 months (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a) the reported treatment failure rates may be confounded by loss to follow-up, which was often of a comparable or greater size to the number retreated. Wagrell et al (2004) reported treatment failure rates during 12–36 months follow-up, but not in the initial 12 months, hence these could not be compared to the cooled HE-TUMT results to establish whether there was any difference between techniques.

Table 45 Summary of cumulative treatment failure rates for HE-TUMT versus TURP

Time point	HE-TUMT %	TURP %	Publication
6 months	2.2	0	Norby et al (2002a)
	6.5	0	D'Ancona et al (1998)
12 months	6.5	4.8	D'Ancona et al (1998)
	12.2	9.6	De la Rosette et al (2003a)
30–36 months	25.8	4.8	D'Ancona et al (1998)
	19.5	11.0	De la Rosette et al (2003a)

In all three studies, treatment failure rates were higher with HE-TUMT and usually resulted from a lack of effectiveness, in contrast to TURP, in which 89 per cent of complications were a result of a complication, such as a urethral stricture or bladder neck stenosis (which required a urethrotomy or bladder neck incision respectively).

Quality of life and sexual function

Quality of life was reported in three studies of cooled HE-TUMT devices using the IPSS QoL index, BPH impact index scores or self-reported questionnaires (de la Rosette et al 2003a/Floratos et al 2001a; Norby et al 2002a; Arai et al 2000).

Quality of life was reported as significantly higher three months after both HE-TUMT and TURP. Furthermore, these improvements were maintained for up to three years in both groups, although the improvements were significantly greater with TURP at three months in Arai et al (2000), at one, two and three years in de la Rosette et al (2003a) but not at six months in Norby et al (2002a). Norby et al (2002a) and Arai et al (2000) both reported that patients' rating of overall satisfaction with treatment was significantly higher following TURP than HE-TUMT.

Two studies specifically examined the effect of cooled HE-TUMT and TURP on sexual function (Francisca et al 1999c, a duplicate of de la Rosette et al 2003a/Floratos et al 2001a; and Arai et al 2000). However, this evidence must be interpreted with caution as a consequence of the fact that the studies used different self-administered questionnaires and, more importantly, there was a poor response to questions on sexual function in both studies (often less than 60% of those randomised). Furthermore, considering the population, a significant proportion already has existing erectile and ejaculatory problems prior to treatment. In both studies, significantly fewer HE-TUMT patients reported a change in sexual function (Francisca et al 1999c) or reported a negative impact on their sex life (Arai et al 2000) compared with TURP patients. In fact, Francisca et al (1999c) reported that HE-TUMT patients were significantly more satisfied with their sexual functioning at three months compared to TURP patients. Fewer patients in the cooled HE-TUMT group reported a decrease in the volume of, or absence of ejaculate after three to six months follow-up compared with the TURP group. In the TURP group, more patients reported morning erections at three months compared with baseline. Higher erectile function scores in the HE-TUMT group in the study by Arai et al (2000) suggested that more sexually active patients may have selected cooled HE-TUMT over TURP.

Sexual dysfunction was examined in a recent review of HE-TUMT versus TURP (de la Rosette et al 2003b) and two reviews of TURP (NHMRC uncomplicated LUTS management, 1996; Kirby et al 1994) (**Table 46**). Erectile dysfunction was reported in more patients after TURP (9.3–15.7%) than after HE-TUMT (4.4%).

Similarly, ejaculatory dysfunction occurred in considerably more TURP patients (63.0–74.4%) than HE-TUMT patients (19.8%).

Table 46 Sexual dysfunction following HE-TUMT and TURP

Publication		Erectile dysfunction %	Retrograde ejaculation %
De la Rosette et al 2003b	**HE-TUMT**	4.4	19.8
	TURP	9.3	63
NHMRC uncomplicated LUTS management 1996	**TURP**	13.6	73.4
Kirby et al 1994	**TURP**	15.7	68

HE-TUMT versus medication

There were no studies comparing HE-TUMT with prazosin or tamsulosin (the most commonly used medication prescribed for BPH in Australia). However, limited evidence was identified for cooled HE-TUMT versus terazosin, of which the highest level of evidence was an 18 month level III-1 study using the Targis® system (Djavan et al 1999e, 2001). In addition, a six-month level III-2 study using the Prostatron® v2.5 system was identified (Witjes et al 1997).

Symptom score

In the study by Djavan et al (1999e, 2001), HE-TUMT scores fell from a baseline mean of 19.4 (moderate-to-severe) to 6.8 (mild) and 7.5 (mild) at six months and 18 months respectively. In contrast, terazosin scores fell from a baseline mean of 18.9 (moderate-to-severe) to 11.0 (moderate) and 11.5 (moderate) at six months and 18 months respectively. The improvements were significantly greater with cooled HE-TUMT compared with terazosin at both time points, although terazosin experienced a more rapid improvement in the initial few weeks. The actual improvement with HE-TUMT is even better when it is considered that nearly half the patients on terazosin had failed treatment by 18 months, and thus the symptom scores are based on the remaining half.

Uroflowmetry

Although the response to terazosin was more rapid, the improvement in Q_{max} was consistently and significantly higher following HE-TUMT compared with terazosin from 12 weeks to 18 months, improving from a baseline mean of 8.3 mL/s and 8.9 mL/s respectively to 13.8 mL/s and 11.3 mL/s respectively at 18 months.

Djavan et al (1999e, 2001) did not present PVR outcomes, although the level III-2 study by Witjes et al (1997) did. Significant improvements were observed at six months relative to baseline across all degrees of obstruction severity in the cooled HE-TUMT group. In contrast, a significant improvement in PVR was only observed in the moderate severity group treated with terazosin.

Treatment failure

The treatment failure rate was significantly lower with HE-TUMT (5.8%) compared with terazosin (41.2%) over 18 months follow-up in the study by Djavan et al (2001). Failed HE-TUMT patients were re-treated with a TURP, whereas most failed terazosin patients were re-treated with cooled HE-TUMT.

Quality of life and sexual function

Quality of life was assessed as part of the IPSS self-administered questionnaire in the study by Djavan et al (1999e, 2001). As with the uroflowmetry results, the improvement with terazosin was more rapid compared to cooled HE-TUMT (first two weeks only). However, from 12 weeks to 18 months, the QoL scores were significantly better in the cooled HE-TUMT group compared with the terazosin group. Improvements observed at six months were maintained for the 18-month study duration.

Sexual function was not examined in the studies comparing HE-TUMT to medication.

HE-TUMT versus ILCP/TUNA

Limited evidence was identified for cooled HE-TUMT versus ILCP and/or TUNA. The highest level evidence available was a six month level II study using the Prostatron® v2.5 system. Two level III-2 studies were also identified: a six month study using the Prostatron® v2.5 system and a three month study using the Dornier UroWave® system.

Symptom score

Symptoms scores for HE-TUMT were significantly improved relative to baseline in all three studies. The improvements were similar to ILCP at six months in one study (Norby et al 2002a), but not as good ILCP at three months in another (Arai et al 2000). The only study comparing HE-TUMT with TUNA indicated that improvements were similar at three months (Arai et al 2000).

Uroflowmetry

Improvements in Q_{max} and PVR were not observed with either HE-TUMT or TUNA in the initial three months (Arai et al 2000), in contrast to ILCP in which there was a significant improvement relative to baseline (and to HE-TUMT). However, by six months in the study by Norby et al 2002a, the improvements with HE-TUMT were significant compared with baseline, and furthermore, were no different to ILCP. Q_{max} improved from a mean of approximately 9 mL/s at baseline to 13 mL/s at six months with HE-TUMT compared with 10 mL/s at baseline to 16 mL/s at six months with ILCP (Norby et al 2002a). PVR decreased from a median of 110 mL to 48 mL with HE-TUMT and 117 mL to 58 mL with ILCP over the same period (Norby et al 2002a).

Treatment failure

Treatment failure was poorly reported for comparative studies of HE-TUMT versus ILCP/TUNA. No ILCP patients were re-treated during six months follow-up in the study by Norby et al (2002a), compared with 2.2 per cent of HE-TUMT patients.

Quality of life and sexual function

Quality of life was assessed using different scales (IPSS QoL and self-reported questionnaire) in two trials (Norby et al 2002a; Arai et al 2000). Based on this limited evidence, significant improvements in quality of life were observed 3–6 months after treatment with HE-TUMT, although the improvements were greater with ILCP and TUNA.

HE-TUMT, ILCP and TUNA were found to have a similar, and minimal impact on sexual function after three months follow-up in the study by Arai et al (2000).

What are the economic considerations?

There is a limited amount of published evidence regarding the cost-effectiveness of HE-TUMT. Blute et al (2000) and Manyak et al (2002) developed a simulation model to evaluate the cost-effectiveness of HE-TUMT relative to TURP and pharmacotherapy (alpha-blocking agent) in patients with moderate-to-severe BPH symptoms over a period of five years. The results of these two studies are derived using the same model. HE-TUMT was found to be cost-effective when compared with the other treatment options included in the evaluation. The cost per quality-adjusted life-year (QALY) gained was US$38,664 for HE-TUMT when compared with pharmacotherapy (in terms of 1999 US dollars). When compared with TURP, HE-TUMT was a dominant option generating superior outcomes at lower costs.

In another study, Walden et al (1998) performed a modelled economic evaluation to examine the two-year cost-effectiveness of LE-TUMT relative to TURP. It is considered that newer second generation (high-energy) TUMT produces superior outcomes to LE-TUMT (de la Rosette et al 2003). Using the Madsen symptom score as the primary indicator of treatment outcome, LE-TUMT was demonstrated to have inferior effectiveness when compared with TURP. However, LE-TUMT incurred lower economic costs over the two-year simulation period. Although the costs of follow-up, late complications and additional treatments were higher for LE-TUMT than TURP, the difference was not large enough to offset the considerably lower initial treatment costs for LE-TUMT. The authors concluded that LE-TUMT is more cost-effective than TURP.

A discussion comparing the results from these studies and the current evaluation is presented in the conclusion section below.

In the following analysis, the cost-effectiveness of HE-TUMT in the treatment of BPH is examined relative to TURP and pharmacotherapy. The analysis will compare the pathways beginning with the initial episode of each of these treatments.
For pharmacotherapy, the only high-quality safety and efficacy data available are derived from a head-to-head trial of HE-TUMT versus terazosin hydrochloride. Hence, the cost-effectiveness of TUMT is compared with that of terazosin treatment. It was assumed that terazosin is representative of the more commonly used alpha-blockers used in the treatment of BPH (prazosin and tamsulosin) in terms of both safety and efficacy.

As a primary goal of BPH treatment is improvement in patient health-related quality of life, an economic evaluation of alternative treatment options should relate costs of treatment to the quality of life improvement achieved through the alleviation of urinary symptoms (Shulz et al 2002). These treatment options may also cause undesirable complications in some patients (ie, side effects), and the associated economic and quality-of-life impacts of these side effects should be included in the analysis. In addition, it is important to incorporate the costs and outcomes of re-treatment for patients failing previous treatment, and the differential procedural mortality risks.

Assessment of value-for-money of HE-TUMT

Why an economic model is required

Economic models of healthcare interventions have a range of advantages and limitations compared with observational studies and other prospectively designed data collection experiments.

A modelled evaluation was deemed necessary to assess the cost-effectiveness of HE-TUMT in order to explore fully the long-term economic and quality-of-life implications of the treatment options for BPH. It is expected that the impact of treatment persist far longer than the duration of the trials considered in the clinical review (ie, five years maximum). Therefore, a modelled evaluation enables a comprehensive and generalisable assessment to be made regarding the cost-effectiveness of HE-TUMT.

Furthermore, the pivotal clinical trials in this evaluation used various symptom scores as surrogate outcome indicators of treatment efficacy. The modelled evaluation translates these surrogate markers into the final outcome in the form of QALYs. In the model, the International Prostate Symptom Score (IPSS) is translated into utility values based on the observed relationship reported in the published evidence (Shulz et al 2002).

In addition, it should be noted that the pivotal clinical trials were not designed to collect resource utilisation data. Hence, the relationship between the short-term and long-term outcomes of treatment and the resource use related to these outcomes had to be modelled. This also allows the model to incorporate resource use that reflects current Australian practice in the management of BPH.

In summary, the modelled approach has the advantages of:

- allowing long-term costs and benefits to be assessed
- translating surrogate outcome indicators into patient-relevant outcomes
- reflecting current Australian management practice.

However, it is also important to bear in mind that the accuracy of the results of a modelled evaluation relies on the quality of input data and the validity of the assumptions underlying the model.

Population in the model

The baseline characteristics of the population included in the primary trials were men (mean age 66.5 years) with LUTS associated with BPH. The mean baseline IPSS score was 19.2, and the mean score of Q_{max} was 8.73 mL/s (d'Ancona et al 1998; Djavan et al 2001; de la Rosette et al 2003a).

Reflecting this, the hypothetical population included in the economic model consists of people aged 65 years old with moderate-to-severe symptomatic BPH. This hypothetical patient cohort also reflects the population that would be eligible for treatment with HE-TUMT if the procedure were available under Medicare.

On the advice of the Advisory Panel, this analysis assumes that patients whose condition is unlikely to be amenable to TURP or TUMT due to a hypocontractile bladder are not included in the patient population under consideration. It was suggested that, in clinical practice, urodynamics are often assessed prior to administering the first procedure in order to identify the group with satisfactory bladder function, ensuring the efficient selection of eligible patients.

Structure of the economic model

A Markov model incorporating a Monte Carlo simulation is used to follow a hypothetical cohort of individuals for 10 years after the first treatment of BPH with one of the following: HE-TUMT, TURP or pharmacotherapy using terazosin. A simulation period of 20 years was employed in an earlier cost-effectiveness assessment of TUNA for the treatment of BPH (MSAC 2002). In the present study, however, a 10-year model was considered more appropriate due to a lack of reliable long-term clinical trial evidence. A simulation period of 10 years is long enough to capture all relevant costs and outcomes associated with any of these treatments, and hence to generate an accurate and reliable evaluation of economic and clinical outcomes without compromising generalisability of the simulation results.

A Markov process is used because patients can be thought of as advancing through different health states, which are associated with differing risks of future events, costs and quality of life. Patients are advanced through the Markov process until death or the end of the simulation process at 10 years. In the absence of long-term data, this process provides a valid estimate of the costs and health outcomes experienced by a cohort of patients after the initial intervention for BPH.

Using Monte Carlo simulation allows the model to retain a 'memory' of each individual's characteristics and past events. Consequently, the model simulates a real life situation where previous clinical interventions affect the choice of future treatment options for the patient, as well as the patient's life expectancy and quality of life. In assessing the relative cost-effectiveness of alternative treatment options for BPH, this property is particularly relevant because each treatment alternative generates different health outcomes in terms of maintained symptomatic remission and occurrence of adverse events, which represent important determinants of the long-term cost-effectiveness. In the economic model, the simulations capture the changes in a key clinical proxy variable (IPSS index) over time. The improvement or deterioration in the IPSS value can be directly linked to a patient's utility value, following published relationships (Shulz et al 2002).

Individuals in the model are advanced through the Markov process in annual cycles. All costs and outcomes are calculated as they occur. The cost-effectiveness is expressed in terms of the cost per additional QALY gained. A discount rate of 5 per cent per annum is applied to all costs and health outcomes.

Figure 5 shows the structure of the model. This is a simplified representation of actual practice, and outlines the key stages of BPH treatment and health states following an intervention. When the model is populated with appropriate inputs, it can be used to address important issues such as the impact that treatment-related adverse events and treatment failures can have on future treatment and patient outcomes. The model also takes account of death from causes unrelated to the treatment of BPH at any simulation cycle.

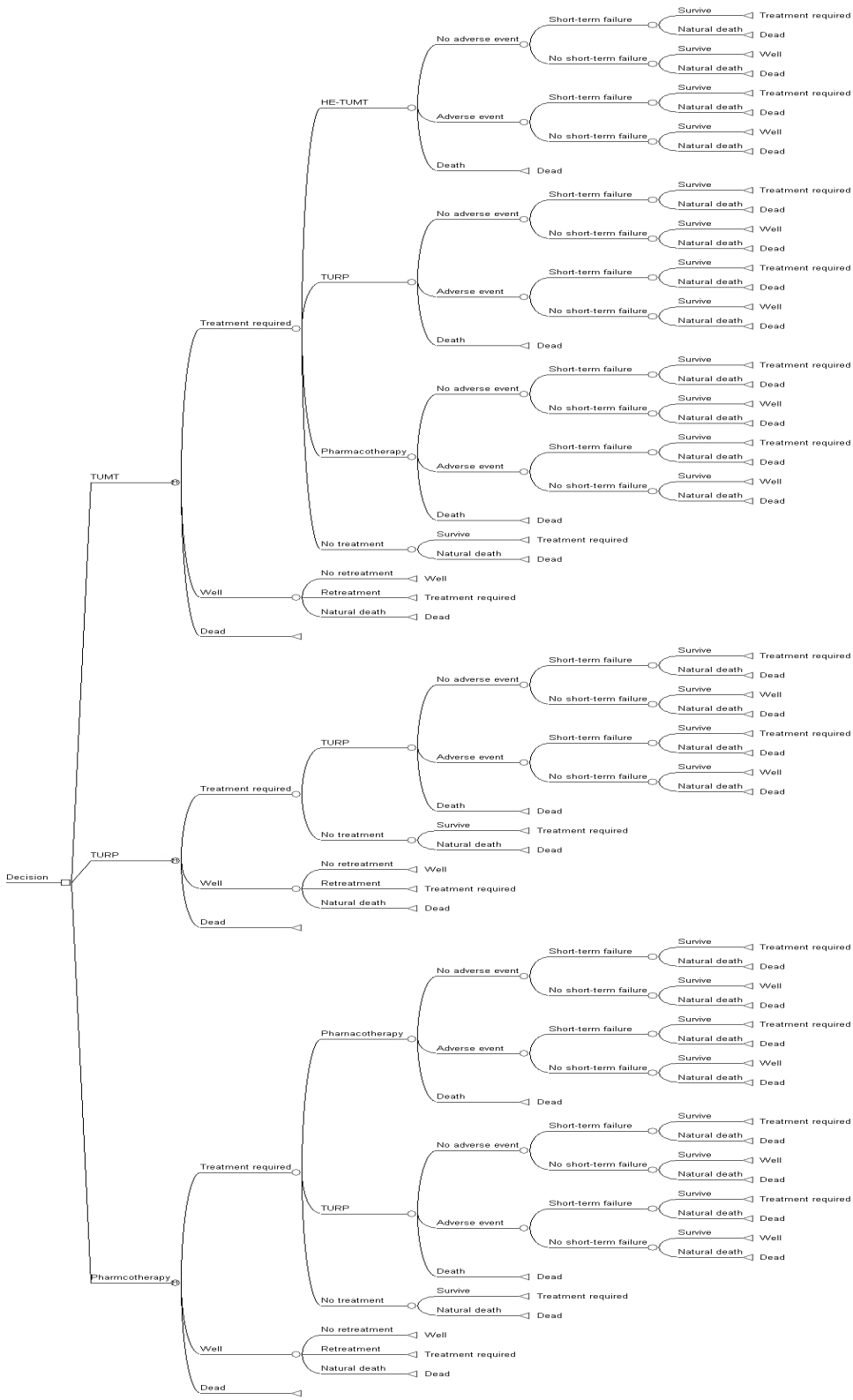

Figure 5 Treatment of BPH in the decision-analytic model

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate

The model has three treatment arms, each representing one of the initial treatments. In each arm, individuals in the hypothetical cohort are classified into one of the following three health states:

- treatment required – the patient requires treatment for BPH
- well – the patient no longer has BPH and does not require treatment
- dead.

At the start of the simulation, all individuals require treatment for BPH. Therefore, all patients begin the simulation in the 'treatment required' state. Patients receive the first episode of treatment described in their respective treatment arm. There are five potential treatment outcomes for each treatment option. The treatment may achieve satisfactory remission of BPH symptoms, either with or without adverse events, or may fail to achieve symptomatic remission, either with or without adverse events. The cost and reduction in utility associated with adverse events are captured in the model. The fifth potential outcome is that the treatment may cause the death of the patient, in which case the patient will enter the 'dead' state, thereby exiting the simulation.

Treatment failure rates (ie, due to a lack of efficacy in symptomatic control and deterioration of BPH symptoms) were modelled from the clinical trial data. In the model, patients who do not require re-treatment due to the treatment failure within 12 months of the previous treatment are assumed to have received a successful treatment. These patients transit to the 'well' state, regardless of whether or not they experienced adverse events.

In this analysis, the lack of symptomatic remission within 12 months of the previous treatment is referred to as 'short-term treatment failure'. Following short-term treatment failure, individuals will undergo an immediate re-treatment in the succeeding simulation cycle. In such cases, the patient remains in the 'treatment required' path and does not transit to the 'well' state at the end of the cycle in which the previous treatment is received.

In each cycle there is a risk of death unrelated to treatment. As in the case of procedural death described above, patients will enter the 'dead' state, thereby exiting the simulation.

As opposed to the short-term treatment failure described above, individuals who are in the 'well' state after treatment may experience symptomatic deterioration in a later cycle due to recurrence of BPH. This recurrence in a later cycle will be referred to as 'long-term treatment failure'. Patients who experience long-term treatment failure will move to the 'treatment required' state and proceed through the treatment pathway described above.

In the HE-TUMT arm, individuals who experience a short-term or long-term treatment failure have TURP, pharmacotherapy or a repeat HE-TUMT as their treatment options. Patients in the TURP arm who experience treatment failure cannot receive HE-TUMT. HE-TUMT is not available for re-treatment in this arm because it represents the existing environment where HE-TUMT is not available. Patients in the pharmacotherapy arm who experience treatment failure are assumed to receive another pharmacotherapy or TURP. Again, for the same reason as in the TURP arm, HE-TUMT is not considered to be a re-treatment option for patients in the pharmacotherapy arm.

In all model arms, it is assumed that patients do not receive more than a total of two episodes of treatment regardless of the treatment options that are administered. Patients who have exhausted all available treatment options in the model remain in the 'treatment required' health state but move down the 'no treatment' path in each cycle.

In order to clarify possible treatment pathways available in the different arms, the treatment algorithms considered in the model are graphically represented in **Figure 6**.

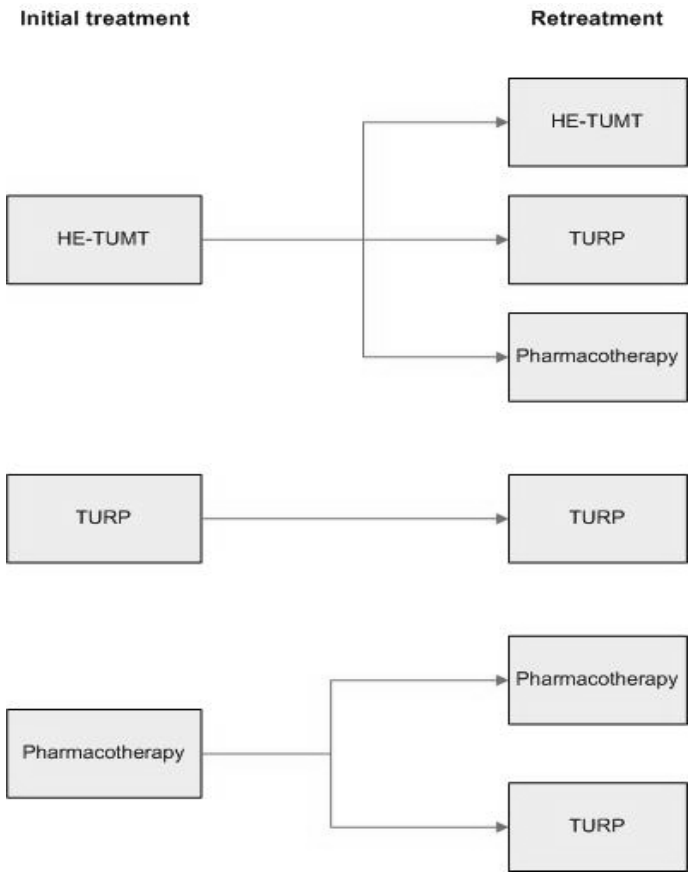

Figure 6 Treatment pathways considered in the model
Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate
Note: Re-treatment is attributable to a lack of efficacy

In the 'treatment required' and 'well' states, a patient's IPSS value is updated in each cycle on the basis of follow-up data from the pivotal trials before being translated into the corresponding utility value. It was assumed that the IPSS of patients who experience short-term or long-term failure returns to the baseline level (ie, the IPSS value prior to the initial treatment), consistent with deterioration in their quality of life. Patients who experienced treatment failure but who have exhausted all available treatment options remain in the simulation, and their IPSS value (and thus utility) remains constant at the baseline level for the remainder of the simulation. This is a conservative assumption since these patients are in fact likely to experience a further deterioration in quality of life when left untreated.

Since annual cycles are used in the simulation, the number of QALYs accrued in each cycle is equivalent to the patient's utility score.

In the model, the administration of HE-TUMT and TURP procedure incurs acute (short-term) costs. These costs are applied at the branch of the decision tree where the procedure takes place. In contrast, the cost of pharmacotherapy is assumed to be incurred as long as patients maintain symptomatic remission (ie, without necessity for re-treatment due to treatment failure) after the first 12 months of therapy. All costs associated with the treatment of adverse events are assumed to be acute (short-term). In contrast, some adverse events considered in the evaluation have a permanent impact on patients' quality of life. This is further discussed below.

All costs are estimated from the perspective of the Australian healthcare system. Indirect and societal costs are not included in the economic model.

Variables used in the economic model

In addition to the variables presented below, the model includes an extensive number of tracking variables, such that individual patient's events can be tracked through the model. This was done to ensure that patients were correctly advanced though the health states of the model and that the impact on utility and costs of their various treatments and treatment outcomes were recorded accurately. Tracking variables also record a patient's IPSS over time, which is translated into a utility value for the calculation of QALYs.

Clinical variables

Variables included in the model to describe the clinical characteristics of the treatment options are summarised in **Table 47**. Risk of death from other causes included in the model is also presented.

Table 47 Clinical variables included in the model

Variable	Description of variable	Value	Source
Baseline IPSS	IPSS prior to the initiation of treatment	19.2	See Appendix H for derivation from d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a)
Change in IPSS scores in successful treatment	Percentage changes in the IPSS scores for patients who continue to achieve satisfactory remission of BPH symptoms		
HE-TUMT			
12 months		−65.5%	See Appendix H for derivation from d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a)
24 months		−59.8%	
36+ months		−56.2%	
TURP			
12 months		−83.5%	See Appendix H for derivation from d'Ancona et al (1998); de la Rosette et al (2003a)
24 months		−78.4%	
36+ months		−86.6%	
Pharmacotherapy			
12 months		−42.3%	See Appendix H for derivation from Djavan et al (2001)
24 months		−40.7%	
36+ months		−39.2%	
Short-term failure with or without side effects	Probability of immediate treatment failure requiring re-treatment (within 12 months of treatment)		
HE-TUMT		0.091	See Appendix H for derivation from d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a)
TURP		0.009	See Appendix H for derivation from d'Ancona et al (1998); de la Rosette et al (2003a)
Pharmacotherapy		0.395	See Appendix H for derivation from Djavan et al (2001)
Long-term failure	Probability of requiring re-treatment per annum (ie, symptom recurrence in the subsequent years)		
HE-TUMT			
24 months		0.065	See Appendix H for derivation from d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a)
36+ months		0.076	
TURP			
24 months		0.010	Advisory Panel
36+ months		0.010	
Pharmacotherapy			
24 months		0.298	See Appendix H for derivation from Djavan et al (2001)
36+ months		0.229	
Procedural mortality	Probability of death from treatment		
HE-TUMP		0.001	MSAC (2002); Advisory Panel
TURP		0.002	MSAC (2002); Advisory Panel
Pharmacotherapy		0[a]	Advisory Panel
Side effects	Probability of treatment-related adverse events		
HE-TUMP		0.285	See Appendix H for derivation from d'Ancona et al (1998), Djavan et al (2001) & de la Rosette et al (2003a); NHMRC (1996); Roehrborn et al (1995); Advisory Panel
TURP		0.986	
Pharmacotherapy		0.072[b]	
Death from other causes	Probability of death from other causes	Age-specific	Australian Bureau of Statistics (2003)

Abbreviations: BPH, benign prostatic hyperplasia; HE-TUMT, high-energy transurethral microwave thermotherapy; IPSS, International Prostate Symptom Score; TURP, transurethral resection of the prostate

[a] *It is expected that there is a very small risk of treatment-related fatal complication in the terazosin therapy. The effect is assumed to be negligible on the overall cost-effectiveness assessment, thus not included in the model. The risk is further minimised in practice, as patients are likely to be assessed prior to the initiation of therapy for eligibility*

[b] *Includes sexual dysfunctions only (see **Table 51** and related discussion)*

The efficacy of treatment is measured in terms of the patient's IPSS over time. As mentioned above, the IPSS value is used to derive the patient's utility value in the model. The effect of each treatment option on the patient's IPSS is established on the basis of a meta-analysis using the data from the primary clinical trials, as presented in **Table 48**. Proportional improvements from baseline are calculated for each time point and entered in the model. Detailed description of the meta-analysis is provided in **Appendix H**.

Table 48 Changes in IPSS values over time

	Mean IPSS ± SE (95% CI)		
	HE-TUMT[a]	**TURP[b]**	**Pharmacotherapy[c]**
Baseline	19.4 ± 0.7 (18.3, 20.5)	19.0 ± 0.9 (17.4, 20.5)	18.9 ± 0.8 (17.5, 20.2)
12 months	6.7 ± 0.7 (5.7, 7.7)	3.2 ± 0.7 (2.1, 4.3)	11.2 ± 0.8 (9.9, 12.5)
24 months	7.8 ± 0.7 (6.6, 8.9)	4.2 ± 0.9 (2.6, 5.7)	11.5 ± 0.8 (10.1, 12.9)
36 months	8.5 ± 0.7 (7.4, 9.6)	2.6 ± 0.7 (1.3, 3.6)	11.8 ± 0.7 (10.7, 12.8)

Abbreviations: CI, confidence interval; HE-TUMT, high-energy transurethral microwave thermotherapy; IPSS, International Prostate Symptom Score; SE, standard error; TURP, transurethral resection of the prostate
[a]Based on d'Ancona et al (1998), Djavan et al (2001) and de la Rosette et al (2003a)
[b]Based on d'Ancona et al (1998) and de la Rosette et al (2003a)
[c]Based on Djavan et al (2001)

A patient's IPSS is assumed to remain at the last observed level available unless the patient experiences long-term treatment failure. In the case of long-term treatment failure, the patient's IPSS is assumed to return to the baseline level.

The short-term outcome of treatment can be remission of BPH symptoms with or without adverse events, or no remission with or without adverse events. These outcomes are assumed to occur within 12 months following the treatment. The 12-month risk of treatment failure for each treatment arm was derived from the primary clinical trials, as presented in **Table 49**. These estimates are derived from a meta-analysis of the clinical trial data. Detailed description of the meta-analysis is given in **Appendix H**.

Table 49 Treatment failure rates from the trials over the three years following the initial intervention

	Treatment failure rate ± SE (95% CI)		
	HE-TUMT[a]	**TURP[b]**	**Pharmacotherapy[c]**
Baseline	–	–	–
12 months	9.1 ± 6.3 (3.2, 19.9)	8.0 ± 6.1 (2.6, 17.5)[d]	39.5 ± 11.9 (20.7, 68.9)
24 months	6.5 ± 5.9 (1.9, 15.6)	1.2 ± 3.5 (0.0, 4.4)	29.8 ± 12.9 (10.7, 61.4)
36 months	7.6 ± 6.2 (2.2, 18.1)	0.0013 ± 0.0512 (0.0, 0.1016)[e]	22.9 ± 15.5 (2.7, 61.0)

Abbreviations: CI, confidence interval; HE-TUMT, high-energy transurethral microwave thermotherapy; SE, standard error; TURP, transurethral resection of the prostate
[a]Based on d'Ancona et al (1998), Djavan et al (2001) and de la Rosette et al (2003a)
[b]Based on d'Ancona et al (1998) and de la Rosette et al (2003a)
[c]Based on Djavan et al (2001)
[d]Treatment failure includes those associated with procedural complications (see below)
[e]This rate is likely to be an underestimate due to the small number of patients followed-up at 3 years. As explained in the text below, only the first year treatment failure rate for TURP is used: for the second year onwards, a rate of 1% per year is used

It is important to note that in this analysis, the need for re-treatment is defined as being due to treatment failure (ie, due to a lack of symptomatic improvement or deterioration in the symptom), as opposed to the treatment of adverse events. The trial data indicate that a large proportion of treatment failure in the TURP arm is attributable to treatment of procedural complications. In d'Ancona et al (1998) and de la Rosette et al (2003a), it was demonstrated that the treatment of procedural complications was the primary reason in eight out of nine patients (89%) who required follow-up treatment after TURP. This means that the risk of re-treatment following TURP due to a lack of symptomatic remission is 0.88 per cent during the first 12 months of treatment. This figure is used in the model.

A meta-analysis of the clinical trial data was also performed to estimate the risk of long-term treatment failure, as shown in **Table 49**. These estimates are used to determine the annual risk of re-treatment due to long-term treatment failure (ie, recurrence of BPH symptoms) in patients who did not experience short-term treatment failure.

Due to the lack of reliable treatment failure data beyond three years, several assumptions were made to simulate treatment outcomes that were not captured in the clinical trials. For TURP, there is strong evidence to suggest that the 10-year risk of treatment failure is roughly 10%. The Advisory Panel corroborated this estimate. Hence, a failure rate of 1 per cent per annum was used in the model following the first year of treatment. For the HE-TUMT and pharmacotherapy arms, the last available values (ie, the estimated risks for the third year) were carried forward until the end of the simulation period. This assumption is associated with a five-year failure rate of 33 per cent for HE-TUMT (**Table 50**). This is consistent with the finding from a long-term non-comparative trial that demonstrated a 34 per cent treatment failure rate at five years (Miller et al 2003).

Table 50 illustrates the patterns of treatment failure for each treatment option based on the trial data and assumptions made above. The simulated incidence of treatment failure will be slightly different in the economic model, as risk of death is incorporated.

Table 50 Risk of short-term and long-term failure associated with the treatment options

	HE-TUMT		TURP		Pharmacotherapy	
	Failure rate	Cumulative number of treatment failures[a]	Failure rate	Cumulative number of treatment failures[a]	Failure rate	Cumulative number of treatment failures[a]
Baseline	–	0.0	–	0.0	–	0.0
Year 1	9.10%	9.1	0.88%[b]	0.9	39.50%	39.5
Year 2	6.50%	15.0	1.00%	1.9	29.80%	57.5
Year 3	7.60%	21.5	1.00%	2.9	22.90%	67.3
Year 4	7.60%	27.4	1.00%	3.8	22.90%	74.8
Year 5	7.60%	33.0	1.00%	4.8	22.90%	80.5
Year 6	7.60%	38.0	1.00%	5.7	22.90%	85.0
Year 7	7.60%	42.8	1.00%	6.7	22.90%	88.4
Year 8	7.60%	47.1	1.00%	7.6	22.90%	91.1
Year 9	7.60%	51.1	1.00%	8.5	22.90%	93.1
Year 10	7.60%	54.8	1.00%	9.5	22.90%	94.7

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate

[a]Out of 100 patients who received the treatment, and assuming no mortality over the 10 years. Only those treatment failures due to a lack of efficacy in symptomatic control are captured

*[a]8% as shown in **Table 49** multiplied by 0.11 (ie, proportion of total re-treatments due to a lack of symptomatic remission)*

These short-term and long-term failure rates are used as probabilities to transit patients to the 'treatment required' state or 'well' state, depending on whether or not the patient requires re-treatment.

The treatment options under consideration differ in the risk and type of treatment-related adverse events that they can cause. **Table 51** summarises the risk of adverse events for each treatment option. These figures are mostly derived from the primary trials included in the safety section above. With regard to ejaculatory dysfunction associated with TURP, the Advisory Panel considered that the data reported by the NHMRC Uncomplicated LUTS Management (1996) study represents the risk in practice more accurately than the findings from the primary trials. The primary clinical trial indicated that terazosin is unlikely to cause any of the adverse events included in this analysis. The advisory panel, however, considers that terazosin is associated with a small risk of ejaculatory dysfunction and erectile dysfunction. For ejaculatory dysfunction, the risk estimate reported in Roehrborn et al (1995) was included in the analysis. For erectile dysfunction, a recommendation from the advisory board was incorporated.

Table 51 Risk of adverse events associated with the treatments

	Urethral stricture/bladder neck stenosis[a]	Ejaculatory dysfunction[b]	Erectile dysfunction[c]	Transfusion[d]	Total
HE-TUMT	0.005	0.220	0.060	0.000	**0.285**
TURP	0.032	0.734	0.110	0.110	**0.986**
Pharmacotherapy	0	0.062	0.010	0	**0.072**

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate
[a]Derived from de la Rosette et al (2003a) and d'Ancona et al (1998)
[b]For HE-TUMT, estimate comes from Norby et al (2002a) and Ahmed et al (1997), out of sexually active men only; for TURP, estimate comes from NHMRC uncomplicated LUTS management guidelines (1996); for pharmacotherapy, estimate comes from Roehrborn (1995)
[c]For HE-TUMT and TURP, estimates come from Wagrell et al (2002, 2004); for pharmacotherapy, estimate is based on the recommendation from the Advisory Panel
[d]Derived from Wagrell et al (2002, 2004) and Norby et al (2002a)
NB: Safety data up to 36 months indicate the incidence of side effects remains relatively stable at 12-month level, except for urethral stricture and bladder neck stenosis in the TURP arm. This favours TURP over other treatment options in the cost-effectiveness evaluation

Table 51 shows that TURP is associated with a considerably higher risk of procedural adverse events than HE-TUMT or pharmacotherapy. The risk of any adverse event is derived as a simple summation of individual adverse event risks (see **Table 51**).
As demonstrated in the following section, the model incorporates weighted average values that collectively account for the economic or quality of life impacts across all possible adverse events. In this way, the overall effects of adverse events on treatment costs and on patients' quality of life are correctly captured in the evaluation. This approach still ensures that the economic and quality of life impacts borne by patients who suffer from multiple complications are appropriately evaluated in the analysis. This implicitly assumes that multiple adverse events have an additive effect on the costs of treatment and on utility values.

There are other treatment-related adverse events that are not considered in the current model. This study only includes ejaculatory dysfunction and erectile dysfunction as possible adverse events caused by pharmacotherapy using terazosin. Terazosin has been shown to have a small risk of causing other adverse reactions such as hypotension. These adverse reactions to terazosin treatment are, however, unlikely to have significant

economic and quality of life impacts and, therefore, they are not considered in the analysis. This will favour the pharmacotherapy in the evaluation of relative cost-effectiveness. Further, the previous section demonstrated that HE-TUMT and TURP are both associated with a small risk of urinary infection, severe incontinence and haematuria. In addition, TURP can cause TUR syndrome. There is little evidence on which to base an accurate determination of the cost and quality of life implications relating to these adverse events and, therefore, they are not considered in the analysis. As the available evidence suggests that TURP is more likely to cause these adverse events than HE-TUMT and pharmacotherapy, it is likely that excluding these adverse events from the evaluation will act against HE-TUMT and pharmacotherapy when assessing the relative cost-effectiveness of these treatments.

It was difficult to determine treatment-related mortality accurately from the included clinical trials. Hence, estimates used in the cost-effectiveness assessment of TUNA for the treatment of BPH (MSAC 2002) were also used in the present analysis for HE-TUMT. As HE-TUMT and TUNA are both minimally invasive procedures, it was assumed that the TUNA estimate also accurately represents the procedural mortality for HE-TUMT. It was assumed that pharmacotherapy does not cause any fatal complications. The advisory panel considered these rates to be reasonable. Risk of death from other causes included in the model is estimated using the Australian life tables (ABS, 2003). It was assumed that BPH itself does not directly result in deaths.

Treatment algorithm variables

Several variables are included to define the treatment algorithms for the three treatment options (see **Figure 6**), as summarised in **Table 52**.

Table 52 Treatment algorithm variables included in the model

Variable	Description	Value	Source
Maximum number of treatment episodes per patient	Total number of treatments one patient can receive over the simulation period		
HE-TUMT			Assumption
TURP		2 in total[a]	
Pharmacotherapy			
Likelihood of re-treatment using:	Probability of receiving a particular treatment alternative following a failure with the previous episode of treatment		
After HE-TUMT:			
HE-TUMT		0.02	Advisory Panel
TURP		0.80	
Pharmacotherapy		0.18	
After TURP:			
HE-TUMT		–	
TURP		1[b]	
Pharmacotherapy		0	
After pharmacotherapy:			
HE-TUMT		–	
TURP		0.5	
Pharmacotherapy[c]		0.5	

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate

[a] *Total number of treatment episodes involving any of the treatment options*

[b] *Re-treatment due to a lack of efficacy only*

[c] *Based on the recommendations of the Advisory Panel who indicated that many patients who fail one medication trial a second medication*

Patients can receive follow-up treatment if they experience a short-term or long-term treatment failure. It was assumed that one patient could receive a total of two treatment procedures involving any of the treatment options during the simulation. This is clearly reflected in the treatment algorithms considered in the model, as presented in **Figure 6**. These hypothetical treatment pathways were established based on the recommendations from the Advisory Panel.

If individuals are unable to receive additional treatment with the assigned alternative because they have exceeded the maximum number of treatment episodes, these patients are assumed to receive no further treatment until they exit the model through death or by reaching the end of the simulation period.

Utility variables

Table 53 summarises the variables relating utility included in the model.

Table 53 Utility variables included in the model

Variable	Description	Value	Source
Base-line utility values	Utility values prior to the initial intervention (derived from the baseline IPSS values)		
HE-TUMT		0.81	d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a) and Schulz et al (2002)
TURP			
Pharmacotherapy			
Utility values following treatment	Utility values following successful treatment		
HE-TUMT		Derived from IPSS (see **Figure 7**)	Schulz et al (2002)
TURP			
Pharmacotherapy			
Loss of utility from adverse events	*Weighted average* utility loss associated with treatment adverse events (% change)		
Permanent adverse event			
HE-TUMT		–3.68%	Ackerman et al (2000); d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a); NHMRC (1996); Roehrborn et al (1995); Advisory Panel
TURP		–3.38%	
Pharmacotherapy		–3.42%	
Temporary adverse event			
HE-TUMT		–5.10%	
TURP		–1.17%	
Pharmacotherapy		–	

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; IPSS, International Prostate Symptom Score; TURP, transurethral resection of the prostate

In the current evaluation, it was necessary to translate baseline IPSS and the changes in IPSS values following treatment into utility values, so that the simulation could capture the treatment outcomes in terms of their impact on patients' quality of life. This was achieved by using the method of Schulz et al (2002). These investigators employed the Health Utility Index (HUI), EuroQol (EQ-5D) and time trade-off methods using a one-year and 10-year time frame to evaluate utility values of subjects' current urinary health states, and examined their relationship with IPSS values. A total of 29 patients were included in the study, most of them suffering from moderate-to-severe BPH with a mean IPSS of 16.24. The findings from this study indicated that mean utility values relating to a participant's current health state (ie, a mean IPSS of 16.24) ranged from

0.79–0.86, as summarised in **Table 54**. The authors also used time trade-off to evaluate a utility value associated with a hypothetical worst-case BPH health state, as shown in **Table 54**. The worst-case health state is defined as an IPSS score of 35, and indicates the most severe BPH symptoms.

Table 54 Utility values in patients with symptomatic BPH

Instrument	Health state	Number of subjects	Range	Mean (SD)
HUI	Current	29	0.39–1.00	0.81 (0.12)
EQ-5D	Current	29	0.62–1.00	0.79 (0.12)
Time trade-off (years)				
1	Current	28	0.13–1.00	0.86 (0.18)
10	Current	28	0.05–1.00	0.80 (0.19)
1	Worst state BPH	26	0.04–1.00	0.54 (0.33)
10	Worst state BPH	26	0.05–1.00	0.48 (0.28)

Abbreviations: BPH, benign prostatic hyperplasia; HUI, Health Utility Index; EuroQol (EQ-5D); SD, standard deviation
Source: Schulz et al (2002)

The authors found that only the time trade-off instrument derived utility values that correlated significantly with IPSS, indicating that these utility values would be most likely to detect symptomatic changes in patients with BPH. In particular, statistically significant correlations were detected for both the current and worst case urinary health state when 1-year time trade-off was employed, while 10-year time trade-off exhibited a significant correlation only in the worst case health state. Hence, the utility values derived from the 1-year time trade-off study were used to determine the utility values at different IPSS values in the economic model.

In this analysis, a linear relationship was assumed to exist between a hypothetical perfect health state with an IPSS of 0 and a utility of 1, and the current health state in the 1-year time trade off study with an IPSS score of 16.24 and a utility of 0.86. A linear relationship was also assumed between the current health state and the worst-case state with an IPSS of 35 and a utility of 0.54. That is to say, utility values of patients will decrease linearly from 1 to 0.86 as the IPSS increases from 0 to 16.24. The calculated change in the utility value associated with a 1-point increase in the IPSS is, therefore, approximately –0.009 between these two points. By the same token, the utility values will decrease linearly from 0.86 to 0.54 at a constant increment by approximately –0.017 as the IPSS score rises from 16.24 to 35. This relationship is represented graphically in **Figure 7**.

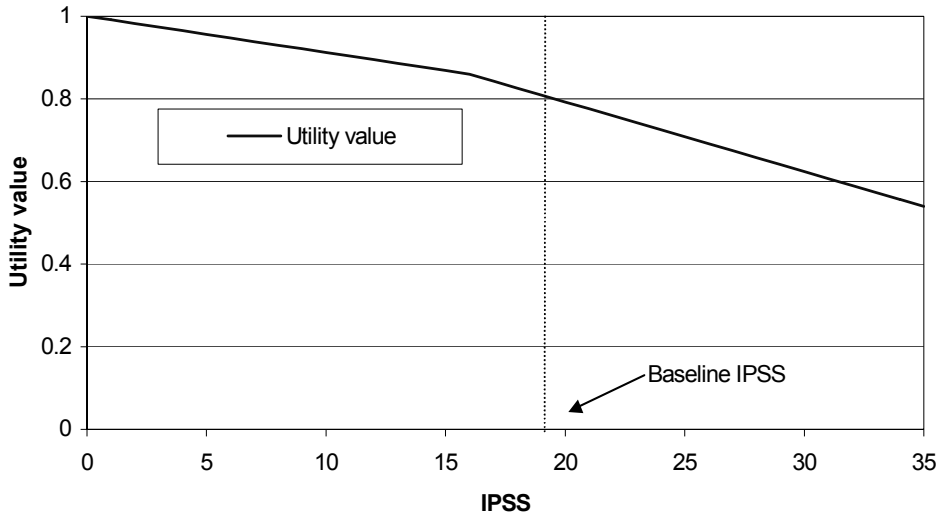

Figure 7 Utility values at different IPSS values
Source: Schulz et al (2002)

The impact of procedural adverse events on quality of life is also incorporated in the economic analysis. Possible treatment-related adverse events included in the model are summarised in **Table 51**. Loss of utility associated with these events is estimated from Ackerman et al (2000). This was the only study that provided the level of detail required in the economic model. Ackerman et al (2000) estimated the utility values, reflecting an individual's preference for specific treatment outcomes, by interviewing 13 men with moderate-to-severe BPH using the standard gamble preference measurement technique. Relevant findings from this study are summarised in **Table 55**.

Table 55 Utility values relating to treatment complications

Outcome	Utility values[a]	Utility loss *versus* no adverse event (%)
Significant remission with:		
No adverse event	0.995	–
Ejaculatory dysfunction	0.966	–2.9%
Erectile dysfunction	0.929	–6.6%
Urethral stricture/bladder neck contracture/stenosis[b]	0.944	–5.1%

Source: Ackerman et al (2000)
[a]The authors presented separate sets of utility values for a risk-averse group and a non-risk-averse group (Ackerman et al 1999). The weighted averages were calculated using the number of subjects in each group
[b]Included as a short-run adverse event (occurring within 30 days of treatment) in Ackerman et al (1999). Other events were considered permanent

In order to identify losses in utility directly related to treatment adverse events, utility values associated with significant remission of BPH symptoms without adverse events and with each of the included adverse events were extracted from the study. Using patients with significant remission is believed to best isolate the disutility attributable to

the adverse event itself. The proportional difference in utility between having no adverse events and each of the adverse events was calculated, as shown in **Table 55**.
As presented in **Table 51**, blood transfusion was also included in the model as a potential procedural adverse event associated with HE-TUMT and TURP. The utility value specific to this health state was not available. It was assumed that blood transfusion does not generate any disutility. As demonstrated in the following section, the economic costs associated with blood transfusion are incorporated in the evaluation.

Table 56 demonstrates calculation of weighted average utility losses associated with the treatment complications caused by each of the treatment options. These weighted average values represent a proportional reduction in utility that is experienced by a patient affected by the treatment adverse event. As noted in **Table 55,** Ackerman et al (2000) made a distinction between permanent and acute adverse events. The authors assumed that if a patient experienced permanent adverse events the patient's quality of life would be affected by the corresponding disutility scores in each cycle over the five-year simulation period unless another treatment was required (Ackerman et al 2000). In the current study, the model is also constructed so that the utility losses of the permanent adverse events are recurrent in each cycle over the simulation period unless the patient receives another episode of treatment.

Table 56 Loss in utility associated with procedural adverse effects (sensitivity analysis)

	Urethral stricture/bladder neck stenosis	Ejaculatory dysfunction	Erectile dysfunction	Transfusion	Total/weighted average utility loss
Utility loss (Table 55)	–5.10%	–2.90%	–6.60%	0%	–
HE-TUMT					
Permanent event					
Risk of adverse event	–	0.220	0.060	–	**0.280**
Relative weight	–	0.79	0.21	–	**1.00**
Weighted utility loss	–	–2.29%	–1.39%	–	**–3.68%**
Temporary event					
Risk of adverse event	0.005	–	–	0.000	**0.005**
Relative weight	1.00	–	–	0.00	**1**
Weighted utility loss	–5.10%	–	–	0.00%	**–5.10%**
TURP					
Permanent event					
Risk of adverse event	–	0.734	0.110	–	**0.844**
Relative weight	–	0.87	0.13	–	**1.00**
Weighted utility loss	–	–2.52%	–0.86%	–	**–3.38%**
Temporary event					
Risk of adverse event	0.032	–	–	0.110	**0.142**
Relative weight	0.23	–	–	0.77	**1**
Weighted utility loss	–1.17%	–	–	0.00%	**–1.17%**
Pharmacotherapy[a]					
Permanent event					
Risk of adverse event	–	0.062	0.010	–	**0.072**
Relative weight	–	0.86	0.14	–	**1.00**
Weighted utility loss	–	–2.49%	–0.92%	–	**–3.42%**

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate
[a]No risks of urethral stricture/bladder neck stenosis or blood transfusion were reported for pharmacotherapy

Table 56 shows that the weighted average utility losses per episode of adverse event are relatively low for TURP when compared with other treatment options. This reflects the magnitude of risk associated with each adverse event relative to the total risk. As shown in **Table 56**, the relative weights attached to erectile dysfunction and urethral stricture/bladder neck stenosis are small in the TURP arm, indicating that these events are relatively less common among all adverse events experienced by patients treated with TURP than by those treated with HE-TUMT or pharmacotherapy. Since these adverse events are associated with large utility losses, the weighted average values in the HE-TUMT arm and the pharmacotherapy arm are further inflated. Yet, the number of individuals affected by these utility losses is still considerably higher in the TURP arm than in other treatment arms (98.6% versus 28.5%/7.2% in total; see **Table 51**).

As mentioned previously, in practice, patients may suffer multiple side effects. By making an assumption that multiple adverse events have an additive effect on a patient's utility value, the use of the weighted average value that collectively accounts for disutilities across all side effects appropriately captures the overall impact on the patient's QALYs. For patients having a side effect, their utility value based on their IPSS is adjusted by the appropriate amount. It was assumed that the impact of temporary adverse events on a patient's utility occurs only in the year of the adverse event, after which time they have been successfully treated for the condition. In contrast, the utility deteriorations caused by permanent adverse events are recurrent at each of the succeeding simulation cycles until the patient receives another episode of treatment due to long-term treatment failure.

Cost variables

Variables used to incorporate the cost inputs in the cost-effectiveness evaluation are summarised in **Table 57**.

Table 57 Cost variables included in the model

Variable	Description	Value	Source
Cost of treatment	Resource cost associated with one episode of treatment		
HE-TUMT		$4034.46	MSAC application; Advisory Panel
TURP		$4969.18	MSAC application
Pharmacotherapy (12 months of terazosin therapy)		$1114.56	Terazosin product information; Schedule of Pharmaceutical Benefits (April 2005); Medicare Benefits Schedule Book (November 2004); advisory panel
Cost of treatment adverse events	Resource cost associated with treatment of adverse events		
HE-TUMT		$144.18	Medicare Benefits Schedule Book (November 2004); d'Ancona et al (1998); Djavan et al (2001); de la Rosette et al (2003a); NHMRC (1996); Roehrborn et al (1995); Advisory Panel
TURP		$159.39	
Pharmacotherapy		$123.40	

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; MSAC, Medical Services Advisory Committee; TURP, transurethral resection of the prostate

Costs of administering HE-TUMT and TURP are obtained from the MSAC application (2004). A small adjustment was made to the HE-TUMT cost quoted in the application. The applicant assumed the surgeon cost associated with HE-TUMT procedure to be

equivalent to that of TURP plus a 25 per cent mark-up. This mark-up was removed, following the advice from the Advisory Panel. This will consequently improve the cost-effectiveness of HE-TUMT.

The estimated cost of TURP included in the application is roughly consistent with the estimates from the National Hospital Cost Data Collection Cost Report Round 7 (2002–2003), as summarised in **Table 58**.

Table 58 Estimated costs associated with TURP

AR-DRG	DRG description	Number of separations	Average length of stay	Average cost (per separation)
M02A	Transurethral prostatectomy with catastrophic or severe CC			
Public		1462	7.77	$7092
Private		1014	8.87	$5243
M02B	Transurethral prostatectomy without catastrophic or severe CC			
Public		6346	3.45	$3976
Private		10,359	3.69	$2492

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; CC, co-morbidities and complications; DRG, Diagnosis Related Groups; TURP, transurethral resection of the prostate
Source: National Hospital Cost Data Collection Cost Report Round 7 2002–03 (http://www.health.gov.au/internet/wcms/Publishing.nsf/Content/health-casemix-costing-fc_r7.htm)

For the base-case analysis, the cost of TURP is assumed to be $4969.18, which incorporates three days of hospitalisation. An Australian retrospective study by Gordon et al (1997) reported that, based on the data from 549 patients received TURP, the average length of hospital stay following the surgery was 2.55 days. Therefore, in the sensitivity analysis, the cost with five days of hospitalisation ($5909.18) is used, as also proposed in the MSAC application. The cost of HE-TUMT does not include any overnight hospital stay, but it incorporates a hospital day stay.

The estimated cost of pharmacotherapy using terazosin was not provided in the MSAC application. Terazosin hydrochloride is currently available for subsidised use only through the Repatriation Pharmaceutical Benefit Scheme (RPBS). The listing details of terazosin are summarised in **Table 59**. Prices paid in the private market are also shown.

Table 59 RPBS listing details of terazosin (Hytrin®) and private market prices

PBS code	Formulation and strength	Maximum quantity (pack size)	Price	
			RPBS	Private
4397K	Tablet 2 mg	28	$38.55	$59.75
4398L	Tablet 5 mg	28	$56.47	$87.54
4399M	Tablet 10 mg	28	$84.34	$130.78

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefit Scheme
Source: Schedule of Pharmaceutical Benefits (April 2005); E-MIMS

Based on the product information provided in the Monthly Index of Medical Specialties (MIMS), the average daily dose of terazosin therapy for BPH is assumed to be 7.5 mg, with 50 per cent of patients receiving 5 mg/day and the remaining patients receiving 10 mg/day. Using this assumption and the price information presented in **Table 59**, the cost of terazosin therapy can be calculated, as shown in **Table 60**.

Table 60 Cost of terazosin therapy (medication costs only)

Daily dose	Unit price		Annual costs[a]	
	RPBS	Private	RPBS	Private
5 mg	$56.47	$87.54	$677.64	$1050.48
10 mg	$84.34	$130.78	$1012.08	$1569.36
7.5 mg (average)	$70.41	$109.16	$844.86	$1309.92

Abbreviation: RPBS, Repatriation Pharmaceutical Benefit Scheme
[a]Assumes one pack accounts for one month of therapy

As mentioned previously, it is assumed that patients continue to receive terazosin therapy as long as they are not confronted by the necessity for re-treatment, creating a continuing cost at each simulation cycle. It is further assumed that patients require monthly general practitioner consultations, comprising six level A and six level B consultations each year. Hence, the total cost associated with one course of terazosin therapy can be estimated, as shown in **Table 61**. The costs under the RPBS are used for the baseline analysis and, in the sensitivity analysis; the cost estimate based on the private market price is employed.

Table 61 Annual cost of terazosin therapy

Resources	Cost	
	RPBS	Private
Medication	$844.86	$1309.92
Monthly general practitioner consultation		
Level A at $14.10 each	$84.60	$84.60
Level B at $30.85 each	$185.10	$185.10
Total cost per annum	**$1114.56**	**$1579.62**

Abbreviation: RPBS, Repatriation Pharmaceutical Benefit Scheme
Source: Medicare Benefits Schedule Book (November 2004); ***Table 60***

Estimated costs associated with the treatment of adverse events are summarised in **Table 62**. As revealed in the primary trials included in the clinical evaluation, the frequency and severity of procedural side effects associated with TURP is likely to be greater than with HE-TUMT.

In estimating the cost of treating adverse events several assumptions have been made, as follows.

- Treatment of urethral stricture is represented by an AR-DRG code of L66Z, incurring a cost of $1308 per episode (based on the public hospital cost estimate)
- The cost associated with bladder neck stenosis was assumed to be same as that of urethral stricture
- Ejaculatory dysfunction and erectile dysfunction both attract a total of four level B consultations.

Based on these assumptions, the average cost of treating one episode of the various adverse events can be calculated on the basis of reported risks, as shown in **Table 62**. It is further assumed that the treatment of adverse events is completed within one

simulation cycle (ie, 12 months), and thus any associated economic impacts are also absorbed within that cycle. This eliminates the necessity for distinction between permanent and temporary adverse events.

Table 62 Cost of treating adverse events

	Urethral stricture/ bladder neck stenosis	Ejaculatory dysfunction	Erectile dysfunction	Transfusion	Total/weighted average cost
Cost of treatment	$1308.0	$123.4	$123.4	$101.4	–
HE-TUMT					
Risk of adverse event	0.005	0.220	0.060	0.000	**0.285**
Relative weight	0.02	0.77	0.21	0.00	**1.00**
Weighted cost	$22.9	$95.3	$26.0	$0.0	**$144.18**
TURP					
Risk of adverse event	0.032	0.734	0.110	0.110	**0.986**
Relative weight	0.03	0.74	0.11	0.11	**1.00**
Weighted cost	$42.5	$91.9	$13.8	$11.3	**$159.39**
Pharmacotherapy					
Risk of adverse event	0.000	0.062	0.010	0.000	**0.062**
Relative weight	0.00	0.86	0.14	0.00	**1.00**
Weighted cost	$0.0	$106.1	$17.3	$0.0	**$123.40**

Abbreviations: HE-TUMT, high-energy transurethral microwave thermotherapy; TURP, transurethral resection of the prostate.
*Source: **Table 51***

As in the case of utilities, by taking a weighted average that collectively accounts for the treatment costs across all adverse events, the overall economic implications will be appropriately captured. Although the cost of treatment per patient is largely comparable amongst the treatments, the number of individuals incurring the cost is considerably higher for TURP than for HE-TUMT and pharmacotherapy.

These estimates are considerably lower than the estimates employed in the cost-effectiveness assessment of TUNA for the treatment of BPH (MSAC 2002). In this earlier assessment, it was estimated that the annual costs of treating a patient who experienced the procedural side effects was, on average, $500, which were then applied to both TURP and TUNA arms (MSAC 2002). In this study, a cost of $500 is used for all treatment arms in a sensitivity analysis.

As mentioned above, those patients who receive no further treatment following a treatment failure do not incur any healthcare costs in the model, although in practice these patients are likely to undergo 'watchful waiting', which may involve small costs associated with medical consultations.

Results

Base-case analysis

The following tables summarise the base-case results of the 10-year cost-effectiveness analysis comparing HE-TUMT with TURP or pharmacotherapy. Results are shown for the pathways beginning with the initial episode of each of these treatments. All estimates are discounted at 5 per cent per annum.

Table 63 indicates that the treatment pathway beginning with HE-TUMT is associated with higher costs than TURP, but at lower costs than pharmacotherapy. The incremental cost associated with the HE-TUMT pathway is estimated to be $485, relative to TURP over the period of 10 years. When compared with pharmacotherapy, the HE-TUMT pathway is shown to generate a cost saving of –$496.

Table 63 Estimated cost of treatment over 10 years

	Average cost per patient over 10 years					
	Initial treatment		Follow-up		Total	Incremental cost of HE-TUMT
	Intervention[a]	*Adverse events*	*Intervention*[a]	*Adverse events*		
HE-TUMT	$4034	$41	$1803	$51	$5929	–
TURP	$4969	$157	$308	$10	$5444	$485
Pharmacotherapy	$3242	$8	$3111	$64	$6424	-$496

[a]*HE-TUMT, TURP or pharmacotherapy*

The effectiveness of each treatment pathway was captured in terms of patients' QALYs in the model, as shown in **Table 64**. The treatment pathway beginning with HE-TUMT was shown to generate greater improvement in QALYs than the pathway commencing with pharmacotherapy, over the 10-year simulation period. However, the HE-TUMT arm was associated with a smaller number of QALYs than the TURP arm.

Table 64 Estimated quality-adjusted life-years (QALYs) over 10 years

	Average QALYs per patient over 10 years	Additional QALYs associated with HE-TUMT
HE-TUMT	6.56	–
TURP	6.72	–0.16
Pharmacotherapy	6.35	0.21

By combining the economic and clinical outcomes presented in **Table 63** and **Table 64**, the relative cost-effectiveness of HE-TUMT was evaluated. This is shown in **Table 65**.

Table 65 Incremental cost-effectiveness ratio

	Incremental cost associated with HE-TUMT	Additional QALYs associated with HE-TUMT	Cost per QALY gained
HE-TUMT	–	–	–
versus TURP	$485	–0.16	HE-TUMT dominated
versus pharmacotherapy	–$496	0.21	HE-TUMT dominates pharmacotherapy

The treatment pathway commencing with HE-TUMT was found to dominate pharmacotherapy, producing superior effectiveness at lower costs. In contrast, the analysis indicated that HE-TUMT is dominated by TURP, having inferior effectiveness at higher costs. The accuracy and generalisability of these results are dependent on the

accuracy of the data inputs and assumptions detailed previously. Sensitivity analyses performed are demonstrated in the following section.

Table 63 and **Table 64** indicate that the simulation results logically reflect the efficacy and safety information incorporated in the model. Patients who received HU-TUMT as a primary intervention incurred lower costs than those treated with TURP during the acute phase, but their follow-up costs are considerably higher than for patients treated with TURP. This effect is attributable to the high treatment failure rate associated with HE-TUMT. Similarly, the treatment pathway beginning with pharmacotherapy has high follow-up costs, reflecting its poor efficacy in symptomatic control. It was also demonstrated that the favourable efficacy profiles associated with TURP compensate for the high acute TURP treatment cost, keeping the overall treatment costs down. During the acute phase, the cost of procedural adverse events was estimated to be relatively high for TURP. This trend is reversed during the follow-up phase. This was an expected result because patients treated with TURP are less likely to experience treatment failure. Patients who experience treatment failure following HE-TUMT or pharmacotherapy are retreated using TURP, and the majority of these patients experience a procedural adverse event.

Table 64 portrays the relative efficacy of these treatment alternatives. Given the data inputs and assumptions made for the base-case analysis, these results also suggest that the favourable risks of procedural adverse events and procedural mortality associated with HE-TUMT relative to TURP, do not generate sufficient QALY benefit to compensate for the lower effectiveness in symptom control.

It should be noted that these results relate the treatment pathways beginning with the initial episode of each of these treatments. Since the pathways for HE-TUMT and pharmacotherapy both involve TURP in case of treatment failure, it is expected that their overall QALY estimates would deteriorate if TURP were not available as a follow-up treatment option. This point is further investigated in the following sensitivity analyses.

Sensitivity analysis

The reliability of the results of any economic model is dependent on the robustness of the key inputs and assumptions. The derivation of the inputs in the current model is described above. In order to investigate the impact of changes in the key inputs on the relative cost-effectiveness of HE-TUMT, a series of sensitivity analyses were conducted. The results of the sensitivity analyses are presented in **Table 66**.

The cost difference between the HE-TUMT and TURP arms is shown to diminish even with a relatively small change in the cost inputs. Similar impacts were also observed as a result of changes made to the failure rates of HE-TUMT. Further, the cost-effectiveness results were found to be sensitive to changes in the baseline utility score. When utility scores representing the quality of life of patients diagnosed with moderate-to-severe BPH are sufficiently higher than the base-case level, the HE-TUMT arm was shown to deliver the best outcome. The pharmacotherapy arm was the next best option in these circumstances. By using a high base-line utility score, differences between the alternative interventions, in terms of their ability in improving the patient's quality of life (via improvement in the IPSS score), carry less weight in the simulation. This also makes the QALY estimates more sensitive to their differences in the risks of causing undesirable side effects.

Table 66 Sensitivity analysis

	Average cost per patient over 10 years (incremental cost of HE-TUMT)	Average QALYs per patient over 10 years (incremental QALYs with HE-TUMT)	Cost per QALY gained
1. Longer hospital stay following TURP procedure (5 days) and higher pharmacotherapy cost			
HE-TUMT	$6310	6.56	–
TURP	$6443 (–$132)	6.72 (–0.16)	HE-TUMT is less effective, but at lower costs
Pharmacotherapy	$8636 (–$2325)	6.35 (0.21)	HE-TUMT dominates pharmacotherapy
2. Scenario 1 and high treatment cost of adverse event ($500)			
HE-TUMT	$6521	6.56	–
TURP	$6799 (–$278)	6.72 (–0.16)	HE-TUMT is less effective, but at lower costs
Pharmacotherapy	$8798 (–$2,277)	6.35 (0.21)	HE-TUMT dominates pharmacotherapy
3. Higher baseline utility value (0.96)			
HE-TUMT	$5929	6.99	–
TURP	$5444 ($485)	6.93 (0.06)	$8682
Pharmacotherapy	$6424 (–$496)	6.97 (0.02)	HE-TUMT dominates pharmacotherapy
4. Higher utility loss associated with treatment side effects (x 2 from the base-case)			
HE-TUMT	$5929	6.45	–
TURP	$5444 ($485)	6.50 (–0.05)	HE-TUMT dominated
Pharmacotherapy	$6424 (–$496)	6.27 (0.18)	HE-TUMT dominates pharmacotherapy
5. Different treatment pathways (involving the same treatment option for the primary and follow-up treatments)			
HE-TUMT	$5678	6.51	–
TURP	$5445 ($233)	6.71 (–0.20)	HE-TUMT dominated
Pharmacotherapy	$5597 ($81)	6.16 (0.35)	$230
6. 50% improvement in HE-TUMT annual failure rate over the first 5 years following the treatment			
HE-TUMT	$5299	6.57	–
TURP	$5444 (–$146)	6.72 (–0.15)	HE-TUMT is less effective, but at lower costs
Pharmacotherapy	$6424 (–$1126)	6.35 (0.22)	HE-TUMT dominates pharmacotherapy
7. No long-term treatment failure after 5 years for HE-TUMT and for pharmacotherapy			
HE-TUMT	$5264	6.58	–
TURP	$5455 (-$191)	6.72 (–0.14)	HE-TUMT is less effective, but at lower costs
Pharmacotherapy	$6487 (–$1223)	6.37 (0.21)	HE-TUMT dominates pharmacotherapy
8. No long-term treatment failure after 5 years for HE-TUMT			
HE-TUMT	$5237	6.58	–
TURP	$5444 (–$208)	6.72 (–0.14)	HE-TUMT is less effective, but at lower costs
Pharmacotherapy	$6424 (–$1188)	6.35 (0.23)	HE-TUMT dominates pharmacotherapy

The first two analyses in **Table 66** concern the assumptions relating to the costs of treatment. In these scenarios, the QALY estimates remain unaffected from the base-case analysis. The first analysis investigates the relative cost-effectiveness of these treatment options should TURP require two additional hospital admission days (the base-case analysis assumed three days' hospitalisation). This new assumption increased the TURP procedural cost by $940. This analysis also employed the high-end estimate for the cost of pharmacotherapy ($1579.62; see **Table 61**). In this scenario, the HE-TUMT arm was associated with lower costs than TURP. The cost difference between the HE-TUMT arm and the pharmacotherapy arm further widened in favour of HE-TUMT.

Another analysis was performed to investigate the situation where, in addition to the aforementioned higher TURP and pharmacotherapy costs, the average cost of treating adverse events were higher, costing $500 per episode. As shown in **Table 66**, this assumption further widens the cost difference between the HE-TUMT arm and the TURP arm. A cost difference similar to that observed in the previous scenario was again demonstrated between the HE-TUMT arm and the pharmacotherapy arm. The increase in the cost of adverse events did not alter the fundamental conclusions regarding the relative cost-effectiveness of HE-TUMT drawn from the previous sensitivity analysis.

Sensitivity analyses demonstrated that plausible changes to the assumptions about economic variables make the HE-TUMT arm cheaper than the TURP arm, and consequently overturn the dominance of TURP over HE-TUMT. This means that the claim of dominance demonstrated in the base-case analysis rests on the differences in the QALY outcomes. As such, sensitivity analyses on the utility values were conducted.

First, the base-line utility score is increased from 0.81 to 0.96. This new value corresponds to the base-line utility estimate employed in the cost-effectiveness analyses performed by Blute et al (2000) and Manyak et al (2002). It should be noted that this estimate is derived from a study population of 13, which indicates that the validity of this estimate may be still questionable. Efficacy and safety data are not altered in performing this scenario. Schulz et al (2002) was also used to establish the link between the utility score and IPSS.

Table 66 presents that under this assumption; the QALYs achieved by patients in the HE-TUMT arm are greater than those in both comparator arms. Estimated treatment costs remained unaffected at the base-case level under this scenario. The cost-effectiveness ratio achieved by the HE-TUMT arm was estimated to be $8,682 when compared with the TURP arm. When compared with pharmacotherapy, HE-TUMT still remains the dominant strategy, although the incremental effectiveness associated with the HE-TUMT arm is now only marginal (0.02).

Using a high baseline utility value leaves little room to differentiate three treatment strategies in terms of their efficacy in improving the IPSS score and consequently patients' quality of life. The impact of treatment failure is also less significant, as the recurrence of BPH has a relatively small impact on patients' QALYs when compared with the base-case scenario. As a result, the QALY estimates in this analysis are now more susceptible to the quality of life impact associated with the treatment adverse events, which, in particular, favour the outcome for the pharmacotherapy arm. Although not shown in **Table 66**, when the baseline utility value of 0.90 is used, the QALY estimate for HE-TUMT, TURP, and pharmacotherapy is 6.83, 6.83, and 6.72, respectively.

Another analysis protocol was conducted to test the impact of greater quality of life implications associated with the treatment adverse events. The weighted average utility losses presented in **Table 53** were doubled for the purpose of this analysis. In this scenario, incremental QALY differences between HE-TUMT and both other interventions decrease, but not sufficient to alter the fundamental cost-effectiveness results obtained from the base-case analysis.

Alternative treatment pathways were also explored. Treatment pathways that involved the same treatment for both the initial and follow-up treatment were incorporated in the model. When compared with the base-case results, a small reduction in the estimated QALYs was observed for the HE-TUMT arm, and a relatively large deterioration in the estimated QALYs has been demonstrated for the pharmacotherapy arm. This accurately reflects the relative efficacy profiles of these treatment options. A notable reduction in cost in the pharmacotherapy arm is also observed, making this arm cheaper than the HE-TUMT arm. This is because patients were re-treated using a less costly treatment option (ie, pharmacotherapy). However, the HE-TUMT is still associated with a superior efficacy, making it a highly cost-effective treatment option at cost per QALY of $230. The TURP arm is unaffected under this scenario, since patients are always re-treated with TURP in the base-case analysis. Therefore, the HU-TUMT pathway is shown to represent a cost-effective treatment strategy when compared with the pharmacotherapy pathway, while HE-TUMT remains dominated by TURP under this scenario.

A sensitivity analysis was performed on the five-year failure rate associated with HE-TUMT. The impact of improvement in the annual failure rates by 50 per cent over these years was investigated here, as shown in **Table 66**. This effectively decreases the cumulative failure rate at five years from 33 per cent to 18 per cent for the HE-TUMT arm (see **Table 50**). As conducted in the base-case analysis, the last available estimates (ie, Year 5) are carried forward until the end of simulation for HE-TUMT and other two treatment strategies. It was demonstrated that this change in the failure rate improved the cost and QALY estimates for HE-TUMT from the base-case analysis. In particular, the total costs in the HE-TUMT arm was now estimated to be slightly lower than that of the TURP arm.

In addition to the five-year failure rate above, reliable long-term clinical outcomes data are not available for HE-TUMT and pharmacotherapy. In the base-case analysis, the last available observations were carried forward until the end of simulation. It is likely that the long-term treatment failure rates have an important impact on the relative cost-effectiveness of these treatment options. In order to investigate this, two sets of sensitivity analyses have been performed.

First, the occurrence of treatment failure is assumed to stop after five years for the HE-TUMT and pharmacotherapy arms. That is, the cumulative rates remain stable after five years at 33.0 per cent for the HE-TUMT arm and 80.5 per cent for the pharmacotherapy arm (see **Table 50**). The second analysis has been performed by applying this new assumption only to the HE-TUMT arm, and by employing the base-case treatment failure rates for the pharmacotherapy arm.

The results in **Table 66** indicate that under both scenarios the HE-TUMT arm achieves large cost reductions and a slight improvement in the number of QALYs. In these scenarios, the extents of cost reductions are large enough to offset the additional costs demonstrated for HE-TUMT over TURP in the base-case analysis. The QALY outcomes of HE-TUMT, however, remain inferior to those of TURP. Relative to the

pharmacotherapy arm, the HE-TUMT arm remains to be a dominant strategy. It should be noted that a slight increase in the cost for the pharmacotherapy arm is attributable to the increased likelihood of patients' successfully continuing on the pharmacotherapy treatment.

These analyses indicate that the cost-effectiveness results are sensitive to the cost inputs and the baseline utility value. The failure rates of HE-TUMT also have important implications. Results from scenario three (see **Table 66**) indicated that HE-TUMT could be cost-effective when compared with TURP if the quality of life of a patient with moderate-to-severe BPH is represented by a utility value that is not as low as the base-case level (ie, 0.81). When findings from scenarios two and three are combined, HE-TUMT is shown to be a dominant strategy over TURP. A similar result can be expected if treatment failure associated with HE-TUMT is in fact better than the level assumed in the base-case analysis. The analyses show that HE-TUMT remains to be a dominant or highly cost-effective treatment alternative when compared with pharmacotherapy.

Conclusions

Safety

The comparative safety of HE-TUMT, TURP, ILCP and terazosin is based on seven primary studies (5 level II, 2 level III-1), which varied from three to 36 months in duration. Including four level II studies and one level III-1 study for HE-TUMT versus/TURP; one level III-1 study for HE-TUMT versus terazosin and one level III-1 study for HE-TUMT versus ILCP/TUNA. Additionally, secondary evidence for HE-TUMT consisting of non-comparative and single-arm studies of one to 60 months duration was included. However, the rates in these lower levels of evidence tended to vary more widely and were thus used simply as supportive evidence.

The majority of patients experienced mild and transient dysuria and haematuria following both HE-TUMT and TURP. However, most other adverse events occurred less commonly following HE-TUMT compared with TURP, including serious haematuria (1.9% versus 6.5% respectively), transfusions (0% versus 8–13% respectively), incontinence (1.0% versus 2.2% respectively), urethral strictures and bladder neck stenosis (0.5% versus 6.8% respectively), and the potentially serious TUR syndrome (0% versus 2–4% respectively). Adverse events were poorly reported for ILCP/TUNA, although urethral strictures and bladder neck stenosis occurred more commonly (2.1%) than in the HE-TUMT group (0.5%). Urinary tract infections (UTIs) were reported in a similar proportion of HE-TUMT patients (16%) and TURP patients (14%), but were by far the most common after ILCP (61%). Adverse events associated with terazosin included dizziness (13.5%), asthenia (7.7%), headache (5.8%), hypotension (1.9%), nausea (1.9%) and postural dizziness (1.9%).

Due to poor reporting and poor follow-up of questionnaires, it was difficult to accurately determine the impact of HE-TUMT and TURP on sexual function from the included studies. These results were further confounded by the fact that many patients in this population tend to have problems with sexual function at baseline. Nevertheless, based on this limited evidence it appears that HE-TUMT results in potentially much lower rates of ejaculatory and erectile dysfunction compared to TURP. This is consistent with several recent reviews, in which the rate of erectile dysfunction and ejaculatory dysfunction associated with HE-TUMT (4.4% and 19.8% respectively) were lower than with TURP (9.3–15.7% and 63.0–74.4% respectively) (de la Rosette et al 2003b; NHMRC uncomplicated LUTS management, 1996; Kirby et al 1994).

Mortality was not reported with ILCP/TUNA or terazosin, was low with HE-TUMT (1.1%) and slightly higher with TURP (1.6%). Deaths were generally stated as not related to treatment and are probably principally driven by the co-morbid conditions in this population. No cases of fistula formation were reported after HE-TUMT in the primary studies, although three cases were reported in the secondary studies (two of these were with LE-TUMT, and one with HE-TUMT, and all were a result of operator error).

Effectiveness

The evidence for the comparative efficacy of HE-TUMT versus TURP was based on five level II studies, one level III-1 study, and three level III-2 studies. Trials varied in duration from three months to 36 months. Six studies used cooled HE-TUMT (five with the Prostatron® v2.5 system and one with the Dornier UroWave® system) and three studies used non-cooled HE-TUMT (ProstaLund®).

There were no studies comparing HE-TUMT with prazosin or tamsulosin (the most commonly used medication prescribed for BPH in Australia). However, limited evidence was identified for cooled HE-TUMT versus terazosin, of which the highest level of evidence was an 18 month level III-1 study using the Targis® system. In addition, a six month level III-2 study using the Prostatron® v2.5 system was identified.

Limited evidence was identified for cooled HE-TUMT versus ILCP and/or TUNA. The highest level evidence available was a six month level II study using the Prostatron® v2.5 system. Two level III-2 studies were also identified: a six month study using the Prostatron® v2.5 system and a three month study using the Dornier UroWave® system.

The three primary outcomes assessed in this report were symptom scores (IPSS, AUA scores), maximum urinary flow rates (Q_{max}) and post-void residual volume (PVR). Changes in symptom scores are considered the most important indication of treatment success. Other important outcomes considered were treatment failure rates, quality of life and sexual function.

Symptom scores

In patients with moderate-to-severe symptoms at baseline, cooled and non-cooled HE-TUMT lead to significant improvements in symptoms (as assessed by the IPSS index and AUA scores) for up to three years.

Improvements tended to occur more rapidly (ie, within three months) with TURP, ILCP and terazosin compared to HE-TUMT. Limited evidence suggested HE-TUMT and TUNA had a similar degree of improvement at three months.

Symptomatic improvement at six months with HE-TUMT was similar to that with TURP and ILCP (ie, all improved to mild severity) but greater than with terazosin (which improved to moderate severity).

Long-term data demonstrated that the improvements with HE-TUMT were not as great as that with TURP at three years. This was due to a slow decline in effectiveness with HE-TUMT over this period such that symptom severity had risen to moderate, compared to TURP in which symptoms remained stable (mild).

Uroflowmetry

Although initially TURP, terazosin and ILCP showed a more rapid improvement in Q_{max} by six months, improvements in Q_{max} following HE-TUMT were similar to ILCP (Norby et al 2002a), similar or less than TURP (d'Ancona et al 1998; Wagrell et al 2002/2004; Norby et al 2002a) and significantly better than terazosin (Djavan et al 1999c, 2001).

Long-term results indicate that HE-TUMT leads to significant improvements in Q_{max} relative to baseline from 12 months for up to a total of three years follow-up, although there is a gradual decline in Q_{max} values over this period. HE-TUMT remained

significantly better than terazosin over an 18 months period (Djavan et al 2001). In contrast, HE-TUMT was similar (d'Ancona et al 1998) or worse (de la Rosette et al 2003a/Floratos et al 2001a; Wagrell et al 2004) compared with TURP over this period.

Improvements in PVR following HE-TUMT were mixed, with some studies indicating no long-term improvement, and others indicating some improvement. Limited evidence indicated the improvements at six months were similar to that from ILCP, and possibly better than that from terazosin. However, TURP showed a rapid and significantly better improvement in PVR compared to HE-TUMT that was sustained for up to three years.

Treatment failure

Although loss to follow-up may confound estimates, cooled HE-TUMT consistently had a higher cumulative treatment failure rate compared to TURP at one-year follow-up (6.5–12.2% versus 4.8–9.6% respectively) and three years follow-up (19.5–25.8% versus 4.8–11.0% respectively) (d'Ancona et al 1998; de la Rosette et al 2003a/Floratos et al 2001a).

However, HE-TUMT had a much lower rate of treatment failure at 18 months (5.8%) compared with terazosin (41.2%) (Djavan et al 2001).

Limited evidence after six months follow-up indicated HE-TUMT had a higher treatment failure rate (2.2%) compared with ILCP (0.0%) (Norby et al 2002a).

Treatment failure following HE-TUMT was usually as a result of a lack of effectiveness, in contrast to TURP, in which 89 per cent of complications were a result of a complication, such as a urethral stricture or bladder neck stenosis (which required a urethrotomy or bladder neck incision respectively).

Quality of life and sexual function

HE-TUMT and TURP resulted in significant improvements in quality of life that were maintained for up to three years. However, the improvements were significantly greater following TURP.

Terazosin lead to a more rapid improvement in quality of life compared to HE-TUMT, however, the improvements were ultimately not as great as with HE-TUMT from six months up to 18 months.

Limited short-term evidence indicated that the improvements following ILCP and TUNA might have been greater at three to six months follow-up.

Although the evidence examining the impact of these procedures on sexual function was limited and poorly reported, and biased by poor response rate and significant levels of dysfunction at baseline, there was a trend, supported by recent reviews, indicating that HE-TUMT has a minimal impact on sexual function, causing much lower rates of erectile and ejaculatory dysfunction compared to TURP. There was no evidence examining the comparative impact of HE-TUMT and medication on sexual dysfunction, and very limited short-term evidence indicated that the impact of ILCP, TUNA is similar to HE-TUMT.

Cost-effectiveness

The cost-effectiveness of alternative treatment pathways that begin with HE-TUMT, TURP or pharmacotherapy (terazosin hydrochloride) in patients with moderate-to-severe

BPH has been evaluated. Under the base-case scenario, the treatment pathway beginning with HE-TUMT was found to be a dominant treatment strategy compared with the pathway starting with pharmacotherapy, generating superior effectiveness at lower costs. However, the pathway beginning with HE-TUMT was dominated by that commencing with TURP.

A series of sensitivity analyses have been performed. It is demonstrated that when a high value for the baseline utility scare is applied, the health outcomes in the HE-TUMT arm become superior to those in the comparator arms. This was found to be so because when the quality of life of a patient experiencing moderate-to-severe BPH is high at the baseline, differences between the alternative interventions in terms of their ability to improve the patient's quality of life (via improvement in the IPSS score) have relatively small importance in the evaluation. Further, this also makes the QALY estimates more susceptible to the differential risks of undesirable side effects associated with the alternative interventions. In addition, the cost difference between the HE-TUMT and TURP arms is shown to diminish even with a slight change in the cost assumptions, which indicates that the treatment costs can be considered largely comparable between the two treatment pathways. A similar impact on the treatment costs was also observed when treatment failure associated with HE-TUMT was improved from the base-case level. As such, when these situations simultaneously occur in practice, HE-TUMT may represent a dominant strategy over TURP. The analyses showed that HE-TUMT was very likely to represent a dominant or highly cost-effective treatment alternative when

It is somewhat difficult to draw a direct comparison between the results from this study and other published evidence, due to differences in the model design and underlying assumptions. Striking differences in simulation results can be found between the current study and Blute et al (2000) and Manyak et al (2002). Blute et al (2000) and Manyak et al (2002) demonstrated that HE-TUMT was cost-effective compared with pharmacotherapy, but found it to be a dominant treatment option when compared with TURP. In these studies, the baseline utility score associated with moderate-to-severe BPH was significantly higher than in the current study (0.96 versus 0.81). As discussed above, the use of a low baseline utility score may provide greater opportunity for TURP to exhibit a positive effect on patients' quality of life attributable to enhanced efficacy in symptomatic control and remission maintenance, compared with other treatment options. Also, the model used by Blute et al (2000) and Manyak et al (2002) allowed patients in the TURP arm to be retreated three times, while the patients initially treated

This might have unfavourably inflated the treatment costs in the TURP arm.

Walden et al (1998) performed a modelled economic evaluation to examine the two-year cost-effectiveness of LE-TUMT relative to TURP. It demonstrated that LE-TUMT was associated with inferior effectiveness, but LE-TUMT incurred lower economic costs when compared with TURP. Based on these simulation results, the authors concluded that LE-TUMT is more cost-effective than TURP. Given the large differences between the current study and Walden et al (1998) in their study scope and analytical approach (eg, study intervention, evaluation length and outcome measurement), it is very difficult to meaningfully compare their results. However, it is interesting to note that a similar pattern of economic occurrence shown in Walden et al (1998) was also observed in the current evaluation (ie, TUMT being associated with lower initial costs accompanied by higher follow-up costs than TURP).

Recommendation

MSAC recommended that on the strength of evidence pertaining to high-energy transurethral microwave thermotherapy public funding should be supported for this procedure.

– The Minister for Health and Ageing accepted this recommendation on 28 November 2005 –

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Samantha Robertson	Department representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research

Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1076
Transurethral microwave thermotherapy

Dr Michael Kitchener (Chair) MBBS, FRACP Senior Visiting Nuclear Physician Queen Elizabeth Hospital, Adelaide	MSAC Member
Associate Professor Michael Cleary MBBS (UQ), FACEM, MHA (UNSW), AFACHSE Executive Director Medical Services The Prince Charles Hospital Health Service District	MSAC Member
Dr William Lynch MBBS MSc FRACS Consultant Urologist The St George Hospital, Sydney	Australian and New Zealand Association of Urological Surgeons (ANZAUS) nominee
Dr Gerard Testa MBBS FRACS Consultant Urological Surgeon Blacktown, Westmead, Prince of Wales and Sutherland Hospitals	ANZAUS nominee
Mr Don Baumber QDH Convenor, Gold Coast Prostate Cancer Support and Information Network Chair, Support and Advocacy Committee, Prostate Cancer Foundation of Australia (PCFA) Director, PCFA Director, Cancer Alliance Network Australia	Consumers' Health Forum of Australia nominee

Evaluators for MSAC application 1076

Dr Nathan Walters BSc (Hons) PhD	M-TAG Pty Ltd, a unit of IMS Health
Mr Koji Makino BCom MCom	M-TAG Pty Ltd, a unit of IMS Health

Members from the Department of Health and Ageing for MSAC application 1076

Ms Brenda Campe Project Manager	Health Technology Section Medicare Benefits Branch

Appendix C Studies included in the review of safety

Table 67 shows the studies included in the review of safety. Duplicate publications of the same trial have been grouped together (identified by the thicker black border) and separated by dotted lines. In addition to this, studies in which patients have been recruited from the same centre(s) during an identical or overlapping period have also been grouped together within a thicker black border; however, they have not been separated by dotted lines. These studies, while they may contain different numbers of patients, are likely to have considerable overlap in terms of the included patients and if not identified, would result in double-counting of events. During data extraction, no assumptions were made about the occurrence of an event; entries in data fields were based on whether a publication explicitly stated that an event had occurred or not (ie, a zero value was placed *only* if reported). In comparative trials, even if one treatment arm reported an event, unless the other treatment arm explicitly stated that the event had not occurred, "–" was entered into the field.

Table 67 Adverse events in the included trials for the safety review

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Ahmed 1997	RCT	6	United Kingdom Eastbourne Hospital	Prostatron® v2.5	30	7	1/30 (3.3)	1/30 (3.3)	–	4/30 (13.3)	0/30 (0.0)	0/30 (0.0)	0/30 (0.0)	All patients reported temporary dysuria; constipation and haematuria in all patients for up to 24 hours. The patient with the UTI also had epididymo-orchitis and haematuria requiring hospitalisation. 2 patients had catheters for 10 days and 1 for 6 weeks
				TURP	30	26	3/30 (10.0)	–	–	12/30 (40.0)	4/30 (13.3)	3/30 (10.0)	0/30 (0.0)	Blood transfusion (n = 4). One of the patients with a UTI developed septicaemia. Two patients had catheters in for 4 weeks
Albala 2000	RCT	12	America Multicentre	TherMatrx®	130	28	–	0/130 (0.0)	–	0/130 (0.0)	–	0/130 (0.0)	–	Urgency (5.3%), bladder spasms (0.7%), dysuria (0.7%). No pain was noted; no rectal damage fistula was noted. Re-catheterisation (n=19)
Albala 2002	RCT	12	America Multicentre	TherMatrx®	121	44	–	11/121 (9.1)	–	0/121 (0.0)	–	0/121 (0)	–	Bladder spasm (4.1%), dysuria (6.6%). No patient experienced urgency, no rectal damage fistula was noted, and no pain was noted. Re-catheterisation (n = 20)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Alivizatos 2005	Case series	12	Greece	ProstaLund®	38	51	3/33 (9.1)	15/33 (45.5)	8/33 (24.2)	–	–	–	–	Haematuria did not require any intervention; 5/33 (15.2%) patients had bladder stones; 19/33 (57.6%) patients had irritative symptoms eg frequency, urgency, nocturia, pain during micturition; 1/33(3.0%) patients required suprapubic catheterisation
Arai 2000	Case-control study	3	Japan Kurashiki Hospital February 1995–August 1997	UroWave®	34	9	–	–	6/31 (18.2)	–	–	–	–	Only evaluated in patients completing questionnaire at baseline and 3 months
				TURP	55	19	–	–	12/39 (30.8)	–	–	–	–	
				ILCP	42	9	–	–	2/38 (5.3)	–	–	–	–	
				TUNA	42	9	–	–	7/31 (18.9)	–	–	–	–	
Berger 2003	Case series	24	Austria University of Innsbruck August 1997–March 2001	Targis®	78	50	14/78 (18.0)	19/78 (24.4)	–	–	–	–	–	Urinary retention (n = 15): 5 patients redeveloped urinary retention while in another 10 patients urinary retention persisted after TUMT treatment. Epididymitis (n = 2). Prolonged catheterisation was noted in 6 patients, haematuria was resolved within three weeks of treatment, irritative urinary symptoms occurred in all patients but resolved within 2 weeks

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Blute 1996	RCT	12	America Mayo Clinic	Prostatron®	78	123	–	54/78 (69.2)	–	–	–	–	–	Urethral bleeding (n = 16), urethral discharge (n = 2), urinary retention (n = 20), other urinary tract problems (n = 11), reproductive (n=8), rectal (n = 4), systemic (n = 2), gastrointestinal (n = 3), renal (n = 1), neurologic (n = 2). No adverse effects effecting the cardiovascular, respiratory, musculoskeletal, and dermatologic or oral/ophthalmic systems were reported. There were no reports of sexual dysfunction
Cavarretta 2001	Case series	12	Italy Bortolo Hospital December 1998– July 2000	Prostatron®	25	1	–	–	–	–	–	–	–	Bilateral orchiepididymitis (n = 1). Haematuria was transient in nature. 2 patients did not regain spontaneous micturition
Dahlstrand 1997	Case-control study	3	Sweden Sahlgrenska Hospital	Prostatron® v2.5 +Foley Catheter	15	0	–	–	–	–	–	–	–	There was no serious complications, four of the patients were hospitalised overnight after the treatment
				Prostatron® v2.5+SR-PGA stent	15	4	–	–	–	–	–	–	–	Irritative symptoms (n = 4)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Francisca 1999b	**Case series**	**48**	**Netherlands Nijmegen Hospital 1993–**	**Prostatron® v2.5**	**357**	–	–	–	–	–	–	–	**5/357 (1.4)**	**No serious complications occurred**
D'Ancona 1997a	Case series	24	Netherlands Nijmegen Hospital October 1993–December 1996	Prostatron® v2.5	301	3	–	–	–	–	–	3/301 (1.0)	7/301 (2.3)	Unable to void after removal of catheter (n = 3), 3 patients received bladder neck incisions (assumed this was for bladder neck stenosis). Death/illness were not separated, thus (n = 7) is an overestimate: noted as not related therapy
D'Ancona 1999	Case series	12	Netherlands Nijmegen Hospital October 1993–July 1996	Prostatron® v2.5	247	2	–	–	–	–	–	2/247 (0.81)	7/247 (2.8)	Bladder neck stenosis treated with bladder neck incision; urethral strictures treated with urethrotomy. Death/illness were not separated, thus (n = 7) is an overestimate: noted as not related to therapy
Floratos 2000	Case series	12	Netherlands Nijmegen Hospital October 1993–March 1999	Prostatron® v2.5/3.5	41	1	–	–	–	–	–	–	6/41 (14.6)	Pain during procedure (n = 1). Treatment failed in 9 patients. Deaths were from severe cardiopulmonary insufficiency or cancer

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
De Wildt 1996	Case series	12	Netherlands Nijmegen Hospital October 1993–August 1994	Prostatron® v2.5	85	31	–	–	–	18/85 (21.2)	0/85 (0.0)	0/85 (0.0)	3/85 (3.5)	Diminished ejaculatory volume (n = 6), epididymitis (n = 6), anticoagulants were used in 18 patients: blood clot retention (n = 1). Prolonged catheterisation required in 10% of patients. During catheterisation 25% of patients reported bladder spasms; 7% perineal discomfort; 76% haematuria, After catheter removal 60% of patients experienced irritative complaints of urgency or frequency, 29% of patients used antibiotics after treatment. Complaints resolved after 2–3 weeks. No stress incontinence reported. Deaths were due to terminal heart failure (not treatment related), pulmonary failure (alpha1-antitrypsine deficiency), and metastasised GI tumour

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
De la Rosette 1996	Prospect -ive case series	12	Netherlands Germany United Kingdom Italy Multicentre, April 1993–July 1994	Prostatron® v2.5	116	NR	–	–	–	See comme nt	–	0/116 (0.0)	2/116 (1.7)	Treatment failure (n = 3), irritative voiding complaints were noted in a large number of patients up to 2–4 weeks, most patients experienced transient haematuria during first few days, a third of patients with antegrade ejaculation at the start of the study had retrograde ejaculation at the end of the study. Deaths were due to terminal heart failure (not treatment related), pulmonary failure (alpha1-antitrypsine deficiency)
D'Ancona 1997b	RCT	12	Netherlands Nijmegen Hospital January 1994–August 1995	Prostatron® v2.5	31	14	5/31 (16.0)	0/31 (0)	–	–		0/31 (0.0)	1/31 (3.2)	Irritative voiding symptoms (n = 9). No Patient required a transfusion. Death non-treatment related
				TURP	21	10	1/21 (4.8)	3/21 (14.3)	–	–	–	1/21 (4.8)	0/21 (0.0)	Irritative voiding symptoms (n = 4), cystectomy for bladder cancer (n = 1). No patient required a transfusion
D'Ancona 1998	RCT	30	Netherlands Nijmegen Hospital January 1994–August 1995	Prostatron® v2.5	31	0	–	–	–	–	–	0/31 (0.0)	1/31 (3.2)	Prolonged catheterisation was required. Death non-treatment related
				TURP	21	4	–	–	–	–	–	1/21 (4.8)	0/21 (0.0)	Cystectomy for bladder cancer (n = 1); dementia (n = 2)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
De la Rosette et al (2003a)	RCT	36	Netherlands Nijmegen Hospital	Prostatron® v2.5	82	3	–	–	–	–	–	1/82 (1.2)	2/82 (2.4)	Treatment failure in 16 patients of which cystolithotripsy (n = 2) and urethral strictures (n = 1) treated with internal optical urethrotomy. Deaths unrelated to treatment. (1 death before treatment but not stated which treatment group this was randomised to)
			January 1996–March 1997	TURP	73	11	–	–	–	–	–	5/73 (6.9)	2/73 (2.7)	Prostate carcinoma (n = 4). Treatment failure requiring further treatment in 8 patients: physiotherapy for stress incontinence (n = 1), anticholinergic for severe storage symptoms (n = 1), bladder neck incision for bladder neck stenosis (n = 3), internal optical urethrotomy for urethral strictures (n = 2). Deaths unrelated to treatment. (1 death before treatment but not stated to which treatment group this was randomised)
Floratos 2001a	RCT	36	Netherlands Nijmegen Hospital	Prostatron® v2.5	82	3	–	–	–	–	–	1/82 (1.2)	2/82 (2.4)	Treatment failure requiring further treatment in 14 patients: cystolithotripsy (n = 2) and urethral strictures (n = 1) treated with internal optical urethrotomy. Deaths unrelated to treatment. (1 death before treatment but not stated to which treatment group this was randomised)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
			January 1996–March 1997	TURP	73	11	–	–	–	–	–	5/73 (6.9)	2/73 (2.7)	Prostate carcinoma (n = 4). Treatment failure requiring further treatment in 8 patients: physiotherapy for stress incontinence (n = 1), anticholinergic for severe storage symptoms (n = 1), alpha-blockers for persisting lower urinary tract symptoms (n = 1), bladder neck incision for bladder neck stenosis (n = 3), internal optical urethrotomy for urethral strictures (n = 2). Deaths unrelated to treatment. (1 death before treatment but not stated to which treatment group this was randomised)
Francisca 1999c	RCT	12	Netherlands Nijmegen Hospital	Prostatron® v2.5	74	22	–	–	12/50 (24.0)	–	7/35 (20)	1/74 (1.4)	0/74 (0.0)	Lack of ejaculation and erectile dysfunction reported at 3 months (out of those answering the question). Urinary Retention (n = 2), urethral strictures treated with internal optical urethrotomy
			January 1996–March 1997	TURP	73	46	–	–	30/44 (68.1)	–	9/53 (17)	2/73 (2.7)	2/73 (2.7)	Lack of ejaculation and erectile dysfunction reported at 3 months (of those answering the question). Bladder carcinoma (n = 1), prostate carcinoma (n = 4), urethral strictures treated with internal optical urethrotomy

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Francisca 2000	RCT	12	Netherlands Nijmegen Hospital January 1996–March 1997	Prostatron® v2.5	74	3	–	–	–	–	–	1/74 (1.4)	0/74 (0.0)	Urinary retention (n = 2), urethral strictures treated with internal optical urethrotomy
				TURP	73	7	–	–	–	–	–	2/73 (2.7)	2/73 (2.7)	Bladder carcinoma (n = 1), prostate carcinoma (n = 4); urethral strictures treated with internal optical urethrotomy
De la Rosette 2000	Case series	12	Netherlands Nijmegen Hospital February 1998–April 1999	Prostatron® v3.5	108	37	10/108 (9.3)	–	–	–	–	1/108 (0.93)	1/108 (0.9)	Epididymitis (n = 1), bladder spasms (n = 25). Several patients had minimal haematuria that resolved in three weeks; at the 3-month evaluation all treatment related complaints were resolved. Urethral strictures treated with urethrotomy
Francisca 1999a	Case series	6	Netherlands Nijmegen Hospital February 1998–September 1998	Prostatron® v3.0	57	66	14/57 (25.0)	–	–	–	–	–	–	Epididymitis (3%), urgency (64%), discomfort (25%). No serious complications occurred, all complications resolved within 3 months
Floratos 2001b	Case series	12	Netherlands Nijmegen Hospital July 1998–July 1999	Prostatron® v3.5	22	1	–	–	–	–	–	1/22 (4.6)	–	Treatment failed in 5 patients, lack of efficacy in 4 patients, adverse event in other

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
David 2004	Retrosp-ective case series	5.6	America Multicentre	ProstaLund®	102	23	–	–	–	–	–	–	–	Epididymitis (n = 4), post-treatment infection (n = 5); re-catheterisation (n=14). Treatment failure requiring further treatment: suprapubic cystostomy tube in 1 due to prolonged retention, and with TURP in another. Irritative voiding symptoms occurred for up to 2–6 weeks
Dicuio 2002	Case series	1	Sweden, Sahlgrenska Hospital October 1998–February 2000	Prostatron® + Medication	89	180	14/89 (16.0)	23/89 (26.0)	–	–	–	–	1/89 (1.1)	Urinary retention (15%), bladder spasms (81%), perineal discomfort (65%). All complications resolved within the first 4 weeks. Bladder spasms associated with catheter. Death due to cardiac infarction the day after treatment: cardiologist judged this unrelated to treatment
Djavan 1998	RCT	3	Austria University of Vienna	Targis® + Sedoanalgesia	22	0	0/22 (0.0)	–	–	–	–	–	0/22 (0.0)	No urinary retention ≥ 2 weeks, no patient reported blood loss, UTI, or re-catheterisation
				Targis® + Topical Anaesthesia	23	0	0/23 (0.0)	–	–	–	–	–	0/23 (0.0)	No urinary retention ≥ 2 weeks, no patient reported blood loss, UTI, or re-catheterisation
Djavan 1999e	RCT	6	Austria University of Vienna	Targis®	51	7	3/51 (5.6)	–	1/51 (2.0)	–	–	–	–	Haemospermia (n = 1), Epididymitis (n = 1), urinary retention ≥ 1 week (n = 1). No dizziness, asthenia, headache, hypotension, nausea or postural dizziness was observed

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
				Terazosin	52	17	0/52 (0.0)	–	0/52 (0.0)	–	–	–	–	Dizziness (n = 7), asthenia (n = 4), headache (n = 3), hypotension (n = 1), nausea (n = 1), postural dizziness (n = 1). No epididymitis, haemospermia or urinary retention ≥ 1 week was observed
Djavan 2001	RCT	18	Austria University of Vienna	Targis®	51	12	4/51 (7.8)	–	3/51 (5.9)	–	–	–	–	Haemospermia (n=2), epididymitis (n = 2), urinary retention > 1 week (n = 1). No dizziness, asthenia, headache, hypotension, nausea, postural dizziness was observed
				Terazosin	52	23	0/52 (0.0)	–	0/52 (0.0)	–	–	–	–	Dizziness (n = 9), asthenia (n = 5), headache (n = 4), hypotension (n = 2), nausea (n = 2), postural dizziness (n = 1). No epididymitis, haemospermia, or urinary retention > 1 week was observed

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Djavan 1999d	Case series	1	Austria University of Vienna	Targis® + Prostatic Bridge	54	35	2/54 (3.7)	–	0/54 (0.0)	25/54 (46.3)	4/54 (7.4)	–	–	Ejaculatory and erectile dysfunction calculated as new cases at 1 month compared with baseline: 3 patients at baseline had no ejaculation compared to 2 at 1 month. Retrograde ejaculation was seen in 4 patients at baseline and 29 at 1 month. Severe erectile dysfunction in 4 at baseline and 8 at 1 month (by score). Early catheter removal (n = 6). No cases of epididymitis or haemospermia were recorded in these patients. Second treatment arm (TUMT + standard catheterisation) was the cohort from Djavan et al (1999a)
Djavan 1999f	RCT	3	Austria University of Vienna	Targis® + Tamsulosin	41	8	1/41 (2.4)	–	2/41 (4.9)	–	–	–	–	Urinary retention ≥ 1 week (n = 1), dizziness (n = 1), headache (n = 1), haematospermia (n = 2). Micturition status represented by dysuria, haematuria, incontinence, subjective discomfort, subjective urine flow
				Targis® – Tamsulosin	40	9	2/40 (5.0)	–	1/40 (2.5)	–	–	–	–	Urinary retention ≥ 1 week (n = 5), haematospermia (n = 1). Micturition status represented dysuria, haematuria, incontinence, subjective discomfort, subjective urine flow

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Djavan 1999c	Prospective case series	3	Austria University of Vienna	Targis®	31	2	1/31 (3.2)	–	–	–	–	–	–	Epididymitis (n = 1)
Djavan 2000a	Prospective case series	4	NR University of Vienna	Targis®	29	3	2/29 (6.9)	–	–	–	–	–	0/29 (0.0)	Epididymitis (n = 1)
Djavan 2000b	Case series	12	Austria University of Vienna	Targis®	71	1	–	–	–	–	–	–	–	Urinary retention (n = 1); treatment failure (n = 1)
Eliasson 1998b	RCT	6	Sweden NR	Prostcare Low Effect Prostcare	98	84	0/98 (0.0)	66/98 (67.4)	–	0/98 (0.0)	1/98 (1.0)	1/98 (1.0)	–	Urinary retention (n = 5) occurred within first 24 hours post treatment. All haematuria was transient. Epididymitis (n = 2), Pain limited treatment (n = 11). No prostatitis was observed in patients, no patient experienced haematospermia. The urethral stricture was a result of thermal injury and also resulted in complete and lasting erectile dysfunction and a deep skin injury (see Sjodin 1997)
				High Effect Prostcare	98	146	1/98 (1.0)	67/98 (68.4)	–	0/98 (0.0)	–	0/98 (0.0)	–	Urinary retention (n = 11) occurred within first 24 hours post treatment. Haematospermia (n = 4), and haematuria were transient. Prostatitis (n = 1); pain limited treatment (n = 62). No cases of epididymitis

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
				High Effect Base Prostcare	31	59	1/31 (3.2)	25/31 (80.7)	–	0/31 (0.0)	–	0/31 (0.0)		Urinary retention (n = 12) occurred within first 24 hours post treatment. Haematospermia (n = 3) and haematuria were transient. Pain limited treatment (n = 18). No patient in this group experienced epididymitis or prostatitis
Sjodin 1997	Case study	–	Sweden Umea University	TUMT	1	1	–	–	–		–	–	–	Third degree burn (n = 1)
Eliasson 1996	Case series	12	Sweden Boden Hospital & Umea University	Prostcare	120	0	–	–	–	0/120 (0.0)	–	–	–	No serious side effects were observed
Eliasson 1995	Case series	12	Sweden Boden Hospital and Umea University	Prostcare	172	133	4/172 (2.3)	106/172 (61.6)	–	0/172 (0.0)	–	–	–	Urine retention (n = 10), bladder spasms (n = 8), haematospermia (n = 2), rectal bleeding (n = 2), epididymitis (n = 1). Most cases of haematuria were resolved in the first 3 days and there were no complications due to this bleeding

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
Eliasson 1998a	Case series	12	Sweden Umea University	Prostcare	32	34	0/32 (0.0)	–	–	–	–	–	–	Urinary retention (n = 28) appears to occur initially after treatment, Incontinence (n = 1), transient haematospermia (n = 5). Varying levels of pain during procedure, majority of patients had haematuria or urethral bleeding, some patients suffered sloughing, and several patients experienced detrusor instability for a few weeks. No stress incontinence. 8 patients with lack of ejaculation had had it before treatment: 3 probably had retrograde ejaculation (sperm cells present in urine). Decrease in erectile function in 6/23 who had normal function before treatment; improvement in 5/9 who had severely reduced or no erection before treatment; reduced ejaculation in 13/23 with normal ejaculation prior to therapy; improvement in 2/9 with reduced or no ejaculation prior to therapy

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
Trachtenberg 1994														
Goldfarb 1995	Case series	12	Canada Toronto Hospital	UroWave®	62	55	0/62 (0.0)	50/62 (80.0)	2/62 (3.2)	–	–	–	–	Gross haematuria was intermittent in nature and stopped in all patients within 6 weeks. No patient required a transfusion, no patient noticed a change in potency, and no hospitalisations were noted, most common complaint was discomfort during procedure, no patient experienced incontinence, and haematuria was transient in nature. Re-catheterisation (n =)
Gravas 2003 ('Study C' in ProstaLund submission to FDA, 2002)	Prospective case series	12	Netherlands Academic Medical Centre November 1999–September 2000	ProstaLund®	41	87	15/41 (36.6)	2/41 (5.0)	7/41 (17.1)	–	–	–	0/41 (0.0)	Vasovagal reaction (n = 2), epididymitis (n = 1), urosepsis (n = 1), bladder spasms (n = 17), dysuria (n = 10), urgency (n = 7), pain (n = 5), frequency (n = 5), urinary retention (n = 3), incontinence (n = 2), penis disorders (n = 2), anus discomfort (n = 1). Main complaints during treatment were urge to void, a burning sensation and perineal discomfort. Lack of ejaculation calculated as change from baseline (n = 7) to 1 year (n = 14)
Hansen 1997	Case-control study	3	Sweden	ProstaLund®	62	–	–	–	–	–	–	–	–	No safety data reported
				TURP	110	–	–	–	–	–	–	–	–	No safety data reported

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Jakubczyk 2002	Case series	6	Poland Warsaw Medical school and Collegium Medicum August 1999–March 2000	Targis®	61	7	4/61 (6.6)	–	–	–	–	1/61 (1.6)	–	Rectal pain (n = 1), epididymitis (n = 1), acute urinary retention associated with the urethral stricture which was treated with urethrotomy
Javle 1996	Case series	12	United Kingdom Royal Liverpool Hospital	Targis®	50	52	8/50 (16.0)	39/50 (78.0)	–	1/50 (2.0)	–	–	–	Acute urinary retention (6%), carcinoma (2%). Haematuria was self-limiting
Kellner 2004	Case series	18	America Beth Israel Hospital April 2000–July 2003	Targis®	39	5	4/39 (10.3)	–	–	–		–	–	Epididymitis (n=1). Treatment failure (n=7)
Krogh 1998	Case series	6	Denmark Herlev Hospital	ProstaLund®	28	9	6/28 (21.4)	–	0/28 (0.0)	0/28 (0.0)	0/28 (0.0)	0/28 (0.0)	–	Urinary retention (n = 3) immediately following treatment. Most of the patients had immediate haematuria which subsided spontaneously, no patient developed incontinence
Kurita 1996	Case series	30	Japan Hamamatsu School of Medicine November 1991–June 1992	Prostcare	43	0	0/43 (0.0)	–	–	–	–	–	–	No urinary retention or major complications, all patients experience urge to urinate and haematuria during treatment

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Lancaster 1997	Case series	12	NR	UroWave®	93	18	–	–	13/93 (14.0)	–	4/93 (4.3)	–	–	Chronic testicular discomfort (n = 1). There were no serious side effects observed, 84% of patients had a TUR like defect in the prostatic fossa. Decreased or lack of ejaculation grouped together (n = 13)
Larson 1995	Case series	1	America Mayo Clinic	Targis®+ Temperature Mapping	15	2	–	–	–	–	–	–	–	Retinal haemorrhage (n = 1), epididymitis (n = 1). Patients typically experienced transient swelling-related difficulty voiding after the procedure
Larson 1996	Case series	–	Multicentre	Targis®	8	0	–	–	–	–	–	–	–	No procedure-related adverse events were noted
Larson 1998b	Case series	–	Multicentre	Targis®	22	0	–	–	–	–	–	–	–	No procedure-related adverse events were noted
Larson 1998a	RCT	6	America Multicentre September 1994–June 1996	Targis®	125	44	8/125 (6.0)	–	5/125 (4.0)	–	–	3/125 (2.4)	1/125 (0.8)	Peri-procedural blood loss (n = 1), epididymitis (n = 3), urinary retention $\geq$ 1 week (n = 10), transient incontinence (n = 5), device adverse event (n = 1), localised tissue abnormalities (n = 6), blood pressure change (n = 2). Haematuria was transient. Death unrelated to treatment
Sall et al 1997	Case report	–	America	Targis®	3	3	2/3	–	–	–	–	3/3	–	Case report of 3 patients with urethral strictures: patients also had transient dysuria and haematuria initially; one went on to receive TUIP

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Lee et al 1995	Case series	12	Singapore	Prostatron®	100	–	7/100 (7.0)	7/100 (7.0)	–	0/100 (0.0)	2/100 (2.0)	–	10/100 (10.0)	Haematuria (gross) did not require further intervention. Deaths were stated as not directly related to TUMT. 28/100 of the patients were in urinary retention at the start of the trial. The remainder were treated for symptoms of bladder obstruction. **Non-retention group:** temporary urinary retention (17/72; 24%); UTI (3/72; 4%); gross haematuria (6/72; 8%); impotence (2/72; 3%) although one patient claimed increased sexual libido; treatment failure (7/72; 9.7%) of whom 5 had TURP, one had repeat TUMT which failed then TURP, 7th had successful repeat TUMT. **Retention group**: UTI (4/28; 14%); gross haematuria (1/28; 3.6%); treatment failure requiring further treatment (6/28; 21%) of whom 4 had a TURP and 2 had indwelling catheter; bulbo-cutaneous fistula (1/28; 3.6%). NB: patient with fistula was in the retention group and had had an indwelling catheter for the previous 6 weeks, which may have been the cause

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Mulvin 1994	Case-control study	3	United Kingdom and Ireland	Prostatron®	20	1	–	–	–	–	–	–	–	Urinary retention (n = 1). No significant urethral injuries, no rectal discomfort or other complication
Miller 2003	Case Series	60	Canada & United Kingdom Multicentre	Targis®	150	7	–	–	7/150 (4.6)	–	–	–	10/150 (6.7)	Post-treatment morbidity was transient and manageable, 14% of patients required a catheter for > 7 days
Ramsey 1998	Case series	36	Canada & United Kingdom Multicentre	Targis®	155	59	17/155 (11.0)	–	7/155 (4.5)	–	–	1/155 (0.7)	–	Hospitalisation (n = 7), epididymitis (n = 4), acute incontinence (n = 3), cerebrovascular accident (n = 1). Re-catheterisation due to urinary retention (n = 19)
Ramsey 1997	Case series	12	Canada & United Kingdom Multicentre	Targis®	154	58	19/154 (13.0)	–	0/154 (0.0)	–	0/154 (0.0)	1/154 (0.7)	1/154 (0.6)	Hospitalisation (n = 7), (due to nausea/dizziness (n = 1); irritative symptoms with urinary retention (n = 3); evaluation of voiding function (n = 4); myocardial infarction (n = 1); cerebrovascular accident (n = 1)). Acute urinary incontinence (n = 3), urinary retention >1 week (n = 17), epididymitis (n = 5), hypertension (n = 3), carcinoma (n = 1). Most urinary retention and UTIs were transient in nature. Death judged unrelated to treatment
Naqvi 2000	Case series	24	Pakistan Dow Medical College September 1995–March 1998	Prostatron® v2.5	200	245	–	80/200 (40.0)	–	2/200 (1.0)	–	–	–	Epididymo-orchitis (n = 3). Dysuria or burning micturition in 80% of patients lasting for 2–4 weeks. Haematuria was transient lasting 1–3 days

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
Norby 2002a	RCT	6	Denmark Kolding Hospital May 1996–November 1999	Prostatron® v2.0/2.5	46	29	14/46 (30.0)	–	–	6/27 (22)	2/22 (9)	0/46 (0.0)	–	Retrograde ejaculation and erectile dysfunction only evaluated in those that completed questionnaire at baseline and 6 months. Bleeding (n = 1), urinary retention (n = 4), headache (n = 1), tinnitus (n = 1), no transfusion was necessary for these patients, no patient suffered from TUR syndrome, no penile oedema were noted, no patients reported incontinence
				ILCP	48	46	27/48 (61.0)	–	–	9/29 (31.0)	4/14 (29)	1/48 (2.1)	–	Retrograde ejaculation and erectile dysfunction only evaluated in those that completed questionnaire at baseline and 6 months urinary retention (n = 4), penile oedema (n=1); no transfusion or bladder evacuation was necessary for these patients, no patient suffered from TUR syndrome, no persistent retention was noted, no patient reported headaches, incontinence or persistent tinnitus

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI n/N (%)	Haematuria n/N (%)	Lack of ejaculation n/N (%)	Retrograde ejaculation n/N (%)	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures n/N (%)	Deaths n/N (%)	Other
				TURP	24	17	3/24 (14.0)	–	–	7/14 (50.0)	1/7 (14)	1/24 (4.2)	–	Retrograde ejaculation and erectile dysfunction only evaluated in those that completed questionnaire at baseline and 6 months. Transfusion (n = 2), TUR syndrome (n = 1) (this patient was one who required transfusion and who also developed stricture); retention (n = 1), stress incontinence (n = 1), no bladder evacuation was necessary for these patients, no persistent retention was noted, there was no reports of penile oedema, headaches or persistent tinnitus
Norby 2002b	RCT	6	Denmark Kolding Hospital May 1996–November 1999	Prostatron® v2.0/2.5	45	2	–	–	–	–	–	–	–	Blood clotting (n = 1), urinary retention (n = 1). Hospitalised after treatment (n = 5)
				ILCP	43	1	–	–	–	–	–	–	–	Removal of a fractured laser tip (n = 1). UTI or retention caused some patients to be hospitalised
				TURP	21	4	–	–	–	–	–	–	–	Transfusion (n = 2), TUR syndrome (n = 1), urethral stricture (n = 1)
Osman 2003	Case series	12	Egypt Mansoura University October 1998–October 2000	Targis®	40	2	–	–	–	–	–	2/40	0/40 (0.0)	Prolonged catheterisation was required in 20% of patients, bladder neck incision carried out on patients with bladder neck contracture (n = 2). All patients completed 1 year follow-up

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Pace 2001	Case series	6	Italy University of Bari April 1998–May 1999	Prostatron®	61	35	13/61 (21.3)	–	–	9/61 (14.8)	–	–	–	Urgency/bladder spasms (n = 9), urge incontinence (n = 1), bowel urge (n = 1), epididymitis (n = 2)
Roehrborn 1998	RCT	6	America & Canada NR	UroWave®	147	163	11/147 (7.5)	20/147 (13.6)	See comments			0/147 (0.0)	–	Sexual dysfunction including haematospermia and ejaculatory problems (n = 44), irritative voiding symptoms mainly dysuria and urgency (n = 32), pain (n = 13), gastrointestinal disturbances (n = 10), prostatic abnormalities (n = 8), urinary retention (n = 8), miscellaneous (n = 17). Pain within the first 3 days of treatment (n = 129), haematuria (n = 55), bladder spasms (n = 32), dysuria & urgency (n = 29), rectal disorders (n = 5), hypertension (n = 2), apnoea (n = 1), syncope (n = 1), nausea (n = 1), haemoptysis (n = 1). No incontinence

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Trachtenberg 1998	RCT	6	America & Canada	UroWave®	147	137	13/147 (8.8)	19/147 (12.9)	See comments			1/147 (0.7)	–	Ejaculatory dysfunction (n = 40), Irritative voiding (n = 30), urinary retention (n = 9), scrotal abscess (n = 6), rectal disorder (n = 8), pelvic pain (n = 5), penile disorder (n = 5), bladder spasm (n = 1). Patients commonly experienced pain, bladder spasms, urethral bleeding and haematuria on day of treatment; no patient experienced a split urinary stream. All other adverse effect were not reported as they were transient or not significant
Schelin 2001	Case series	12	Sweden Kalmar Hospital August 1997–June 1999	ProstaLund®	24	8	7/24 (29.2)	1/24 (4.2)	–	–	–	–	–	Temporary catheter care (n = 1), catheter retained (n = 5)
Schelin 2002	Retro-spective case-control study	3	Sweden Kalmar Hospital	ProstaLund® + Mepivacaine Epinephrine	15	–	–	–	–	–	–	–	–	Asymptomatic tachycardia was observed
				ProstaLund® – Mepivacaine Epinephrine	35	–	–	–	–	–	–	–	–	–

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Study B, ProstaLund submission to	RCT	6	Switzerland, October 1998 – October 2001	ProstaLund®	42	–	–	–	–	–	–	–	0/42 (0.0)	Results are combined with two other studies (Wagrell et al 2002; Gravas et al 2003) and divided into different time periods. Individual results besides mortality could not be specifically determined or allocated to one or the other trials
FDA, PMA P010055 SSED				TURP	20	–	–	–	–	–	–	–	0/20 (0.0)	
Terai 1995	Retro-spective case-control study	6	Japan, Kyoto University September 1992– April 1994	Prostatron® v2.5	40	1	–	–	–	–	–	–	–	Epididymitis (n = 1). Mild transient haematuria occurred in nearly all patients, 21 patients required catheterisation after procedure
Thalmann 2002	Prospect-ive case Series	24	Switzerland University of Berne	Targis®	200	49	47/200 (24.0)	–	–	–	–	–	15/200 (7.5)	Blood pressure elevated (n = 1), epididymitis (n = 1). 171 patients experienced temporary therapy discomfort. Deaths were non-treatment related
Thalmann 1999	Prospect-ive case series	12	Switzerland University of Berne	Targis®	134	32	27/134 (20.0)	0/134 (0.0)	3/134 (2.2)	–	–	–	7/134 (5.2)	Blood pressure elevated (n = 1), Epididymitis (n = 1). 3 patients had severe coagulopathy and 24 were receiving oral anticoagulants. Temporary therapy discomfort experienced by 101 patients. Deaths due to non-treatment related cardiovascular disease, all were treatment failures who required a second HE-TUMT

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Tomera 1998	Case series	–	USA	Prostatron® v2.5	16	0	–	–	–	–	–	–	–	No significant adverse effects, slight nausea but no emesis occurred most likely related to remifentanyl, while some patients reported urge to urinate, bladder spasms were rare
Tomera 2000	Case series	3	USA April 2000–August 2000	Prostatron® v3.5	16	0	–	–	–	–	–	–	–	Subjective discomfort after treatment was subjectively less than previous TUMT treatments, some patients reported post-treatment dysuria. No other complications
Yokoyama 2004	Case control series	12	Japan, Okayama School of Medicine, June 1997–March 2000	Targis® (60min)	27	11	–	–	–	–	–	2/27 (7.4)	–	Urinary retention (n = 5), epididymitis (n = 4)
			Okayama School of Medicine May 2000–March 2003	Targis® (30min)	31	4	–	–	–	–	–	0/31 (0.0)	–	Urinary retention (n = 2), Epididymitis/prostatitis (n = 2)
Wagrell 2002, Wagrell 2003	RCT	12	Scandinavia & United States	ProstaLund®	100	96	18/100 (18)	1/100 (1)	–	–	6/100 (6)	–	0/100 (0.0)	**Non-serious events:** Haematuria (13%), micturition urgency (37%), urinary retention (19%), transient incontinence (3%) **Serious events:** urine retention (n = 1)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
			Multicentre, October 1998–November 1999	TURP	46	50	9/46 (20)	4/46 (8.7)	–	–	5/46 (11)	–	1/46 (2.2)	**Other non-serious events:** Haematuria (39%), micturition urgency (13%), urinary retention (13%), transient incontinence (13%) **Serious events:** TUR syndrome (n = 1), urosepsis (n = 1), clot retention (n = 1)
Wagrell 2004	RCT	36	Scandinavia & United States Multicentre	ProstaLund®	80	19	0/80 (0.0)	1/80 (1.3)	–	–	6/80 (7.5)	–	0/80 (0.0)	**NB: Results for 12–36 month:** other events include: prostate-specific antigen increase (n = 4), urgency (n = 2), urinary retention (n = 2), incontinence (n = 1), urethral disorder (n = 1), haematuria (n = 3). No epididymitis, back pain or myelitis was noted in these patients **Serious events (12–36 months):** bladder calculus (n = 1); prostatic disorder (n = 1); haematuria (n = 1)

Paper	Study design	Time months	Location /patient recruitment	Treatment device	Total patients	Total events	UTI	Haematuria	Lack of ejaculation	Retrograde ejaculation	Erectile dysfunction or impotence	Urethral stricture / bladder neck stenosis or contractures	Deaths	Other
							n/N (%)	n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
			October 1998–November 1999	TURP	39	20	1/39 (2.6)	0/39 (0.0)	–	–	6/39 (15.4)	–	1/46 (2.2)	**NB: Results for 12–36 month:** Urgency (n = 5), incontinence (n = 2), urethral disorder (n = 3), epididymitis (n = 1), back pain (n = 1), myelitis (n = 1), haematuria (n =0). No increases in prostate-specific antigen or urinary retention were noted in these patients. No additional serious events (12–36 months). No additional deaths during the 12–36 month period: the one reported death occurred in the first 12 months (Wagrell et al 2002)
Kobelt 2004	RCT	12	Scandinavia & United States	ProstaLund®	100	4	–	–	–	–	–	–	–	Haematuria, haemorrhage and sepsis (n = 4)
			Multicentre	TURP	46	7	–	–	–	–	–	–	–	Haematuria, haemorrhage and sepsis (n = 7)
Witjes 1997	Case-control study	6	Netherlands January 1992–November 1995	Watchful waiting	121	–	–	–	–	–	–	–	–	No safety data reported
				Terazosin	60	–	–	–	–	–	–	–	–	
				HE-TUMT	136	–	–	–	–	–	–	–	–	
				Laser	83	–	–	–	–	–	–	–	–	
				TURP	87	–	–	–	–	–	–	–	–	

Appendix D Studies included in the review of efficacy: study design and quality assessment

Table 68 Relevant published and unpublished systematic reviews of HE-TUMT identified

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
Hoffman et al 2004	Systematic review of randomised controlled trials Objective: to evaluate the efficacy and safety of TUMT (Prostatron® 2.0, 2.5; ProstaLund®) compared with TURP in men with symptomatic BPH	Any trial published between 1966 to December 2003, International	6 studies (540 patients in total)	Included studies: enrolling men with symptomatic BPH, comparing TUMT (high or low energy) with TURP, randomly assigned patients, ≥ 10 patients, patient follow-up ≥ 6 months, reported urinary symptom and/or flow data. Excluded: studies of hyperthermia, thermo-ablation or thermotherapy using transrectal approaches	I	• Adequate search strategy of appropriate databases • Appropriate inclusion criteria applied by two independent reviewers. Included studies assessed for quality (adequacy of concealing randomised treatment allocation, blinding, and follow-up) • Characteristics and results of individual studies appropriately summarised. Appropriate pooling of results	**Limited applicability** Applicable only for comparison of TUMT to TURP Only included randomised controlled trials: other non-randomised comparative studies not examined Includes studies of low-energy and high-energy TUMT

Table 69 Relevant published and unpublished studies of HE-TUMT identified

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
D'Ancona et al 1997b, 1998	Prospective, open, randomised controlled trial Objective: Compare cooled HE-TUMT (Prostatron® v2.5) and TURP in patients with BPH	1994–1995 Netherlands	52	Men ≥ 45 years old (range 52–89; average 69) with symptomatic BPH > 3 months (Madsen score ≥ 8; peak flow rate 15 mL/s, minimum voided volume 100 mL, post-void residual ≤ 350 mL); prostate length 25–50 mm, volume 30–100 cm^3; candidates for TURP Excluded: prostate cancer, prior prostate surgery, enlarged median lobe, medicated for prostate or bladder	II	Open label (no indication of blinding) Randomisation procedure not stated – not clear that concealment was adequate Objective and subjective outcomes. Not stated that assessors were unaware of the treatment undertaken by patient Patients evaluated at 12 months: HE-TUMT = 27/31 (87%) TURP = 17/21 (81%) Patients evaluated at 30 months: HE-TUMT = 17/31 (55%) TURP = 12/21 (57%)	Included patients applicable to present patient population in research question
De la Rosette et al 2003a Floratos et al 2001a Francisca et al 1999c, 2000	Prospective, open, randomised controlled trial Objective: Durability of cooled HE-TUMT (Prostatron® v2.5) and TURP for patients with LUTS suggestive of bladder outflow obstruction, and effects on sexual function and quality of life	January 1996 – March 1997	155	Patients ≥ 45 years old (range 54–77; average 67) with lower urinary tract symptoms suggestive of bladder outflow obstruction persisting > 3 months (prostate volume ≥ 30 cm^3, prostatic urethra ≥ 25 mm; Madsen score ≥ 8; minimum flow rate ≤ 350 mL) Excluded: Patients with prostatitis, UTI, prostate cancer; isolated middle lobe, previous prostatic surgery	II	Open label (no indication of blinding) Randomisation procedure not stated – not clear that concealment was adequate. Floratos et al 2001a & Francisca et al 1999c appear to be duplicates, although different numbers stated for randomisation. TURP group numbers were the same (73), however it appears more patients were added in Floratos et al 2001a (Francisca et al 1999c = 74; Floratos et al 2001a = 83) Other objective and subjective outcomes (including self-administered questionnaire). Not stated that assessors were unaware of the patients' treatments Number included in analysis: HE-TUMT = 78/82 (95%) TURP = 66/73 (90%) However, number evaluated varied by outcome and follow-up period: eg number evaluated for symptoms (de la Rosette, 2003): 1 year: HE-TUMT = 58/82 (71%) TURP = 48/73 (66%) 3 year: HE-TUMT = 35/82 (43%) TURP = 33/73 (45%)	Included patients applicable to present patient population in research question

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
Norby et al 2002a, 2002b	Prospective, open, randomised controlled trial Objective: To compare efficacy and frequency of complications of ILCP, TURP/TUIP and cooled LE/HE-TUMT (Prostatron® 2.0/2.5) in patients with symptomatic BPH	May 1996 – November 1999 Denmark	118	Patients ≥ 50 years old (average 66); IPSS ≥ 7; QoL ≥ 3; obstructed according to ICS nomogram or Q_{max} < 12 mL/s; PVR ≤ 350 mL or catheterised; prostatic ureter ≥ 25 mm Excluded: suspicion of prostate cancer, previous prostate operation, UTI, medication known to affect voiding	II	Open label (no indication of blinding) Randomisation procedure not stated – not clear that concealment was adequate Other objective & subjective outcomes. Not stated that assessors were unaware of the patient's treatment Study stopped at final date for financial reasons. Recalculation of the power based on number of evaluable patients at 6 months decreased from 90% to 85% Evaluated patients at 6 months: HE-TUMT = 44/46 (96%) TURP/TUIP = 22/24 (92%) ILCP = 44/48 (92%)	Patients received LE-TUMT if prostate volume < 30 mL and HE-TUMT if prostate volume ≥ 30 mL In the TURP/TUIP group, patients underwent TURP or TUIP according to surgeon's decision
'Study B'[c]	Prospective, open, randomised controlled trial Objective: To compare the efficacy and safety of non-cooled HE-TUMT (ProstaLund®) with TURP in patients with clinical BPH	October 1998 – October 2001 1 centre in Switzerland	62	Patients ≥ 45 years old (average 68) with symptomatic BPH, IPSS ≥ 13, prostate volume 30–100 mL, Q_{max} < 13 mL/s on a voided volume > 125 mL Excluded: previous surgical treatment for prostate; presence of median lobe; prostatitis or prostate cancer; UTI; concomitant medication for prostate within 6 weeks	II	Open label (no indication of blinding) The treatment allocation was double-blind & sealed randomisation envelopes were used 12-month follow-up: 1 patient withdrawn after randomisation but before treatment, group not specified. 6 withdrew before 12 months (3 in each group). LOCF used in analyses: HE-TUMT = 42/42 (100%) TURP = 19/19 (100%)	Included patients applicable to present patient population in research question
Wagrell et al 2002, 2003, 2004, Kobelt et al 2004	Prospective, open, randomised controlled trial Objective: To compare the efficacy and safety of non-cooled HE-TUMT (ProstaLund®) with TURP in patients with clinical BPH	October 1998 – October 2001 Switzerland and USA	154	Patients ≥ 45 years old (average 68) with symptomatic BPH, IPSS ≥ 13, prostate volume 30–100 mL, Q_{max} < 13 mL/s on a voided volume > 125 mL Excluded: previous surgical treatment for prostate; presence of median lobe; prostatitis or prostate cancer; UTI; concomitant medication for prostate within 6 weeks	II	Open label (no indication of blinding) The treatment allocation was double-blind & sealed randomisation envelopes were used Objective & subjective outcomes. Not stated that assessors were unaware of treatments Patients evaluated at 1 year for IPSS/QoL analysis: HE-TUMT = 93/103 (90%) TURP = 43/51 (84%) Patients evaluated at 3 years for IPSS/QoL analysis: HE-TUMT = 68/103 (66%) TURP = 35/51 (69%)	Included patients applicable to present patient population in research question

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
Ahmed et al 1997	Prospective, open, randomised controlled trial Objective: Compare cooled HE-TUMT (Prostatron® v2.5) with TURP for treatment of symptomatic, uncomplicated, obstructive BPH	Not stated UK	60	Patients ≥ 55 years old (range 56–88; average 69) with moderate to severe symptomatic uncomplicated BPH (AUA score > 12; Flow rate <15mL/s; PVR < 300mL; Pdet max > 70 cmH_2O; prostate volume 25–100 mL), unequivocally obstructed as assessed from the Abrams-Griffith nomogram Exclude: Generally or technically unsuitable (including previous prostatic surgery); prominent middle lobe; previous drug treatment for BPH; complicated BPH (including obstructive uropathy and acute or chronic urinary retention)	III–1	Open label (no indication of blinding) Objective and subjective outcomes. Not stated that assessors were unaware of the treatment undertaken by patient Randomisation through patients selecting sealed envelope – not clearly indicated that concealment was adequate. However, patients failing to complete treatment or follow-up were substituted 12 month follow-up: as stated, discontinuers were substituted, therefore 100% follow-up	Includes symptomatic patients with moderate-to-severe symptoms
Djavan et al 1999e, 2001	Prospective, open, pseudo-randomised controlled trial Objective: To compare the efficacy and safety of cooled HE-TUMT (Targis®) with alpha-blocker treatment (terazosin) for BPH	Austria	103	Patients 45–85 years old (average 65) with moderate to severe BPH (IPSS ≥ 9); peak flow rate < 12 mL/s with voided volume ≥ 150 mL; prostatic urethra 30–50 mm in length Excluded: alpha-blocker treatment in last 3 months; previous medication or surgery for prostate; PVR > 250 mL; acute urinary retention; prostatitis or prostate cancer; prostate volume > 100 cm^3	III–1	Open label (no indication of blinding) Randomisation procedure alternated the group assignments of consecutive patients one-by-one 6 month follow-up: IPSS/QoL/flow: HE-TUMT = 50/51 (98%) Terazosin = 43/52 (83%) However, treatment failures were followed up to determine what further treatment they received Patients evaluated at 18 months: IPSS/QoL/flow: HE-TUMT = 47/51 (92%) Terazosin = 29/52 (56%) However, treatment failures were followed up to determine what further treatment they received	Included patients applicable to present patient population in research question

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
Arai et al 2000	Prospective controlled before-and-after study Objective: Impact of cooled HE-TUMT (Dornier UroWave®), TURP, ILCP & TUNA on QoL & sexual function	1995–1997 Japan	204	Men aged 52–84 years (mean age varied from 66–70 across treatment arms) with symptomatic BPH Exclude prostate cancer. If alpha-blockers not stopped 2 weeks before treatment	III–2	Selection bias: Selection was primarily on patients views of the benefits including symptom improvements versus risks Some differences in baseline variables (prostate volume larger in ILCP/TUNA than TURP/HE-TUMT; post void residual volume greater in TURP than HE-TUMT; erectile function score higher in HE-TUMT than TURP suggesting sexually active patients selected HE-TUMT over TURP). No apparent adjustment Mostly subjective outcomes (QoL, questionnaires, symptoms scores). Not stated that assessors were unaware of the treatment undertaken by patient Patients evaluated at 3 months: 84.8% overall TURP = 55/65 (84.6%) HE-TUMT = 34/40 (85%) ILCP = 42/48 (87.5%) TUNA = 42/51 (82.4%)	Applicable to research question population
Hansen et al 1997	Prospective controlled before-and-after study Objective: To evaluate the performance of a simple home flow test in the examination and follow-up of patients treated with TURP or non-cooled HE-TUMT (ProstaLund®) for LUTS suggestive of bladder outlet obstruction	Sweden	172	Patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (age not reported)	III–2	Selection bias: Decisions to perform HE-TUMT or TURP based on diagnostic work-up: digital rectal examine, PSA, creatinine, symptom evaluation, uroflowmetry, and cystoscopy. Residual urine and urine culture Subjective outcome for symptom improvement. Objective outcomes also measured but poorly reported Patient characteristics poorly reported 3 months follow-up: not reported	Limited applicability as baseline patient characteristics not reported

Study author/s & year	Study design	Setting (year, site)	N	Study population	NHMRC level	Study quality	Applicability
Witjes et al 1997	Prospective controlled before-and-after study Objective: Symptomatic and urodynamics effects of watchful waiting, alpha-blocker (terazosin), laser therapy, cooled HE-TUMT (Prostatron® v2.5) or TURP in patients with lower urinary tract symptoms and various degrees of bladder outlet obstruction	January 1992 – November 1995 Netherlands	487 (668 initially)	Patients with lower urinary tract symptoms and various degrees of bladder outlet obstruction (mean age varied with treatment and degree of severity from 60–70 years of age) Excluded: patients previously treated with laser resection of prostate, 5 alpha-reductase inhibitors, alpha blockers in the previous 4 weeks, or TUMT; prostate cancer	III–2	Selection bias: Therapy was recommended based on severity of symptoms and grade of bladder outlet obstruction or patient preference Consecutive patients on watchful waiting, laser therapy, HE-TUMT or terazosin from the Nijmegen clinic were followed. Patients treated with TURP were from a different hospital. 27% of patients dropped out before the second investigation at 6 months. Follow-up: Watchful waiting = 121/178 (68%) terazosin = 60/97 (62%) laser therapy = 83/114 (73%) HE-TUMT = 136/180 (76% TURP = 87/99 (88%) difficult to determine, numbers of patients in each group indicated, however, footnotes on IPSS outcome indicates not all patients evaluated at endpoint	Groups divided into mild, moderate and severe bladder outlet obstruction

Appendix E Criteria used for assessing the quality of the evidence

The following criteria may be employed in assessing the quality of the evidence (other criteria may also be used) for studies included in the review:

Systematic reviews and meta-analyses

- Was an adequate search strategy used?
- Did it include appropriate search terms and databases?
- Could the search terms and/or choice of databases have been improved upon?
- Were the inclusion criteria appropriate and applied in an unbiased way?
- Were pre-specified inclusion criteria applied independently by two people?
- Were the studies assessed for quality (relating to the minimisation of biases)?
- Were appropriate quality issues assessed independently by two people?
- Were the characteristics and results of individual studies appropriately summarised?
  - Were summary descriptive tables of subjects, intervention, outcomes etc provided and estimates of treatment effect displayed? How adequate were they (ie, did they contain sufficient information)?
- Were the methods used for pooling the data appropriate?
- Were sources of heterogeneity explored?

Randomised controlled trials

- Blinding
  - Were the trials double–blind, single blind or not blinded?
  - Was an objective outcome used?
- Concealment of treatment allocation
  - Was the treatment adequately concealed?
- Were all randomised participants included in the analysis?

Case-series

- Was subject selection representative of eligible patients or was a group selected? If there was a selected group, is the basis for their selection explained?
- Were outcome measures blind to pre/post intervention? If not, was an objective outcome measure used?
- What percentage of subjects was followed up?

Quasi-experimental and 'cohort' studies

- Subject selection
  - Was the 'new technology' group representative of eligible patients?
  - Was the comparison group representative of eligible patients?
  - If either group was selected, is the basis for their selection explained?
- Comparability of groups
  - Were the new technology group and the comparison group comparable on demographic characteristics and clinical features?
  - If not, was adjusted analysis used or were the results adjusted for differences?
- Measurement of outcomes
  - Were outcome measures blind to the technology used? If not, were objective outcome measures used?
- Was the same method of measurement used across comparison groups?
- Completeness of follow-up
  - What percentage of subjects was followed up?

Case-control studies

- Were the cases a representative sample of all eligible cases or a selected group (eg, volunteers)?
  - Was the case definition adequate?
  - Was there an independent validation of outcomes (blind to exposure status); or were outcomes taken from medical records; or self-reported without independent validation?
  - Were the controls from the same population as the cases and were the same exclusion criteria used, or were a selected group used (eg, hospital controls)?
  - Were the controls free of outcome and, if so, was there independent validation or was validation based on medical records or self-reported?
- Were the groups comparable on demographic characteristics and important potential confounders?
  - If not, were the results adjusted for differences?
- In ascertaining whether subjects have been exposed to the technology under investigation, were they blinded to case-control studies?
- Were all selected subjects included in the analysis?
  - If not, what percentage of subjects in both cases and controls was followed up?

Appendix F Literature search strategies

Medline search strategy

The search strategy used to identify relevant studies of HE-TUMT for the treatment of LUTS in BPH patients in Medline is presented in **Table 70.**

Table 70 HE-TUMT Medline strategy

Search term		Results
1	microwaves/	6762
2	microwave$1.ti,ab.	7659
3	or/1–2	9154
4	3 and exp diathermy/	456
5	3 and exp hyperthermia, induced/	1348
6	or/4–5	1348
7	(microwave adj (thermotherapy or diathermy)).ti,ab.	321
8	(microwave adj (treatment or therapy)).ti,ab.	302
9	or/7–8	602
10	9 and (high?energy or energy or heat$).ti,ab.	213
11	9 and trans?urethral.ti,ab.	284
12	or/10–11	366
13	(tumt or he?tumt or plft).ti,ab.	184
14	(prostatron or prostasoft or prostalund).ti,ab.	82
15	(targis or core?therm).ti,ab.	90
16	or/6,12–15	1530
17	prostatic hyperplasia/	12323
18	exp urination disorders/	30645
19	exp urological manifestations/	4277
20	bladder neck obstruction/	2508
21	(bph or luts or boo).ti,ab.	4555
22	(prostat$2 adj3 (hyperplasia or hypertroph$2 or enlarge$)).ti,ab.	9072
23	(prostatism or prostatic adenoma or adenofibromyomatosis).ti,ab.	991
24	(lower urinary tract symptom$1).ti,ab.	1225
25	(bladder adj3 (obstruction or strangulation or stenosis)).ti,ab.	2051
26	(obstructio vesicae urinariae).ti,ab.	0
27	exp rectal fistula/	2860
28	((vesicorectal or urethrorectal or prostatorectal) adj fistula$1).ti,ab.	100
29	(fistula recti or rectal fistula).ti,ab.	117
30	or/17–29	49103
31	16 and 30	407

EMBASE search strategy

The search strategy used to identify relevant studies of HE-TUMT for the treatment of LUTS in BPH patients in EMBASE is presented in **Table 71.**

Table 71 HE-TUMT EMBASE strategy

Search term		Results
1	transurethral microwave thermotherapy/	184
2	exp hyperthermic therapy/	4214
3	microwave therapy/	89
4	diathermy/	1458
5	microwave radiation/	4415
6	microwave$1.ti,ab.	7811
7	or/3–6	9940
8	2 and 7	576
9	or/1,8	641
10	(microwave adj (thermotherapy or diathermy)).ti,ab.	280
11	(microwave adj (treatment or therapy)).ti,ab.	223
12	or/10–11	485
13	12 and (high?energy or energy or heat$).ti,ab.	201
14	12 and trans?urethral.ti,ab.	251
15	or/13–14	336
16	(tumt or he?tumt or plft).ti,ab.	161
17	(prostatron or prostasoft or prostalund).ti,ab.	65
18	(targis or core?therm).ti,ab.	26
19	or/9,15–18	772
20	prostate hypertrophy/	10112
21	exp micturition disorder/	28977
22	bladder obstruction/	651
23	(bph or luts or boo).ti,ab.	4212
24	(prostat$2 adj3 (hyperplasia or hypertroph$2 or enlarge$)).ti,ab.	8070
25	(prostatism or prostatic adenoma or adenofibromyomatosis).ti,ab.	552
26	(lower urinary tract symptom$1).ti,ab.	1255
27	(bladder adj3 (obstuction or strangulation or stenosis)).ti,ab.	57
28	(obstructio vesicae urinariae).ti,ab.	0
29	rectum fistula/	402
30	rectovesical fistula/	27
31	rectourethral fistula/	49
32	prostate rectum fistula/	10
33	(fistula recti or rectal fistula).ti,ab.	59
34	((vesicorectal or urethrorectal or prostatorectal) adj fistula$1).ti,ab.	59
35	or/20–34	41014
36	19 and 35	362

Cochrane Library search strategy

The search strategy used to identify relevant studies of HE-TUMT for the treatment of LUTS in BPH patients in the Cochrane Library is presented in **Table 72.**

Table 72 HE-TUMT Cochrane strategy

	Search term	Results
1	exp microwaves [Mesh Term]	108
2	microwave*	254
3	or/1–2	254
4	exp diathermy [Mesh Term]	332
5	exp hyperthermia, induced [Mesh Term]	590
6	or/4–5	590
7	3 and 6	74
8	microwave near (thermotherapy, diathermy)	69
9	Microwave near (treatment, therapy)	131
10	or/8–9	161
11	high*energy or energy or heat*	10584
12	trans*urethral	1059
13	or/11–12	11589
14	10 and 13	91
15	tumt or he*tumt or plft	41
16	prostatron or prostasoft or prostalund	14
17	targis or core*therm	5
18	or/7,14–17	119

Manual search strategy

A manual search of the bibliographies of the papers identified by the searches of the above databases identified a further two publications relevant to the application.

Appendix G FDA public health notification

FDA public health notification: Serious injuries from microwave thermotherapy for benign prostatic hyperplasia

(Available at http://www.fda.gov/cdrh/safety/bph.html)

October 11, 2000

Dear Colleague:

This is to notify you of the potential for serious thermal injury and related complications associated with the use of microwave energy to treat benign prostatic hyperplasia (BPH), and to provide information that can help avoid these complications. Although the use of microwave thermotherapy for the treatment of BPH has been demonstrated to be safe and effective, and more than 25,000 procedures have been performed, we are concerned about some unexpected procedure-related complications that have occurred since the marketing of these devices.

Currently marketed devices include the Prostatron® (Edap Technomed, Inc.) and the Targis System® (Urologix, Inc). Dornier Medical Systems, Inc. has received approval to market their UroWave® System but is not yet marketing it. We are working with the manufacturers to ensure that labelling and training programs address these complications.

Nature of the problem

Since 1996, we have received reports of 16 thermal injuries related to microwave thermotherapy systems. Of these, 10 resulted in fistula formation and 6 resulted in clinically significant tissue damage to the penis or urethra. These injuries may not be apparent at the time of treatment, and may take hours or days to develop. (Note that the original labelling for these devices did not list fistula formation as a procedure-related complication.) The reported injuries have required colostomies, partial amputation of the penis, and/or other therapeutic interventions.

We have identified several factors that may have contributed to the injuries noted:

- Incorrect placement or undetected migration of either the treatment catheter or the rectal temperature sensors;
- Failure of the physician to remain with the patient throughout the entire treatment duration;
- Failure to pause treatment when the patient is communicating serious pain;
- Over-sedation of the patient, which compromises his ability to communicate pain;
- Treatment of patients who have undergone prior radiation therapy to the pelvic area;
- Treatment of patients whose prostate sizes are outside the ranges specified in the labelling; and

- Leakage from the balloons used to retain either the urethral catheter or the rectal temperature sensor in the correct anatomical position;

Recommendations

When considering a patient for microwave thermotherapy for BPH, ensure that he meets the device's indications, including the criteria for eligible prostate size indicated for the specific system being used. Additionally, it is important to verify that the patient has not had prior radiation therapy to the pelvic area, as these patients are at increased risk of rectal fistula formation. Furthermore, the labelling of each device lists specific patient populations for which safety and effectiveness of this therapy are unknown (eg, those with prostate cancer).

When discussing the procedure with the patient, it is important to ensure that he understands the risks and benefits listed in the labelling of the specific device. He should also understand the duration of the procedure, the level of pain or discomfort that should be considered normal, the importance of telling the physician of any unusual pain during treatment, how to operate any emergency stop button, and the need to remain as still as possible during treatment.

Carefully follow the instructions for use provided with these microwave systems. Note that they require the physician to continually supervise the procedure throughout the entire treatment period. The physician must (1) verify that the retention balloons of the urethral catheter and rectal temperature sensor probe are free of leaks, and (2) confirm the placement of the urethral catheter and rectal temperature sensor using acceptable methods (eg, direct visualization, ultrasound imaging) both prior to treatment and other specified times consistent with the manufacturer's recommendations. Either patient movement or component breakage may cause migration of a properly placed urethral catheter or rectal temperature sensor.

Be careful not to over-sedate the patient. As patient perception of pain is an important safety mechanism to ensure that the heating of the tissue is not excessive, general or spinal anaesthesia should not be used.

Closely monitor the patient and the equipment throughout the entire treatment, and manually pause treatment if the patient complains of excessive pain or anything unusual occurs.

Background

Microwave thermotherapy systems are intended to heat the prostate, resulting in the necrosis of periurethral prostatic tissue, to provide relief of urinary symptoms in patients with obstructive BPH. These devices heat the prostate to therapeutic levels using microwave energy delivered by an antenna contained within a specially designed urethral catheter. The catheter is designed so that when the balloon is seated at the neck of the bladder, the active portion of the antenna is positioned within the prostate. To prevent overheating, the systems circulate cooling fluid through the urethral catheter to protect the urethral tissue from excessive heat and automatically vary microwave energy output during treatment based on information supplied by temperature sensors placed posterior to the prostate within the rectum. Treatment may last from 30 to 60 minutes.

Because the catheter and/or the rectal temperature sensors can migrate during treatment, and because the correct placement of both of these components is critical for safe and

effective treatment, the labelling for all these devices instructs the treating physician to: (1) verify that the urethral catheter (and rectal temperature sensor probe, if applicable) has a working retention balloon prior to placement, and (2) verify the proper position of both the urethral catheter and the rectal temperature sensors prior to and at specified time intervals consistent with the manufacturer's recommendation for treatment. These requirements are intended to help ensure that catheter or rectal temperature sensor migration does not occur in a manner which would cause undetected excessive heating of surrounding tissues or the delivery of therapeutic heating levels to areas of the body that are not intended to receive treatment. The labelling for microwave thermotherapy devices also instructs the treating physician to monitor the equipment and patient during treatment, and manually reduce or pause the microwave power if the patient experiences excessive pain or extreme heating is observed.

Reporting adverse events to FDA

The Safe Medical Devices Act of 1990 (SMDA) requires hospitals and other user facilities to report deaths and serious injuries associated with the use of medical devices. FDA is interested in additional data on adverse events involving the use of microwave thermotherapy systems. When submitting a report, please identify the treatment protocol and catheter type, if known. Healthcare providers that are employed by facilities that are subject to FDA's user facility reporting requirements should follow the reporting procedures established by their facilities. All other providers may submit their reports to MedWatch, FDA's voluntary reporting program. The reports can be submitted by phone at 1-800-FDA-1088; by fax at 1-800-FDA-0178; by mail to MedWatch, Food and Drug Administration, HF-2, 5600 Fishers Lane, Rockville, Maryland 20857, or online at www.accessdata.fda.gov/scripts/medwatch.

Getting more information

If you have questions regarding this letter, please contact the Issues Management Staff, Office of Surveillance and Biometrics (HFZ-510), 1350 Piccard Drive, Rockville, Maryland, 20850, by fax at 301-594-2968, or by e-mail at phann@cdrh.fda.gov. Additionally, a voice mail message may be left at 301-594-0650 and your call will be returned as soon as possible.

All of the FDA medical device postmarket safety notifications can be found on the World Wide Web at http://www.fda.gov/cdrh/safety.html. Postmarket Safety notifications can also be obtained through e-mail on the day they are released by subscribing to our list server. Subscribe at: http://list.nih.gov/cgi-bin/wa?SUBED1=dev–alert&A=1

Sincerely yours,

David W Feigal Jr, MD, MPH
Director
Centre for Devices and Radiological Health
Food and Drug Administration

Appendix H Imputation of data and meta-analysis of HE-TUMT results

Introduction

This summary describes the methods used in analysing summary clinical trials results comparing HE-TUMT to TURP and medication in benign prostatic hyperplasia (BPH). These results are used in the economics.

For each comparator, only long-term studies of the highest level of evidence reporting suitable outcomes (treatment failure rates, IPSS index and adverse events) were used. For HE-TUMT versus TURP, two trials satisfied these criteria, both of which were level II studies with three years follow-up (d'Ancona et al 1998; de la Rosette et al 2003a). For HE-TUMT versus medication, only one study was suitable: an 18-month level III-1 study by Djavan et al (1999e, 2001).

The analyses were carried out in two stages. In the first, summary data for time points other than those reported were imputed for two studies, and the resulting summary data were meta-analysed in the second stage.

Methods

Imputation of data

The first stage of analyses consisted of imputing means, standard deviations and sample sizes for continuous (IPSS and Q_{max}) and number of positive events for a binary (treatment failure rate) outcome. This was necessary as the analyses required results for 12, 24 and 36 months, and two of the three studies reported results for other time points. In general, interpolation (and extrapolation) using curves fitted through existing results were used, and this process was carried out separately for each arm of the two studies. In very few cases quadratic interpolation was required, as in general linear interpolation was sufficient. Imputation of the sample size was required because of evidence of patient dropout over time. The statistical package STATA (v 8.2, Statacorp, 2003) was used to calculate the necessary interpolation polynomials.

Meta-analyses

The meta-analyses were conducted using Bayesian methods (Smith et al 1995). This was because (1) data from only three studies were available, (2) these included summary data from multiple time points, and (3) there were more than two treatments involved. Classical meta-analysis (Hedges and Olkin, 1985; DerSimonian and Laird, 1986; Hardy and Thompson, 1996) assumes a single pair of results (from two treatment arms) for each study. It also assumes that the between-studies-variance is known and with three studies this is rare.

For the treatment failure rates, the following set hierarchical models were used. At the lowest level (arm-specific results), a logit was used:

$$logit(\pi_{ijt}) = a_i + \beta_j \times I(treatment = j) + \delta_t \times I(time = t) + \beta\delta_{jt} \times I(treatment = j \text{ and } time = t),$$

where *i* is the study number, *j* indexes the treatment type and *t* indexes the time point. Therefore $i = 1, 2, 3$; $j = 1$ (HE/TUMT), 2 (TURP), 3 (terazosin); $t = 12, 24, 36$ (months). The parameters *a*, β, δ and $\beta\delta$ (indices omitted) measure study, treatment, time and treatment-by-time interaction effects, respectively. The indicator function I(.), which takes the value 1 if the expression in brackets is true and 0 otherwise, merely formalises the fact that only a few parameters are present in the model for each specific arm.

Interaction terms account for differences in treatment failure rates between treatment types at each time–point. In order to avoid aliasing within parameters sets (excluding *a*'s), the convention of *regression coding*, where the effect corresponding to the first level of any factor (parameter set) is set to 0. The study effects, a_i, $i == 1, 2, 3$, were modeled as normally distributed random effects from a common distribution, so that $a_i \sim N(\alpha, \tau^2)$, where α and τ^2 are unknown parameters; τ^2 is called the *between-studies-variance* (or BSV). The remaining parameters in the logit model were assumed to represent fixed effects. The model is therefore a so-called *random-intercept* model.

In accordance with Bayesian principles (eg, Carlin and Louis 2000), prior distributions are required for α, β_j, δ_t, $\beta\delta_{jt}$, and τ^2. As is standard and conservative practice when little is known about parameter values *a-priori*, vague (*uninformative*) priors were allocated to all. Except for the BSV, the parameters were assumed to be normally distributed. In practice, uninformative normal distributions are specified to having large variances, so that the probability density function is (almost) flat around the prior mean, and thus resemble a uniform distribution. In this case, these parameters were assigned a mean of 0 and variance of one million, or a $N(0, 1{,}000^2)$ prior distribution.

The BSV parameter was assumed to have an inverse gamma distribution, or more precisely, its inverse, the so-called *precision*, was assumed to have a gamma distribution. Specifically, the distribution was $1/\tau^2 \sim$ gamma (0.001, 0.001), a distribution which is quite flat everywhere except for a spike close to 0, or when the BSV is very large which is unlikely to occur with measured data.

Meta-analyses were conducted using WinBUGS (v 1.3, Spiegelhalter et al 2000), a freely available Bayesian analysis package (website: http://www.mrc–bsu.cam.ac.uk/bugs). In general, a burn-in sequence of 1000 iterations preceded a sequence of 10,000 iterations, which was used to estimate results.

An analogous model as described above was used for the meta-analysis of means. A summary of the hierarchical linear models used to analyse these data is as follows.

Lowest level (0):

$m_{ijt} \sim N(\mu_{ijt}, \sigma_{ijt}^2)$,

where $\mu_{ijt} = a_i + \beta_j \times I(\textit{treatment} = j) + \delta_t \times I(\textit{time} = t) + \beta\delta_{jt} \times I(\textit{treatment} = j \text{ and } \textit{time} = t)$.

Level 1:

$a_i \sim N(\alpha, \tau^2)$, $i = 1, 2, 3$.

Level 2:

$\alpha \sim N(0, 1{,}000^2)$;

$\beta_j \sim N(0, 1{,}000^2)$, $j = 1, 2$;

$\delta_t \sim N(0, 1{,}000^2)$, $t = 12, 24, 36$;

$\delta\beta_{jt} \sim N(0, 1{,}000^2)$, $j = 1, 2$, $t = 12, 24, 36$;

$1/\tau^2 \sim \text{gamma}(0.001, 0.001)$.

In keeping with classical meta-analysis, the arm-specific sample standard error of the mean replaced σijt2 in the Level 0 model. A more general approach would involve accounting for the uncertainty in these estimates by defining a prior distribution for the standard error of each treatment type, say an inverse gamma distribution, and estimating the shape parameter of each.

Results: Imputate data

Table 73 Derived treatment failure rates for HE-TUMT versus TURP

Trial/ publication	Treatment arm	Age mean ± SD	N	Cumulative treatment failure rate n/N (%)			
				Baseline	12 months	24 months	36 months
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	0/31 (0)	2/31 (6.4)	6/31 (19.4)	10/31 (30.3)
	TURP	69.6 ± 8.5	21	0/21 (0)	1/21 (4.8)	1/21 (4.8)	1/21 (4.8)

Table 74 Derived IPSS for HE-TUMT versus TURP

Trial/ publication	Treatment arm	Age mean ± SD	N	Mean ± SD (n)			
				Baseline	12 months	24 months	36 months
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	18.3 ± 6.3 (31)	5.0 ± 2.7 (27)	6.9 ± 5.4 (20)	8.9 ± 7.1 (14)
	TURP	69.6 ± 8.5	21	16.7 ± 5.6 (21)	3.4 ± 2.2 (17)	5.3 ± 4.1 (14)	7.3 ± 5.4 (10)

Table 75 Q_{max} for HE-TUMT versus TURP

Trial/ publication	Treatment arm	Age mean ± SD	N	Mean ± SD (n)			
				Baseline	12 months	24 months	36 months
D'Ancona et al 1998	**HE-TUMT**	69.3 ± 5.9	31	9.3 ± 3.9 (31)	17.1 ± 7.8 (27)	16.2 ± 9.3 (20.2)	13.3 ± 9.3 (14.5)
	TURP	69.6 ± 8.5	21	9.3 ± 3.4 (21)	19.3 ± 10.7 (17)	19.2 ± 9.8 (13.8)	19.0 ± 7.1 (9.8)

Table 76 Treatment failure rates for HE-TUMT versus terazosin

Trial/ publication	Treatment arm	Age mean ± SD	N	Cumulative treatment failure rate n/N (%)			
				Baseline	12 months	24 months	36 months
Djavan et al 1999e, 2001	**HE-TUMT**	69.3 ± 5.9	66.2 (8.0)	51	0/51 (0)	2/51 (3.9)	4.5/51 (8.8)
	TURP	69.6 ± 8.5	64.0 (11.4)	52	0/51 (0)	16/52 (30.8)	24.0/52 (46.2)

Table 77 IPSS for HE-TUMT versus terazosin

Trial/ publication	Treatment arm	Age mean ± SD	N	Mean ± SD (n)			
				Baseline	12 months	24 months	36 months
Djavan et al 1999e, 2001	**HE-TUMT**	66.2 (8.0)	51	19.4 ± 3.3 (51)	7.1 ± 2.4 (48.5)	7.7 ± 2.1 (45.5)	8.3 ± 1.8 (42.5)
	Terazosin	64.0 (11.4)	52	18.9 ± 3.5 (52)	11.2 ± 2.7 (36.0)	11.5 ± 2.5 (22.0)	11.8 ± 0.4 (8.0)

Table 78 Q_{max} for HE-TUMT versus terazosin

Trial/ publication	Treatment arm	Age mean ± SD	N	Mean ± SD (n)			
				Baseline	12 months	24 months	36 months
D'Ancona et al 1998	**HE-TUMT**	66.2 (8.0)	51	8.3 ± 1.6 (51)	13.9 ± 2.5 (48.4)	13.8 ± 2.0 (45.7)	13.7 ± 1.4 (43.0)
	Terazosin	64.0 (11.4)	52	8.9 ± 1.7 (52)	11.5 ± 1.3 (36.3)	11.2 ± 0.9 (21.1)	10.9 ± 0.5 (6.0)

Results: Meta-analysis results

Table 79 Meta-analysis results: non-cumulative treatment failure rates

	Treatment failure rate + SE (95% CI)		
	HE-TUMT	**TURP**	**Terazosin**
Baseline	0	0	0
12 months	9.1 ± 6.3 (3.2, 19.9)	8.0 ± 6.1 (2.6, 17.5)	39.5 ± 11.9 (20.7, 68.9)
24 months	6.5 ± 5.9 (1.9, 15.6)	1.2 ± 3.5 (0.0, 4.4)	29.8 ± 12.9 (10.7, 61.4)
36 months	7.6 ± 6.2 (2.2, 18.1)	0.001257 ± 0.0512 (0.0, 0.1016)	22.9 ± 15.5 (2.7, 61.0)

Table 80 Meta-analysis results: IPSS

	Mean + SE (95% CI)		
	HE-TUMT	**TURP**	**Terazosin**
Baseline	19.4 ± 0.7 (18.3, 20.5)	19.0 ± 0.9 (17.4, 20.5)	18.9 ± 0.8 (17.5, 20.2)
12 months	6.7 ± 0.7 (5.7, 7.7)	3.2 ± 0.7 (2.1, 4.3)	11.2 ± 0.8 (9.9, 12.5)
24 months	7.8 ± 0.7 (6.6, 8.9)	4.2 ± 0.9 (2.6, 5.7)	11.5 ± 0.8 (10.1, 12.9)
36 months	8.5 ± 0.7 (7.4, 9.6)	2.6 ± 0.7 (1.3, 3.6)	11.8 ± 0.7 (10.7, 12.8)

Table 81 Meta-analysis results: Q_{max}

	Mean + SE (95% CI)		
	HE-TUMT	**TURP**	**Terazosin**
Baseline	8.9 ± 1.3 (7.4, 10.6)	8.0 ± 1.3 (6.3, 9.6)	9.5 ± 1.3 (8.1, 11.3)
12 months	15.0 ± 1.3 (13.4, 16.8)	22.4 ± 1.8 (19.4, 25.4)	12.3 ± 1.3 (10.8, 14.1)
24 months	13.6 ± 1.3 (12.1, 15.3)	19.4 ± 2.0 (16.0, 22.7)	11.3 ± 1.3 (9.9, 13.1)
36 months	11.0 ± 1.3 (9.5, 12.7)	20.7 ± 2.0 (17.3, 24.0)	9.7 ± 1.3 (8.3, 11.5)

Appendix I International Prostate Symptom Score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?							
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?							
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?							
Urgency Over the last month, how difficult have you found it to postpone urination?							
Weak stream Over the past month, how often have you had a weak urinary stream?							
Straining Over the past month, how often have you had to push or strain to begin urination?							
	None	**1 time**	**2 times**	**3 times**	**4 times**	**5 times or more**	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?							
Total IPSS score							

Quality of life due to urinary symptoms	**Delighted**	**Pleased**	**Mostly satisfied**	**About equally satisfied and dissatisfied**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?							

Total score: 0–7 Mildly symptomatic; 8–19 moderately symptomatic; 20–35 severely symptomatic

Abbreviations

AIHW	Australian Institute of Health and Welfare
ANZAUS	Australian and New Zealand Association of Urological Surgeons
AR-DRG	Australian Refined Diagnosis Related Group
AUA	American Urological Association
BOO	bladder outflow obstruction
BPH	benign prostatic hyperplasia
CC	comorbidities and complications
CI	confidence interval
DRG	diagnosis related group
FDA	Food and Drug Administration (USA)
HE-TUMT	high-energy transurethral microwave thermotherapy
HIC	Health Insurance Commission (now *Medicare Australia*)
HUI	health utility index
ILCP	interstitial laser coagulation of the prostate
IPSS	International Prostate Symptom Score
ITT	intention to treat
LE-TUMT	low-energy transurethral microwave thermotherapy
LPURR	linearised passive urethral resistance relations
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NR	not reported
PBS	Pharmaceutical Benefits Scheme
Pdet max	voiding pressure at maximum flow
PVR	post-void residual volume
Q_{max}	maximum urinary flow rate
QoL	quality of life
RPBS	Repatriation Pharmaceutical Benefits Scheme
SE	standard error
TUIP	transurethral incision of the prostate
TUMT	transurethral microwave thermotherapy
TUNA	transurethral needle ablation
TURP	transurethral resection of the prostate
UTI	urinary tract infection

References

Ackerman SJ, Rein AL, Blute M, Beusterien K, Sullivan EM, Tanio CP, Manyak MJ, Strauss MJ (2000). Cost-effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: Part I – methods. *Urology*. 56(6): 972–980.

Ahmed M, Bell T, Lawrence WT, Ward JP, Watson GM (1997). Transurethral microwave thermotherapy (Prostatron version 2.5) compared with transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: A randomised, controlled, parallel study. *British Journal of Urology*. 79(2): 181–185.

Albala DM, Turk TM, Fulmer BR, Koleski F, Andriole G, Davis BE, Eure GR, Kabalin JN, Lingeman J, Nuzzarello J, Sundaram C (2000). Peri-urethral transurethral microwave thermotherapy for the treatment of benign prostatic hyperplasia: an interim one-year safety and efficacy analysis using the TherMatrx TMx-2000. *Techniques in Urology*. 6(4): 288–293.

Albala DM, Fulmer BR, Turk TM, Koleski F, Andriole G, Davis BE, Eure GR, Kabalin JN, Lingeman JE, Nuzzarello J, Sundaram C (2002). Office-based transurethral microwave thermotherapy using the TherMatrx TMx-2000. *Journal of Endourology*. 16(1): 57–61.

Arai Y, Aoki Y, Okubo K, Maeda H, Terada N, Matsuta Y, Maekawa S, Ogura K (2000). Impact of interventional therapy for benign prostatic hyperplasia on quality of life and sexual function: a prospective study. *Journal of Urology*. 164(4): 1206–1211.

Australian Bureau of Statistics (2003). *Deaths* (Cat no. 3302). Canberra.

Australian Government Department of Health and Ageing (2004). *Medicare Benefits Schedule*. Canberra.

Australian Government Department of Health and Ageing (2004). National Hospital Cost Data Collection Cost Report Round 7 2002–2003, Canberra (available from http://www.health.gov.au/internet/wcms/Publishing.nsf/Content/health-casemix-costing-fc_r7.htm)

Australian Government Department of Health and Ageing (2005). *Schedule of Pharmaceutical Benefits*. Canberra.

Berger AP, Niescher M, Spranger R, Steiner H, Bartsch G, Horninger W (2003). Transurethral microwave thermotherapy (TUMT) with the Targis System: A single-centre study on 78 patients with acute urinary retention and poor general health. *European Urology*. 43 (2): 176–180.

Blute ML, Patterson DE, Segura JW, Tomera KM, Hellerstein DK (1996). Transurethral microwave thermotherapy versus sham treatment: A double-blind randomised study. *Journal of Endourology*. 10(6.): 565–573.

Blute M, Ackerman SJ, Rein AL, Beusterien K, Sullivan EM, Tanio CP, Strauss MJ, Manyak MJ (2000). Cost effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: Part II–results. *Urology*. 56(6): 981–987.

Carlin BP and Louis TA (2000). *Bayes and empirical Bayes methods for data analysis* (Second ed). Boca Raton, Florida: Chapman and Hall/CRC Press, Chapter 2.

Cavarretta L, Scremin E, Cucciarre G, Todeschini M, Novella G, Tasca A (2003). High-energy microwave thermotherapy in the treatment of benign prostatic hyperplasia, *Urologia Internationalis*. 71(1): 10–15.

D'Ancona FC, Francisca EA, Debruyne FM, de la Rosette JJ (1997a). High-energy transurethral microwave thermotherapy in men with lower urinary tract symptoms. *Journal of Endourology*. 11(4): 285–289.

D'Ancona FC, Francisca EA, Witjes WP, Welling L, Debruyne FM, de la Rosette JJ (1997b). High-energy thermotherapy versus transurethral resection in the treatment of benign prostatic hyperplasia: Results of a prospective randomised study with one year of follow-up. *Journal of Urology*. 158(1): 120–125.

D'Ancona FC, Francisca EA, Witjes WP, Welling L, Debruyne FM, de la Rosette JJ (1998). Transurethral resection of the prostate versus high-energy thermotherapy of the prostate in patients with benign prostatic hyperplasia: Long-term results. *British Journal of Urology*. 81(2): 259–264.

D'Ancona FCH, Francisca EAE, Hendriks JCM, Debruyne FMJ, de la Rosette JJ (1999). High-energy transurethral thermotherapy in the treatment of benign prostatic hyperplasia: Criteria to predict treatment outcome. *Prostate Cancer & Prostatic Diseases*. 2(2): 98–105.

Dahlstrand C, Grundtman S, Pettersson S (1997). High-energy transurethral microwave thermotherapy for large severely obstructing prostates and the use of biodegradable stents to avoid catheterisation after treatment. *British Journal of Urology*. 79(6): 907–909.

David RD, Grunberger I, Shore N, Swierzewski III SJ (2004). Multicenter initial US experience with CoreTherm – monitored feedback transurethral microwave thermotherapy for individualized treatment of patients with symptomatic benign prostatic hyperplasia. *Journal of Endourology*. 18(7): 682–685.

De la Rosette JJ, de Wildt MJ, Hofner K, Carter SS, Debruyne FM, Tubaro A (1996). High-energy thermotherapy in the treatment of benign prostatic hyperplasia: Results of the European Benign Prostatic Hyperplasia Study Group. *Journal of Urology*. 156(1): 97–101; discussion 101–102.

De la Rosette JJ, Francisca EA, Kortmann BB, Floratos DL, Debruyne FM, Kiemeney LA (2000). Clinical efficacy of a new 30-min algorithm for transurethral microwave thermotherapy: Initial results. *BJU International*. 86(1): 47–51.

De la Rosette JJ, Floratos DL, Severens JL, Kiemeney LA, Debruyne FM, Pilar LM (2003a). Transurethral resection versus microwave thermotherapy of the prostate: A cost-consequences analysis. *BJU International*. 92(7): 713–718.

De la Rosette JJ, Laguna MP, Gravas S, and de Wildt MJ (2003b). Transurethral microwave thermotherapy: The gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? *Journal of Endourology*. 17(4): 245–251.

De Wildt MJ, Debruyne FM, de la Rosette JJ (1996). High-energy transurethral microwave thermotherapy: A thermoablative treatment for benign prostatic obstruction. *Urology*. 48(3): 416–423.

DerSimonian R and Laird N (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*. 7:177–188.

Devonec M, Berger N, Perrin P (1991). Transurethral microwave heating of the prostate – or from hyperthermia to thermotherapy. *Journal of Endourology*. 5: 129.

Dicuio M, Knutson T, Vesely S, Damber JE, Dahlstrand C (2004). 30-minutes TUMT. Use of the visual analogue scale to investigate patients' pain perception, different cocktail options and tolerability during 30 minutes' treatment. *Urologia Internationalis*. 73(2): 130–136.

Djavan B, Shariat S, Schafer B, Marberger M (1998). Tolerability of high-energy transurethral microwave thermotherapy with topical urethral anaesthesia: Results of a prospective, randomised, single-blinded clinical trial. *Journal of Urology*. 160(3 Pt.1): 772–776.

Djavan B, Ghawidel K, Basharkhah A, Hruby S, Bursa B, Marberger M (1999a). Temporary intraurethral prostatic bridge-catheter compared with neoadjuvant and adjuvant alpha-blockade to improve early results of high-energy transurethral microwave thermotherapy. *Urology*. 54(1): 73–80.

Djavan B, Seitz C, Fakhari M, Ghawidel K, Marberger M (1999b). Prevention of temporary prostatic obstruction after high-energy microwave thermotherapy by placement of prostatic bridge catheter. [French]. *Progres en Urologie*. 9(2): 261–270.

Djavan B, Seitz C, Ghawidel K, Basharkhah A, Bursa B, Hruby S, Marberger M (1999c). High-energy transurethral microwave thermotherapy in patients with acute urinary retention due to benign prostatic hyperplasia. *Urology*. 54(1): 18–22.

Djavan B, Fakhari M, Shariat S, Ghawidel K, Marberger M (1999d). A novel intra-urethral prostatic bridge catheter for prevention of temporary prostatic obstruction following high-energy transurethral microwave thermotherapy in patients with benign prostatic hyperplasia. *Journal of Urology*. 161(1): 144–51.

Djavan B, Roehrborn CG, Shariat S, Ghawidel K, Marberger M (1999e). Prospective randomised comparison of high-energy transurethral microwave thermotherapy versus alpha-blocker treatment of patients with benign prostatic hyperplasia. *Journal of Urology*. 161(1): 139–143.

Djavan B, Shariat S, Fakhari M, Ghawidel K, Seitz C, Partin AW, Roehrborn CG, Marberger M (1999f). Neo-adjuvant and adjuvant alpha-blockade improves early results of high-energy transurethral microwave thermotherapy for lower urinary tract symptoms of benign prostatic hyperplasia: A randomised, prospective clinical trial. *Urology*. 53(2): 251–259.

Djavan B, Wammack R, Ghawidel K, Alavi S, Hasenzagel C, Dobronski P, Stoklosa A, Jakubcky T, Borkowski A, Marberger M (2000a). Microwave thermotherapy in patients with chronic urinary retention. *Techniques in Urology* 6(4): 278–281.

Djavan B, Bursa B, Basharkhah A, Seitz C, Remzi M, Ghawidel K, Hruby S, Marberger M (2000b). Pre-treatment prostate-specific antigen as an outcome predictor of targeted transurethral microwave thermotherapy. *Urology*. 55(1): 51–57.

Djavan B, Seitz C, Roehrborn CG, Remzi M, Fakhari M, Waldert M, Basharkhah A, Planz B, Harik M, Marberger M (2001). Targeted transurethral microwave thermotherapy versus alpha-blockade in benign prostatic hyperplasia: Outcomes at 18 months. *Urology*. 57(1): 66–70.

Eliasson TU, Abramsson LB, Pettersson GT, Damber JE (1995). Responders and non-responders to treatment of benign prostatic hyperplasia with transurethral microwave thermotherapy. *Scandinavian Journal of Urology & Nephrology*. 29(2): 183–191.

Eliasson T, Abramsson LB, Pettersson GT, Damber JE (1996). Sexual function before and after transurethral microwave thermotherapy for benign prostatic hyperplasia. *Scandinavian Journal of Urology & Nephrology*. 30(2): 99–102.

Eliasson T, Damber JE (1998a). Temperature controlled high-energy transurethral microwave thermotherapy for benign prostatic hyperplasia using a heat shock strategy. *Journal of Urology*. 160(3 Pt.1): 777–781; discussion: 781–782.

Eliasson T, Abramsson L, Damber JE (1998b). Importance of thermal dose and antenna location in transurethral microwave thermotherapy for benign prostatic hyperplasia. *Journal of Endourology*. 12(6): 581–589.

Feldman SL (1997). Urology: A market poised for expansion. *Wessels, Arnold and Henderson Industry Report*. Wessels, Arnold & Henderson: Minneapolis USA, pp. 13–18.

Floratos DL, Sonke GS, Francisca EA, Kiemeney LA, Kortmann BB, Debruyne FM, de la Rosette JJ (2000). High-energy transurethral microwave thermotherapy for the treatment of patients in urinary retention, *Journal of Urology*. 163(5): 1457–1460.

Floratos DL, Kiemeney LA, Rossi C, Kortmann BB, Debruyne FM, de la Rosette JJ (2001a). Long-term follow-up of randomised transurethral microwave thermotherapy versus transurethral prostatic resection study. *Journal of Urology*. 165(5): 1533–1538.

Floratos DL, Sedelaar JP, Kortmann BB, Aarnink RG, Wijkstra H, Debruyne FM, de la Rosette JJ (2001b). Intra-prostatic vasculature studies: Can they predict the outcome of transurethral microwave thermotherapy for the management of bladder outflow obstruction? *Prostate*. 46(3): 200–206.

Francisca E, d'Ancona FC, Debruyne F, de la Rosette JJ (1999a). Results of patients treated with the 30-minute high-energy transurethral microwave thermotherapy protocol (TUMT 3.0). *European Urology*. Supplement 35: 52.

Francisca EA, d'Ancona FC, Debruyne F, et al (1999b). High-energy transurethral microwave thermotherapy (TUMT 2.5) in the treatment of BPH: Results of a prospective study with 4-year follow-up. *European Urology*. Supplement 35: 52.

Francisca EA, d'Ancona FC, Meuleman EJ, Debruyne FM, de la Rosette JJ (1999c). Sexual function following high-energy microwave thermotherapy: Results of a randomised, controlled study comparing transurethral microwave thermotherapy to transurethral prostatic resection. *Journal of Urology*. 161(2): 486–490.

Francisca EA, d'Ancona FC, Hendriks JC, Kiemeney LA, Debruyne FM, de la Rosette JJ (2000). A randomised study comparing high-energy TUMT to TURP: Quality-of-life results. *European Urology.* 38(5): 569–575.

Goldfarb B, Bartkiw T, Trachtenberg J (1995). Microwave therapy of benign prostatic hyperplasia. *Urologic Clinics of North America.* 22(2): 431–439.

Gonzalez RR, Te AE. (2003). How do transurethral needle ablation of the prostate and transurethral microwave thermotherapy compare with transurethral prostatectomy? *Current Urology Reports.* 4: 302–303.

Gordon NS, Hadlow G, Knight E, Mohan P (1997). Transurethral resection of the prostate: Still the gold standard. *Australian and New Zealand Journal of Surgery.* 67(6): 354–357.

Gravas S, Laguna MP, de la Rosette JJ (2003). Efficacy and safety of intraprostatic temperature-controlled microwave thermotherapy in patients with benign prostatic hyperplasia: Results of a prospective, open-label, single-center study with one-year follow-up. *Journal of Endourology.* 17(6): 425–430.

Hansen MV, Zdanowski A (1997). The use of a simple home flow test as a quality indicator for male patients treated for lower urinary tract symptoms suggestive of bladder outlet obstruction. *European Urology.* 32(1): 34–38.

Hardy R and Thompson SG (1996). A likelihood approach to meta-analysis with random effects. *Statistics in Medicine.* 15: 619–629.

Hedges LV and Olkin I (1985). *Statistical methods for meta-analysis.* San Diego: Academic Press, Chapter 5.

Hoffman RM, MacDonald R, Monga M, Wilt TJ (2004). Transurethral microwave thermotherapy versus transurethral resection for treating benign prostatic hyperplasia: A systematic review. *BJU International.* 94(7): 1031–1036.

Jakubczyk T, Stoklosa A, Borkowski A, Habrat W, Dobrowolski Z (2002). Transurethral microwave thermotherapy: First experiences in Poland. *BJU International.* 89(7): 767–770.

Javle P, Blair M, Palmer M, Jenkins SA, Parsons KF (1996). The role of an advanced thermotherapy device in prostatic voiding dysfunction. *British Journal of Urology.* 78(3): 391–397.

Kellner DS, Armenakas NA, Brodherson M, Heyman J, Fracchia JA (2004). Efficacy of high-energy transurethral microwave thermotherapy in alleviating medically refractory urinary retention due to benign prostatic hyperplasia. *Urology.* 64 (4): 703–706.

Kirby R, Kirby M, Fitzpatrick J, Fitzpatrick A (1994) *Shared care for prostatic diseases.* Isis Medical Media, Oxford: p. 111.

Kobelt G, Spangberg A, Mattiasson A (2004). The cost of feedback microwave thermotherapy compared with transurethral resection of the prostate for treating benign prostatic hyperplasia. *BJU International.* 93(4): 543–548.

Krogh J, Hansen F, Nordling J (1998). Transurethral microwave thermotherapy for treatment of benign prostatic hyperplasia: Results obtained with the ProstaLund device. *World Journal of Urology*. 16(2): 115–119.

Kurita Y, Ushiyama T, Suzuki K, Fujita K, Kawabe K (1996). Transrectal ultrasonography to predict the clinical outcome of transurethral microwave thermotherapy in patients with benign prostatic hyperplasia. *International Journal of Urology*. 3(6.): 448–453.

Larson TR, Collins JM (1995). An accurate technique for detailed prostatic interstitial temperature-mapping in patients receiving microwave thermal treatment. *Journal of Endourology*. 9(4): 339–347.

Larson TR, Bostwick DG, Corica A (1996). Temperature-correlated histopathologic changes following microwave thermo-ablation of obstructive tissue in patients with benign prostatic hyperplasia. *Urology*. 47(4): 463–469.

Larson TR, Blute ML, Bruskewitz RC, Mayer RD, Ugarte RR, Utz WJ (1998a). A high-efficiency microwave thermo-ablation system for the treatment of benign prostatic hyperplasia: Results of a randomised, sham-controlled, prospective, double-blind, multicenter clinical trial. *Urology*. 51(5): 731–742.

Larson TR, Collins JM, Corica A (1998b). Detailed interstitial temperature mapping during treatment with a novel transurethral microwave thermo-ablation system in patients with benign prostatic hyperplasia. *Journal of Urology*. 159(1): 258–264.

Lee KT, Tan HH, Li MK, Cheng WS, Rekhraj IR, Foo KT (1995). Transurethral microwave thermotherapy (TUMT) for benign prostatic hyperplasia (BPH) – our first 100 cases. *Singapore Medical Journal*. 36(2): 181–184.

Manyak MJ, Ackerman SJ, Blute ML, Rein AL, Buesterien K, Sullivan EM, Tanio CP, Strauss MJ (2002). Cost-effectiveness of treatment for benign prostatic hyperplasia: An economic model for comparison of medical, minimally invasive, and surgical therapy. *Journal of Endourology*. (1): 51–56.

Medical Services Advisory Committee (2002). *Assessment Report: Transurethral needle ablation (TUNA) for the treatment of benign prostatic hyperplasia*. Commonwealth of Australia, Canberra.

Miller PD, Kastner C, Ramsey EW, Parsons K (2003). Cooled thermotherapy for the treatment of benign prostatic hyperplasia: Durability of results obtained with the Targis System. *Urology*. 61(6.): 1160–1164; discussion 1164–1165.

Naqvi SA, Rizvi SA, Hasan AS (2000). High-energy microwave thermotherapy in patients in urinary retention. *Journal of Endourology*. 14(8): 677–681.

NHMRC Clinical Practice Guidelines (1996). *The management of uncomplicated lower urinary tract symptoms in men*. Australian Government Publishing Service: Canberra. p. 26.

NHMRC (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines*. National Health and Medical Research Council, Canberra.

NHMRC (2000). *How to use the evidence: assessment and application of scientific evidence*. National Health and Medical Research Council, Canberra.

Norby B, Frimodt-Moller PC (2000). Development of a urethro-rectal fistula after transurethral microwave thermotherapy for benign prostatic hyperplasia. *BJU International*. 85(4): 554–555.

Norby B, Nielsen HV, Frimodt-Moller PC (2002a). Transurethral interstitial laser coagulation of the prostate and transurethral microwave thermotherapy versus transurethral resection or incision of the prostate: Results of a randomised controlled study in patients with symptomatic benign prostatic hyperplasia. *BJU International*. 90(9): 853–862.

Norby B, Nielsen HV, Frimodt-Moller PC (2002b). Cost-effectiveness of new treatments for benign prostatic hyperplasia: Results of a randomised trial comparing the short-term cost-effectiveness of transurethral interstitial laser coagulation of the prostate, transurethral microwave thermotherapy and standard transurethral resection or incision of the prostate. *Scandinavian Journal of Urology & Nephrology*. 36(4): 286–295.

Osman Y, Wadie B, El Diasty T, Larson T (2003). High-energy transurethral microwave thermotherapy: Symptomatic versus urodynamic success. *BJU International*. 91(4): 365–370.

Pace G, Selvaggio O, Palumbo F, Selvaggi FP (2001). Initial experience with a new transurethral microwave thermotherapy treatment protocol '30-minute TUMT'. *European Urology*. 39(4): 405–411.

ProstaLund Operations AB H1S6LS. 'Study B': Submission to FDA (2002) (PMA P01005 SSED). http://www.fda.gov/cdrh/pdf/p010055.html: 1–24.

Ramsey EW, Miller PD, Parsons K (1997). A novel transurethral microwave thermal ablation system to treat benign prostatic hyperplasia: results of a prospective multicenter clinical trial. *Journal of Urology*. 158(1): 112–118; discussion 118–119.

Ramsey EW, Miller PD, Parsons K (1998). Transurethral microwave thermotherapy in the treatment of benign prostatic hyperplasia: Results obtained with the Urologix T3 device. *World Journal of Urology*. 16(2): 96–101.

Roehrborn CG (1995). The newly established guidelines for the diagnosis and management of benign prostatic hyperplasia. *Current Opinion in Urology*. 5: 30–34.

Roehrborn CG, Preminger G, Newhall P, Denstedt J, Razvi H, Chin LJ, Perlmutter A, Barzell W, Whitmore W, Fritzsch R, Sanders J, Sech S, Womack S (1998). Microwave thermotherapy for benign prostatic hyperplasia with the Dornier UroWave: Results of a randomised, double-blind, multicenter, sham-controlled trial. *Urology*. 51(1): 19–28.

Sall M, Bruskewitz RC (1997). Prostatic urethral strictures after transurethral microwave thermal therapy for benign prostatic hyperplasia. *Urology*. 50(6): 983–985.

Schelin S (2001). Microwave thermotherapy in patients with benign prostatic hyperplasia and chronic urinary retention. *European Urology*. 39(4): 400–404.

Schelin S (2002). Mediating transurethral microwave thermotherapy by intraprostatic and periprostatic injections of mepivacaine epinephrine: Effects on treatment time, energy consumption, and patient comfort. *Journal of Endourology.* 16(2): 117–121.

Schulz MW, Chen J, Woo HH, Keech M, Watson ME, Davey PJ (2002). A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *Journal of Urology.* 168(1): 155–159.

Sjodin JG, Eliasson T, Erlandson BE, Loyd D (1997). Thermal injury during TUMT. *Scandinavian Journal of Urology & Nephrology.* 31(6): 561–564.

Smith TC, Spiegelhalter DJ, Thomas SL (1995). Bayesian approaches to random-effects meta-analysis: A comparative study. *Statistics in Medicine.* 14: 2685–2699.

Spiegelhalter D, Thomas A and Best N (2000). *WinBUGS version 1.3 User Manual.* Cambridge University: MRC Biostatistics Unit.

Statacorp (2003). Stata Statistical Software: Release 8.0. College Station, Texas: Stata Corporation.

Terai A, Shichiri Y, Onishi H, Arai Y, Oishi K, Takeuchi H, Yoshida O (1995). Increasing the thermal dose in transurethral microwave thermotherapy produces no improvement in therapeutic efficacy. *International Journal of Urology.* 2(3): 186–190.

Terazosin product information (accessed via Monthly Index of Medical Specialties [MIMS]).

Thalmann GN, Graber SF, Bitton A, Burkhard FC, Gruenig O, Studer UE (1999). Transurethral thermotherapy for benign prostatic hyperplasia significantly decreases infravesical obstruction: results in 134 patients after one year. *Journal of Urology.* 162(2): 387–393.

Thalmann GN, Mattei A, Treuthardt C, Burkhard FC, Studer UE (2002). Transurethral microwave therapy in 200 patients with a minimum follow-up of two years: Urodynamic and clinical results. *Journal of Urology.* 167(6): 2496–2501.

Tomera KM, Tomera FM (1998). The Tomera technique: High-energy transurethral thermotherapy with low energy morbidity. *Alaska Medicine.* 40(1): 3–5.

Tomera KM, Tomera FM, Clark WR (2000). Initial and superior experience with 30-minute TUMT. *Techniques in Urology.* 6(4): 276–277.

Trachtenberg J, Roehrborn CG (1998). Updated results of a randomised, double-blind, multicenter, sham-controlled trial of microwave thermotherapy with the Dornier UroWave in patients with symptomatic benign prostatic hyperplasia. UroWave Investigators Group. *World Journal of Urology.* 16(2): 102–108.

Vos T, Mathers C (1999). AIHW: Human services standards book; benign prostatic hypertrophy. Available: http://www.aihw.gov.au/bod/bod_yld_by_disease/o_genitourinary/o2_prostate.xls

Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, Schain M, Larson T, Boyle E, Duelund J, Kroyer K, Ageheim H, Mattiasson A (2002). Feedback microwave thermotherapy versus TURP for clinical BPH– a randomised, controlled, multicenter study. *Urology.* 60(2): 292–299.

Wagrell L, Schelin S, Nordling J, Larsson T, Mattiasson A (2003). ProstaLund microwave feedback treatment compared with TURP for treatment of BPH: A prospective, randomised, multicentre study [abstract]. *Australia and New Zealand.Journal of Surgery.* 73: A146.

Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, Schain M, Larson T, Boyle E, Duelund J, Kroyer K, Ageheim H, Mattiasson A (2004). Three-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: A prospective, randomised, multicenter study. *Urology.* 64(4): 698–702.

Waldén M, Acosta S, Carlsson P, Pettersson S, Dahlstrand C (1998). A cost-effectiveness analysis of transurethral resection of the prostate and transurethral microwave thermotherapy for treatment of benign prostatic hyperplasia: Two-year follow-up. *Scandinavian Journal of Urology and Nephrology.* 32(3): 204–210.

Witjes WP, Robertson A, Rosier PF, Neal DE, Debruyne FM, de la Rosette JJ (1997). Urodynamic and clinical effects of non-invasive and minimally invasive treatments in elderly men with lower urinary tract symptoms stratified according to the grade of obstruction. *Urology.* 50(1): 55–61.

Yokoyama T, Tsugawa M, Nagai A, Kumon H (2004). High-energy transurethral microwave thermotherapy in patients with benign prostatic hyperplasia: comparative study between 30- and 60-minute single treatments. *Acta Medica Okayama.* 58(3): 151–156.