NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: The PLASMA system for transurethral resection and haemostasis of the prostate

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **Original EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **EAC assessment report update** – an update to the original EAC assessment report produce by an external assessment centre
3. **Assessment report overview update**– an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Review Decision –** documentation detailing the decision to schedule a standard update of the guidance and bring the topic to committee to review new evidence.
6. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
7. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Cedar

Healthcare Technology Research Centre

External Assessment Centre Report

The TURis system for transurethral resection of the prostate

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None

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The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Abbreviations

TURiS	Transurethral Resection in Saline
TURP	Transurethral resection of the prostate
mTURP	Monopolar transurethral resection of the prostate
TUR	Transurethral resection syndrome, characterised by fluid overload and hyponatraemia
EAC	External Assessment Centre
LOS	Length of (hospital) stay
TUIP	Transurethral incision of the prostate
RCT	Randomised control trial
RR	Relative risk
NNT	Number needed to treat
ARR	Absolute risk reduction
CI	Confidence Interval
LUTS	Lower urinary tract symptoms
BPH	Benign prostatic hyperplasia
BPE	Benign prostatic enlargement
EAU	European Association of Urology
TUMT	Transurethral microwave therapy
TUNA	Transurethral needle ablation of the prostate
HoLEP	Holmium laser enucleation of the prostate
TUVP	Transurethral vaporisation of the prostate
MHRA	Medicines and Healthcare Products Regulatory Agency (UK regulatory body)
FDA	Food and Drug Administration (US regulatory body)
WHO	World Health Organisation
MAUDE	Manufacturer and User Facility Device Experience, FDA database

EMA	European Medicines Agency
SD	Standard deviation
W	Watts
IPSS	International prostate symptom score
Qmax	Maximum flow rate
BPVP	bipolar plasma vaporization of the prostate
QoL	Quality of life
TURis-V	TURis Plasma Vaporisation
TURB	Transurethral resection of the bladder
IIEF-5	International Index of Erectile Function, 5 item version
BOO	Bladder Outlet Obstruction
Na	Sodium
K	Potassium
Cl	Chlorine
IIEF-ED	International Index of Erectile Function
Hb	Haemoglobin
NS	Not significant
mM mmol/l	millimolar millimole per litre
IQR	Interquartile range
mOsm/L	milliosmoles per litre
Qave	Average flow rate
I^2	Measure of the degree of inconsistency across studies in a meta-analysis
df	Degrees of freedom
SGD	Singapore dollar
MA	Meta-analysis

HES	Hospital episode statistics
NEC	Not elsewhere classifiable
CC Score	Critical care score
RBC	Red blood cells

Contents

1 Summary

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

Evidence from randomised trials clearly shows that TURis has a better safety profile compared to mTURP in terms of avoidance of TUR syndrome and reducing the need for blood transfusion. TURis is cost saving for existing Olympus customers but is not proven to be cost saving for non-Olympus customers based on the EAC's critique of the economic submission. There is uncertainty around the clinical evidence for different complications that can lead to possible reduction in readmission to hospital. These outcomes are not consistently reported in randomised studies and hence the potential for TURis to further reduce resource use is not clear.

Scope of the sponsor's submission

The EAC finds that the sponsor has made a reasonable interpretation of the scope. Several TURis related procedures are absent from the sponsor's submission. These are the vaporization procedure using the button electrode, the hybrid technique of resection/vaporization using loop/button electrodes, enucleation of the prostate, and TUIP using a needle electrode. Clinical experts generally agreed that these excluded techniques are novel or rare uses of TURis. There appears to be a different evidence base for the TURis vaporization procedure to that of resection with TURis.

Summary of clinical evidence submitted by the sponsor

There are a total of eight RCTs available as full papers providing evidence for TURis. Additional observational studies do not identify any further insight to outcomes following TURis procedures. No randomized studies originate from the UK and some represent use of TURis in countries where procedural decisions (e.g. discharge from hospital) may differ substantially to the UK. All of the randomized trials provide a head to head comparison of TURis with mTURP and the patient populations are broadly similar in terms of important baseline factors.

Summary critique of clinical evidence submitted by the sponsor

TUR syndrome

The sponsor claims that TURis practically eliminates the risk of TUR syndrome associated with mTURP. The EAC supports this claim and calculates a RR 0.18 (95% CI 0.05, 0.61) in favour of TURis based on meta-analysis of six randomised studies (Figure 2). This is associated with a number needed to treat (NNT) of 50, meaning that 50 patients must be treated with TURis (instead of mTURP) to prevent one case of TUR syndrome.

Blood transfusion

The sponsor claims that TURis reduces the need for blood transfusion. The EAC supports this claim and calculates a RR 0.35 (95% CI 0.19, 0.64) in favour of TURis based on meta-analysis of six randomised studies (Figure 4). This is associated with a NNT value of 20, meaning that 20 patients must be treated with TURis (instead of mTURP) to prevent one case of blood transfusion.

Procedure duration

Evidence from randomised trials does not find that procedures are significantly shorter using TURis compared to mTURP. An EAC meta-analysis of five randomised studies found the difference in procedure time (TURis minus mTURP) to be -1.36 minutes (95% CI -3.69, 0.98) minutes (Figure 23). The result is not statistically significant and the size of the observed difference is small and unlikely to transfer to a real life resource saving.

Clot retention

Evidence from randomised trials does not indicate that TURis reduces clot retention compared to mTURP. An EAC meta-analysis of five randomised trials (Figure 6) indicates there is no statistically significant effect in favour of TURis: RR (TURis/mTURP) 0.54 (95% CI 0.26, 1.13).

Readmission due to haemorrhage

Evidence from randomised trials does not indicate that TURis reduces re-admission due to haemorrhage compared to mTURP. In an EAC meta-analysis of three randomised trials the RR of readmission due to haemorrhage (TURis/mTURP) is 0.53 (95% CI 0.22, 1.25, p = 0.15)

i.e. not a statistically significant result since the confidence interval includes the null value of 1.

Readmission (any cause)

The EAC notes that one RCT recorded readmission for any cause (Fagerstrom 2011). In this study the rate of readmission was 5/98 cases (5.1%) in the TURis arm compared to 14/87 (16.1%) in the mTURP arm, p = 0.011. There is variability across randomised studies in the reporting of adverse events leading to readmission and there is poor reporting of rates of readmission by cause.

Hospital stay

The sponsor's meta-analysis contains visible heterogeneity with a clear outlying study that found a statistically significant reduction in hospital stay of 1.2 days in favour of TURis (Chen 2009). No other randomised study reported a significant difference in favour of TURis for hospital stay. The EAC's meta-analysis of two studies, excluding the outlier found no statistically significant effect in favour of TURis: mean difference in hospital stay (TURis minus mTURP): -0.19 (95% CI -0.46, 0.07) days (Figure 12). The size of the observed difference is small and unlikely to transfer to a real life resource saving. As an alternative method we included the data from Chen 2009 in a random effects model. This too found no statistically significant effect.

Urethral strictures / bladder neck contractures

Evidence from randomised studies indicates that there is no difference in the rates of urethral stricture or bladder neck contracture between TURis and mTURP. An EAC meta-analysis (Figure 26) of six studies found the RR (TURis/mTURP) to be 1.08 (95% CI 0.69, 1.68), p = 0.74. Randomised studies appear to report data on the incidence of these adverse outcomes in a fairly consistent manner.

Repeat procedure due to incomplete resection

Evidence from randomised studies indicates that there is no difference in the rates of repeat procedure due to incomplete resection between TURis and mTURP. An EAC meta-analysis

(Figure 29) of three studies found the RR (TURis/mTURP) to be 0.76 (95% CI 0.42, 1.40), p = 0.38. There is again some variation in the reporting of this outcome across studies, which leads to uncertainty in the EAC's result.

Evidence from randomised trials does not indicate that catheters are removed significantly earlier following TURIs than following mTURP. As was the case for hospital stay, the sponsor's analysis contained outlying data from the Chen 2009 study. In an EAC fixed effects meta-analysis of two studies (without the Chen 2009 data) the mean difference (TURis minus mTURP) in time to catheter removal was -0.09 (95% CI -0.25, 0.06) days, p = 0.24. This result is not statistically significant.

Summary of economic evidence submitted by the sponsor

There was no relevant published economic evidence so the sponsor's economic evidence comprises a de novo model. The model showed a cost saving for TURis compared with mTURP for existing Olympus customers and non Olympus customers. The structure of the model was suitable for the decision problem. The main drivers of the model were length of hospital stay and cost of a hospital bed-day and the cost of consumables for mTURP. Sensitivity analysis showed that the model was robust.

Summary critique of economic evidence submitted by the sponsor

As described in the summary critique of clinical evidence the claimed reduction in length of stay for TURis was not supported by the evidence. When the difference in length of stay between TURis and mTURP is entered as zero to the model the result is no longer cost saving. The sponsor overestimated the cost of mTURP consumables for non-Olympus customers using generic consumables and underestimated the cost for Olympus customers. The cost of blood transfusion was overestimated. Overall the model showed mTURP to be cheaper for non-Olympus customers. For existing Olympus customers the model shows a small cost saving compared with mTURP.

Summary of any additional work carried out by the External Assessment Centre

In section 3.8 the EAC has reproduced meta-analyses conducted by the sponsor but with changes including

- inclusion of additional RCT data
- correction of data entry errors or of double counting of patients
- exploring whether studies published in non-English language papers are pivotal to the analyses
- seeking a valid response to the problem of heteogenity.

The EAC also conducted additional meta-analyses for repeat procedures due to incomplete resection, readmission to hospital due to haemorrhage and incidence of urethral strictures and bladder neck contractures.

The EAC used the revised clinical inputs and also in some instances revised cost and resource use in the sponsor's de novo model. We included a scenario where TURis was assumed to reduce the rate of readmission (all causes, Fagerstrom 2011).

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The sponsor has provided a comprehensive overview of the clinical context that is relevant to the decision problem, and cites credible sources of information.

Medical conditions that lie behind male lower urinary tract symptoms (LUTS) are stated as benign prostatic hyperplasia (BPH) that can lead to benign prostatic enlargement (BPE), leading to LUTS. In terms of prevalence the submission states that around 60% of men who are of age 60 years or more have some degree of prostate enlargement, with LUTS occurring in 30% of men older than 65 years. The submission describes serious complications that can result from LUTS, including severe urinary tract infections, urinary retention or renal failure, and notes that LUTS can considerably reduce men's quality of life.

The clinical pathways for treatment are presented from European guidelines and the submission makes reference to relevant NICE guidance products.

Briefly, education and lifestyle advice, or medical therapies are usually the first line of treatment options that a clinician considers. Medical therapies include muscarinic receptor antagonists, 5alpha-reductase inhibitor, alpha 1-blockers and vasopressin analogues (EAU guidelines).

The sponsor refers to NICE CG97, which recommends that clinicians should offer surgery only if voiding symptoms are severe or if drug treatment and conservative management options have been unsuccessful or are not appropriate. Also presented is an algorithm from EAU guidance, to guide clinicians in choosing the appropriate surgical treatment in this group of men.

Considerations include patient choice, prostate volume, anaesthetic risk, anticoagulant therapy and the local availability of different techniques.

A list of different surgical options is briefly presented, based on EAU guidance:

- TUIP: transurethral incision of the prostate
- TURP: transurethral resection of the prostate
- Laser enucleation
- Laser vaporisation
- TUMT: transurethral microwave therapy
- TUNA: transurethral needle ablation of the prostate

- Open prostatectomy
- HoLEP: holmium laser enucleation of the prostate
- Stent

NICE CG97 states that TURP is a surgical treatment option for men with all prostate sizes, though TUIP is an option where the prostate volume is < 30g and, where prostate volume is > 80g, TURP, TUVP or HoLEP, or open prostatectomy are surgical options.

Of these treatments, Transurethral Resection in Saline (TURis) is a modification of TURP and may be used in the same patient group that undergo TURP.

The sponsor has described the differences between TURis and standard TURP. Briefly, TURis is a bipolar electrosurgical technique, and standard TURP is a monopolar electrosurgical technique. Electrosurgery delivers electrical energy from a generator unit to the operation site, to cut tissue or coagulate bleeding blood vessels.

In monopolar TURP (mTURP) the active electrode is at the end of the resectoscope, delivering energy to the operation site and the return electrode is a conductive sticky pad placed elsewhere on the patient's skin, usually on the thigh. Also mTURP requires irrigation with a nonconductive fluid (glycine, mannitol or sorbitol). These fluids are not isotonic with blood and may be absorbed by the body during surgery. Fluid absorption may lead to a rare, but potentially serious condition called TUR syndrome, characterised by fluid overload and hyponatraemia. The sponsor cites the incidence of TUR syndrome as between 0.5%-8% with a reported mortality rate of 0.2%-0.8%.

In TURis, the active and return electrodes are both located within the working element of the resectoscope. Therefore no external return electrode is required and saline may be used as the irrigating fluid. Saline is near isotonic with blood and a claimed benefit of TURis is that the risk of TUR syndrome is eliminated. TURis uses higher energy settings than mTURP.

For clarity we use the terms TURis to represent (bipolar) TURis supplied by Olympus, and 'mTURP' to represent TURP procedures undertaken with any monopolar system. The EAC notes that other bipolar technologies exist but are outside the scope of this evaluation, which considers TURis as a single technology.

2.2 Overview of sponsor's description of ongoing studies

The sponsor identified one ongoing study listed below and provided sufficient detail.

- Evaluation of the Effects of Different Prostate Surgeries on Urinary and Sexual Function, ClinicalTrials.gov Identifier: NCT01810068

Another trial not identified by the sponsor is detailed below however it is not clear when the results will be published.

Multicentre randomised cotrolled trial comparing bipolar with monopolar transurethral resection of the prostate, JPRN-UMIN000010801. The study is being undertaken in Japan with target sample size n=100. The primary end point in this study is safety, with a focus on perioperative findings such as operation time, decline of sodium level, clot retention, transfusion, and any other symptom relating to the procedures. Key secondary outcomes are efficacy findings for patients after 36 months of follow-up including development of urethral stricture.

2.3 Critique of sponsor's definition of the decision problem

2.3.1 Population

The clinical evidence submitted matches the patient population defined in the scope. The study samples of the randomised trials are broadly homogenous for age and baseline clinical factors. Exclusion criteria are broadly similar across the randomised studies and include: known or suspected cancer, neurogenic bladder, previous prostate surgery, urethral stricture, and coagulopathy.

There is a minor heterogeneity in that the majority of randomised trials excluded from analysis men in whom prostate cancer was an incidental finding following surgery, whereas a minority of trials would not exclude such cases.

The study by Chen 2009 included men with baseline prostate volume > 50 ml, resulting in the largest mean prostate volumes of the randomised studies. There is some subgroup analysis of men with large prostate glands (> 60 ml) and men on anticoagulant therapy in one randomised trial (Michielsen 2011).

2.3.2 Intervention

The TURis technology was first CE marked in 2003. The sponsor's submission includes the most recent (dated 2012) certificate awarded by a notified body and confirming compliance of TURIs with EC Directive 93/42/EEC Annex II Article 3.

The TURis technology described in the sponsor's submission is within the description of the technology defined in the scope. Upon beginning to independently examine the evidence base for TURis, the EAC observed that the published literature includes studies of the TURis technology used in different ways. We therefore sought clarification with the sponsor and with clinical experts for the relevance to the decision problem of the following TURis procedures:

- Resection

- Vaporisation
- Hybrid technique of resection/vaporisation
- Enucleation
- TUIP

Resection

The sponsor has interpreted the decision problem to apply to the use of TURis only in this way. In a TURis resection procedure the surgeon usually uses a loop electrode and selects the 'cut' or 'coagulate' modes via foot pedals. The loop electrode comes in four sizes: 'small', 'medium', 'large' and 'band'. The surgeon chooses loop size according to the size of the prostate. The band electrode is thicker, giving deeper heat penetration. Resection generates chips of resected tissue. The roller electrode is used in some cases (after the loop electrode) to provide additional smoothing and coagulation. This is at the surgeon's discretion; perhaps 80% of cases use only the loop electrode, and 20% both loop and roller electrodes.

Vaporisation

The term 'vaporisation' has two uses. Firstly *vaporisation as an effect* describes how TURis delivers energy during any procedure, including resection, above.

Secondly *vaporisation as a procedure* refers to use of a button electrode to ablate prostate tissue without the generation of chips, and making available no tissue for histological examination. The sponsor has interpreted the decision problem to exclude the use of TURis for *vaporisation procedures*.

Hybrid technique of resection/vaporisation

This describes a procedure that involves both resection and vaporisation with the button electrode. The sponsor has interpreted the decision problem to exclude the use of TURis for hybrid procedures.

Enucleation

This is a procedure requiring a different electrode and which has a steep learning curve for the surgeon. The sponsor has interpreted the decision problem to exclude the use of TURis for enucleation.

TUIP

TURis enables TUIP procedures where prostate volume is < 30g, using a needle electrode. The sponsor has interpreted the decision problem to exclude the use of TURis for TUIP procedures.

Expert advice on the intervention

Three expert advisors commented on the relevance of TURis when used for vaporisation procedures, hybrid procedures, enucleation and TUIP. One expert advisor considered that all four procedures were novel or rarely used. A second expert advisor considered vaporisation, hybrid technique and enucleation to be not mainstream procedures, but that TUIP may be in use where the theatre is already using Olympus equipment. A third expert advisor described all four procedures as recognised uses of TURIs, with the exception of enucleation, since true enucleation requires open surgery or HoLEP. One expert advisor stated that he used the button electrode, presumably for the vaporisation (or hybrid) technique.

In summary the EAC feels that the sponsor's interpretation of the intervention is reasonable. It seems reasonable to consider TURis enucleation as outside of the scope, considering that the technique has a steep learning curve (and that expert advice states that true enucleation is a HoLEP laser technique). A caveat concerns TURis *vaporisation procedure* or *hybrid procedure*. The sponsor has not focused on these techniques or provided evidence on these techniques. It is difficult to discern subtleties of techniques from study abstracts but *vaporisation/hybrid techniques* appear to have a smaller evidence base but distinct from mainstream use of TURis. One clinical expert reported use of the button electrode in his routine practice.

2.3.3 Comparator(s)

The comparator described in the sponsor's submission matches that of the final scope. The comparator is mTURP and there are numerous suppliers of monopolar systems. The monopolar procedure may also use both loop and roller electrodes to cut and coagulate prostate tissue.

Some observational studies have a proportion of non-TURP procedures in their comparator groups that are outside of the Scope. Also some randomised trials are three-arm in nature, comparing for example, TURis versus mTURP versus *TURis vaporisation procedure*.

2.3.4 Outcomes

The outcomes defined in the scope are:

- Hospital length of stay

- Procedural blood loss and blood transfusion requirement
- Time of removal of urinary catheter post-operatively
- TUR syndrome
- Re-admittance for repeat procedures
- Duration of surgical procedure
- Healthcare associated infection
- Quality of life
- Device-related adverse events

The sponsor's submission focuses on the results of meta-analyses (TURis versus mTURP) for six outcomes as follows:

- Incidence of TUR syndrome
- Incidence of blood transfusion
- Incidence of clot retention
- Difference in hospital stay
- Difference in time to removal of urinary catheter
- Difference in procedure time

The submission does not include a meta-analysis of re-admittance for repeat procedures. The EAC performed a meta-analysis for this outcome in two scenarios, namely repeat procedure due to incomplete resection, and readmission due to haemorrhage, although there was not a large volume of reliable data.

The sponsor removed healthcare associated infection as an outcome. The included studies report complications following TURis and mTURP and the EAC has collected data in section 3.6 wherever it was available. However healthcare associated infection does not appear to be a pivotal outcome measure in a comparison between TURis and mTURP.

The sponsor added post-operative incidence of clot retention as an outcome in the submission. Although this was not specified in the scope, clinical experts advise that it is an important outcome.

The submission does not focus heavily on quality of life, as this outcome does not appear in the meta-analyses or the economic model. Section 7.9.1 of the sponsor's submission briefly cites studies that indicate that TURis is equivalent to mTURP for quality of life-related outcomes and functional outcomes. Section 3.6 of this report lists both quality of life-related outcomes and functional outcomes for each study, but neither group of outcomes are pivotal in the comparison of TURis and mTURP, because the two techniques are equivalent in these respects.

The sponsor has sought data for adverse events and provides a summary in section 7.7 of the submission. The sponsor has not performed a meta-analysis of longer term complications following surgery i.e. urethral strictures and bladder neck stenoses. The EAC performed meta-analyses for these outcomes.

None of the submitted evidence originates from the UK, so meta-analyses performed by the sponsor (or by the EAC) may be affected by differences in clinical practice between countries. For example, differences in discharge critieria following surgery may affect hospital stay.

2.3.5 Cost analysis

The cost analysis covers the two scenarios specified in the scope namely, hospitals which are currently using the Olympus TURP system in a monopolar configuration, and hospitals which are not currently using the Olympus TURP system in a monopolar configuration. The difference in scenarios is reflected in the cost of capital equipment. However the difference in cost is reduced because the model assumes that the Olympus generator is supplied without capital cost to hospitals performing 150 TURis cases per year. The remaining capital costs in either scenario are for three resectoscopes (and sub components) per Olympus generator.

Clinical experts confirmed that the case mix in the model in terms of consumable electrodes is reasonable.

The cost perspective is reasonable, accepting that TURis does not appear to impact upon social services.

The time horizon is not specified but covers the short term postoperative period (e.g. 1 month or so). The time horizon does not permit modelling of longer term complications (urethral strictures and bladder neck contractures) but evidence from randomised trials indicates that rates of these two complications are similar following TURis and mTURP.

The sponsor has undertaken one-way sensitivity analysis on each of the model inputs, a threshold analysis of each model variable to identify the point at which the model becomes cost neutral and a probabilistic sensitivity analysis in the model for each model parameter.

2.3.6 Subgroups

The scope specified two subgroups of interest: individuals with prosthetic lower limbs because in mTURP, the return electrode is normally placed on the patient's thigh, and patients with cardiac pacemakers, due to the risk of electrical interference caused by electrosurgery current. Both the sponsor and the EAC identified no evidence for TURis used in either group. The sponsor included subgroup analysis from Michielsen 2011 for TURis used in men with large (> 60 g) prostate volume and men on oral anticoagulant therapy. There are no striking differences in outcomes following TURis in either subgroup to the wider population of men with LUTs, and neither subgroup is considered specifically in the economic model.

Both the sponsor and the EAC have not highlighted any issues related to equality.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

3.1.1 Retrieval of published clinical evidence

The sponsor searched the following databases:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R)
- EMBASE
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2014
- EBM Reviews - Cochrane Central Register of Controlled Trials January 2014,
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2014,
- EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2014,
- EBM Reviews - Health Technology Assessment 1st Quarter 2014
- Econlit 1886 to February 2014

The reference lists of identified systematic reviews were also searched.

The sources searched provide reasonable coverage of likely published evidence though the following would have made the search for published evidence more rigorous

- search of conference proceedings
- reference list checking of included studies
- contact of authors of included studies to check for other data

3.1.2 Retrieval of unpublished clinical evidence

The sponsor searched their own organisational records for any relevant unpublished data. The sponsor also searched ClinicalTrials.gov for ongoing studies and MHRA and FDA databases for adverse events. The sources searched provide reasonable coverage of likely unpublished evidence. A search of the WHO International Clinical Trials Registry Platform together with the additional sources 1. and 3. listed above would have made the search for unpublished evidence more rigorous.

3.1.3 Search strategy

The strategy has been assessed in accordance with the PRESS checklist (Peer Review of Electronic Search Strategies). The search strategy used by the sponsor is comprehensive using a range of Medical Subject Headings and free-text terms together with Boolean and proximity operators. The sponsor stated that both RCTs and non-RCTs were to be included. The study design terms used by the sponsor in the search strategy is not sufficient to identify all potential studies. The Cochrane Collaboration have validated study design filters for identifying RCTs however study design filters for non-RCTs have not been validated. Therefore to ensure that both RCTs and non-RCTS are retrieved a search should be performed without terms that describe study designs.

3.2 Critique of the sponsor's study selection

A flow diagram of study selection was included in the sponsor's submission. This was mostly clearly presented except for how the 1116 records were obtained in relation to the number of records identified by the database searches presented in the sponsor's appendix. The sponsor did not identify any unpublished studies.

The sponsor's study inclusion criteria are in keeping with the Scope, and restrict to English language papers and English language abstracts.

3.3 Included and excluded studies

3.3.1 Sponsor's included and excluded studies

The sponsor describes its submission of clinical evidence as 14 randomised trials (Abascal Junquera et al. 2006;Akman et al. 2013;Chen et al. 2009;Chen et al. 2010;Fagerstrom et al. 2009;Fagerstrom et al. 2011;Goh 2010;Goh 2009;Gulur 2010a;Gulur 2010b;Michielsen et al. 2007;Michielsen et al. 2010a;Michielsen et al. 2010b;Rose et al. 2007) and 10 observational studies (Bertolotto 2009;Fumado 2011;Giulianelli 2012;Ho et al. 2007;Jun Hyun 2012;Lee et al. 2011;Michielsen et al. 2010c;Michielsen et al. 2011;Petkov, I 2011;Puppo et al. 2009).

3.3.2 EAC literature search

The EAC conducted an independent search for clinical and economic evidence relevant to the scope. The methods are presented in Appendix 1. Briefly, we searched of the following sources: Medline, Medline in Process, Embase, The Cochrane Library, HEED, EconLit, Web of Science, National Technical Information Service database, NHS Evidence, Pubmed, International Clinical Trials Registry Platform, Clinicaltrials.gov, MAUDE, MHRA and EMA. In addition, citation tracking of the sponsor's included studies was performed in Web of Science and the reference lists of the sponsor's included studies as well as relevant systematic reviews were checked for other relevant publications. We also contacted the author of every randomised trial with a general request for additional study information.

This did not yield any extra data, although subsequent, specific queries led to clarifications by authors in several instances.

Figure 1 shows the EAC's study selection process. The EAC included:

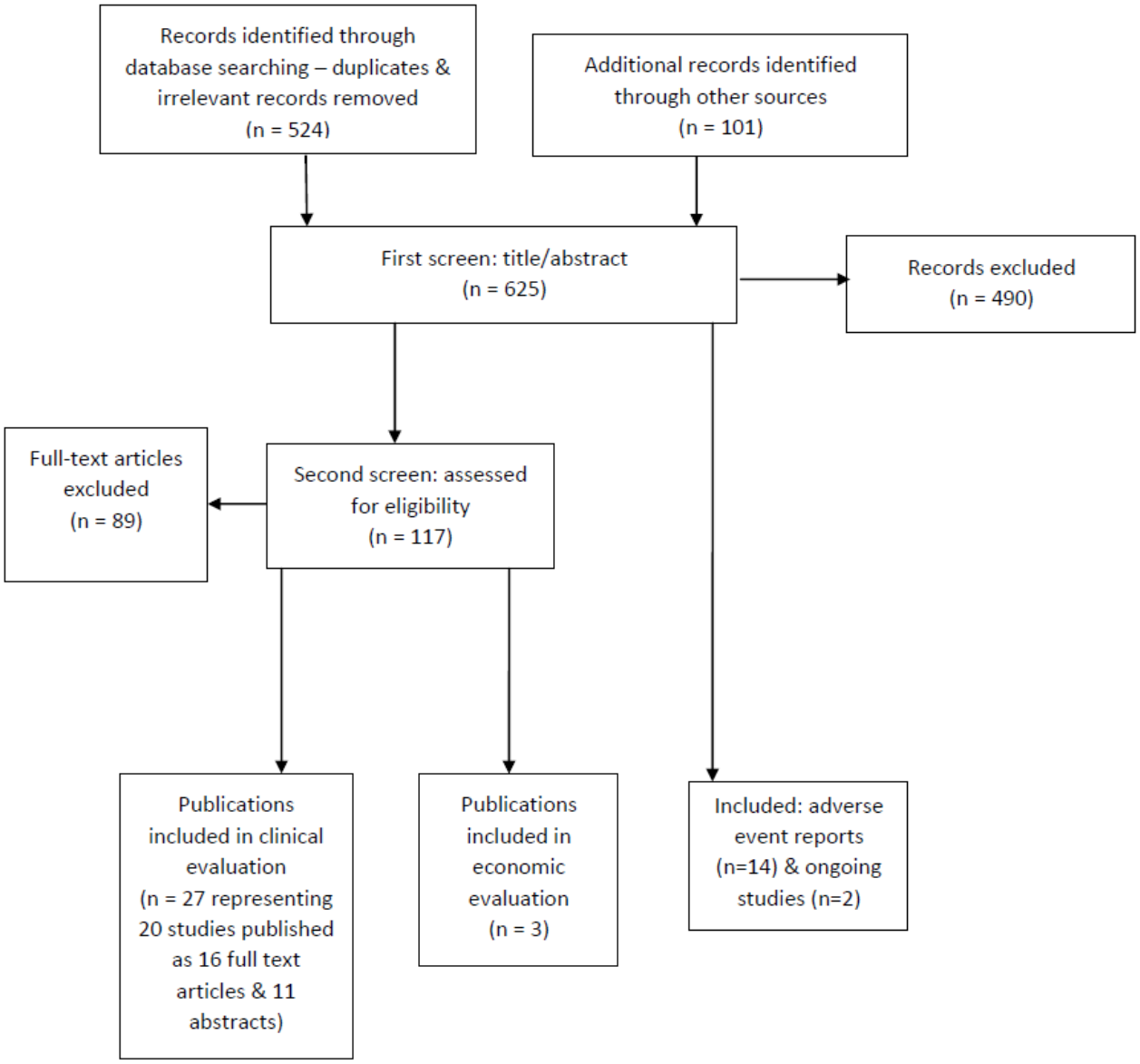
27 clinical study publications representing 20 studies (16 full text articles and 11 abstracts)

published economic evaluations

14 adverse incident reports

2 ongoing studies.

Figure 1: EAC's study selection flowchart



3.3.3 EAC-selected studies and nomenclature

All of the sponsor's included papers were identified by the EAC's literature search and all of them present data that are relevant to the scope, so the EAC did not exclude any of the papers. However having examined the papers the EAC describes the body of evidence comparing TURis with mTURP, pointing out the following characteristics:

- Distinction between studies available as full papers in English language, full papers in non-English language but with English language abstracts, and studies available only as conference abstracts.

- There are instances where multiple papers or abstracts report data from the same randomised trial. This is not made explicit and is problematic in the 5 papers published by Michielsen and colleagues (Michielsen, Debacker, De, V, Van, Kaufman, Braeckman, Amy, Keuppens, Michielsen, Debacker, De Boe, Van Lersberghe, Kaufman, Braeckman, Amy, & Keuppens 2007;Michielsen, Coomans, Braeckman, Umbrain, Michielsen, Coomans, Braeckman, & Umbrain 2010a;Michielsen, Coomans, Michielsen, & Coomans 2010b;Michielsen, Coomans, Peeters, Braeckman, Michielsen, Coomans, Peeters, & Braeckman 2010c;Michielsen, Coomans, Van, Braeckman, Michielsen, Coomans, Van Lersberghe, & Braeckman 2011), and led the sponsor to double count cases in one meta-analysis. The same issue is not made explicit in the case of 4 abstracts from the same team (Goh 2010;Goh 2009;Gulur 2010a;Gulur 2010b), but no double counting occurred. The Fagerstom study is based on two papers (Fagerstrom, Nyman, Hahn, Fagerstrom, Nyman, & Hahn 2009;Fagerstrom, Nyman, Hahn, Fagerstrom, Nyman, & Hahn 2011), but the authors reported this clearly and it is not problematic.

- The EAC considers two papers classed as observational studies by the sponsor to be subgroup analyses from a larger randomised trial (Michielsen, Coomans, Peeters, Braeckman, Michielsen, Coomans, Peeters, & Braeckman 2010c;Michielsen, Coomans, Van, Braeckman, Michielsen, Coomans, Van Lersberghe, & Braeckman 2011).

- Distinction between randomised trials and observational studies

- Additional studies identified and included by the EAC: we found two additional randomised trials (Geavlete et al. 2011;Ho, Yip, Lim, Fook, Foo, Cheng, Ho, Yip, Lim, Fook, Foo, & Cheng 2007) and one additional observational study (Shum et al. 2014).

- A lead author confirmed to the EAC that two studies conducted at the same centre in China are separate studies (Chen 2009, Chen 2010).

- The EAC obtained translation to English of the Rose 2007 study on the basis that its data are pivotal to readmission due to haemorrhage. The EAC did not obtain translation of the paper by Abascal Junquera 2006 because its data are not pivotal to any outcome.

Therefore the volume and type of studies providing evidence on TURis, and are shown below. For ease of reference, we will refer to each study by 'EAC nomenclature' i.e. using the lead author name and year of latest publication.

There are seven randomised trials published as full papers and in English language as shown in Table 1.

Table 1 Randomised trials published as full papers

Randomised trial (EAC nomenclature)	**Paper(s)**
Akman 2013	(Akman, Binbay, Tekinarslan, Tepeler, Akcay, Ozgor, Ugurlu, Muslumanoglu, Akman, Binbay, Tekinarslan, Tepeler, Akcay, Ozgor, Ugurlu, & Muslumanoglu 2013)
Chen 2009	(Chen, Zhang, Liu, Lu, Wang, Chen, Zhang, Liu, Lu, & Wang 2009)
Chen 2010	(Chen, Zhang, Fan, Zhou, Peng, Wang, Chen, Zhang, Fan, Zhou, Peng, & Wang 2010)
Fagerstrom 2011	(Fagerstrom, Nyman, Hahn, Fagerstrom, Nyman, & Hahn 2009;Fagerstrom, Nyman, Hahn, Fagerstrom, Nyman, & Hahn 2011)
Geavlete 2011	(Geavlete, Georgescu, Multescu, Stanescu, Jecu, Geavlete, Geavlete, Georgescu, Multescu, Stanescu, Jecu, & Geavlete 2011)

Ho 2007	(Ho, Yip, Lim, Fook, Foo, Cheng, Ho, Yip, Lim, Fook, Foo, & Cheng 2007)
Michielsen 2011	(Michielsen, Debacker, De, V, Van, Kaufman, Braeckman, Amy, Keuppens, Michielsen, Debacker, De Boe, Van Lersberghe, Kaufman, Braeckman, Amy, & Keuppens 2007;Michielsen, Coomans, Braeckman, Umbrain, Michielsen, Coomans, Braeckman, & Umbrain 2010a;Michielsen, Coomans, Michielsen, & Coomans 2010b;Michielsen, Coomans, Peeters, Braeckman, Michielsen, Coomans, Peeters, & Braeckman 2010c;Michielsen, Coomans, Van, Braeckman, Michielsen, Coomans, Van Lersberghe, & Braeckman 2011)

There is also one randomised trial available only as four conference abstracts (Table 2)

Table 2: Randomised trials available only as conference abstracts

Randomised trial (EAC nomenclature)	**Abstracts**
Goh 2010	(Goh 2010;Goh 2009;Gulur 2010a;Gulur 2010b)

There are two randomised trials reported in non-English language papers with English language abstracts (Table 3). For these studies the EAC extracted data by informal means to determine whether they were pivotal to our meta-analyses (See section 3.8). The Abascal-Junquera study was not pivotal to any analysis, and was not translated to English by a formal agency. The data from this study extracted by the EAC are shown in Appendix 2, but the data are not tabulated elsewhere in this report. The Rose 2007 study was formally translated to English due to its pivotal role in meta-analysis of the outcome readmission due to haemorrhage, and its data are tabulated in this report.

Table 3: Randomised trials reported in non-English language papers with English language abstracts

Randomised trial (EAC nomenclature)	Abstracts
Abascal Junquera 2006	(Abascal Junquera, Cecchini, Salvador, Martos, Celma, Morote, Abascal Junquera, Cecchini Rosell, Salvador Lacambra, Martos Calvo, Celma Domenech, & Morote Robles 2006)
Rose 2007	(Rose, Suttor, Goebell, Rossi, Rubben, Rose, Suttor, Goebell, Rossi, & Rubben 2007)

There are four observational studies published as full papers (Table 4).

Table 4: Observational studies published as full papers

Observational study (EAC nomenclature)	Papers
Ho 2006	(Ho et al. 2006)
Lee 2011	(Lee, Ryu, Lee, Park, Yum, Han, Lee, Ryu, Lee, Park, Yum, & Han 2011)
Puppo 2009	(Puppo, Bertolotto, Introini, Germinale, Timossi, Naselli, Puppo, Bertolotto, Introini, Germinale, Timossi, & Naselli 2009)
Shum 2014	(Shum, Mukherjee, Teo, Shum, Mukherjee, & Teo 2014)

There are five observational studies available as abstracts (Table 5).

Table 5: Observational studies available as abstracts

Observational study (EAC nomenclature)	**Papers**
Bertolotto 2009	(Bertolotto 2009)
Fumado 2011	(Fumado 2011)
Giulianelli 2012	(Giulianelli 2012)
Hyun 2012	(Jun Hyun 2012)
Petkov 2011	(Petkov, I 2011)

3.3.4 Key features of studies: randomised trials published as full papers

Table 6: Randomised trial: Akman 2013

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men with symptomatic BPH that required surgery owing to urinary retention or failed medical therapy. **Exclusion criteria:** Patients with neurogenic bladder dysfunction, previous prostatic or urethral surgery, prostate cancer, bladder calculus or coagulopathy.	Turkey	**TURis group:** Mean 67.4 (SD 9.3) years **mTURP group:** Mean 67.7 (SD 7.7) years	**TURis group:** Mean 18.8 (SD 2.4) **mTURP group:** Mean 18.5 (SD 2.7)	**TURis group:** Mean 7.2 (SD 2.9) ml/s **mTURP group:** Mean 8.0 (SD 3.6) ml/s	**TURis group:** Mean 59.7 (SD 24.9) ml **mTURP group:** Mean 55.9 (SD 23.9) ml	RCT comparing TURis 26 F resectoscope at 200 W (cut) and 100 W (coagulate) Versus MTURP 26 F resectoscope at 80 – 100 W (cut) and 50 – 70 W (coagulate) with Mannitol. Patients received spinal or general anaesthesia. **Follow-up:** 12 months **Surgeon:** Not reported	286 men were enrolled, 257 were analysed for long term outcomes. **TURis group:** n = 127 **mTURP group:** n = 130 **Withdrawals:** 23 men were lost to follow up and 6 died during follow up. The short term outcomes are based on 286 men.

Table 7: Randomised trial: Chen 2009

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Age > 55 years Symptomatic BPH Prostate volume > 50 ml IPSS ≥18 Q max < 15 ml/s. All men had failed medical therapy with alpha-blockers or 5-alpha reductase inhibitors. **Exclusion criteria:** Suspected prostate cancer, bladder calculus, neurogenic bladder, previous prostate surgery & urethral stricture.	China	Assume mean (SD) as paper does not specify. **TURis group:** 72.6 (6.5) years **mTURP group:** 71.8 (6.3) years	Assume mean (SD) as paper does not specify. **TURis:** 25.8 (7) **mTURP:** 26.7 (6.5)	Assume mean (SD) as paper does not specify. **TURis:** 7.8 (3.7) ml/s **mTURP:** 8.2 (4.5) ml/s	Assume mean (SD) as paper does not specify. **TURis:** 78.4 (16.4) ml **mTURP:** 76.8 (17.5) ml	RCT comparing: TURis 26 F resectoscope at 180 W (cut), 100 W (coagulate) Versus MTURP 26 F resectoscope at 120 W (cut), 70 W (coagulate) with Mannitol 4% solution. Spinal anaesthesia was used in all cases. **Follow-up:** 6 months **Surgeons:** Not reported	45 patients were enrolled, 40 were analysed: **TURis group:** n=21 **mTURP group:** n=19 **Withdrawals:** 4 patients withdrew before surgery and one was found to have prostate cancer

Table 8: Randomised trial: Chen 2010

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men in whom TURP was indicated due to BPH, who had failed medical therapy. **Exclusion criteria:** Severe pulmonary disease, allergy to alcohol, prostate cancer, bladder calculus, neurogenic bladder dysfunction, previous prostate surgery, urethral stricture, coagulopathy.	China	**TURis group:** Mean 69.7 (SD 7.6) years **mTURP group:** Mean 71.2 (SD 6.3) years	**TURis group:** Mean 22.8 (SD 5.7) **mTURP group:** Mean 21.8 (SD 6.2)	**TURis group:** Mean 7.1 (SD 3.7) ml/s **mTURP group:** Mean 7.9 (SD 3.5) ml/s	**TURis group:** Mean 60.2 (SD 18.7) ml **mTURP group:** Mean 59.1 (SD 17.3) ml	RCT comparing: TURis at 180 W (cut), 100 W (coagulate) with 1% ethanol added to the saline Versus mTURP at 120 W (cut), 70 W (coagulate) with mannitol 4% / ethanol 1%. Resectoscope sizes are not reported. Irrigation fluid uptake was monitored with a breathalyser. **Follow-up:** 2 years **Surgeons:** An experienced surgeon.	100 men were randomised and analysed. **TURis group:** n = 50 **mTURP group:** n = 50 **Withdrawals:** None.

Table 9: Randomised trial: Fagerstrom 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men with symptomatic BPH requiring surgery due to failed medical therapy or urinary retention and a TRUS-estimated prostatic value of 30 – 100 ml. **Exclusion criteria:** Prostate cancer, core biopsy of prostate within 3 months before scheduled surgery, neurogenic bladder dysfunction, urethral strictures. Patients with prostates of size < 30 ml underwent TUIP and those with prostates > 100 ml underwent open prostatectomy.	Sweden	**TURis group:** Mean 69.5 (SD 7.2) years **mTURP group:** Mean 72.7 (SD 8.4) years	**TURis group:** Mean 21.7 (SD 6.9) **mTURP group:** Mean 20.4 (SD 7.6)	Not reported	**TURis group:** Mean 55.6 (SD 18.2) ml **mTURP group:** Mean 58.2 (SD 17.6) ml	RCT comparing TURis using 24F resectoscope, 280 W (cut) and 100 W (coagulate). Ethanol 1% was added to the saline. Versus MTURP using 24F resectoscope 130 W (cut) and 50 W (coagulate) and mannitol 3%, ethanol 1% irrigation fluid In both groups fluid uptake was monitored with an alcometer. Blood loss was measured with a photometer. **Follow-up:** 18 months **Surgeon:** Two residents performed 14 evaluable operations, all others performed by 10 specialists in urology with ≥ 5 years of urological experience.	202 men were randomised, 185 were analysed **TURis group:** n = 98 **mTURP group:** n = 87 **Withdrawals:** 17 men were excluded: TUIP: 4 Withdrawal: 3 Bladder cancer: 3 Prostate cancer: 3 Otherwise ineligible: 4

Table 10: Randomised trial: Geavlete 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men with bladder outlet obstruction and : Qmax <10 mL/s IPSS > 19 Prostate volume 30 - 80 ml. **Exclusion criteria:** Severe comorbidities, previous prostate surgery, history of prostate cancer, abnormal digital rectal examination, increased prostate-specific antigen.	Romania	Stated for the whole study as mean 67 (range 51–83) years	**TURis Group:** 24 (20-32) **mTURP group:** 24.2 (20-31)	**TURis Group:** 6.1 (3.9-9.2) ml/s **mTURP group:** 6.4 (4.4-9.5) ml/s	**TURis Group:** 53.7 (30-79) ml **mTURP group:** 54.8 (32-80) ml	3-arm RCT comparing: TURis with standard resection loop Versus mTURP with 26 F resectoscope and sterile water Versus BPVP with button electrode (data not shown) **Follow-up:** 18 months **Surgeons:** Not reported	**TURis group:** n = 170 **mTURP group:** n = 170 **Withdrawals:** Not reported

Table 11: Randomised trial: Ho 2007

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men of age > 50 years with TURP indicated due to failure of medication, IPSS > 18, Qmaz < 15 ml/s, acute urinary retention or a failed trial of voiding without urinary catheter, recurrent urinary tract infection, haematuria. **Exclusion criteria:** Documented or suspected prostate cancer, bladder calculus, neurogenic bladder, previous prostate surgery, renal impairement/hydronephrosis, urethral stricture.	Singapore	**TURis group:** Mean 66.6 (SD 6.8) years **mTURP group:** Mean 66.5 (SD 7.2) years	**TURis group:** Mean 22.6 (SD 5.5) **mTURP group:** Mean 24.6 (SD 6)	**TURis group:** Mean 6.8 (SD 4.8) ml/s **mTURP group:** Mean 6.5 (SD 3.2) ml/s	**TURis group:** Mean 56.5 (SD17.9) ml **mTURP group:** Mean 54.8 (SD 19.2) ml	RCT comparing: TURis with 26F resectoscope, 180 W (cut), 100 W (coagulate) Versus MTURP with 26F resectoscope, 100 W (cut), 50W (coagulate) and glycine 5%. **Follow-up:** 12 months	100 men were randomised an analysed. **TURis group:** n = 50 **mTURP group:** n = 50 **Withdrawals:** None

Table 12: Randomised trial: Michielsen 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men with bladder outlet obstruction due to BPH with IPSS ≥ 13, QoL index ≥ 3 and Qmax < 15 ml/s. **Exclusion criteria:** Neurogenic bladder, prostate cancer, previous prostatic or urethral surgery, bladder stones.	Belgium	**TURis group:** Mean 72.1 (SD 9.4) years **mTURP group:** Mean 72.4 (SD 9.0) years **Sub-group analysis** **Large (>60g) BPH:** **TURis group:** Mean 71.88 (SD ± 8.78) years **mTURP group:** Mean 70.12 (SD ±7.95) years **Oral anticoagulants:** **TURis group:** Mean 75.11 (SD ±7.83) years **mTURP group:** Mean 73.64 (SD ±9.0) years	Not reported	Not reported for the whole sample. **Sub-group analysis** **Large (>60g) BPH:** **TURis group:** Mean 7.08 (SD ± 2.77) ml/s **mTURP group:** Mean 7.87 (SD ± 3.43) ml/s **Oral anticoagulants:** not reported	**TURis group:** Mean 45 (SD 18.3) cc **mTURP group:** Mean 53.9 (SD 23.6) cc Data are based on a subset of 263 (TURis) and 255 (mTURP) patients **Sub-group analysis** **Large (>60g) BPH: TURis group:** Mean 78.30(SD ± 11.83) ml **mTURP group:** Mean 78.85 (SD ±14.94) ml **Oral anticoagulants: TURis group:** Mean 55.11 (SD ±16.29) ml **mTURP group:** Mean 55.61 (SD ±24.01) ml	RCT comparing: TURis with 24F resectoscope, 270 W (cut), 75 W (coagulate) Versus MTURP with 24F/26F resectoscope, 175 W (cut), 75 W (coagulate), glycine 1.5% **Follow-up:** Stated as 32.1 months (mTURP) and 31.4 months (TURis), based on a subset of 263 (TURis) and 255 (mTURP) patients **Surgeons:** In the first 238 patients (reported in the 2007 paper) the following procedures were performed by staff/trainee surgeons: TURis: 81/38 mTURP: 112/8 Total 193/46	550 randomised **TURis group:** n = 285 **mTURP group:** n = 265 **Withdrawals:** Not reported. The 2007 paper reports on 238 patients as follows: **TURis group:** n = 118 **mTURP group:** n = 120 **Sub-group analysis** **Large (>60g) BPH: TURis group:** n=33 **mTURP group:** n=33 **Oral anticoagulants:** **TURis group:** n=98 **mTURP group:** n=78

Table 13: randomised trial: Rose 2007

Note: the EAC arranged translation of the paper from German to English by an agency accredited to the to the BS EN 15038 translation standard.

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients with bladder tumours or enlarged prostate **Exclusion criteria:** Not known	Germany	**TURis group:** **mTURP group:**	Not reported	Not reported	Not reported	RCT comparing TURis Versus MTURP **Follow-up:** Not known **Surgeons:** Not known	128 patients in total, 56 treated for bladder cancer, 72 treated for prostate enlargement. **TURis group:** n = 38 (prostate) **mTURP group:** n = 34 (prostate) **Withdrawals:** Not known

3.3.5 Key features of studies: randomised trial published in conference abstract form

Table 14: Randomised trial: Goh 2010

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients with benign prostatic obstruction. **Exclusion criteria:** Not reported	Multicentre Country/ies not reported	**TURis group:** 72 years **mTURP group:** 73 years Reported as 'comparable' (p = 0.65 in 156 patients; p = 0.3 in 210 patients)	Not reported	Not reported	Based on 156 patients: **TURis group:** 71.6 cc **mTURP group:** 73.6 cc Reported as 'comparable' (p=0.75) Based on 210 patients: **TURis group:** 68.9 cc **mTURP group** 69.8 cc (p = 0.8)	Abstracts only RCT comparing: TURis Versus mTURP **Follow-up:** 12 months **Surgeons:** Not reported	210 patients were recruited and randomised. The first 156 patients were followed-up with IPSS scores and flow rates. **TURis group:** n = 110 (80 followed up) **mTURP group:** n = 100 (76 followed up) **Withdrawals:** Not reported

3.3.6 Key features of studies: observational studies published as full papers

Table 15: Observational study: Ho 2006

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Clinical significant BPH **Exclusion criteria:** Suspected prostate cancer, bladder calculus, neurogenic bladder, previous TURP, urethral stricture, renal impairment or obstructive hydronephrosis	Singapore	Mean 66 yrs (range 50 – 87)	Mean 22.6 (range not reported)	Mean 6.5 ml/s (range not reported) n=23	Mean 32.7cc (range 18.3-89.2)	Uncontrolled before and after evaluation of TURis, 200W (cut), 100 W (coagulate) Regional anaesthesia was used in all but two cases. **Follow-up:** 12 months, n=15 mean 10.7months (3-12) **Surgeon:** Not reported	45 patients were enrolled, **Withdrawals:** 30 men were lost at 12 mth follow-up

Table 16: Observational study: Lee 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men who underwent TURP, TURis or TURis-V for BPH. Indications for surgery were Qmax < 15ml/s, IPSS of ≥ 12, and American Society of Anesthesiologists classification of ≤2. **Exclusion criteria:** Prostate cancer, neurogenic bladder, UTI, urethral stricture, previous prostate surgery, chronic renal failure, receiving anticoagulant therapy.	Korea	**TURis group:** 70.16 years ±4.32 **TURP group:** 69.79 years ±6.33 **TURis-V group:** 73.40 years ±7.62	**TURis group:** 25.26 ±3.31 **TURP group:** 23.77 ±4.41 **TURis-V group:** 24.47 ±5.10	**TURis group:** 8.74 ml/s ±2.28 **TURP group:** 8.38 ml/s ±3.90 **TURis-V group:** 8.07 ml/s ±3.56	**TURis group:** 68.83ml ±14.94 **TURP group:** 62.34ml ±18.25 **TURis-V group:** 61.45ml ±21.59	Retrospective comparative cohort TURis 24 Fr resectoscope Versus Monopolar TURP 24Fr resectoscope with Urosol Versus TURis-plasma vaporisation (TURis-V) (out of scope) **Follow-up:** 6 months **Surgeons:** Single surgeon	Data from 73 consecutive men were analysed. **TURis group:** n = 19 **TURP group:** n = 39 **TURis-V group:** n = 15 **Withdrawals:** All completed 6mth follow-up

Table 17: Observational study: Puppo 2009

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Diagnosis of BPH with Qmax <10 ml/s, IPSS >13, PV 20-80 ml. **Exclusion criteria:** Not reported	Italy	**TURis group:** Median 66.5 years (47-86)	**TURis group:** Median 24 (13-35)	**TURis group:** Median 6 ml/s (0-10)	**TURis group:** Median 52 ml (20-80	Uncontrolled, before and after study TURis 26 Fr resectoscope, cutting 280 W & coagulation 120 W **Follow-up:** 6 months **Surgeons:** Not reported	**TURis group:** n =376 **Withdrawals:** All completed 6 month follow-up

Table 18: Observational study: Shum 2014

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients with indications for TURP (failed medical treatment, intolerable adverse effects from medical treatment, urinary retention, other BPH complications) **Exclusion criteria:** Large prostatic capsular defect, bladder neck incision after resection, peri-operative haemodynamic instability, peri-operative fever.	Singapore	Mean 70.8 years ±8.6	**TURis Group:** 18.6 ±7.8 **TURP group:** n/a Excludes patients with urinary retention who were on a urinary catheter immediately before the procedure	**TURis Group:** 9.8 ±3.7 ml/s **TURP group:** n/a Qmax reported as 'peak flow'. Excludes patients with urinary retention who were unable to void before the procedure.	**TURis Group:** not reported **TURP group:** n/a	Uncontrolled before and after TURis with 26 F resectoscope , cutting at 280 W and coagulation at 100 W with spinal anaesthesia **Follow-up:** 6 months **Surgeons:** Report implies that the 3 authors performed the procedures. 14 patients underwent other procedures in the same setting (cystolitholapaxy, inguinal hernia repair & ureteric stenting).	**TURis group:** n=100 **TURP group:** n/a **Withdrawals:** The authors report that all 100 patients completed at least 6 months of postoperative follow-up, but state that 82% attended a review at 6 months, implying that 18 patients may have been withdrawn.

3.3.7 Key features of studies: observational studies published in conference abstract form

Table 19: Observational study: Bertolotto 2009

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients undergoing TURP, TUIP or TURB, treated with TURis with a follow up of at least 6 months **Exclusion criteria:** Not reported	Not reported	Not reported	Not reported	Not reported	median 52ml	Abstract only Retrospective cohort (casenote review) **Follow-up:** Minimum 6 months **Surgeons:** Not reported	1000 consecutive records of patients treated using TURis. **mTURP group:** n = 376 **TUIP group:** n = 144 **TURB group:** n = 480 **Withdrawals:** Not reported (retrospective study)

Table 20: Observational study (abstract): Fumado 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients treated with TURis for TURP **Exclusion criteria:** Patients with less than 12 months of follow-up	Not reported	**TURis group:** Mean 69.7 (range 50-89) years **TURP group:** n/a	**TURis group:** Mean 23.2 (range 8-34) **TURP group:** n/a	**TURis group:** Mean 8.2 (range 2-15) ml/s **TURP group:** n/a	**TURis group:** Mean 61 (range 24-134) cc **TURP group:** n/a	Abstract only Cohort study **Follow-up:** 12 months **Surgeons:** Single surgeon	**TURis group:** n = 120 **TURP group:** n = n/a **Withdrawals:** None (study may be retrospective)

Table 21: Observational study: Giulianelli 2012

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients with LUTS (from BOO to BPE) who underwent TURP **Exclusion criteria:** Responders to drug therapies	Not reported	**All patients:** Mean age 65.5 (range 48-83) years	Not reported	Not reported	Not reported	Abstract only Non-randomised study comparing: TURis using Surgmaster scapel Versus MTURP Versus Plasmakinetic energy (Gyrus system) **Follow-up:** 12 months **Surgeons:** Single surgeon	320 consecutive patients enrolled, the first 160 being a historical reference group. **TURis group:** n = 160 **mTURP group:** n = 80 **Plasmakinetic group:** n = 80 **Withdrawals:** Not reported

Table 22: Observational study: Hyun 2012

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Men with benign prostate hyperplasia **Exclusion criteria:** Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Abstract only Retrospective casenote review comparing: TURis Versus mTURP Versus TURis Plasma Vaporisation (TURis-V) **Follow-up:** 6 months **Surgeons:** Single surgeon	73 consecutive records reviewed **TURis group:** n = 19 **mTURP group:** n = 39 **TURis-V group:** n = 15 **Withdrawals:** All patients were assessed perioperatively, and 'most' were followed-up to 6 months.

Table 23: Observational study: Petkov 2011

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Patients with symptomatic BPH **Exclusion criteria:** Not reported	Not reported	Not reported. Pre-op characteristics comparable in both groups.				Prospective comparative cohort comparing: TURis Versus Monopolar TURP **Follow-up:** 1 month **Surgeon:** Not reported	45 men were enrolled **TURis group:** n = 21 **TURP group:** n = 24 **Withdrawals:** None reported

3.4 Overview of methodologies of all included studies

The sponsor's submission relies on the evidence provided by the randomised trials. Table 24 in Section 3.4.1 provides a summary of all randomised trials that the EAC considers eligible for inclusion, and this is followed in Section 3.4.2 by narrative descriptions of each study in turn. The observational studies have less influence in the submission, and these are summarised in a brief narrative in Section 3.4.3.

3.4.1 Tabulated description of the randomised studies

Table 24: summary of the randomised trials

Study	Country	Design	Population size	Follow-up	Quality
Akman 2013	Turkey	TURis v monopolar TURP	286 men were enrolled, 257 were analysed for long term outcomes. **TURis group:** n = 127 **mTURP group:** n = 130	12 months	The paper does not report the method of randomisation, whether blinding was performed, or a sample size calculation.
Chen 2009	China	TURis v monopolar TURP	45 patients enrolled, 40 analysed: **TURis group:** n=21 **mTURP group:** n=19	6 months	The paper does not report: method of randomisation, sample size calculation, methods for statistical analysis or whether any competing interests exist.
Chen 2010	China	TURis v monopolar TURP	100 patients randomised and analysed. **TURis group:** n = 50 **mTURP group:** n = 50	2 years	The capsular perforation data are shown for breathalysed men only, because measured fluid absorption was analysed against operating time in men with and without capsular perforation. There was a strong correlation between operating time and fluid absorption in both groups.
Fagerstrom 2011	Sweden	TURis v monopolar TURP	202 men were randomised, 185 were analysed **TURis group:** n = 98 **mTURP group:** n = 87	18 months	The study was powered to detect a 30% difference in blood loss. Method of randomisation was random number table. The paper does not report whether patients or assessors of outcome were blinded to random allocation. Intermittent irrigation (versus continuous irrigation with Reuter's trocar) varied slightly between groups: 81% in the TURis group and 71% in the MTURP group.
Geavlete 2011	Romania	3-arm RCT: TURis v BPVP v monopolar TURP	340 **TURis group:** n = 170 **mTURP group:** n = 170	18 months	Data are not shown for the third study arm: BPVP. P values not shown here as relate to three patient groups (ANOVA or Chi square), not two. The paper does not state whether average values are means, nor whether measures of spread are ranges. Both patients and assessors of outcome were blinded to allocation.

Study	Country	Design	Population size	Follow-up	Quality
Goh 2010	Not reported	TURis v monopolar TURP	210 patients were recruited and randomised. The first 156 patients were followed-up with IPSS scores and flow rates. **TURis group:** n = 110 (80 followed up) **mTURP group:** n = 100 (76 followed up)	12 months	Abstracts only. It is not clear for all of the outcomes whether they refer to the entire sample (210 patients) or only those which were followed-up for 12 months (156 patients)
Ho 2007	Singapore	TURis v monopolar TURP	100 men were randomised an analysed. **TURis group:** n = 50 **mTURP group:** n = 50	12 months	All cases had histologically confirmed BPH. 45 patients had acute urinary retention. Randomisation was by computer programme. No sample size calculation is reported. Study appears to be unblinded. There were no losses to follow-up at 12 months.
Michielsen 2011	Belgium	TURis v monopolar TURP	550 randomised **TURis group:** n = 285 **mTURP group:** n = 265	32.1 months (mTURP) & 31.4 months (TURis), based on a subset of 263 (TURis) and 255 (mTURP) patients	The data is published in three papers, where each patient sample is included in the subsequent sample. The three samples are 238 patients (Jan2005-Jun 2006), 518 patients (Jan 2005-Jan 2009) and 550 patients (Jan 2005-Aug 2009). The lead author confirmed this. The numbers of men who were ineligible for inclusion or who did not consent to enter the trial, are not available. Loss to follow-up is not reported.
RRose 2007	Germany	TURis v monopolar TURP	128 patients in total, 56 treated for bladder cancer, 72 treated for prostate enlargement. **TURis group:** n = 38 (prostate) **mTURP group:** n = 34 (prostate)	Not reported	Data extracted from English language abstract and tabulated results in the German language peer reviewed journal publication. All data cited are for patients with enlarged prostate (not those treated for bladder cancer).

3.4.2 Narrative description of the randomised studies

This section provides a narrative description of randomised studies with the main results. More detailed results from the randomised studies are tabulated in section 3.6.

The Turkish randomised trial by Akman et al. 2013 allocated 286 patients to TURis or mTURP. Inclusion criteria were symptomatic BPH requiring surgical intervention due to urinary retention or failed medical therapy. 257 patients were analysed. Baseline prostate volumes were 59.7 ml (TURis) and 55.9 ml (mTURP). Mean procedure duration was 54 min (TURis) versus 58.7 min (mTURP), p = 0.03. There were zero versus 2 cases of TUR syndrome in each group respectively, and 3 versus 8 cases of blood transfusion (p=0.2) and 1 versus 2 cases of clot retention requiring recatheterisation, respectively. Time to removal of the catheter was at a mean of 2.4 days postoperatively in the TURis group, versus 2.6 days in the mTURP group. Hospital stay was mean 2.5 days versus 2.7 days respectively. At 12 months follow up Improvements in IPSS and Qmax at 12 months were similar in both groups. There were 8 cases of urethral stricture / bladder neck contracture in the TURis group versus 6 in the mTURP group.

The Chinese randomised trial by Chen et al. 2009 studied men with large prostate glands: 78.4 ml (TURis) and 76.8 ml (mTURP). The study randomly allocated 45 patients to TURis or mTURP. Inclusion criteria were age > 55 years, symptomatic BPH, prostate volume > 50 ml, IPSS > 18, Qmax < 15 ml/s and previous failure of medical therapy. Baseline prostate volumes were 78.4 ml (TURis) and 76.8 ml (mTURP). Procedure duration was 88 minutes (TURis) versus 105 minutes (mTURP), p = 0.001. There were zero and 1 cases of TUR syndrome, respectively, and 1 versus 3 cases of blood transfusion, respectively. Catheter removal occurred at 2.5 postoperative days (TURis) versus 3.4 days (mTURP). Respective values for hospital stay were 3.0 days versus 4.2 days, p = 0.001, making this the only study to find a statistically significant advantage in hospital stay arising from TURis. At 6 months follow up there was little difference between groups for IPSS and Q_{max}.

The same team of authors published results of another randomised study in 2010 (Chen 2010) and the authors confirmed that this is a different study to the one described above. 100 men who had failed medical therapy and in whom surgery was warranted were randomly allocated to TURis or mTURP. Baseline prostate volume was mean 60.2 ml (TURis) and 59.1 ml (mTURP). Procedure duration was 59 minutes (TURis) versus 60 minutes (TURP), p = 0.82. There were no cases of TUR syndrome in either group (this also confirms that this is a different study to the one above). 1 patient (TURis) and 3 patients (mTURP) required blood transfusions, p = 0.62. Respective rates of clot retention were zero cases versus 2 cases, p = 0.49. The study did not report the time to removal of catheter or hospital stay. At 2 years follow up there was no difference between groups for functional outcomes including IPSS, Q_{max} and IIEF-5.

The trial by Fagerstrom 2011 randomised 202 men to TURis or mTURP, and analysed 185 men, with reasons given for withdrawals. Men had a baseline prostate volume of 30 – 100 ml on ultrasound. Baseline prostate volumes were mean 55.6 ml (TURis) and mean 58.2 ml (mTURP). Procedure duration was mean 62 minutes (TURis) versus mean 66 minutes (mTURP). There were zero cases of TUR syndrome in the TURis group versus 3 in the mTURP group (data confirmed by lead author). Respective rates of blood transfusion were 4 versus 10 cases, p < 0.01. Catheters were removed at a median of 20 hours in both groups and 8 (TURis) versus 10 (mTURP) men were discharged with catheter in situ. Hospital stay was median 51 hours (TURis) versus median 52 hours (mTURP). The rate of re-admission (any cause) was 5/98 (TURis) versus 14/87 (mTURP), p < 0.011; respective values for repeat procedures due to incomplete resection were 2

cases versus 4 cases, and respective values for readmission due to haemorrhage were 2 cases versus 7 cases. IPSS improved greatly in both groups, with no between-group difference at 3 weeks and with the benefit sustained through 18 months of follow up.

The Romanian randomised trial by Geavlete 2011 allocated 340 men with bladder outlet obstruction, Qmax <10 ml/s, IPSS >19 and prostate volume 30-80 ml to TURis or mTURP. Baseline prostate volume was 53.7 ml (TURis) and 54.8 ml (mTURP). Procedure duration was 52.1 minutes (TURis) versus 55.6 minutes (mTURP). There were zero (TURis) versus 3 (mTURP) cases of TUR syndrome. Respective values for blood transfusion were 3 versus 11, and for clot retention 2 versus 7. Time to removal of catheter was 46.3 hours (TURis) versus 72.8 hours (mTURP). Respective values for hospital stay were 3.1 days versus 4.2 days. The rate of readmission due to haemorrhage was 2 cases (TURis) versus 6 cases (mTURP). The authors reported 'retreatment rate' as 16 cases (TURis) versus 15 cases (mTURP); these events appear distinct from data on sclerosis and stricture and the EAC interpreted them as representing repeat procedure due to incomplete resection. Functional outcomes at 18 months were similar between groups for IPSS and Qmax.

Goh 2010 conducted a multicentre randomised study (countries not reported) and published results in four conference abstracts. 210 men with benign prostatic obstruction were randomly allocated to TURis or mTURP. Baseline prostate volume was 71.6 cc (TURis) and 73.6 cc (mTURP). Procedure duration was 38 minutes (TURis) versus 35 minutes (mTURP), p = 0.3. There were zero cases of TUR syndrome in the TURis group versus 3 cases in the mTURP group. Time to removal of catheter was 48 hours (TURis) versus 52 hours (mTURP), p = 0.97. Respective values for hospital stay were 90 hours versus 103 hours, p = 0.06. The authors reported IPSS and Qmax at 12 months follow up as comparable. The complication rate was 25% TURis versus 30% mTURP, p = 0.1 (follow up length not reported).

The randomised study by Ho 2007 was conducted in Singapore and randomly allocated 100 men of age >50 years with IPSS >18 and Qmax <15 ml/s to TURis versus mTURP. Baseline prostate volume was mean 56.5 ml (TURis) and mean 54.8 ml (mTURP). Procedure duration was mean 59 minutes (TURis) versus mean 58 minutes (mTURP). There were zero cases of TUR syndrome in the TURis group versus 2 cases in the mTURP group, p < 0.05. There were 2 cases of blood transfusion; 1 case in each group. Clot retention occurred in 3 cases (TURis) versus 2 cases (mTURP). At 12 months follow up IPSS and Qmax values were similar between groups.

The study by Michielsen 2011 randomly allocated a total of 550 men with IPSS >13 and Qmax <15 ml/s to TURis versus mTURP. There is significant duplicate reporting in 3 published papers, and in addition the study undertook subgroup analysis of outcomes in men with large baseline prostate volume (> 60 g) and men on oral anticoagulant medication. For these reasons the denominator values for many outcome measures varied across the published papers. Baseline prostate volume was mean 45 cc in 263 men (TURis) and mean 53.9 cc in 255 men (mTURP). Procedure duration was mean 52.1 minutes (TURis) versus mean 50.9 minutes (mTURP), p = 0.357. There were 0/285 cases of TUR syndrome in the TURis group versus 2/265 cases in the mTURP group. 4/118 men required blood transfusion (TURis) versus 1/120 men (mTURP), p = 0.211. Clot retention occurred in 4/118 patients (TURis) versus 6/120 patients (mTURP), p = 0.749. Time to removal of catheter was mean 1.64 days (TURis) versus mean 1.64 days (mTURP), p = 0.815. Respective values for hospital stay were mean 3.72 days (TURis) versus mean 3.89 days (mTURP), p = 0.773. There were 0/118 cases of revision due to incomplete resection in the TURis group versus 2/120 cases in the mTURP group.

Of men with large prostate glands, 33 were randomly allocated to TURis and 33 to mTURP. Mean prostate volumes were 78.5 ml and 78.9 ml, respectively. There was no statistically significant difference in mean procedure time between TURis (67 minutes) and mTURP 59 minutes, p = 0.131, or mean hospital stay (3.9 versus 3.6 days, respectively, p = 0.748). TUR syndrome occurred in zero cases versus 1 case, respectively, p = 1.000.

Of men on oral anticoagulants, 98 were randomly allocated to TURis and 78 to mTURP. Baseline prostate volumes were 55.1 ml and 55.6 ml, respectively. Mean procedure duration was longer in the TURis group (67 minutes) than in the mTURP group (37 minutes, p <0.0001). Respective mean volumes of tissue resected were 30.1 g versus 26.3 g, p = 0.282. One patient in the TURis group required blood transfusion versus 2 in the mTURP group, p = 0.585. Respective values for mean postoperative drop in haemoglobin were 1.3 g/dl and 1.2 g/dl, p = 0.603. There was also little difference in incidence of clot retention (13 versus 12 cases respectively, p = 0.828) and mean length of hospital stay (4.4 versus 4.9 days respectively, p = 0.330).

The randomised trial conducted in Germany by Rose 2007 allocated 128 men to TURis versus mTURP. Procedure duration was 55 minutes (TURis) versus 35 minutes (mTURP), p = 0.005. There were no cases of TUR syndrome in either study group. There were 4 cases of readmission due to haemorrhage in the TURis group versus 1 case in the mTURP group.

3.4.3 Narrative summary of the observational studies

The sponsor identified 10 observational studies however two of these (Michielsen 2010 & 2011) are reports of two different sub-groups of patients from the randomised controlled trial (Michielsen 2011). Of the remaining 8 observational studies 3 were published as full papers and 5 as abstracts only. The EAC identified an additional observational study (Shum 2014). None of the studies reported as full papers were conducted in the UK and the country in which the study was conducted was not reported in any of the abstracts. No additional data was gained from the observational studies to that reported by the RCTs. As reported by the sponsor, the outcomes reported from the observational studies were consistent with those from the RCTs.

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor conducted critical appraisal using a form adapted from the Centre for Reviews and Dissemination 2008 guidance for undertaking reviews in health care (Centre for Reviews and Dissemination 2008). Forms for each study were included in the submission. A summary comment on the quality of each of the studies would have been useful to capture any significant bias or conflict of interest.

The EAC has little concern around the sponsor's critical appraisal. The sponsor's claims tend to rely upon randomised trial evidence (over observational study evidence) and this is a reasonable approach. The randomised trials have limitations including small sample sizes in some cases, and, with some studies lacking a clear description of the primary outcome measure or sample size calculation. The randomised studies are seldom blinded.

3.6 Results

3.6.1 Results of randomised studies published as full papers

Table 25: Results of randomised study: Akman 2013

Outcome	TURis (n = 143)	mTURP (n = 143)	p value	Comments
Procedure duration*	Mean 54 (SD 21) min	58.7 (SD 16.8) min	p = 0.03	
Volume of tissue resected	Not reported	Not reported	Not reported	
TUR syndrome*	0/127 (0%) patients	2/130 (1.5%) patients	Not reported	
Postoperative change in Na	Mean -1.3 (SD 3.8) mEq/l	Mean -2.82 (SD 5.8) mEq/l	p = 0.03	
Postoperative change in K	Mean 0.03 (SD 0.5) mEq/l	Mean -0.18 (SD 0.4) mEq/l	p = 0.06	
Postoperative change in Cl	Mean 0.16 (SD 5.9) mEq/l	Mean -1.27 (SD 6.0) mEq/l	p = 0.16	
Need for blood transfusion*	3/127 (2.4%) patients	8/130 (6.2%) patients	p = 0.2	
Mean postoperative drop in Hb	Mean 1.2 (SD 0.9) g/dl	Mean 1.41 (SD 1.23) g/dl	p = 0.1	
Clot retention*	1/127 (0.8%)patients	2/130 (1.5%) patients	Not reported	Stated as re-catheterisation due to clot retention
Time to removal of catheter*	Mean 2.4 (SD 1.0) days	Mean 2.6 (SD 1.2) days	Not reported	
Hospital stay*	Mean 2.5 (SD 1.3) days	Mean 2.7 (SD 1.4) days	p = NS	
Readmission due to haemorrhage	Not reported	Not reported		
Need for repeat procedure due to incomplete resection	Not reported	Not reported		
Functional outcomes				
IPSS at 12 months	Mean 10.3 (SD 3.0)	Mean 10.8 (SD 2.9)	Not reported	127 (TURis) and 130 (mTURP) men were followed up for 12 months or more.
Qmax at 12 months	Mean 17.1 (SD 3.1) ml/s	Mean 16.3 (SD 4.7) ml/s	Not reported	p < 0.001 for the difference from baseline within each group. 127 (TURis) and 130 (mTURP) men were followed up for 12 months or more.

Table continues....

...Akman 2013 continued

Quality of life outcomes	Not reported	Not reported	Not reported	
Other outcomes				
Urethral stricture / bladder neck contracture	8/127 (6.3%) patients	6/130 (4.6%) patients	p = 0.7	Stated as reoperation within 1 year for urethral stricture or bladder neck contracture. 127 (TURis) and 130 (mTURP) men were followed up for 12 months or more.
International Index of Erectile Function (IIEF-ED)	12-month IIEF-ED score improved slightly relative to preoperative values in both groups but the differences were not statistically significant			Data presented graphically in paper. 127 (TURis) and 130 (mTURP) men were followed up for 12 months or more.
EAC comments on study quality The paper does not report the method of randomisation, whether blinding was performed, or a sample size calculation.				

Table 26: Results of randomised study: Chen 2009

Outcome	TURis (n = 21)	mTURP (n = 19)	p value	Comments
Procedure duration*	88 (18) min	105 (17) min	p = 0.001	Assume mean (SD) as not reported
Volume of tissue resected	56.5 (10.8) g	55.3 (9.7) g	p = NS	Assume mean (SD) as not reported
TUR syndrome*	0/21 (0%) cases	1/19 (5%) cases	Not reported	The study measured blood sodium and potassium (data not shown here)
Mean postoperative drop in sodium	6.9 (0.7) mM	14.8 (1.8) mM	p = 0.001	Assume (SD) as not reported
Hypokalemia	2/21 (9.5%) cases	1/19 (5.3%) cases	Not reported	
Need for blood transfusion*	1/21 (4.8%) cases	3/19 (15.8%) cases	Not reported	
Mean postoperative drop in Hb	1.4 g/dl	2.5 g/dl	p = 0.001	
Clot retention*	Not reported	Not reported	Not reported	
Time to removal of catheter*	2.5 (0.8) days	3.4 (0.9) days	p = 0.11	Assume mean (SD) as not reported
Hospital stay*	3.0 (0.5) days	4.2 (0.7) days	p = 0.001	Assume mean (SD) as not reported
Readmission due to haemorrhage	Not reported	Not reported	Not reported	
Need for repeat procedure due to incomplete resection	Not reported	Not reported	Not reported	
Functional outcomes				
IPSS at 3 months	9.6 (6.4)	10.6 (5.5)	Not reported	Assume mean (SD) as not reported
IPSS at 6 months	7.9 (6.6)	7.6 (5.4)	Not reported	Assume mean (SD) as not reported
Qmax at 3 months	23.5 (9.5) ml/s	24.9 (10.2) ml/s	Not reported	Assume mean (SD) as not reported
Qmax at 6 months	23.2 (10.3) ml/s	24.4 (9.6) ml/s	Not reported	Assume mean (SD) as not reported
Quality of life outcomes	Not reported	Not reported	Not reported	
Other outcomes				
Urethral stricture / bladder neck contracture	Not reported	Not reported	Not reported	
Total complications	4/21 (19%) cases	8/19 (42%) cases	Not reported	
Obturator nerve reflex	2/21 (9.5%) cases	3/19 (15.7%) cases	Not reported	
Need for catheter re-insertion	1/21 (4.8%) cases	1/19 (5.3%) cases	Not reported	
EAC comments on study quality The paper does not report the method of randomisation, sample size calculation, methods for statistical analysis or whether any				

competing interests exist.

Table 27: Results of randomised study: Chen 2010

Outcome	TURis (n = 50)	mTURP (n = 50)	p value	Comments
Procedure duration*	59 (SD 19) min	60 (SD 18) min	p = 0.82	
Volume of tissue resected	40 (SD 16) g	38.9 (SD14.5) g	p = 0.31	
TUR syndrome*	0 patients	0 patients	-	
Fluid absorption detected	17/45 (37.8%) patients	25/38 (65.8%) patients	p = 0.015	45 (TURis) and 38 (mTURP) patients were able to use the breathalyser.
Mean fluid absorption	208 (SD 344) ml	512 (SD 706) ml	p < 0.001	Based on 45 (TURis) and 38 (mTURP) patients; see above
Serum sodium decrease	3.4 (SD 1.4) mmol/l	6.3 (SD 2.9) mmol/l	p < 0.001	
Capsular perforation	9/45 (20%) patients	15/38 (39%) patients	Not reported	Data presented for breathalysed men only.
Need for blood transfusion*	1/50 (2%) patients	3/50 (6%) patients	p = 0.62	
Mean postoperative drop in Hb	1.1 (SD 0.6) g/dl	1.6 (SD 0.7) g/dl	p = 0.008	
Clot retention*	0 patients	2/50 (4%) patients	p = 0.49	Reported as re-catheterisation
Time to removal of catheter*	Not reported	Not reported		
Hospital stay*	Not reported	Not reported		
Readmission due to haemorrhage	Not reported	Not reported		
Need for repeat procedure due to incomplete resection	Not reported	Not reported	Not reported	
Functional outcomes				
IPSS at 24 months	3.7 (SD 2.7)	3.8 (SD2.6)	p = 0.59	
Qmax at 24 months	25.5 (SD 9.0) ml/s	2.8 (SD 8.3) ml/s	p = 0.72	
IIEF-5 at 24 months	20.4 (SD 6.0)	19.6 (5.9)	p = 0.65	
Quality of life outcomes	Not reported	Not reported		
Other outcomes				
Urethral stricture / bladder neck contracture	3/50 (6%) patients	5/50 (10%) patients	p = 0.71	Stated as re-operation rate for urethral stricture / bladder neck contracture
Urethral stricture	2/50 (4%) patients	3/50 (6%) patients	p = 1.0	Within 6-24 months postoperatively
Bladder neck contracture	1/50 (2%) patients	2/50 (4%) patients	p = 1.0	Within 6-24 months postoperatively

Table continues...

Stress incontinence	0 patients	2/50 (4%) patients	p = 0.49	Within 6-24 months postoperatively
Retrograde ejaculation	8/22 (36%) patients	9/18 (50%) patients	p = 0.52	Within 6-24 months postoperatively. Presumably 22 (TURis) and 18 (mTURP) men were sexually active.
Transitory urge incontinence	8/50 (16%) patients	10/50 (20%) patients	p = 0.79	In the acute period

EAC comments on study quality

The capsular perforation data are shown for breathalysed men only, because measured fluid absorption was analysed against operating time in men with and without capsular perforation. There was a strong correlation between operating time and fluid absorption in both groups.

Table 28: Results of randomised study: Fagerstrom 2011

Outcome	TURis (n = 98)	mTURP (n = 87)	p value	Comments
Procedure duration*	Mean 62 (SD 23) min	Mean 66 (SD 23) min	p = NS	
Volume of tissue resected	Mean 27.3 (SD 15.1) g	Mean 26.3 (SD 13.2) g	p = NS	
TUR syndrome*	0/98 (0%)	3/87 (3.5%) patients	Not reported	Confirmed by lead author
Termination of procedure due to fluid uptake	2 patients	4 patients	Not reported	Detected by presence of irrigation ethanol in blood
Need for blood transfusion*	4/98 (4%) patients	10/87 (11%) patients	p < 0.01	
Mean postoperative drop in Hb	Median 5.54 (IQR 9.91, 2.43) %	Median 9.59 (IQR 16.88, 5.51) %	p < 0.001	
Blood loss during surgery	Median 235 (IQR 127 – 415)	Median 350 (IQR 175 – 660)	p < 0.001	Stated as a 34% reduction in the TURis group.
Blood loss after surgery	Median 8.9 (IQR 0 – 34.0)	Median 13.5 (IQR 2.0 – 54.4)	p = NS	
Blood loss (total)	Median 262 (IQR 150 – 472)	Median 399 (IQR 186 – 855)	p < 0.001	The difference between groups related mostly to intraoperative blood loss.
Clot retention*	Not reported	Not reported		
Time to removal of catheter*	Median 20 (range 13 – 115) hours	Median 20 (range 13 – 262) hours	p = NS	Excludes men who were discharged with a catheter
Discharged with catheter	8/98 (8.2%) patients	10/87 (11.5%) patients	p = NS	
Hospital stay*	Median 51 (range 22 – 163) hours	Median 52 (range 27 – 365) hours	p = NS	
Rate of readmission due to haemorrhage	2/98	7/87		Stated as due to bleeding
Rate of readmission (any cause)	5/98 readmissions	14/87 readmissions	p < 0.011	Includes bleeding, infection & other causes. Readmission was associated with larger haemorrhage per minute during resection.
Need for repeat procedure due to incomplete resection	2/98 (2.0%) 1 internal urethrotomy 1 TUIP for bladder neck stenosis	4/87 (4.6%) 1 TUIP 3 re-TURP		Additional data on stricture/stenosis are reported below. There may be overlap.
Functional outcomes				
IPSS	IPSS score reduced greatly in both groups from baseline values to approximately 7 by approximately 3 weeks. This benefit was sustained throughout the 18 month follow-up in both groups and there was no between group difference after 3 weeks. Timed			Presented graphically in paper

	micturition (seconds to first decilitre) showed similar sustained improvements in both groups.	

Table continues...

Quality of life outcomes	Bother score reduced in both groups from 4 at baseline to 1 at 3 weeks. The score was 1 at 18 months in both groups.			Scale 0 – 6, 6 representing the most bother.
Other outcomes	In the mTURP group there were four cases of repeat surgeries due to incomplete resections (TUIP or mTURP).			
Urethral stricture / bladder neck contracture				
Urethral stricture during follow-up	2/98 (2%) patients	1/87 (1.1%) patients	Not reported	2011 paper
Bladder neck stenosis	1/98	0/87		2011 paper
Resection speed	Mean 0.46 (SD 0.21) g/min	Mean 0.40 (SD 0.15) g/min	$p < 0.05$	
Resection radicality	Mean 48.8 (SD 21.0) %	Mean 45.3 (SD 15.9) %	p = NS	
EAC comments on study quality The study was powered to detect a 30% difference in blood loss. Method of randomisation was random number table. The paper does not report whether patients or assessors of outcome were blinded to random allocation. Intermittent irrigation (versus continuous irrigation with Reuter's trocar) varied slightly between groups: 81% in the TURis group and 71% in the MTURP group.				

Table 29: Results of randomised study: Geavlete 2011

Outcome	TURis (n = 170)	mTURP (n = 170)	p value	Comments
Procedure duration*	52.1 (21-79) min	55.6 (23-84) min	-	
Volume of tissue resected	Not reported	Not reported	-	
TUR syndrome*	0/170 (0%) patients	3/170 (1.8%) patients	-	
Need for blood transfusion*	3/170 (1.8%) patients	11/170 (6.5%) patients	-	
Postoperative drop in Hb	1.2 (0.2-1.9) g/dl	1.6 (0.3-2.5) g/dl	-	
Clot retention*	2/170 (1.2%) patients	7/170 (4.1%) patients	-	
Time to removal of catheter*	46.3 (36-72) hours	72.8 (48-96) hours	-	
Hospital stay*	3.1 (2-4) days	4.2 (3-6) days	-	
Rate of readmission due to haemorrhage	2/170 (1.2%) patients	6/170 (3.5%) patients	-	Stated as due to haemorrhage
Need for repeat procedure due to incomplete resection	16/170 (9.4%) patients	15/170 (8.8%) patients	-	Stated as 'retreatment rate' and distinct from data on sclerosis and stricture'
Functional outcomes			-	
e.g. IPSS at 18 months	7.9 (3-18)	8.3 (1-17)	-	
e.g. Qmax at 18 months	20.6 (11.4-33.5) ml/s	20.2 (11.1-33.0) ml/s	-	
Quality of life outcomes	The quality of life scores were similar at baseline and at each follow-up point to 18 months.			The paper does not report the scale for the score.
Urethral strictures / bladder neck stenosis				
Urethral strictures	11/170(6.5%)	9/170 (5.3%)	-	
Bladder neck stenosis	6/170 (3.5%)	7/170 (4.1%)	-	Stated as sclerosis

EAC comments on study quality

Data are not shown for the third study arm: BPVP. P values are not shown here because in the study they relate to three patient groups (ANOVA or Chi square), not two. The paper does not state whether average values are means, nor whether measures of spread are ranges. Both patients and assessors of outcome were blinded to allocation.

Table 30: Results of randomised study: Ho 2007

Outcome	TURis (n = 50)	mTURP (n = 50)	p value	Comments
Procedure duration*	Mean 59 (SD 18) min	Mean 58 (SD 16) min	p = NS	
Volume of tissue resected	Mean 29.8 (SD 11.2) g	Mean 30.6 (SD 9.8) g	p = NS	
TUR syndrome*	0/50	2/50	p < 0.05	
Decline in serum Na	Mean 3.2 (SD 0.5) mmol/l	Mean 10.7 (SD 1.8) mmol/l	p < 0.05	
Or related outcome				
Need for blood transfusion*	1/50	1/50	p = NS	
Mean postoperative drop in Hb	Mean 1.2 (SD 0.6) g/dl	Mean 1.8 (SD 0.4) g/dl	p = NS	
Clot retention*	3	2	p = NS	
Time to removal of catheter*	Not reported	Not reported		
Hospital stay*	Not reported	Not reported		
Readmission due to haemorrhage	Not reported	Not reported		
Need for repeat procedure due to incomplete resection	Not reported	Not reported	Not reported	
Functional outcomes				
IPSS at 3 months	The authors state that IPSS scores were similar between groups to 12 months follow-up. IPSS at 12 months in both groups is approximately 6.			Based on graphically presented data.
Qmax at 3 months	Qmax was similar between groups at 12 months at approximately 18 ml/s			Based on graphically presented data.
Quality of life outcomes				
Other outcomes				
Urethral strictures / bladder neck stenosis	3/50	1/50	p = NS	Data are for stricture only, treated with urethral dilation.
Urinary tract infection	2/50	2/50	p = NS	
Failed trial without catheter	5/50	4/50	p = NS	

EAC comments on study quality

All cases had histologically confirmed BPH. 45 patients had acute urinary retention. Randomisation was by computer programme. No sample size calculation is reported. Study appears to be unblinded. There were no losses to follow-up at 12 months.

Table 31: Results for randomised study: Michielsen 2007, Michielsen 2010a, Michielsen 2010b, Michielsen 2010c, Michielsen 2011

Outcome	TURis (n = 285)	mTURP (n = 265)	p value	Comments
Procedure duration*	Mean 52.1 (SD 22.5) min	Mean 50.9 (SD 22.2) min	p = 0.357	Data for a subset of 263 (TURis) and 255 (mTURP) patients
Subgroup analysis	Mean 67 (SD 18) min	Mean 59 (SD 23) min	p = 0.131	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean 57 (SD 22) min	Mean 37 (SD 19) min	p = 0.000	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Weight of tissue resected	Mean 17.6 (SD 11.5) g	Mean 19.2 (SD 15.0) g	p = 0.173	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean 30.12 (SD 15.21) g	Mean 26.31 (SD 13.25) g	p = 0.282	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean 19.44 (SD 11.53) g	Mean 20.21 (SD 11.88) g	p = 0.670	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
TUR syndrome*	0/285 (0%) patients	2/265 (0.8%) patients	Not reported	
Subgroup analysis	0/33 (0%) patients	1/33 (3%) patients	p = 1.000	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	0/98 (0%) patients	0/78 (0%) patients		Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Change in serum Na	Mean -1.5 (SD 1.1) mmol/l	Mean -2.5 (SD 3.3) mmol/l	p < 0.001	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean – 1.30 (SD 2.49) mmol/l	Mean – 3.12 (SD 3.20) mmol/l	p =0.012	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Change in serum K	Mean -0.2 (SD 0.4) mmol/l	Mean -0.1 (SD 0.6) mmol/l	p = 0.042	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean – 0.20 (SD 0.44) mmol/l	Mean – 0.17 (SD 0.53) mmol/l	p =0.803	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Change in serum Cl	Mean 1.3 (SD 2.6) mmol/l	Mean 0.5 (SD 3.1) mmol/l	p = 0.002	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean 1.61 (SD 2.71) mmol/l	Mean -0.42 (SD 4.03) mmol/l	p = 0.019	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Need for blood transfusion*	4/118 (3.4%) patients	1/120 (0.8%) patients	p = 0.211	Data for the first 118 (TURis) patients and the first 120 (mTURP)

				patients
	1/98 (1%)	2/78 (3%)	p = 0.585	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Mean postoperative drop in Hb	Mean 1.3 (SD 1.2) g/dl	Mean 1.2 (SD 1.1) g/dl	p = 0.658	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean -1.80 (SD 1.35) mg/dl	Mean -1.33 (SD 0.97) mg/dl	p = 0.114	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean -1.29 (SD 0.99) mg/dl	Mean -1.21 (SD 0.92) mg/dl	p = 0.603	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Clot retention*	4/118 (3.4%) patients	6/120 (5%) patients	p = 0.749	Data for the first 118 (TURis) patients and the first 120 (mTURP) patients
Subgroup analysis	4/33 (12%)	2/33 (6%)	p = 0.672	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	13/98 (13%)	12/78 (15%)	p=0.828	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Time to removal of catheter*	Mean 1.64 (SD 1.33) days	Mean 1.64 (SD 0.86) days	p = 0.815	Data for a subset of 263 (TURis) and 255 (mTURP) patients
Subgroup analysis	Mean 1.58 (SD 0.83) days	Mean 1.67 (SD 0.78) days	p = 0.748	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean 1.79 (SD 1.78) days	Mean 1.77 (SD 1.02) days	p = 0.942	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Hospital stay*	Mean 3.72 (SD 2.62) days	Mean 3.89 (SD 3.18) days	p = 0.773	Data for a subset of 263 (TURis) and 255 (mTURP) patients
Subgroup analysis	Mean 3.88(SD 2.43) days	Mean 3.64 (SD 3.56) days	p = 0.748	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean 4.35(SD 3.14) days	Mean 4.91(SD 3.56) days	p = 0.330	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Readmission due to haemorrhage	Not reported	Not reported		
Need for repeat procedure due to incomplete resection	0/118 patients	2/120 patients	Not reported	It is unclear why revision was performed. Data for the first 118 (TURis) patients and the first 120 (mTURP) patients
Functional outcomes	Not reported	Not reported		

Quality of life outcomes	Not reported	Not reported		

.....Michielsen continued

Other outcomes				
Urethral stricture	4/263 (1.5%) patients	6/256 (2.3%) patients	p = 0.539	Stricture only. Data for a subset of 263 (TURis) and 255 (mTURP) patients. All cases required reintervention.
Subgroup analysis	0/33 (0%) patients	0/33 (0%) patients	p = 1.000	Stricture only. Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Bladder neck contracture	1/33 (3%) patients	2/33 (6%) patients	p = 1.000	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Resection speed	Mean 0.36 (SD 0.22) g/min	Mean 0.40 (SD 0.32) g/min	p = 0.100	Data for 285 (TURis) and 265 (mTURP) patients
Subgroup analysis	Mean 0.45(SD 0.17) g/min	Mean 0.46 (SD 0.18) g/min	p = 0.823	Large (>60g) BPH: 33 (TURis) & 33 (mTURP) patients
Subgroup analysis	Mean 0.38(SD 0.25) g/min	Mean 0.62(SD 0.40) g/min	p = 0.000	Oral anticoagulants: 98 (TURis) & 78 (mTURP) patients
Early complications	9%	11%	p = NS	Data for the first 118 (TURis) patients and the first 120 (mTURP) patients .This included clot retention (above)
Postoperative urinary retention	3/118 (2.5%)	5/120 (4.2%)	p = 0.722	Data for the first 118 (TURis) patients and the first 120 (TUR.P) patients
EAC comments on study quality The data is published in three papers, where each patient sample is included in the subsequent sample. The three samples are 238 patients (Jan2005-Jun 2006), 518 patients (Jan 2005-Jan 2009) and 550 patients (Jan 2005-Aug 2009). The lead author confirmed this. The numbers of men who were ineligible for inclusion or who did not consent to enter the trial, are not available. Loss to follow-up is not reported.				

Table 32: Results for randomised study: Rose 2007

Outcome	TURis (n = 38)	mTURP (n = 34)	p value	Comments
Procedure duration*	55 min	35 min	reported=0.005	
Volume of tissue resected	42 g	31 g	Not reported	
TUR syndrome*	0/38 patients	0/34 patients	Not reported	
Bleeding-related revisions	4/38 (10.5%)	1/34 (2.9%)	Not reported	
Drop in serum sodium	0 mmol/l	1.1 mmol/l	Not reported	
Need for blood transfusion*				
Mean postoperative drop in Hb	1.0 g/dl	1.0 g/dl	Not reported	
Clot retention*	Not reported	Not reported		
Time to removal of catheter*	64 h	49 h	Not reported	
Hospital stay*	Not reported	Not reported		
Rate of readmission due to haemorrhage	4/38	1/34	Not reported	'Revision surgeries due to postoperative bleeding'. It is unclear whether patients were sent home then readmitted.
Need for reoperation due to incomplete resection	Not reported	Not reported		
Functional outcomes	Not reported	Not reported		
e.g. IPSS at 3 months	Not reported	Not reported		
e.g. Qmax at 3 months	Not reported	Not reported		
Quality of life outcomes	Not reported	Not reported		
Other outcomes				
Urethral strictures / bladder neck contracture	Not reported	Not reported		
Adductor muscle contraction	0/38 patients	0/34 patients	Not reported	
Capsular perforation	0/38 patients	0/34 patients	Not reported	

EAC comments on study quality

Data extracted from English language abstract and tabulated results in the German language peer reviewed journal publication. All data cited are for patients with enlarged prostate (not those treated for bladder cancer).

3.6.2 Results of randomised studies available as conference abstracts

Table 33: Results of randomised study (abstract): Goh 2010

Outcome	TURis (n = 80 or 110)†	mTURP (n = 76 or 100)†	p value	Comments
Procedure duration*	38 min	35 min	p = 0.3)	
Volume of tissue resected	Not reported	Not reported	Not reported	
TUR syndrome*	0 patients	3/100 (3%) patients	Not reported	Abstract states ”in the bipolar arm 3 patients had symptoms only with minimal changes in serum Na”
Fluid absorption	548 ml	1015 ml	p < 0.001	
Post-operative sodium	138.7 mmol/L	135.8 mmol/L	p < 0.001	
Capsular perforations	25 cases	27 cases	p = 0.5	
Serum osmolarity	289 mOsm/L	284 mOsm/L	p < 0.001	
Need for blood transfusion*	Not reported	Not reported	Not reported	
Mean postoperative drop in Hb	Not reported	Not reported	Not reported	
Clot retention*	Not reported	Not reported	Not reported	
Time to removal of catheter*	48 hours	52 hours	p = 0.97	
Hospital stay*	90 hours	103 hours	p = 0.06	p value stated as p50.06; assumed to be a typographical error
Readmission due to haemorrhage	Not reported	Not reported	Not reported	
Need for repeat procedure due to incomplete resection				
Functional outcomes				
IPSS at 12 months	Reported as ‘comparable’. No values provided		p = 0.9	
Qmax at 12 months	Reported as ‘comparable’. No values provided		p = 0.5	
Quality of life outcomes	Reported as ‘comparable’. No values provided		p = 0.3	
Other outcomes				
Complication rate	25%	30%	p = 0.1	Follow-up length not reported
Surgeon rated flow characteristics	7	7.7	p = 0.01	Scale 0-10, 10 represents best performance
Surgeon rated clarity of vision	7.5	8	p = 0.007	Scale 0-10, 10 represents best performance
Surgeon rated loop	7	7.5	p = 0.04	Scale 0-10, 10

resection volume				represents best performance

Table continues...

Surgeon rated coagulation	Stated as favourable in the monopolar arm	p = 0.02	
Surgeon rated haemostasis	Stated as favourable in the monopolar arm	p = 0.04	

EAC comments on study quality

Abstracts only.

† It is not clear for all of the outcomes whether they refer to the entire sample (210 patients) or only those which were followed-up for 12 months (156 patients)

3.6.3 Results of observational studies published as full papers

Table 34: Results for observational study: Ho 2006

Outcome	TURis (n = 45)	TURP (n = 0)	p value	Comments
Procedure duration*	Mean 42 (range 15 - 75) min	n/a	n/a	
Volume of tissue resected	Mean 25.3 (range 12 - 46) g	n/a	n/a	
TUR syndrome*	0/45 (0%)	n/a	n/a	
Decline in serum Na	Mean 2.2 (range 1- 6) mmol/l	n/a	n/a	
Or related outcome	n/a	n/a	n/a	
Need for blood transfusion*	2/45 (4.4%)	n/a	n/a	
Mean postoperative drop in Hb	Mean 1.4(range 0.8 – 6.4) g/dl	n/a	n/a	
Clot retention*		n/a	n/a	
Time to removal of catheter*	Mean 2 (1 – 21) days	n/a	n/a	
Hospital stay*	2 days (range 1-6) days	n/a	n/a	
Rate of readmission	Not reported	n/a	n/a	
Functional outcomes				
IPSS at 12 months	Mean 6.5, range not reported (n=15)			
Qmax at 12 months	18.3 ml/s, range not reported (n=15), p<0.05, significant at all follow-up intervals compared to preoperative values, NB 22 patients with acute retention of urine did not have preoperative Qmax			
Quality of life outcomes				
Other outcomes				
Urinary tract infection	4/45 (8.9%)	n/a	n/a	
Stricture	1/45 (2.2%)	n/a	n/a	
Prostate cancer	2/45 (4.4%)	n/a	n/a	
EAC comments on study quality 22 patients had acute urinary retention. Follow-up at 12 months was not complete.				

Table 35: Results for observational study: Lee 2011

Outcome	TURis (n = 19)	TURP (n = 39)	TURis-V (n = 15)	p value	Comments
Procedure duration*	71.84 min ±24.96	73.85 min ±29.70	58.67 min ±28.88	p = 0.211	
Weight of tissue resected	16.87 g ± 6.64	12.27 g ± 8.67	Not reported	p = 0.047	p value here for TURis vs TURP only.
TUR syndrome*	Not reported				
Decline in serum Na	1.46 mmol/l ±3.42	0.05 mmol/l ±3.30	0.50 mmol/l ±3.06	p = 0.165	
Need for blood transfusion*	1/19 (5.3%)	3/39 (7.7%)	0/15 (0%)	p = 0.538	
Mean postoperative drop in Hb	0.71 mg/dl ±1.09	0.77 mg/dl ±1.33	0.19 mg/dl ±1.14	p = 0.302	
Clot retention*	1/19 (5.3%)	4/39 (10.3%)	0/15 (0%)	p = 0.389	
Time to removal of catheter*	4.05 days ±0.40	4.26 days ±0.99	2.80 days ±0.41	p < 0.001	
Hospital stay*	6.00 days ±0.58	6.66 days ±1.22	4.86 days ±0.52	p < 0.001	
Rate of readmission	Not reported				
Functional outcomes					
IPSS at 6 months	Graphical information only, pre-op v post-op comparison, significant improvement in all groups			p < 0.01	
Qmax at 6 months	Graphical information only, pre-op v post-op comparison, significant improvement in all groups			TURP: p < 0.01 TURis: p < 0.05	
Quality of life outcomes	Graphical information only, pre-op v post-op comparison, significant improvement in all groups			p < 0.01	Method for ascertaining QoL was not described.
Other outcomes	Not reported				
Urinary tract infection					
Stricture					
Prostate cancer					

EAC comments on study quality

Retrospective analysis, small sample size, with limited statistical power. With the exception of resection weight, p values for outcomes are used to compare the 3 methods, (including TURis-V). Confidence intervals are not reported.

Table 36: Results for observational study: Puppo 2009

Outcome	TURis (n = 376)	TURP (n=0)	p value	Comments
Procedure duration*	Median 42 min (14-92)	n/a	n/a	
Volume of tissue resected	Median 24.6 ml (3.4-64)	n/a	n/a	
TUR syndrome*	0/376 (0%)	n/a	n/a	
Decline in serum Na	1.46 mg/dl ±3.42	n/a	n/a	
Need for blood transfusion*	7/376 (1.9%)	n/a	n/a	
Median postoperative drop in Hb	0.8 g/dl (0.4-8)	n/a	n/a	
Clot retention*	11/376 (2.9%)	n/a	n/a	Reported as 'early' postoperative clot retention
Time to removal of catheter*	Median 3 days (3-14)	n/a	n/a	
Hospital stay*	Median 4 days (3-7)	n/a	n/a	
Rate of readmission	Not reported	n/a	n/a	
Functional outcomes				
IPSS pre/post-op Qmax pre/post-op Qmax at 6 months	Pre-op median 24 (13-35), post-op median 5 (0-25) Pre-op Qmax median 6 ml/s (0-10), post-op median 19 ml/s (6-39) 17/376 (4.5%) Qmax <15 ml/s			
Quality of life outcomes	Not reported			
Other outcomes				
Bladder neck contracture	4/376 (1.1%)			
Stricture	11/376 (2.9%)			

EAC comments on study quality

Uncontrolled, before and after study, with limited follow-up data at 6 months. Limited data analysis. Equipment donated by Olympus but authors state no competing financial interests.

Table 37: Results for observational study: Shum 2014

Outcome	TURis (n = 100)	TURP	p value	Comments
Procedure duration*	74.3 min ±24.8	n/a	-	
Volume of tissue resected	32.7 g ±15.1	n/a	-	
TUR syndrome*	0/100 (0%)	n/a	-	
Change in serum Na	-0.7 mmol/L ±3.0	n/a		
Change in creatinine	-1.5 micromol/L ±33.1	n/a		
Need for blood transfusion*	0/100 (0%)	n/a	-	
Mean postoperative drop in Hb	0.2 g/dL ±1.0	n/a	-	
Clot retention*	2/100 (2%)	n/a	-	Included in readmission
Time to removal of catheter*	Mean 15.0 hrs	n/a	-	no SD reported
Hospital stay*	Approx. 1 day	n/a	-	'Many' patients were discharged within 23 hours after surgery.
Rate of readmission	6/100 (6%)	n/a	-	
Functional outcomes			-	
IPSS at 6 months	9.2 ±6.3	n/a	-	
Qmax at 6 months	17.6 ml/s ±8.7	n/a	-	Reported as 'peak flow'
Quality of life outcomes	Pre: 4.4 ±1.1, 6 months: 1.8 ±1.2			Mean post-op score of 1.8 is reported to show that patients were 'pleased' or 'mostly satisfied'.
Other outcomes				
Urinary tract infection	4/100 (4%)			
Urethral stricture	1/100 (1%)			Included in readmission
Bladder neck contracture	3/100 (3%)			Included in readmission

EAC comments on study quality

Uncontrolled, before and after study. 40 patients had pre-operative urinary retention and were therefore excluded from some pre-operative measures (eg IPSS, Qmax) . The authors report that all 100 patients completed at least 6 months of postoperative follow-up, but stated that 82% attended a review at 6 months, implying that some may have been withdrawn. Patients with perioperative haemodynamic instability were excluded, which may have concealed any incidence of TUR syndrome.

3.6.4 Results for observational study (abstract): Bertolotto 2009

Table 38: Results for observational study: Bertolotto 2009

Outcome	TURis (n = 376)	mTURP (n = 0)	p value	Comments
Procedure duration*	42 min	n/a	n/a	median
Volume of tissue resected	24.6 g	n/a	n/a	median
TUR syndrome*	0 patients	n/a	n/a	
Need for blood transfusion*	7/376 (1.9%) patients	n/a	n/a	
Median postoperative drop in Hb	0.9 g/dl	n/a	n/a	
Clot retention*	11/376 (2.9%) patients	n/a	n/a	
Time to removal of catheter*	3 days	n/a		median
Hospital stay*	4 days	n/a	n/a	
Rate of readmission	5/376 (1.3%) patients	n/a	n/a	Minimum 6 months follow-up
Functional outcomes	Not reported	n/a	n/a	
Quality of life outcomes	Not reported	n/a	n/a	
Other outcomes				
Urethral stricture	15/376 (4.0%) patients	n/a	n/a	Minimum 6 months follow-up
Death	0 patients	n/a	n/a	Minimum 6 months follow-up

EAC comments on study quality

Abstract only.

The study also reported outcomes for patients treated using TURis for TUIP and TURB.

Table 39: Results for observational study: Fumado 2011

Outcome	TURis (n = 120)	mTURP (n = 0)	p value	Comments
Procedure duration*	Mean 64 (range 13-120) min	n/a	n/a	
Volume of tissue resected	Mean 24 (range 4-66) g	n/a	n/a	
TUR syndrome*	Not reported	n/a	n/a	
Need for blood transfusion*	Not reported	n/a	n/a	
Mean postoperative drop in Hb	Not reported	n/a	n/a	
Clot retention*	Not reported	n/a	n/a	
Time to removal of catheter*	Not reported	n/a	n/a	
Hospital stay*	Mean 27 (range 11-95) hours	n/a	n/a	
Rate of readmission	Not reported	n/a	n/a	
Functional outcomes				
IPSS at 12 months	4.7	n/a	n/a	Likely mean but no SD
Qmax at 12 months	25 ml/s	n/a	n/a	Likely mean but no SD
Quality of life outcomes				
IPSS QoL at 12 months	Decrease from 4.9 to 1.0 (79.6%)	n/a	n/a	
Other outcomes				
Major complications	0 patients	n/a	n/a	
Incontinence at 12 months	0 patients	n/a	n/a	
EAC comments on study quality Abstract only.				

Table 40: Results for observational study: Giulianelli 2012

Outcome	TURis (n = 160)	mTURP (n = 80)	Plasmakinetic (n = 80)	p value	Comments
Procedure duration*	Not reported			Not reported	
Volume of tissue resected	Not reported			Not reported	
TUR syndrome*	Not reported			Not reported	
Need for blood transfusion*	9/320 (2.8%) patients			Not significant	
Clot retention*	Not reported			Not reported	
Time to removal of catheter*	Mean 24 hours			'Similar'	
Hospital stay*	Mean 48 hours			'Similar'	
Rate of readmission	11/320 (3.4%) patients			Not significant	
Functional outcomes					
IPSS at 12 months	Significant change from baseline			Not significant between groups	
Qmax at 12 months	Significant change from baseline			Not significant between groups	
Qave at 12 months	Significant change from baseline			Not significant between groups	
Quality of life outcomes	Significant change from baseline			Not significant between groups	
Other outcomes					
Death	None			N/A	In 48 hours post-TURP
Bladder neck contracture	7/320 (2.1%) patients			Not significant	**included in 'readmissions'*
Urethral stenosis	4/320 (1.25%) patients			Not significant	***included in 'readmissions'*

EAC comments on study quality

Abstract only.

Concluded "no statistical differences in efficacy and safety aside from which energy we used", which appears to be an error in translation as elsewhere the authors reported no statistically significant differences *between* energy sources.

Table 41: Results of observational study: Hyun 2012

Outcome	TURis (n = 19)	mTURP (n = 39)	TURis-V (n = 15)	p value	Comments
Procedure duration*	71.84 ± 24.96 min	73.85 ± 29.70 min	58.67 ± 28.88 min	p = 0.211	Shortest time presented.Where ± is used, the authors used the symbol +.
Volume of tissue resected	Not reported	Not reported	Not reported	Not reported	
TUR syndrome*					
Serum sodium changes	No significant changes in changes of serum sodium before and after procedure				Not clear whether differences refer to before/after or between groups
Need for blood transfusion*	1/19 (5.3%)	3/39 (7.7%)	0/15 (0%)	Not reported	
Postoperative drop in Hb	No significant changes in changes of haemoglobin levels before and after procedure				Not clear whether differences refer to before/after or between groups
Clot retention*	1/19 (5.3%)	4/39 (10.3%)	0/15 (0%)	Not reported	
Time to removal of catheter*	TURis-V significantly decreased catheter duration in comparison with mTURP and TURis			p < 0.001	
Hospital stay*	TURis-V significantly decreased 'hospital day' in comparison with mTURP and TURis			p < 0.001	
Rate of readmission	Not reported	Not reported	Not reported	Not reported	
Functional outcomes	Not reported	Not reported	Not reported	Not reported	
Quality of life outcomes	Not reported	Not reported	Not reported	Not reported	
Other outcomes					
Irrigation fluid volume	TURis-V significantly decreased irrigation fluid volume used during procedure in comparison with mTURP and TURis			p = 0.016	
Postoperative irrigation duration	TURis-V significantly decreased postoperative irrigation duration in comparison with mTURP and TURis			p < 0.001	
EAC comments on study quality Abstract only.					

Table 42: Results of observational study: Petkov 2011

Outcome	TURis (n = 21)	TURP (n = 24)	p value	Comments
Procedure duration*	Not reported	Not reported	p = NS	
Volume of tissue resected	Not reported	Not reported	p = NS	
TUR syndrome*	Not reported	Not reported		Authors conclude reduced risk of TUR syndrome
Postoperative decrease in Na	2.4 mmol/l + 1.6	9.1mmol/l + 2.8	P < 0.001	
Postoperative change in K	Not reported	Not reported		
Postoperative change in Cl	Not reported	Not reported		
Need for blood transfusion*	Not reported	Not reported		
Mean postoperative drop in Hb	Not reported	Not reported	p = NS	
Clot retention*	Not reported	Not reported		
Time to removal of catheter*	2.7 days	3.6 days	P < 0.001	
Hospital stay*	3.5 days	4.6 days	P <0 .001	
Rate of readmission	Not reported	Not reported		
Functional outcomes				
IPSS & Qmax	Improvements were comparable between two groups at first month of follow-up			
Quality of life outcomes	Not reported	Not reported	Not reported	
Other outcomes	Not reported	Not reported	Not reported	
EAC comments on study quality Abstract only				

3.7 Description of the adverse events reported by the sponsor

The sponsor has sought data for adverse events and provides a summary in section 7.7 of the submission. The sponsor has not performed a meta-analysis of longer term complications following surgery i.e. urethral strictures and bladder neck stenoses. The EAC performed meta-analyses for these outcomes.

The sponsor reported a total of 4 adverse events, identified from the MHRA (2 events) and FDA MAUDE (2 events). These are shown in Table 43. One of the events appears to be shown twice.

Table 43: adverse events identified by the sponsor

Database	Reference Number	Affected part	Detail
MHRA	2012/011/012/401/007	WA22302D	Problem arose during a TURis procedure. Scrub Nurse believed the loop broke due to over pressure applied by the surgeon. Not used by a Urologist but instead in a Gynaecology procedure, different purpose to that of the scope.
MHRA	2014/001/023/601/004	WA22302D	During a TURis procedure the loop broke during use. Not used by a urologist but instead in a Gynaecology procedure, different purpose to that of the scope.
FDA (MAUDE)	9610773-2012-00070	WA22366A	Teflon body exhibited failure mode of burning of the contacts. It cannot be excluded that inappropriate handling by the user and insufficient contact between electrode and the working element.
FDA (MAUDE)	9610773-2012-00020	WA22332D	Loop broke after third activation cycle. Mechanical break suggested, although item not returned by hospital for full investigation.

In addition the EAC identified further adverse events. These are listed in Table 44.

Table 44: Additional adverse events identified by the EAC

Database	Reference Number	Affected part	Detail
FDA (MAUDE)	8010047-2012-00286	UES-40	During the TURis procedure no abnormality was observed and the user performed the procedure successfully. On (b)(6) 2012, the pt returned to the user with some difficulties and pain. The user performed cystoscopy and necrosis and urethral burns were found. Then the pt was kept in the hospital.

FDA (MAUDE)	MW5031246	FAS electrode	Olympus Surgmaster bipolar procedure: The pt underwent a TURP and during the procedure the bipolar electrode loop broke off. The loop wire was intentionally left in the pt. A post-op pelvic ct scan showed 2 metal fragments within the anterior prostate. Ct scan done on (b)(6) 2013.
FDA (MAUDE)	9610773-2012-00049	A22001A	During a three hour transurethral resection of the prostate of (b)(6) pt with bipolar resection in saline equipment, the pt's bladder ruptured. Gas collection in the bladder and the hazard of rupture caused by spark ignition is a known side-effect. It is recommended to flush the bladder regularly during the procedure. There are strong indications for inadvertence and lack of experience of the user as the flushing was reportedly done sporadically only and a procedure of 3 hours for a prostate resection can be considered extraordinarily long. Thus, the case is assessed to be the consequence of a user error.
FDA (MAUDE)	8010047-2012-00352	GEI	Bipolar unit was used for a TURP. The machine would not coagulate at times. The unit only worked about 50% of the time and prolonged the length of the surgery. The cord to the hand piece, as well as the hand piece itself, and the electrode were all replaced and tried. None of these attempts were successful. Biomed was called into the room and could not identify the problem. The cause was not identified.
FDA (MAUDE)	2662751	FJL resectoscope	TURP done with an olympus resectoscope (bipolar working element). The porcelan (beak) came off the inner sheath of the resectoscope inside the patient's prostatic urethra. The broken instructment piece was retrieved with cystoscope and flexible alligator grasper. The item was sent to ims for repair. It was deemed unrepairable. A replacement was ordered.

FDA (MAUDE)	8010047-2012-00195	KNS	During a transurethral enucleation with bipolar (TUEB) the pt had gone into cardiac arrest then become a vegetative state. The physicians performed a transesophageal echocardiography after the procedure, there were air in the pt's heart. One of the physician thought that the pt had developed air embolism, but the other physician could not determine whether the air had been generated during the TUEB procedure. Additionally, the pt had a diabetes as preexisting disorder. Manufacturer Narrative No abnormality was found with the device. The exact cause of the pt's outcome could not be conclusively determined, however, it was likely to be caused by the complication of tueb or the pt's preexisting disorder.
FDA (MAUDE)	9610773-2011-00027	A2642	During TURP the bipolar electrode broke, melted, and burned up. There was no device fragment reported to have fallen inside the patient. The procedure was completed with unspecified device. There was no patient injury reported. The manufacturer's evaluation confirmed that the returned inner sheath has a non-Olympus insulation tip, and the insulation tip exhibited evidence of thermal damage. In addition, the insulation material at the distal end was severely damaged with a large portion missing. The cap from the tension ring was loose, with worn out sealant. There were minor stain and scratches on the trocar sheath.
FDA (MAUDE)	9610773-2011-00018	A22201C	During a TURP bipolar procedure, the subject device reportedly disintegrated. There was no pt harm reported. The intended procedure was reportedly completed with a different unspecified electrode. The cause of the reported phenomenon could not be conclusively determined.

FDA (MAUDE)	2045838	WA22306D	One hour into this transurethral resection (tur), the error code alarmed on the olympus bipolar machine. The surgeon tried trouble shooting, then took the scope apart and noticed that the loop had come apart. The red part from the metal loop.
FDA (MAUDE)	9610773-2010-00040	WA22557C	During a TURP) procedure with vaporization in saline, the users switched from one model of electrode to the subject device. Upon initial activation of the subject device, while contacting tissue, the pt reportedly exhibited some movement on the surgical table. The user stopped the application of energy, and then reactivated the electrode, and the pt again reportedly exhibited movement. The users disconnected the subject device from the concomitant devices, repositioned and reconnected the electrode, and the pt was said to have exhibited movement again upon the next attempt to use the device. The electrode was then removed from use, replaced with another electrode, and the procedure was completed. Visual inspection revealed damage on one of the electrode arms at the junction of the gray inner and outer sheaths.
FDA (MAUDE)	1727828	WA22306D	While performing a TURP procedure with an olympus bipolar resectoscope, the loop portion of the electrode broke off. The portion of the loop was seen under direct visualization in the bladder. Attempted to remove the broken off piece of loop but visualization was lost and the location was unknown. A portable x-ray was used to locate the lost piece. The procedure was completed and the patient was taken to recovery.

FDA (MAUDE)	1727848	09286POOL001	During TURP using the olympus bipolar machine, the disposable loop (resection electrode) broke off in the bladder. The broken off portion of the loop was not visualized. A cystoscope was used to visualize the bladder and urethra; the loop was not found. The specimen was checked for the loop, as well as the drapes and floor. A portable x-ray was ordered and read as negative. Cystoscopy was performed one last time and still nothng was visualized.

The adverse event that appears to be the most common (several reported cases) is breakage or degeneration of the electrode, potentially leaving debris in the patient. In one case this was attributed to use of a non-Olympus component, and in another case the event occurred in a gynaecological procedure. There is at least one case of reported failure to coagulate (cause not identified) and a case of a patient presenting after surgery with necrosis and urethral burns. There is a case of suspected air embolism leading to cardiac arrest, but the precise cause was not determined. There is also a reported case of bladder rupture attributed to poor surgical technique: a prolonged TURP procedure (3 hours) with insufficient irrigation. There is also a case of patient movement during treatment.

Two reported cases of adverse events appear may be linked to enucleation or vaporisation procedures. The EAC cannot be certain that every case relates to TURis and the reactive reporting mechanism of adverse events permits both duplication of reporting and potentially under reporting, such that a reliable estimate of the rate of events is unfeasible. Finally the EAC would suggest that the adverse events are considered in the context of those that arise during mTURP.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor performed meta-analysis of data from randomised trials comparing TURis versus mTURP for six outcome measures: TUR syndrome, blood transfusion, clot retention, time to catheter removal, hospital stay and procedure duration.

The EAC reproduced the sponsor's meta-analyses and made adjustments according to conditions as follows:

- adding data from additional randomised trials identified by the EAC
- removing data that are duplicated in the sponsor's analysis due to repeat publication
- correction of data entry errors

- exploring the use of random effect models in analyses with evident study heterogeneity
- exploring the exclusion of outlying studies observed to generate heterogeneity (using a fixed effect model)
- exploring the effect of removing data from randomised studies available as abstracts only (which does not enable a critical appraisal)
- exploring the effect of adding or removing data from randomised studies published in Spanish or German language, to determine whether the data are of pivotal importance to the economic model.

One or more of the adjustments were applied to each analysis on a case-by-case basis. All meta-analyses performed by the EAC are summarised in Appendix 3.

TUR syndrome

The sponsor's meta-analysis of TUR syndrome included data from six randomised studies (Abascal-Junquera 2006, Akman 2013, Chen 2010, Goh 2010, Michielsen 2011, Rose 2007). The pooled relative risk of TUR syndrome was 0.28 (95% CI 0.08, 1.02) and is not statistically significant since the confidence interval includes the null value of 1, representing no difference in risk between treatments. Three of the included studies had zero rates of TUR syndrome in both the TURis and mTURP arms, and therefore can provide no information on relative risk (Abascal 2006, Chen 2010, Rose 2007). The sponsor applied a continuity correction using a risk of 0.5 in both arms as follows:

Abascal 2006 RR (TURis/mTURP) = 0.5/24 x 21/0.5 = 0.88

Chen 2010 RR (TURis/mTURP) = 0.5/50 x 50/0.5 = 1

Rose 2007 RR (TURis/mTURP) = 0.5/38 x 34/0.5 = 0.90

The calculations generate relative risks for each of the three studies that are equal, or close to, the null value of 1, as we would expect with near equal numbers of subjects in each group (TURis and mTURP). This approach may bias the analysis against TURis and the sponsor acknowledges this. Methods manuals for meta-analysis (Cochrane & CRD) state that a reasonable approach is to exclude studies with zero events in both arms. For this reason the EAC excluded the three studies with zero rates of TUR syndrome in both arms (Abascal 2006, Chen 2010, Rose 2007).

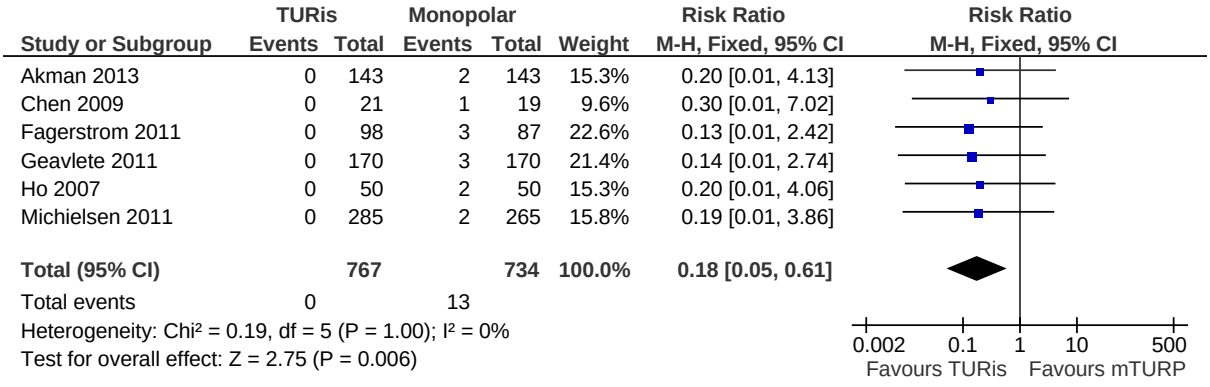
The EAC also excluded data from a randomised study that was available only as a conference abstract (Goh 2010) and which has no evidence of having been peer-reviewed.

The EAC added data from 4 additional randomised studies that the sponsor had not included (Ho 2006, Chen 2009, Fagerstrom 2011, Geavlete 2011).

For the Michielsen publications the EAC's meta-analysis contains only the data from the latter relevant publication with the most complete accrual.

The EAC fixed effect analysis provides a RR of TUR syndrome of 0.18 (95% CI 0.05, 0.61), p = 0.006 in favour of TURis (Figure 2). There is little heterogeneity evident. This result is statistically significant and provides strong evidence to support the claim that TURis reduces the risk of TUR syndrome. If the abstracted data from Goh 2010 is included in the EAC analysis there is very little change: RR 0.17 (95% CI 0.05, 0.53) in favour of TURis, p = 0.002. The EAC feels that the most robust analysis excludes the Goh 2010 data on the basis that it is abstracted data only.

Figure 2: Forest plot of EAC meta-analysis of TUR syndrome

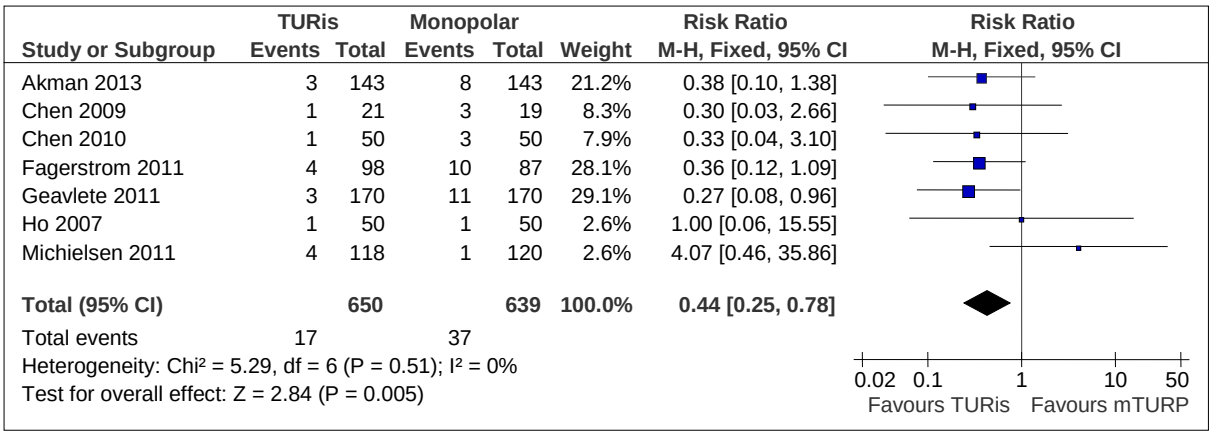


The relative risk of 0.18 (95% CI 0.05, 0.61) in Figure 2 represents an absolute difference in risk of -0.02 (95% CI -0.03, -0.01). This corresponds to a number-needed-to-treat (NNT) value of 50 (95% CI 33, 100). This means that 50 patients would need to be treated with TURis in order to prevent one case of TUR syndrome.

Blood transfusion

The sponsor's meta-analysis of blood transfusion initially included data from four randomised studies (Akman 2013, Chen 2010, Fagerstrom, Michielsen 2007) and found the pooled RR to be 0.52 (95% CI 0.26, 1.04) in favour of TURis. The confidence interval includes the null value of 1 and the result is not statistically significant. The EAC added data from three additional randomised studies (Chen 2009, Ho 2006, Geavlete 2011), resulting in a pooled RR of 0.44 (95% CI 0.25, 0.78), p = 0.005, in favour of TURis. This result is statistically significant, and without substantial heterogeneity (Figure 3).

Figure 3: Forest plot of fixed effect EAC meta-analysis of Blood transfusion



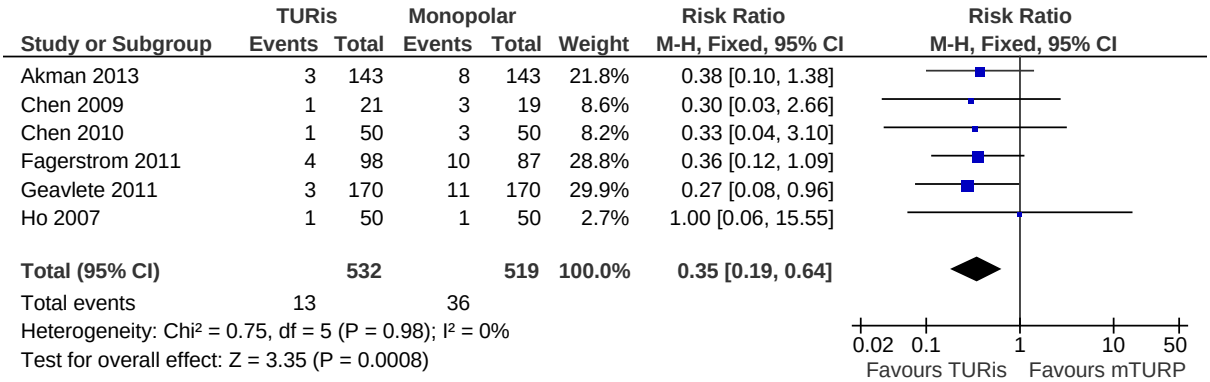
The sponsor repeated their initial meta-analysis but with omission of data from Michielsen 2011 on the basis that in the study a greater proportion of TURis procedures than mTURP procedures were performed by trainee surgeons, resulting in longer operating times and associated with greater blood loss. The EAC feels that this is a reasonable action on the grounds of heterogeneity (Table 45).

Table 45: Skill mix of surgeons for TURis and mTURP procedures in Michielsen 2007

	Staff	Trainees	Total
mTURP	112 (93%)	8 (7%)	120
TURis	80 (68%)	38 (32%)	118

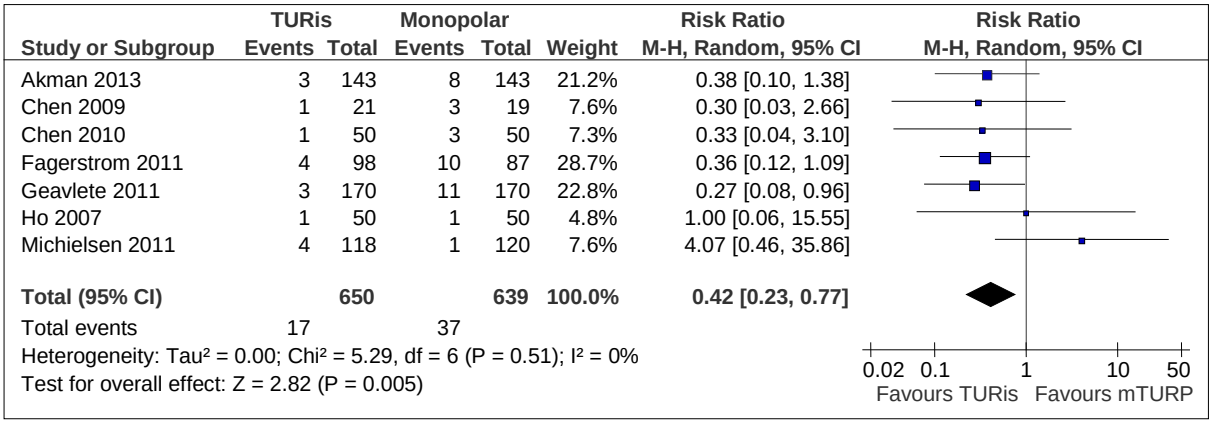
The EAC explored the impact of removing the same data from its analysis. The pooled RR became 0.35 (95% CI 0.19, 0.64), p = 0.0008, in favour of TURis, with little heterogeneity evident (Figure 4).

Figure 4: Forest plot of EAC fixed effect meta-analysis of Blood transfusion, excluding data from Michielsen 2011



As an alternative approach the EAC explored using a random effects model, including the data from Michielsen 2011. This generated a RR of 0.42 (95% CI 0.23, 0.77) in favour of TURis, p = 0.005 (Figure 5).

Figure 5: Forest plot of random effect EAC meta-analysis of Blood transfusion



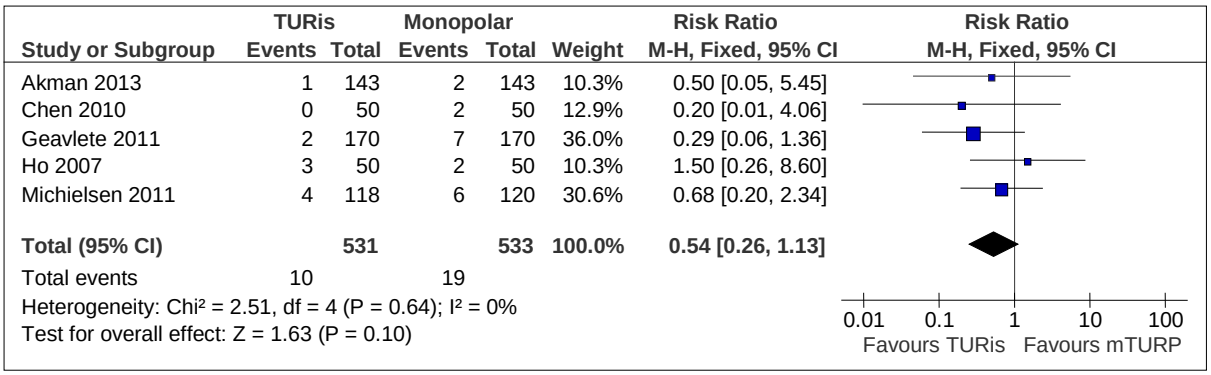
All three analyses indicate that TURis is associated with lower risk of blood transfusion.

Of the three approaches listed above the one judged by the EAC is the second approach (Figure 4) i.e. fixed effects meta-analysis with exclusion of data from Michielsen 2011. The pooled RR of 0.35 (95% CI 0.19, 0.64), p = 0.0008, in favour of TURis corresponds with an ARR of -0.05 (95% CI -0.07, -0.02) in favour of TURis. This represents a NNT of 20 (95% CI 14, 50), meaning that 20 patients need to be treated with TURis in order to prevent one case of blood transfusion.

Clot retention

The sponsor's meta-analysis of clot retention included data from two randomised studies (Akman 2013, Michielsen 2007) and the pooled RR (TURis/mTURP) was 0.63 (95% 0.21, 1.90). The confidence interval includes the null value of 1 and the result is not statistically significant. The EAC added data from three additional randomised studies (Chen 2010, Geavlete 2011, Ho 2006) and the RR (TURis/mTURP) changed to 0.54 (95% CI 0.26, 1.13), p = 0.10, and without obvious heterogenerity. This result is also not statistically significant (Figure 6).

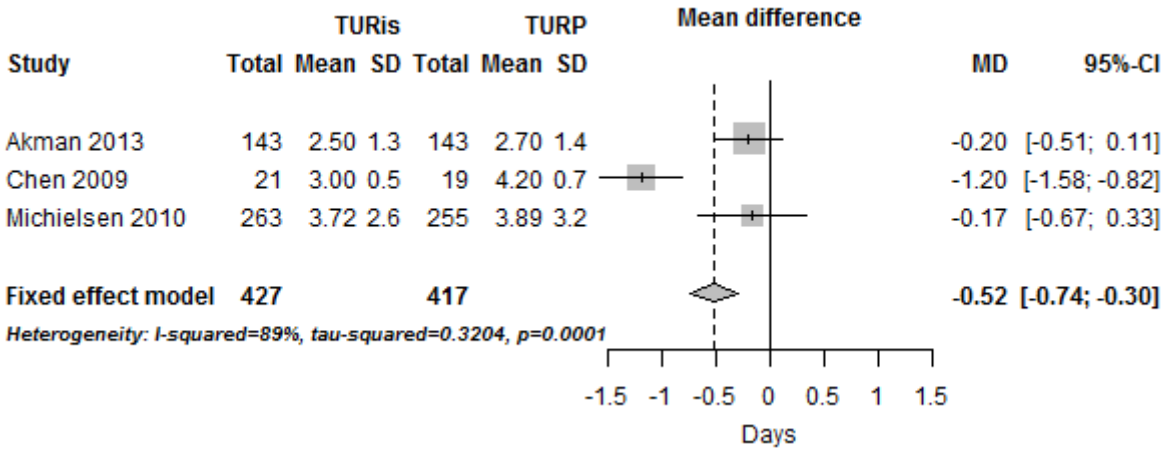
Figure 6: Forest plot of EAC fixed effect meta-analysis of clot retention



Hospital stay

The sponsor's meta-analysis of hospital stay included data from three randomised studies (Akman 2013, Chen 2009, Michielsen 2011 (shown as Michielsen 2010)). The pooled mean difference in hospital stay between groups (TURis minus mTURP) was -0.52 (95% CI -0.74, -0.30) days, p = 0.0001. This result is statistically significant since the confidence interval excludes the null value of zero difference between groups and it suggests that hospital stay is, on average, half a day shorter following TURis than following mTURP (Figure 7)

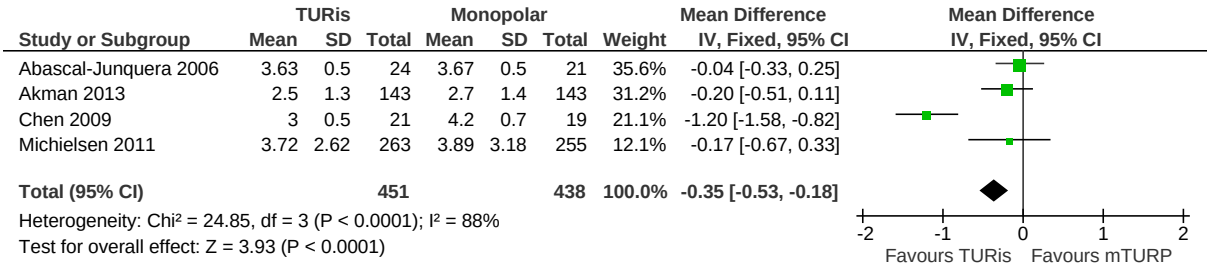
Figure 7: Sponsor's fixed effects meta analysis of hospital stay (reproduced directly from the submission, page 80)



However there is visible heterogeneity in the individual effects of the three included studies, with the Chen 2009 study driving the pooled estimate in favour of TURis.

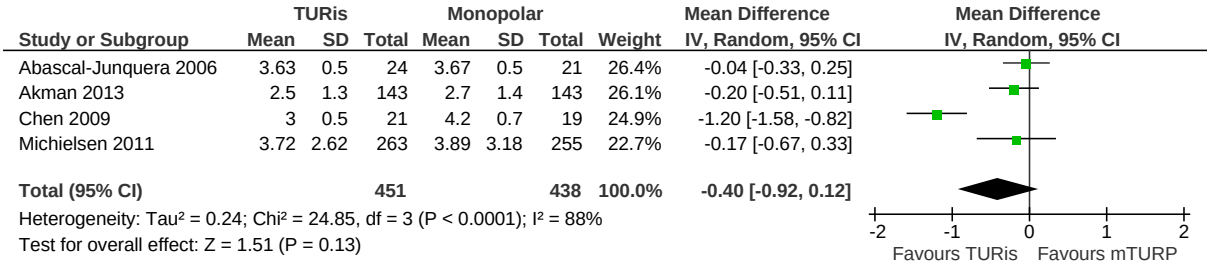
As an initial step the EAC added to the analysis data from a randomised trial published in a Spanish-language paper (Abascal-Junquera 2006). In a fixed effects model the effect was to slightly attenuate the size of the difference in favour of TURis, although it remained statistically significant: RR -0.35 (95% CI -0.53, -0.18), p < 0.0001. The profound heterogeneity remained (Chi^2 = 24.85, df = 3, p < 0.0001, I^2 = 88%), Figure 8.

Figure 8: Forest plot of EAC meta-analysis of hospital stay with data from Abascal-Junquera 2006 (fixed effects model)



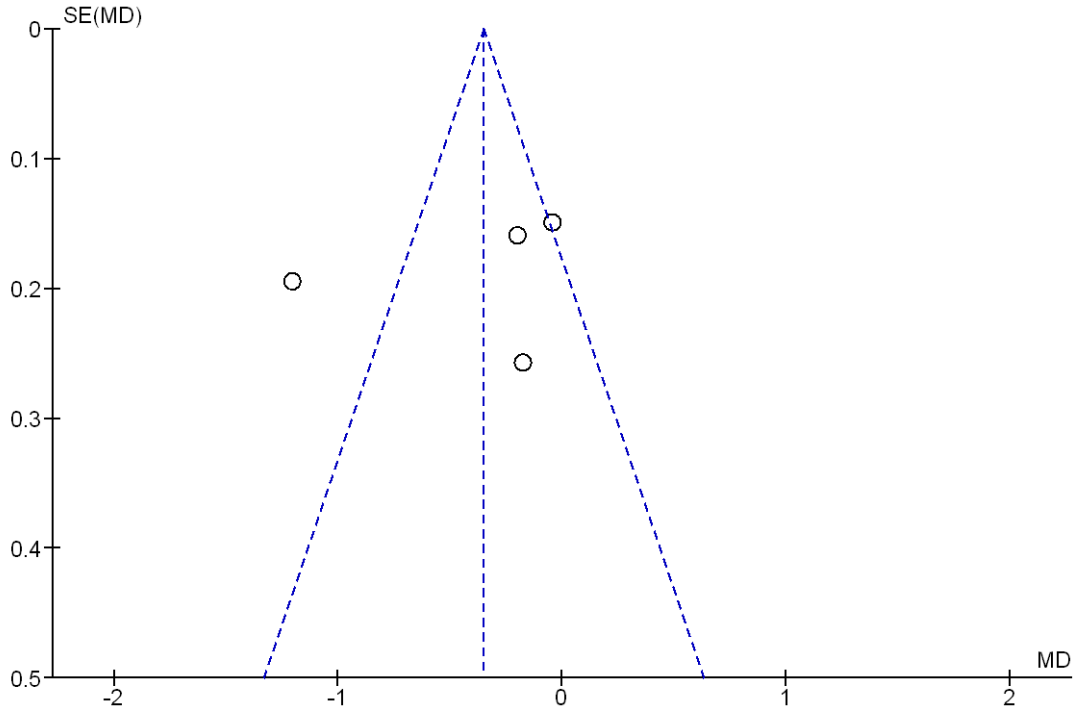
The EAC explored the effect of the same analysis as above but using a random effects model. This generates a pooled mean difference in hospital stay between groups (TURis minus mTURP) of -0.40 (95% CI -0.92, 0.12) days, p = 0.13. The result is not statistically significant as the confidence interval contains the null value of zero (Figure 9).

Figure 9: Forest plot of EAC meta-analysis of hospital stay with data from Abascal-Junquera 2006 (random effects model)



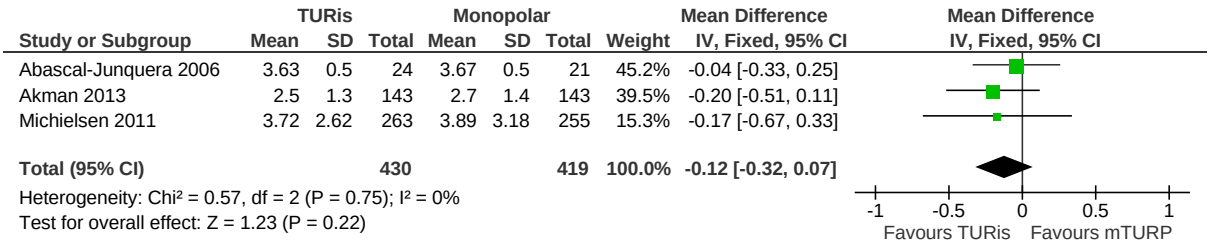
We examined the Chen 2009 study. The heterogeneity is easily visualised in a funnel plot (Figure 10), which plots the mean difference in hospital stay for each study on the X axis and the standard error of the mean difference for each study on the Y axis (descending). The Chen 2009 study is a clear outlier, lying to the left of the funnel.

Figure 10: Funnel plot illustrating heterogeneity between studies reporting data on length of hospital stay.



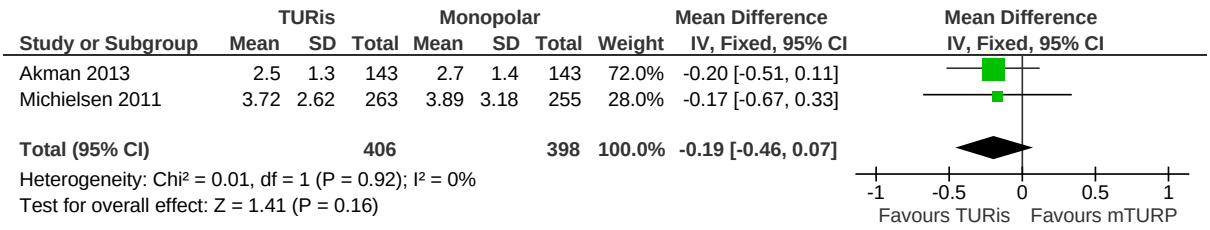
The Chen 2009 study was conducted in China and we considered that length of hospital stay is likely to be influenced by local practice in addition to purely clinical factors. On this basis we judged that we should exclude the Chen 2009 data from the meta-analysis. With removal of this data in a fixed effect model there was no discernable heterogeneity. The pooled mean difference in hospital stay between groups (TURis minus mTURP) was -0.12 (95% CI -0.32, 0.07) days, p = 0.13. The result is not statistically significant as the confidence interval crosses the null value of 1 (Figure 11).

Figure 11: Forest plot of EAC meta-analysis of hospital stay excluding data from Chen 2009 (fixed effects model)



Finally we explored whether data from the Spanish-language paper (Abascal-Junquera 2006) are pivotal to the analysis. Removal of this study resulted in only a small change to the RR and its confidence interval: RR -0.19
(95% CI -0.46, 0.07), p = 0.16, with the result being not statistically significant (Figure 12).

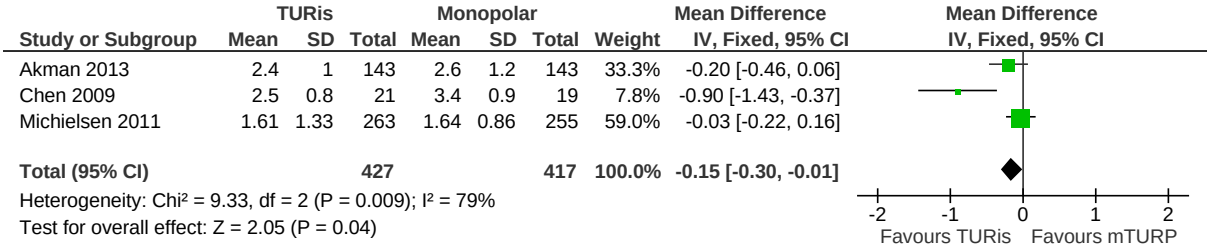
Figure 12: Forest plot of EAC meta-analysis of hospital stay excluding data from Chen 2009 and Abascal-Junquera 2006 (fixed effects model)



Time to removal of urinary catheter

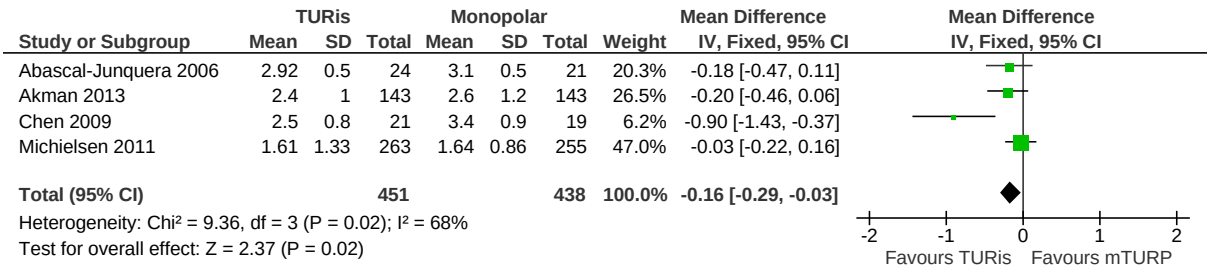
The sponsor's meta-analysis included data from three randomised studies (Akman, Chen 2009, Michielsen 2010) and used a fixed effects model. The sponsor's pooled estimate of the mean difference (TURis minus mTURP) in time to catheter removal was -0.23 (95% CI -0.38, -0.08) days. The sponsor made a small data error entry: In the Chen 2009 study the correct value for time to catheter removal is 2.5 days in the TURis group, not 1.5 days as entered. The EAC entered the correct value and the mean difference became -0.15 (95% CI -0.30, -0.01), p = 0.04 in favour of TURis, but with significant heterogeneity detected (Chi^2 = 9.33, df = 2, p = 0.009, I^2 = 79%), Figure 13.

Figure 13: EAC reproduction of sponsor's fixed effects meta-analysis of time to catheter removal (with a corrected data entry error)



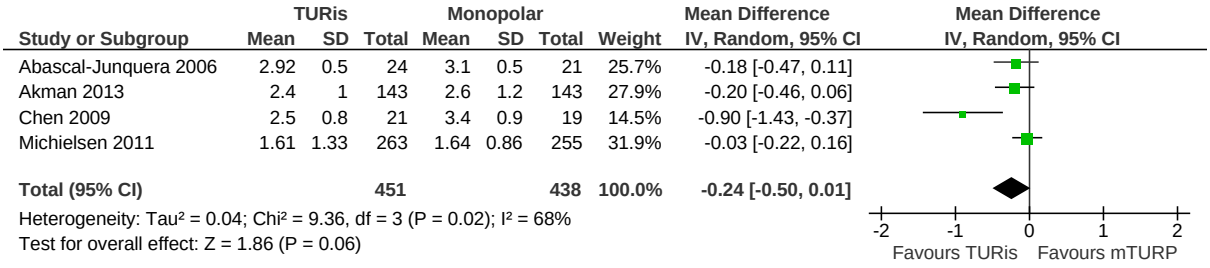
We also added data from an additional study (Abascal-Junquera 2006) published in a Spanish language paper. The Abascal-Junquera 2006 data made very little change to the result: the pooled fixed effect estimate of the mean difference (TURis minus mTURP) in time to catheter removal remained small but statistically significant at -0.16 (95% CI -0.29, -0.03) days, p = 0.02. This analysis also has significant heterogeneity between the studies (Chi^2 = 9.36, df = 3, p = 0.02, I^2 = 68%, Figure 14).

Figure 14: EAC fixed effect meta-analysis of time to catheter removal with additional data from Abascal-Junquera 2006



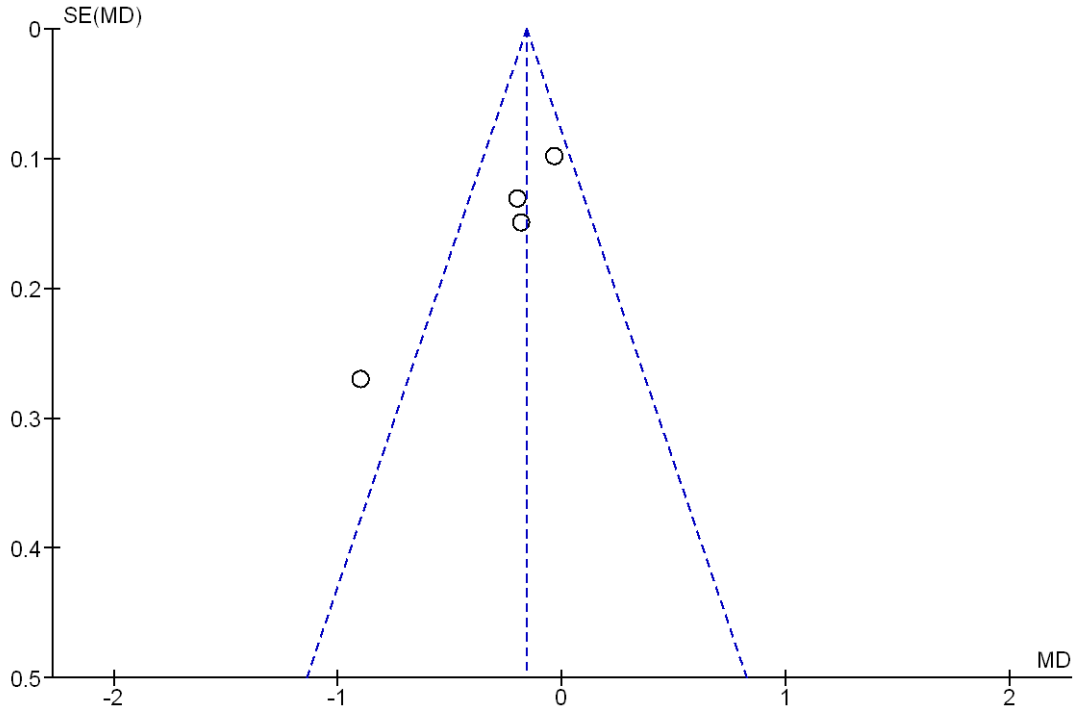
Due to visible heterogeneity we repeated the analysis with a random effects model. This provided a pooled estimate of the mean difference (TURis minus mTURP) in time to catheter removal of -0.24 (95% CI -0.50, 0.01), p = 0.06. The confidence interval includes the null value of zero difference and the result is no longer statistically significant (Figure 15).

Figure 15: EAC random effect meta-analysis of time to catheter removal with additional data from Abascal-Junquera 2006



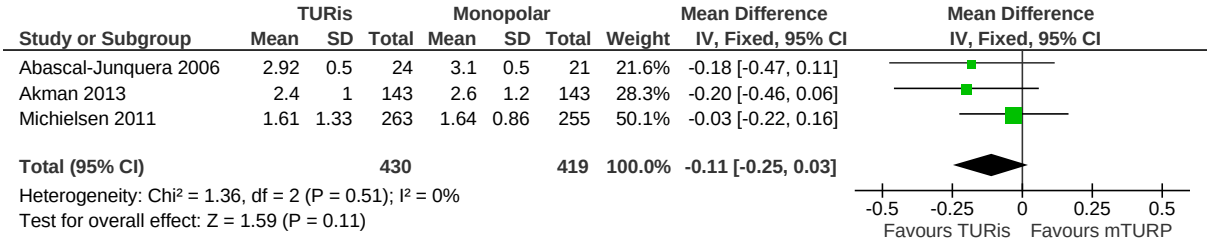
We examined the Chen 2009 study, which appears to introduce the heterogeneity. The study has the smallest patient sample of the four trials. In Figure 16 the Chen 2009 study is a clear outlier, lying to the left of the funnel.

Figure16 : Funnel plot illustrating heterogeneity between studies reporting data on time to catheter removal



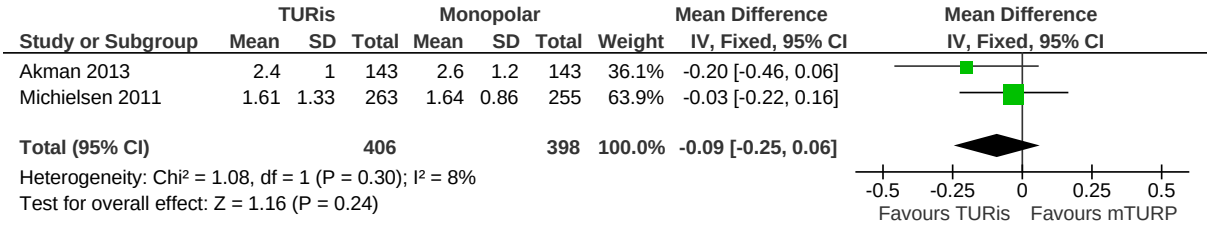
Similar to hospital stay above, we judged that local practice for catheter removal may differ internationally. We examined the effect of removing the Chen 2009 data. In a fixed effect model the mean difference (TURis minus mTURP) in time to catheter removal was -0.11 (95% CI -0.25, 0.03) days, p = 0.11. There is no remarkable heterogeneity but the difference is both small and not statistically significant, since the confidence interval contains the null value of zero (Figure 17).

Figure 17: EAC fixed effect meta-analysis of time to catheter removal with removal of data from Chen 2009



Finally we examined the effect of removing data from the Spanish language paper (Abascal-Junquera 2009) to determine whether it has strong influence (Figure 18). In a fixed effects analysis the mean difference (TURis minus mTURP) in time to catheter removal was -0.09 (95% CI -0.25, 0.06) days, p = 0.24. There is no profound heterogeneity and the difference remains small and not statistically significant (Figure 18). A limitation is that the meta-analysis includes only two studies.

Figure 18: EAC fixed effect meta-analysis of time to catheter removal with removal of data from Abascal-Junquera 2006

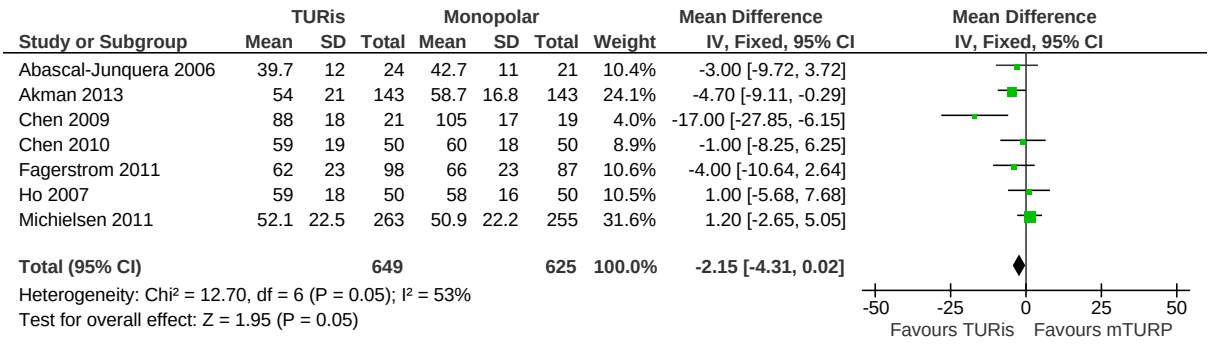


Procedure time

The sponsor's meta-analysis included data from five papers (Akman, Chen 2010, Fagerstrom, Michielsen 2007, Michielsen 2010) and used a fixed effects model. The pooled estimate of the mean difference (TURIs minus mTURP) in procedure time was 0.48 (95% CI -1.81, 2.77) minutes. The confidence interval includes the null value of zero difference and the result is not statistically significant. There was statistical heterogeneity between the studies (I^2 = 82.4%, p = 0.0001).

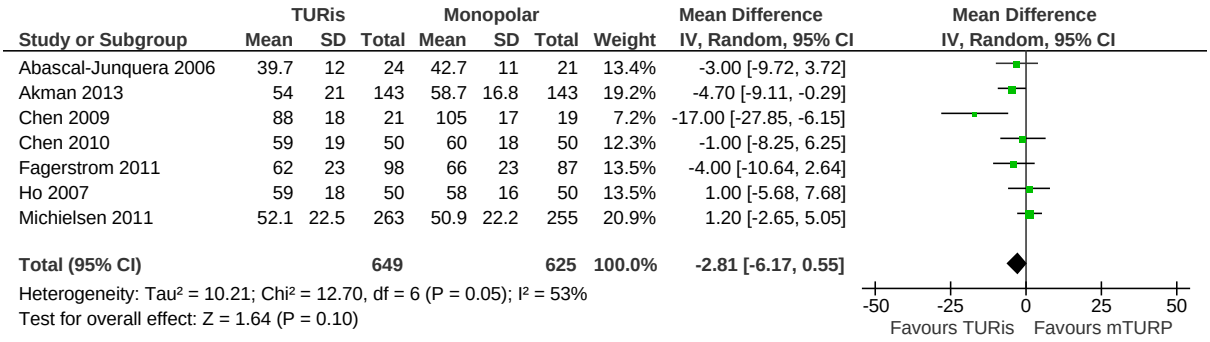
The sponsor repeated their initial meta-analysis but with omission of data from Michielsen 2007 on the basis that in the TURis arm, a greater proportion of procedures were performed by trainee surgeons than in the mTURP arm, resulting in longer operating times. This can be seen as a reasonable action on the grounds of heterogeneity but moreover the EAC established with the lead author that the data in this study are part of the same randomised study published subsequently and also included in the same meta-analysis (Michielsen 2010). Therefore the EAC removed the Michielsen 2007 data and added three additional studies (Abascal Junquera 2006, Chen 2009, Ho 2006), as shown in Figure 19. The pooled estimate of the mean difference (TURIs minus mTURP) in procedure time was -2.15 (95% CI -4.31, 0.02, p = 0.05) minutes. The confidence interval includes the null value of zero difference and the result is not statistically significant. There is also statistical heterogeneity between the studies (Chi^2 = 12.70, df = 6, p = 0.05, I^2 = 53%).

Figure 19 Forest plot of fixed effects meta-analysis of procedure time



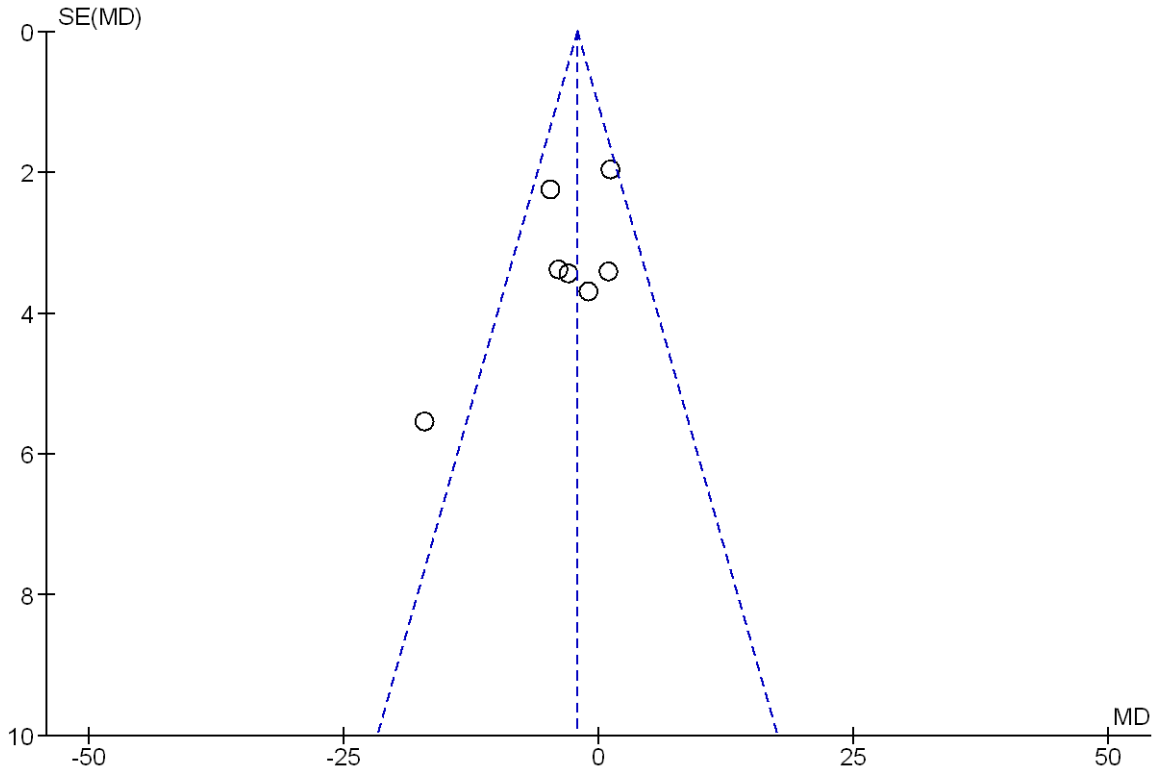
Repeating the analysis in a random effects model provides a pooled mean difference (TURIs minus mTURP) in procedure time of -2.81 (95% CI -6.17, 0.55 p = 0.10) in favour of TURis. The confidence interval includes the null value of zero difference and the result is not statistically significant (Figure 20).

Figure 20: Forest plot of EAC meta-analysis of procedure time (random effects model)



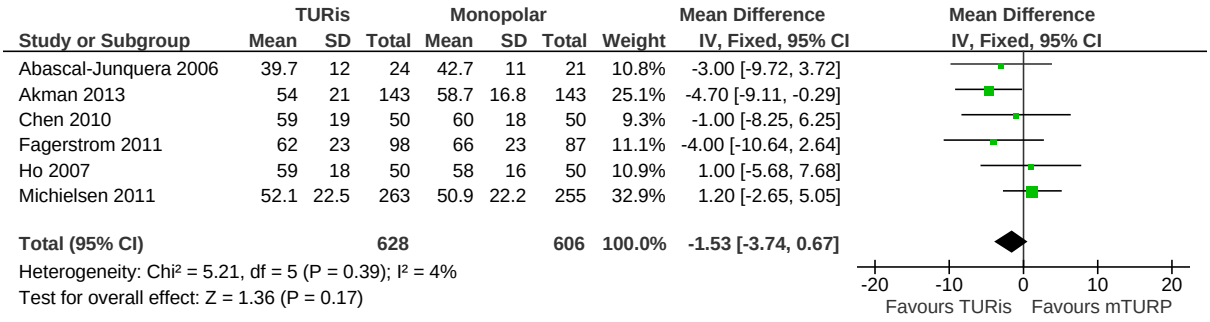
We examined the study by Chen 2009, which introduces visible heterogeneity to the analysis (being noticeably different to Chen 2010, conducted at the same centre). In Figure 21 the Chen 2009 study is again a profound outlier, with a large mean difference in procedure time favouring TURis, and also the largest variability in procedure time.

Figure21: Funnel plot illustrating heterogeneity between studies reporting data on procedure time



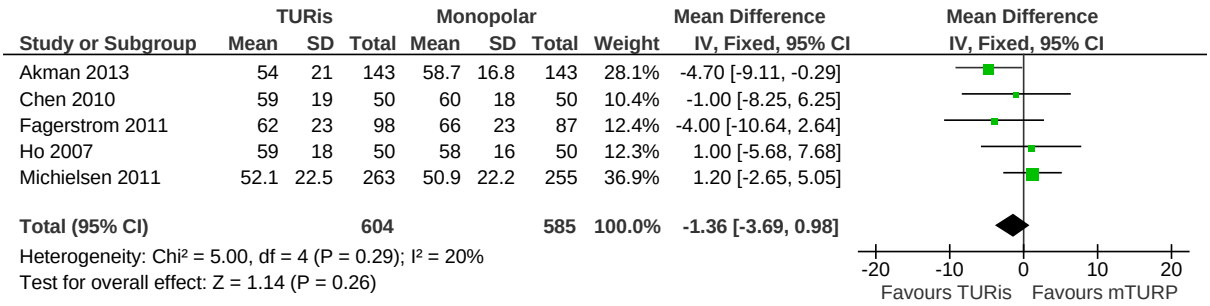
The Chen 2009 study had the largest baseline prostate volumes: mean 78.4 ml (TURis) and mean 76.8 ml (mTURP) and the longest operating times (mean 88 minutes and 105 minutes, respectively). Suspecting that a relationship exists between prostate volume and operating time we explored a fixed effect meta-analysis with removal of the Chen 2009 data. The pooled mean difference (TURIs minus mTURP) in procedure time was -1.53 (95% CI -3.74, 0.67) minutes with p = 0.39 i.e. a small difference which is not statistically significant (Figure 22).

Figure 22: Fixed effects EAC meta-analysis of procedure time with removal of data by Chen 2009



Finally we explored in a fixed effect analysis whether removal of data from the Spanish-language paper (Abascal-Junquera 2006) had much influence on the result (Figure 23). There was only a small change in the result: the pooled mean difference (TURIs minus mTURP) in procedure time was -1.36 (95% CI -3.69, 0.98, p = 0.26) minutes i.e. a small difference and a non-statistically significant result.

Figure 23: Fixed effects EAC meta-analysis of procedure time with removal of data from Abascal-Junquera 2006



3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

In addition to adjustments made to the sponsor's meta-analyses reported in section 3.6, the EAC performed meta-analysis of data from randomised studies for the following outcomes:

- Re-admission due to haemorrhage

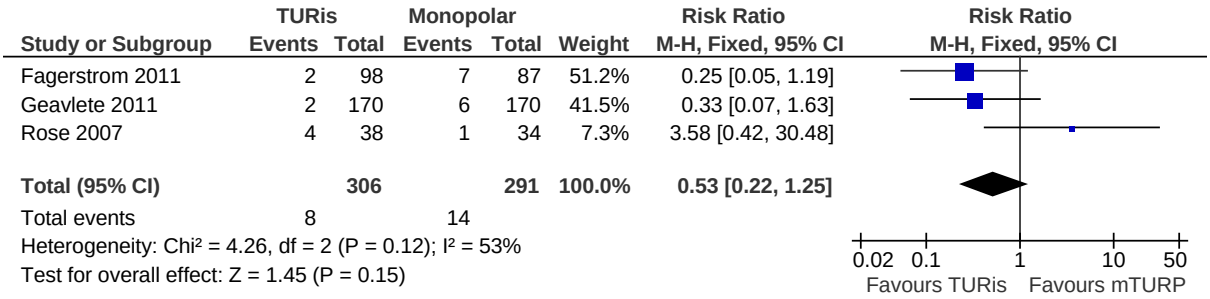
- Urethral strictures and bladder neck contractures
- Repeat procedure due to incomplete resection

Re-admission due to haemorrhage

The EAC explored whether there is a difference between TURis and mTURP in readmission to hospital due to secondary haemorrhage. Expert advice indicated that this can occur at around day 12 post operatively.

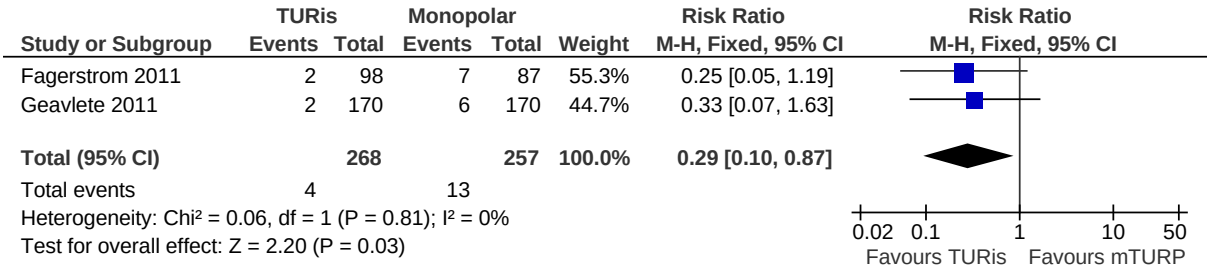
Three studies provided data (Figure 24). The RR (TURis/mTURP) of readmission due to haemorrhage was 0.53 (95% CI 0.22, 1.25, p = 0.15). This result is not statistically significant. There is no obvious heterogeneity between the studies (Figure 24).

Figure 24: Fixed effects meta-analysis of re-admission due to haemorrhage



If the data from the German-language paper (Rose 2007) are excluded the RR becomes 0.29 (95% CI 0.10, 0.87, p = 0.03) in favour of TURis i.e. a statistically significant result since the confidence interval excludes the null value of 1. In this sense the Rose 2007 data are pivotal and should be included (Figure 25).

Figure 25: Fixed effects meta-analysis of re-admission due to haemorrhage, excluding data from Goh 2007



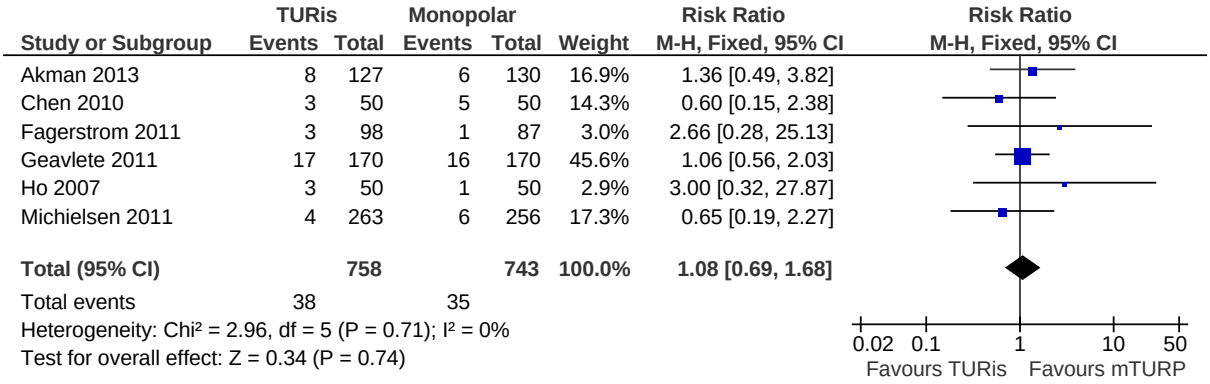
Urethral strictures and bladder neck contractures

In the published literature some authors express a concern that TURis may lead to higher rates of urethral strictures or bladder neck contractures / stenoses. These arise due to tissue damage during surgery and the specific concern arises because TURis uses higher power (W)

than mTURP, and because the return electrode runs current back along the resectoscope inside the urethra. Expert advisors confirmed that it was worth collecting data for these outcomes.

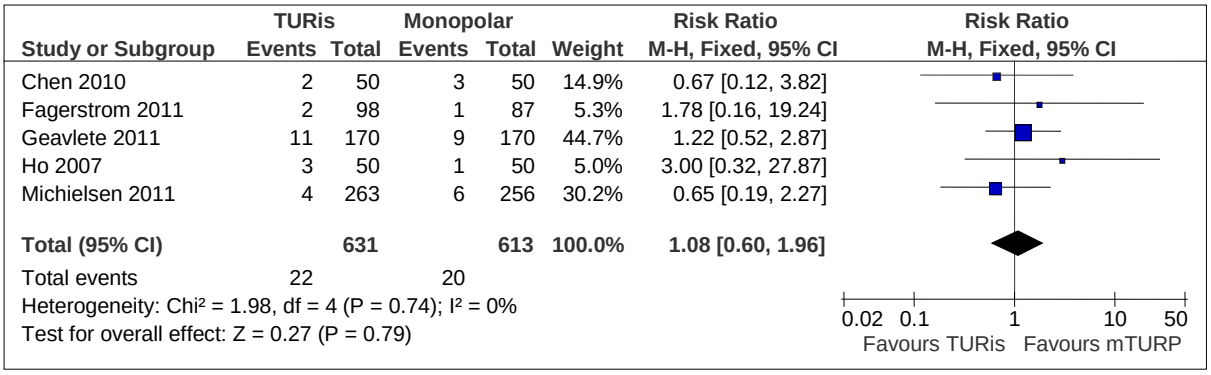
Six studies provide data (Figure 26). Some studies aggregate urethral stricture / bladder neck contracture together whereas others report data separately. For aggregated data, there is little difference in the risk of these two adverse events between groups: RR 1.08 (95% CI 0.69, 1.68, p = 0.74), with no obvious heterogeneity (Figure 26).

Figure 26: EAC fixed effect meta-analysis of urethral stricture / bladder neck contracture (aggregated data)



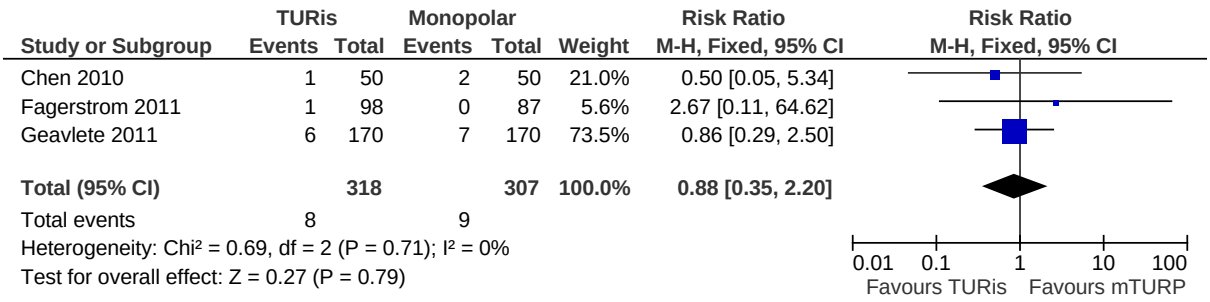
Five studies report data on urethral strictures as a single outcome. In a fixed effects meta-analysis there is little difference in the risk of urethral strictures between TURIs and mTURP: RR 1.08 (95% CI 0.60, 1.96, p = 0.79), with no obvious heterogeneity (Figure 27).

Figure 27: EAC fixed effect meta-analysis of urethral stricture



Three studies report data on bladder neck contracture as a single outcome. In a fixed effects meta-analysis there is little difference in the risk of bladder neck contracture between TURIs and mTURP: RR 0.88 (95% CI 0.35, 2.20, p = 0.79), with no obvious heterogeneity (Figure 28):

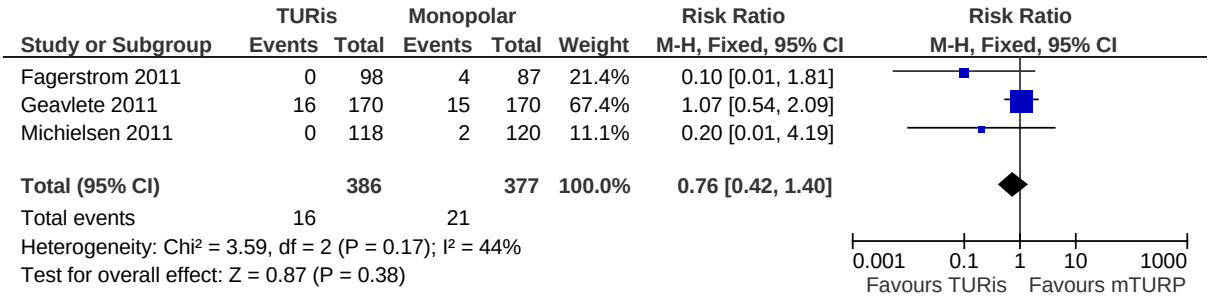
Figure 28: EAC fixed effect meta-analysis of bladder neck contracture



Repeat procedure due to incomplete resection

Three studies provide data. In a fixed effect meta-analysis there is there is little difference in the risk of repeat procedure due to incomplete resection between TURIs and mTURP: RR 0.76 (95% CI 0.42, 1.40, p = 0.38), as shown in Figure 29.

Figure 29: Fixed effects meta-analysis of repeat procedure due to incomplete resection



The analysis of repeat procedures is subject to some uncertainty concerning how events are classified. The study by Fagerstrom reported 2/98 events in the TURis arm: one internal urethrotomy and one TUIP for bladder neck stenosis. We judged that these were surgeries for stricture/contracture and therefore not surgeries due to incomplete resection, and entered zero events in this arm.

The data for Geavlete 2011 refer to 'retreatment rate', but appear to be distinct from data for bladder neck sclerosis and urethral strictures.

The data in Michielsen 2007 are reported as two patients in the mTURP group requiring 'transurethral revision with cauterisation' and appear to be distinct from complications.

Nevertheless it is possible that in all three studies the reported procedures were undertaken for reasons other than incomplete resection, including bleeding or contractures/strictures. For this reason the result should be interpreted with caution.

3.10 Conclusions on the clinical evidence

The EAC presents a response to each claim relating to patient benefits made by the sponsor in the scope. Our responses are shown in Table 46 below. Our responses to the sponsor's

claims relating to healthcare system benefits are presented in our conclusions on the economic submission in Section 5 (Table 56).

Table 46: EAC responses to each claim made by the sponsor relating to patient benefits in the scope

Sponsor's claim re: patient benefits	EAC response
Reduced risk of transurethral resection (TUR) syndrome through the use of a saline irrigation fluid.	We uphold this claim and calculate RR 0.18 (95% CI 0.05, 0.61) in favour of TURis based on meta-analysis of six randomised studies (Figure 2). ARR = -0.02 (95% CI -0.03, -0.01) NNT = 50 (95% CI 33, 100) The NNT estimates that 50 patients must be treated with TURis (instead of mTURP) to prevent one case of TUR syndrome.
Reduced risk of post-operative blood transfusion due to intraoperative bleeding.	We uphold this claim and calculate RR 0.35 (95% CI 0.19, 0.64) in favour of TURis based on meta-analysis of six randomised studies (Figure 4). ARR = -0.05 (95% CI -0.07, -0.02) NNT = 20 (95% CI 14, 50) The NNT estimates that 20 patients must be treated with TURis (instead of mTURP) to prevent one case of blood transfusion.
A shorter surgical procedure leading to fewer intra and post-operative complications and a lower level of hospitalisation.	**Procedure time** Evidence from randomised trials does not find that procedures are significantly shorter using TURis compared to mTURP. An EAC meta-analysis of five randomised studies found the difference in procedure time (TURis minus mTURP) to be -1.36 minutes (95% CI -3.69, 0.98) minutes (Figure 23). The result is not statistically significant and the size of the observed difference is small and unlikely to transfer to a real life resource saving. TURis reduces complications in terms of TUR syndrome and blood transfusion as described above. Our conclusions for other complications are as follows.
As above	**Clot retention** Evidence from randomised trials does not indicate that TURis reduces clot retention compared to mTURP. An EAC meta-analysis of five randomised trials (Figure 6) indicates there is no statistically significant effect in favour of TURis: RR (TURis/mTURP) 0.54 (95% CI 0.26, 1.13)

Sponsor's claim re: patient benefits	EAC response
As above	**Readmission due to haemorrhage** Evidence from randomised trials does not indicate that TURis reduces re-admission due to haemorrhage compared to mTURP. In an EAC meta-analysis of three randomised trials the RR of readmission due to haemorrhage (TURis/mTURP) is 0.53 (95% CI 0.22, 1.25, p = 0.15) i.e. not a statistically significant result since the confidence interval includes the null value of 1.
As above	**Readmission (any cause)** The EAC notes that one RCT recorded readmission for any cause (Fagerstrom 2011). In this study the rate of readmission was 5/98 cases (5.1%) in the TURis arm compared to 14/87 (16.1%) in the mTURP arm, p = 0.011. There is variability across randomised studies in the reporting of adverse events leading to readmission and there is poor reporting of rates of readmission by cause.
As above	**Hospital stay** The sponsor's meta-analysis contains visible heterogeneity with a clear outlying study that found a statistically significant reduction in hospital stay of 1.2 days in favour of TURis (Chen 2009). No other randomised study reported a significant difference in favour of TURis for hospital stay. The EAC's meta-analysis of two studies, excluding the outlier found no statistically significant effect in favour of TURis: mean difference in hospital stay (TURis minus mTURP): -0.19 (95% CI -0.46, 0.07) days (Figure 12). The size of the observed difference is small and unlikely to transfer to a real life resource saving. As an alternative method we included the data from Chen 2009 in a random effects model. This too found no statistically significant effect.
As above	**Urethral strictures / bladder neck contractures** Evidence from randomised studies indicates that there is no difference in the rates of urethral stricture or bladder neck contracture between TURis and mTURP. An EAC meta-analysis (Figure 26) of six studies found the RR (TURis/mTURP) to be 1.08 (95% CI 0.69, 1.68), p = 0.74. Randomised studies appear to report data on the incidence of these adverse outcomes in a fairly consistent manner.

Sponsor's claim re: patient benefits	EAC response
As above	**Repeat procedure due to incomplete resection** Evidence from randomised studies indicates that there is no difference in the rates of repeat procedure due to incomplete resection between TURis and mTURP. An EAC meta-analysis (Figure 29) of three studies found the RR (TURis/mTURP) to be 0.76 (95% CI 0.42, 1.40), p = 0.38. There is again some variation in the reporting of this outcome across studies, which leads to uncertainty in the EAC's result.
Earlier catheter removal time for improved patient comfort.	Evidence from randomised trials does not indicate that catheters are removed significantly earlier following TURIs than following mTURP. As was the case for hospital stay, the sponsor's analysis contained outlying data from the Chen 2009 study. In an EAC fixed effects meta-analysis of two studies (without the Chen 2009 data) the mean difference (TURis minus mTURP) in time to catheter removal was -0.09 (95% CI -0.25, 0.06) days, p = 0.24. This result is not statistically significant.

4 Economic evidence

4.1 Published economic evidence

4.1.1 Critique of the sponsor's search strategy

The sponsor's methods for identifying and selecting economic studies are listed in Table 61 of the submission. The sponsor has searched a comprehensive list of databases and the inclusion and exclusion criteria reflect the scope. In keeping with the sponsor's interpretation of the scope for clinical evidence, economic evidence for TURis vaporisation procedures is excluded.

4.1.2 Retrieval of published economic evidence

The sponsor searched the following databases:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R)
- EMBASE
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2014
- EBM Reviews - Cochrane Central Register of Controlled Trials January 2014,
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2014,
- EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2014,
- EBM Reviews - Health Technology Assessment 1st Quarter 2014
- Econlit 1886 to February 2014

The reference lists of identified systematic reviews were also searched.

The sources searched provide reasonable coverage of likely published evidence though the following would have made the search for published evidence more rigorous

- search of conference proceedings
- reference list checking of included studies
- contact of authors of included studies to check for other data

4.1.3 Retrieval of unpublished economic evidence

Internal research within the sponsor's organisation was searched for any relevant unpublished data. A search of conference proceedings and contacting authors of included

studies to check for other data would have made the search for unpublished evidence more rigorous.

4.1.4 Search strategy

The strategy has been assessed in accordance with the PRESS checklist (Peer Review of Electronic Search Strategies). The search strategy used by the sponsor is comprehensive using a range of Medical Subject Headings and free-text terms together with Boolean and proximity operators and an economic search filter.

4.1.5 Critique of the sponsors study selection

A flow diagram of study selection was included in the sponsor's submission. This was mostly clearly presented except for how the 1116 records were obtained in relation to the number of records identified by the database searches presented in the sponsor's appendix. For the 136 references that were excluded, clarification could be provided that this includes the 24 references for the clinical evidence. The sponsor did not identify any unpublished studies.

4.1.6 Included and excluded studies

The sponsor has identified three economic studies (Gupta 2010;Lourenco T et al. 2008;Sugihara et al. 2012) and the EAC identified one additional clinical study which included an economic estimation (Shum, Mukherjee, Teo, Shum, Mukherjee, & Teo 2014) but has not used them as evidence for TURis due to low applicability to the scope.

4.1.7 Overview of methodologies of all included economic studies

The studies are described below but they add little value to an evaluation of TURis versus mTURP due to:

- consideration of generic bipolar technologies, or unknown bipolar technology (Gupta 2010;Lourenco T, 'Dow J, abi G, everill M, ickard R, & rmstrong N 2008;Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, Homma, Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, & Homma 2012)

- international differences in length of hospital stay acknowledged by authors (Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, Homma, Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, & Homma 2012)

- insufficient detail (Gupta 2010;Shum e. al. 2014).

A health technology assessment (Lourenco T et. al. 2008) compared different sequences of surgical procedures in a Markov model, including minimally invasive procedures, TURP and

ablative procedures. The authors presented clinical evidence for bipolar TURP, but there is no included evidence for TURis, or an economic evaluation of bipolar versus mTURP.

The sponsor has also referred to a Japanese economic analysis based on a retrospective national review of bipolar (1531 cases) and mTURP (5155 cases) procedures (Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, Homma, Sugihara, Yasunaga, Horiguchi, Nakamura, Nishimatsu, Kume, Ohe, Matsuda, & Homma 2012) performed in 222 hospitals. In Japan at the time of study there were two bipolar systems in use: TURis and the Storz AUTOCON II 400. There was no firm method to identify TURis procedures, but a previous national survey (with response rate 42%) suggested that TURis was the bipolar technology used in the vast majority of cases. Cases were identified from a national administrative claims database which accounts for 40% of all acute care inpatient hospitalizations in Japan. Data were collected in two six month intervals: from July 1 to December 31 of 2008 and 2009. Total costs included doctor and administration fees, operation and anaesthesia costs, medications, laboratory tests and imaging tests. The sample excluded low volume centres (defined as fewer than 15 cases and those that practised autologous blood transfusion. Bipolar procedures were concentrated in academic and large volume centres. Cases of mTURP were identified on the basis of sorbitol being used as the irrigation fluid: the absence of sorbitol was assumed to represent a bipolar procedure. Bipolar TURP had longer procedure time (116 minutes) than mTURP (98 minutes, $p < 0.001$). There were 20 cases of homologous transfusion in the bipolar group versus 118 in the monopolar group ($p = 0.018$). Overall postoperative complications favoured bipolar TURP (26 cases) over mTURP (172 cases, $p = 0.001$). Respective values for TUR syndrome were zero versus 16 ($p = 0.029$). Postoperative length of stay was shorter in the bipolar group at 7 days, versus 8 days in the monopolar group ($p = 0.003$). Total mean cost per procedure was US$ 6062 for bipolar TURP and US$ 6103 for mTURP. The authors acknowledged that Japan is characterized by a longer length of hospital stay than Western countries, related to its insurance based healthcare system, and that some monopolar procedures could have been classified as bipolar procedures if the sorbitol use was not registered in the database. The costs used in the study were highly aggregated.

The third study is a conference abstract based on a cost analysis in India (Gupta 2010). The study examined the costs of various surgical treatments performed in the period January 2003 to October 2009 for BPE, including monopolar (584 cases) and bipolar TURP (39 cases, bipolar not specified as TURis). The costs included were manpower cost, cost of surgical and operation theatre equipment and the cost of post operative ward stay. The cost per case for mTURP was estimated as US$ 169.77 for mTURP and US$240.42 for bipolar TURP.

The EAC identified one additional study with cost data. The uncontrolled before and after study reported in sections 3.3 and 3.6 studied 100 patients treated in Singapore with TURis (Shum, Mukherjee, Teo, Shum, Mukherjee, & Teo 2014). Patients were treated according to a catheter-free early discharge protocol, with discharge on postoperative day 1. There were

13 patients discharged with a urinary catheter. 14 patients received simultaneous other surgical procedures such as inguinal hernia repair or cystolitholapaxy. The study included the costs of ward charges, surgical fees, diagnostics, medications, laboratory and radiological investigations and excluded government subsidies. The average bill of the TURis-treated patients discharged from hospital as per protocol on postoperative day 1 was 4768.58 SGD. The authors estimated the cost of a 3 day hospital stay for mTURP as SGD 8768.87. The authors appear to have achieved discharge on postoperative day 1 for all TURis patients (in contrast to the majority of randomised studies) and this study does not provide a direct empirical comparison with mTURP.

4.1.8 Overview and critique of the sponsor's critical appraisal for each study

The sponsor did not critique the economic evidence, as no relevant evidence was identified.

4.1.9 Does the sponsor's review of economic evidence draw conclusions from the data available?

The sponsor did not draw conclusions from the economic evidence, as no relevant evidence was identified.

4.2 De novo cost analysis

Patients

The population in the model is men with lower urinary tract symptoms (LUTS) presumed secondary to benign prostatic hyperplasia (BPH), in whom surgical intervention (TURP) is indicated and this is in accordance with the scope.

Technology

The technology is the TURis system in accordance with the scope.

Comparator(s)

As described in the scope the sponsor's comparator is mTURP.

Model structure

An executable model was provided in Excel format. The model structure is straightforward and is in the form of a simple decision tree. Patients entering the model are either treated with TURis or mTURP. The following complications are included in the base case: TUR syndrome, blood transfusion. Clot retention can be included as an option. There is also an option to include re-operation due to the initial procedure being terminated prior to completion. The time horizon of the model is not defined but it is designed to capture early procedural complications. A discount rate of 3.5% is applied to the capital equipment cost of

TURis beyond the first year. The model perspective is that of the NHS. The EAC considers the basic model structure to be appropriate.

The sponsor lists five assumptions:

1. No difference is assumed in the efficacy of TURis and mTURP in terms of resection weight or radicality

2. The capital cost of mTURP equipment is not considered

3. The cost of an Olympus generator is not considered

4. The risk of TUR syndrome in the TURis arm is 0%

5. TURis electrodes are non-reusable

The EAC agrees with all of these assumptions. None of the published studies have shown a difference in efficacy of TURis compared with mTURP in terms of resection of tissue. No cases of TUR syndrome have been identified in the TURis arm of the published studies, so the assumption of risk of TUR syndrome of 0% is supported. TURis electrodes are single patient use, so it is reasonable to assume that they are not re-used. Olympus manufacture a reusable electrode for TURis but report that demand for it is virtually nil, and that they recommend use of single use TURis electrodes. The model assumes also that electrodes used for mTURP are also single use. This too is a reasonable assumption because expert advisors report that although some centres employ reusable electrodes in mTURP,it is considered best practice to use only single patient use electrodes. It is reasonable to exclude the capital cost of the mTURP equipment if the equipment was provided as part of a contract agreement to purchase electrodes. However hospitals may choose to purchase the capital equipment and then buy consumable items from third party suppliers. In this case the capital equipment cost should be included in the model.

The Olympus generator is provided as part of the product package and therefore it does not need to be considered separately. The model assumes the generator is supplied free of charge as part of a contract to purchase TURis consumables. No discount on consumables is applied for sites already having an Olympus generator.

The EAC identified the following additional assumptions in the model that were not made explicit in the sponsor's submission:

1. The cost of the mTURP consumables is assumed to be 50% of the cost of TURis consumables.

2. There is an assumption that patients admitted for re-operation would undergo the same type of procedure (TURis or mTURP) as the initial operation.

3. The sponsor assumes that 22% of TURis procedures employ a roller electrode in addition to a loop electrode based on sponsor sales data.

4. It is assumed that patients experiencing intra-operative bleeding would require a blood transfusion.

5. The model assumes the mTURP electrodes are single use.

The EAC can find no justification for making the assumption that mTURP consumables are 50% the cost of TURis consumables. Since the sponsor's Tornado charts (sponsor's Figures 14 & 15) show the cost of mTURP consumables to be the third strongest driver of the model, it is important to use the best possible data source for this value, rather than an estimate.

The EAC confirmed the assumptions concerning electrodes used for TURis and mTURP with clinical experts. Clinical advisers noted that some centres use re-useable mTURP electrodes, but that it is best practice to use single use electrodes.

Clinical parameters and variables

Clinical data on complications (TUR syndrome), blood transfusion, and clot retention were taken from the sponsor's meta-analysis. For relative risk of clot retention for TURis vs mTURP, the results of the sponsor's MA were not statistically significant and the confidence interval crosses the null value. The sponsor has used the point estimate of relative risk. Clot retention was included only as an option in the model, and was not included in the base case results. This result should be interpreted with caution due to the lack of statistical significance.

There is the option in the model to include in the calculations the costs of re-operation due to the initial procedure being terminated prior to completion. The percentage of patients needing re-operation is 5% for mTURP and 2% for TURis based on data from the Fagerstrom 2011 study. Other studies include data on re-admissions, but these were not included by the sponsor. On scrutinising the Fagerstrom 2011 study it appears that the two re-operations in the TURis arm were for urethral stricture or scarring. The EAC has combined the results of studies reporting re-operation for incomplete resection in the EAC meta-analysis. The forest plot is shown in Figure 29 of this report. The interpretation of the re-admission data is difficult because of unclear reporting in the studies. In the Fagerstrom 2011 study, the rate of re-admission (any cause) was 5/98 (TURis) versus 14/87 (mTURP), $p < 0.011$. However other studies are less comprehensive in reporting re-admissions, so it is not clear if this is a general finding across all studies. In the model re-admission due to clot retention only is included as an option. Therefore the inclusion of re-admission in the model is subject to uncertainty.

The sponsor presents inputs to their de novo cost model in Table 70 of their submission. The EAC has reproduced the clinical parameters in the table below (as Table 47) and we have added different values for each input where we feel that these improve validity.

Table 47: Clinical parameters in de novo cost model

Variable	Sponsor's value	Sponsor's range or 95% CI (distribution)	Sponsor's source	EAC's value	EAC's range or 95% CI (distribution)	EAC's source
Probability of TUR syndrome with mTURP	1.14% (7/613)	0.30% - 1.98% (Beta)	Meta-analysis of RCTs as described in Section 7 of this dossier. Range: ±25%.	1.77% (13/734)	Range 0.75%, 5.26% 95% CI 1.04%, 3.01%	Mean value of 6 RCTs (Akman, Chen 2009, Fagerstrom, Geavlete, Ho, Michielsen 2010). 95% CI calculator http://vassarstats.net/prop1.html
Probability of TUR syndrome with TURis	0%	-	Although the meta-analysis calculated a relative risk of 0.28, any risk of TUR syndrome is eliminated with TURis (for more detail, see section 9.2.1).	0%		Correspondence with expert advisors and RCT data.
Probability of blood transfusion with mTURP	7.50% (21/280)	4.41% - 10.59% (Beta)	Meta-analysis of RCTs as described in Section 7 of this dossier. Range: ±25%.	5.79% (37/639)	Range 0.83%, 15.79% 95% CI 4.23%, 7.88%	Mean value of 6 RCTs (Akman, Chen 2009, Chen 2010, Fagerstrom, Geavlete, Ho) A clinical expert estimated the figure at 5%, i.e. close to that of the RCT data.
Relative risk of blood transfusion for TURis versus mTURP	RR 0.36	0.16 - 0.80 (Beta)	Mean value and range: meta-analysis of RCTs as described in Section 7 of this dossier.	RR 0.35	95% CI 0.19, 0.64	EAC meta-analysis of 6 RCTs (Akman, Chen 2009, Chen 2010, Fagerstrom, Geavlete, Ho)
Probability of clot retention with mTURP	3.04% (8/263)	-	Meta-analysis of RCTs as described in Section 7 of this dossier Note: this is not considered in the base case analysis	3.56% (19/533)	Range 1.39%, 5% 95% CI 2.29%, 5.61%	5 RCTs (Akman, Chen 2010, Geavlete 2011, Ho, Michielsen 2007) 95% CI: http://vassarstats.net/prop1.html
Relative risk of clot retention for TURis versus mTURP	RR0.63	-	Meta-analysis of RCTs as described in Section 7 of this dossier Note: this is not considered in the base case analysis	RR 0.54	95% CI 0.26, 1.13	EAC meta-analysis of 5 RCTs (Akman, Chen 2010, Geavlete 2011, Ho, Michielsen 2007)

Resource identification, measurement and valuation

Hospital Length of Stay (LOS)

The sponsor took procedural data such as difference in hospital length of stay for TURis compared with mTURP from the sponsor's meta-analysis. The EAC considers this requires careful scrutiny since procedural measures largely reflect local practice. Inspection of the relevant forest plots (Figures 7-10, 19-21) reveals a high degree of heterogeneity resulting from one of the studies (Chen 2009) in all of the procedural measures (hospital LOS, procedure duration, catheterisation time). There are several approaches to coping with heterogeneity in a meta-analysis.

1) Ignore the heterogeneity and do fixed effects meta-analysis

2) Do random effects meta-analysis, which applies when the 'effect' (e.g. difference hospital LOS between TURis and mTURP) is not expected to be the same in all studies

3) Remove the outlier studies.

The fixed effects method is not appropriate for extremely heterogeneous data. The random effects method is less robust than the fixed effects method, particularly when the number of studies is small. The EAC considered that since just one study based in China was very different from the other studies, it was reasonable that the outlier study (Chen 2009) should be removed from the meta-analysis for the procedural measures. It was then possible for the EAC to apply the fixed effects method. The results of the EAC meta-analysis for LOS is that there is no significant difference between LOS for TURis and mTURP.

It is worth noting that the sponsor's claimed reduction in LOS of 0.52 days may not be realisable in clinical practice. Discharge from hospital is subject to hospital procedures and practices, such as the timing of ward rounds and availability of prescription medicines to take home. A time saving of less than 1 day is not always readily achievable.

Although the sponsor took the difference in LOS for TURis compared with mTURP from the meta-analysis, the LOS for mTURP (3.3 days) was taken from HES data 2012-13 and the EAC considers this to be an appropriate data source.

Procedure Complications

The sponsor includes 3 types of complication in the model:

- TUR syndrome
- procedural blood loss requiring a transfusion

- re-admission for clot retention (this is an option in the calculations)

The additional resources required for patients experiencing TUR syndrome were taken by the sponsor from NICE CG97 Appendix F, Table 7. The guideline identified the additional resources as a 2 day stay in a high dependency unit, followed by 2 days on the general ward. The cost for these additional days' stay is taken from national schedule of reference costs 2012-13. The EAC considers this is the best source of available data and that the appropriate codes were used.

Resources required for a blood transfusion in the sponsor's model are taken from a published study (Varney and Guest 2003). The authors included the statement 'The average number of units per transfusion *for each type* was 2.7 units of red blood cells, 2.8 units of fresh frozen plasma, one therapeutic dose of platelets, 9.6 units of cryoprecipitate' (EAC italics). This has been interpreted by the sponsor to mean that each transfusion includes all of these products. Therefore the sponsor has overestimated the resource requirements and hence the cost of blood transfusion. The costs of blood products were taken from the NHS Blood and Transplant 'Blood price list' 2013-14 and this is an appropriate source, although a more recent version is available for 2014-15. The 2.7 units of red blood cells is an average across all patients including major trauma. The EAC contacted clinical advisers to ask about typical transfusion volumes and products following mTURP. Clinical advisers confirmed that 2.7 units of red blood cells is a reasonable estimate for mTURP patients.

Re-operations due to incomplete resection

The cost of re-operation due to the initial procedure being terminated prior to completion is calculated in the sponsor model as the cost of consumables plus the cost of hospital stay. This underestimates the full cost of re-operation since it does not include theatre time. Although the cost per patient of theatre time is the same for TURis and mTURP, the numbers of patients requiring re-operation differ in the two arms according to the sponsor model. The EAC suggests using the NHS reference cost for the cost of a TURP re-operation and adding the extra cost of TURis consumables for the TURis arm would be more realistic. The EAC meta-analysis found no significant difference in the rate of re-operation between mTURP and TURis. Therefore this potential advantage claimed by the sponsor is not supported and has not been modified in the model by the EAC.

4.2.1 Procedural model inputs

Table 48 lists the procedural inputs to the model.

Table 48: Procedural inputs to the model

Row / variable	Sponsor's value	Sponsor's range or 95% CI (distribution)	Sponsor's source	EAC's value	EAC's range or 95% CI (distribution)	EAC's source
Mean length of inpatient stay post prostate resection procedure with mTURP	3.3 days	2.5 – 4.1 days (Gamma)	Hospital Episode Statistics (HES) procedures and interventions 2012-13. M65.3 Endoscopic resection of prostate NEC (50). Range: ±25%.	3.3 days (total hospital stay)	2.7 - 3.89 days	Mean of 2 RCTs (Akman, Michielsen 2010)
Reduction in length of stay associated with TURis	0.52 days	0.30 - 0.74 (Gamma)	Mean value and range: output of meta-analysis. Meta-analysis of RCTs as described in Section 7 of this dossier.	0.19 days	(95% CI -0.46, 0.07) days	EAC's meta-analysis of two studies (Akman, Michielsen 2010), excluding the outlier (Chen 2009) and a Spanish-language paper.
Cost per inpatient day (general ward)	£305	£175 - £360 (Gamma)	Mean value and range: National Schedule of Reference Costs 2012-13. LB25F - Transurethral Prostate Resection Procedures with CC score 0-2. Urology. Elective inpatient excess bed day cost (51)	£305		£305 is from "Elective Inpatient Excess Bed Days" row 1248 in NHS reference costs (Main schedule). https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
Cost per inpatient day (high dependency unit)	£619	-	Mean value: National Schedule of Reference Costs 2012-13. XC07Z - Adult Critical Care, 0 Organs Supported. (51)	£619	Lower/Upper quartile: £398, £772	National schedule of reference costs 2012-13

Incremental cost for a patient experiencing TUR syndrome	£1,848	£1,386 - £2,310 (Gamma)	This reflects the cost of two days in a high dependency unit and two days on a general ward. These assumptions are in line with the economic analysis undertaken for NICE CG97. Costs are taken from the National Schedule of Reference Costs 2012-13 (51). HDU bed day = XC07Z - Adult Critical Care, 0 Organs Supported. General ward bed day = LB25F - Transurethral Prostate Resection Procedures with CC score 0-2. Urology. Excess bed day. Range: ±25%.	£1,848		National Schedule of Reference Costs 2012-13
Incremental cost for a patient requiring a blood transfusion	£920.40	£690 - £1,151 (Gamma)	This represents the cost of the blood components required for a transfusion. Unit costs are taken from the NHS Blood and Transplant, 2013-14 price list (52) and resource use estimates are based on the study by Varney et al (53). Range: ±25%.	£329		1 unit standard red cells = £ 121.85 (NHS Blood and Transplant price list 2014/15. Clinical experts confirm that blood transfusion is used in approximately 5% of cases, using typically 2-3 units. 2.7 seems a sensible value 2.7 x £121.85 = £329.
Cost of re-admission due to clot retention	£2,781	-	National Schedule of Reference Costs 2012-13. LB20D - Infection or Mechanical Problems Related to Genito-Urinary Prostheses, Implants or Grafts, with Interventions, with CC Score 0-3. Non-elective short stay. (51) Note: this is not considered in the base case analysis.	£2,781		National Schedule of Reference Costs
Proportion of patients requiring a repeat procedure – mTURP	5%	-	Fagerstrom 2011 (25) Note: this is not considered in the base case analysis.	5.57% (21/377)	Range 1.67%, 8.82% 95% CI 3.67%, 8.36%	Mean rate of 3 RCTs (Fagerstrom, Geavlete, Michielsen 2007). Subject to some uncertainty around identification of events. 95% CI: http://vassarstats.net/prop1.html

Proportion of patients requiring a repeat procedure – TURis	2%	-	Fagerstrom 2011 (25) Note: this is not considered in the base case analysis.	4.15% (16/386)	Range 0%, 9.41% 95% CI 2.57%, 6.63%	Mean rate of 3 RCTs (Fagerstrom, Geavlete, Michielsen 2007). Subject to some uncertainty around identification of events. 95% CI: http://vassarstats.net/prop1.html
Cost of repeat procedure - mTURP	£1,087.07	-	Set to equal the cost of the initial procedure and hospital stay but excluding the cost of complications. Note: this is not considered in the base case analysis.			Not included in EAC analysis
Cost of repeat procedure - TURis	£1,009.03	-	Set to equal the cost of the initial procedure and hospital stay but excluding the cost of complications. Note: this is not considered in the base case analysis.			Not included in EAC analysis

Technology and comparators' costs

4.2.2 Equipment

The sponsor assumed that 3 sets of TURis capital equipment (excluding generator) would be required per centre, based on Olympus data. This would allow up to 3 TURis operations to be carried out per session but no more because the equipment needs to be cleaned before re-use. The EAC checked this assumption with clinical advisers who confirmed it is reasonable.

The generator is not included in the capital equipment costs for Olympus customers or for non-Olympus customers. This is because the generator is provided to customers free of charge as part of a sales package including an agreed volume of consumables.

Values used for the base case in the sponsor's model are reproduced in Table 49 below, together with any changes by the EAC and their sources.

Table 49: EAC adjustments to sponsor's base case model inputs

Variable	Sponsor's value	Sponsor's range or 95% CI (distribution)	Sponsor's source	EAC's value	EAC's range or 95% CI (distribution)	EAC's source
TURis telescope cost	£3,570	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
TURis light guide cable	£415	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
TURis inner sheath	£735	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
TURis outer sheath	£1,225	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
TURis working element	£2,755	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
TURis saline cable	£205	-	Olympus data on file	Sponsor's value accepted	Sponsor's value accepted	
Total capital cost for TURis – non-Olympus customer	£26,715	£20,036 - £33,394 (Gamma)	Olympus data on file. Comprised of the cost of 3x telescope, 3x light guide cable, 3x inner sheath, 3x outer sheath, 3x working element and 3x saline cable. Range: ±25%.	Sponsor's value accepted	Sponsor's value accepted	
Total capital cost for TURis – existing Olympus monopolar customer	£8,880	£6,660 - £11,100 (Gamma)	Olympus data on file. Comprised of the cost of 3x working element and 3x saline cable. Range: ±25%.	Sponsor's value accepted	Sponsor's value accepted	
Lifespan for TURis capital equipment	7 years	5 - 10 years (Gamma)	Olympus data on file. Range selected to capture variability in the care taken of equipment.	Sponsor's value accepted	Sponsor's value accepted	The HTA had a 10 year time horizon based on 10 years of equipment life (Lourenco T, 'Dow J, abi G, everill M, ickard R, & rmstrong N 2008).
Discount rate for costs	3.5%	0% - 6% (Beta)	Mean value and range: MTEP methods guide (47) HM Treasury Green Book (48)	Sponsor's value accepted	Sponsor's value accepted	

4.2.3 Consumables

Costs of consumables are shown in Table 50 below. One of the key drivers in the sponsor's model is the cost of consumables for mTURP. It is therefore surprising that the input for this parameter is 'assumed to be 50% of overall cost for a TURis procedure'. The EAC searched the NHS supply chain catalogue for the price of mTURP consumables based on clinical advisers' suggestions for typical mTURP electrodes.

The electrodes for TURis are assumed to be single use, which is appropriate. It is assumed that 22% of TURis procedures will employ a roller electrode as well as a loop electrode. This is based on data held on file by the sponsor. There is no explicit assumption about the consumable resources required for mTURP i.e. which types of electrode would be used, only an assumption about the cost. The EAC asked the clinical advisers if these assumptions are reasonable. Clinical advisors indicated that use of roller electrode in 22% of TURis cases is reasonable, and that the roller electrode is used in up to 100% of mTURP procedures. It is on this basis that the EAC calculated the consumable cost per case for mTURP to be £56.84, including 1 loop electrode, 1 roller electrode and 1 return electrode per mTURP case based on NHS supply chain price list for generic consumables.

The sponsor did not include potential cost savings from switching irrigation fluid from glycine to saline, but this potential saving is very small. The EAC has checked the price of the fluids and found that 3L glycine (1.5%) is £13.60 and 3L saline (0.9%) is £12.00. With such a marginal difference in cost the EAC has not modified the model to include the irrigation fluids.

Table 50: Costs of consumables

<table>
<tr><th>Variable</th><th>Sponsor's value</th><th>Sponsor's range or 95% CI (distribution)</th><th>Sponsor's source</th><th>EAC's value</th><th>EAC's range or 95% CI (distribution)</th><th>EAC's source</th></tr>
<tr><td>Overall consumables cost for mTURP per procedure</td><td>£80.57</td><td>£60.43 - £100.71 (Gamma)</td><td>Assumed to be 50% of overall cost of consumables for a TURis procedure. Range: ±25%.</td><td>Olympus List price £137.75

Third party consumables
£56.84

Electrosurgery unit £10 per patient for non-Olympus customers</td><td>±25%:
£14.32, £23.86</td><td>Assumes use of 1 loop electrode & 1 roller/ball in 100% of cases. Based upon NHS Supply Chain list of diathermy equipment costs:
<table>
<tr><th>Item</th><th>Unit cost (£)</th></tr>
<tr><td>Covidien E7506 Diathermy plate standard (solid) with leadwire</td><td>£4.04</td></tr>
<tr><td>Loop electrode (models suitable for mTURP</td><td>£26.40</td></tr>
<tr><td>Roller/ball electrode (models suitable for mTURP</td><td>£26.40</td></tr>
<tr><td>Total</td><td>£56.84</td></tr>
</table></td></tr>
<tr><td>TURis electrode small loop cost</td><td>£1,520 for box of 12</td><td>-</td><td>Olympus data on file.</td><td>Unit cost £126.67</td><td></td><td>£1520/12 = £126.67</td></tr>
<tr><td>TURis electrode medium loop cost</td><td>£1,520 for box of 12</td><td>-</td><td>Olympus data on file.</td><td>Unit cost £126.67</td><td></td><td>£1520/12 = £126.67</td></tr>
<tr><td>TURis electrode roller cost</td><td>£1,880 for box of 12</td><td>-</td><td>Olympus data on file.</td><td>Unit cost £156.67</td><td></td><td>£1880/12 = £156.67</td></tr>
<tr><td>Number of uses per TURis electrode</td><td>1</td><td>-</td><td>Single use per electrode is recommended by Puppo et al, 2009 (43)</td><td></td><td></td><td></td></tr>
<tr><td>Use of TURis rollers as a proportion of all TURis electrode use</td><td>22%</td><td>17% - 28% (Beta)</td><td>Olympus data on file. Range: ±25%.</td><td></td><td></td><td></td></tr>
</table>

Sensitivity analysis

One-way sensitivity analysis

The sponsor undertook one-way sensitivity analysis on each of the model inputs and the results of the most significant inputs were included in a Tornado diagram. The range investigated for each value was in most instances ±25%. The key drivers of the model were the reduction in LOS for TURis compared with mTURP, the cost of a bed-day and the cost of mTURP consumables.

The EAC considered that the range of values for the cost of mTURP consumables (£60.43 - £100.71) was too small, especially since this was an estimate.

The sponsor also presented a threshold analysis of each model variable to identify the point at which the model becomes cost neutral.

Scenarios

The sponsor included 3 scenarios in the model:

a) Considering clot retention and the cost of re-admission

b) Including re-operations due to initial procedure being terminated prior to completion

c) Considering a difference in hospital stay between procedures of 1 day

The EAC considers that re-admission due to clot retention is an important consideration, both in terms of clinical outcome and cost considerations. The EAC meta-analysis found a relative risk of 0.54 for clot retention in TURis, but the result was not statistically significant. Therefore the scenario should be treated with caution. Reporting of re-admissions and complications in the studies was not always clear and thorough. Further research should include reporting of these.

It is a plausible hypothesis that there could be a greater number of re-operations in mTURP if operations were terminated prior to completion because of concerns about increased risks of TUR syndrome in lengthy procedures. The EAC found the analysis of re-operations to be subject to uncertainty because of variations in the way these are described in the published studies. The EAC point estimate of relative risk was 0.76, but this was not statistically significant. Therefore this scenario should be regarded with caution.

There is no evidence to support a difference in hospital stay of 1 day, therefore this scenario does not add to the case for adoption.

The sponsor's model includes a capacity calculation as an option when the user selects 'Consider the effect of a difference in procedure duration on costs'. The calculation is incorrect. When the difference in procedure duration is set to zero minutes, the model calculates a saving of 50 hours' theatre time per year. The EAC meta analysis found no difference in procedure time between mTURP and TURis.

Probabilistic sensitivity analysis

The sponsor included probabilistic sensitivity analysis in the model. Each model parameter was assigned a statistical distribution and the model was run for 1000 simulations, by randomly sampling the distributions and calculating the results of the model each time. The analysis generated a mean cost saving for TURis of £133 per patient for Olympus customers and £115 per patient for non-Olympus customers. TURis remained cost saving in almost all of the simulations.

The sponsor concludes that the probabilistic sensitivity analysis demonstrates that the model is robust.

4.3 Results of de novo cost analysis

Base-case analysis results

The sponsor's base case results are shown in Table 51 below.

Table 51: Sponsor's base case analysis

Procedure	Total cost per patient
TURis – existing Olympus customer	£1043.57
TURis - non-Olympus customer	£1063.01
mTURP	£1177.20
Difference - existing Olympus customer	-£133.63
Difference - non-Olympus customer	-£114.19

The sponsor concluded that TURis is cost saving compared with mTURP, driven by a reduced LOS.

Sensitivity analysis results

The sponsor sensitivity analysis results are reproduced in Table 52 below.

Table 52: Sponsor's sensitivity analysis

Variable	Cost difference with low value	Cost difference with high value	Difference
TURis reduction in hospital stay (days) (0.3 to 0.7; base case 0.5)	-£68	-£201	£133
Inpatient day cost (£175 to £360; base case £305)	-£66	-£163	£97
mTURP consumables cost per procedure (£60 to £101; base case £81)	-£114	-£154	£40
mTURP Blood transfusion rate (5.63% to 9.38%; base case 7.50%)	-£123	-£145	£22
Cost per blood transfusion (£690 to £1,151; base case £920)	-£123	-£145	£22
Roller TURis proportion use (16.5% to 27.5%; base case 22.0%)	-£143	-£126	£17
TURis Blood transfusion relative risk (0.27 to 0.45; base case 0.36)	-£141	-£128	£12

Variable	Cost difference with low value	Cost difference with high value	Difference
mTURP TUR syndrome rate (0.86% to 1.43%; base case 1.14%)	-£129	-£140	£11
Cost per case of TUR syndrome (£1,386 to £2,310; base case £1,848)	-£129	-£140	£11
Cohort size - direct input (100 to 200; base case 150)	-£129	-£137	£7

In the sponsor's sensitivity analysis TURis remained cost saving between £66 and £201 for all low and high values of the inputs. The sponsor concludes that the model is robust.

Subgroup analysis

The sponsor did not present any sub-group analysis. No clinical data on TURis were identified by the sponsor or by the EAC for the two subgroups specified in the scope, namely individuals with prosthetic lower limbs and cardiac pacemakers. The randomized study by Michielsen 2011 undertook subgroup analyses in 66 men with large prostate glands (> 60 ml) and 176 men on oral anticoagulant therapy. These analyses demonstrated that both TURis and mTURP are viable options for treating both groups of men, but there were no remarkable differences between treatment groups for outcomes specified in the scope. We were not able to identify any subgroup in which we would expect the economic outcomes for TURis to differ from economic outcomes in the general population of men treated with TURis.

Model validation

The sponsor carried out an internal validation of the model functionality. Resource use assumptions were presented by the sponsor to an expert adviser. The sponsor states in the

submission that 'Overall, the expert interviewed agreed with the data estimates, sources and assumptions used in the model'.

No published economic studies were found comparing TURis with mTURP, therefore the model could not be validated against any published model.

4.4 Interpretation of economic evidence

The sponsor correctly interprets the results presented.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

As discussed in Section 3.8 of this report, the EAC has re-worked a number of the meta-analyses to include additional evidence identified by the EAC, and because of different study selections. Therefore it was necessary to re-run the model with the revised clinical outcome data. We have also checked the resource inputs to the model and made some changes to resource use and costs. The revised inputs to the model have a significant impact on the results of the model. The impact of these changes is described in section 4.6.1 of this report.

The EAC has conducted a quality check of the sponsor model. This is included as Appendix 4. The quality appraisal shows that the model was well constructed, and clearly described.

The EAC has investigated sub-groups described in the scope and those identified in the published literature, but found no evidence about the sub-groups in the scope and no pertinent differences from the general patient population for sub-groups identified from the literature.

There are different purchasing arrangements possible for capital equipment items such as an electrosurgery unit. The equipment may be purchased outright, leased, or may be loaned from the supplier as part of a contract to purchase a minimum number of consumable items per year. If equipment is purchased outright, the hospital may choose to purchase suitable third party consumables, such as those available from NHS supply chain. Provided companies are able to provide documentation to confirm compatibility with specified goods including generators (ideally indicating relevant model numbers), users are free to utilise appropriate products from any manufacturer. It is the responsibility of the end user to obtain written confirmation of compatibility between items such as generators and related consumables.

For existing Olympus customers we assumed that the hospital has been loaned the electrosurgery unit and pays Olympus for their brand of mTURP consumables as part of a contract agreement. For non-Olympus customers we have assumed that the hospital owns an existing electrosurgery unit generator and purchases third party mTURP consumables from NHS supply chain.

We found the threshold value for the cost of TURis consumables to be £83 for non-Olympus customers i.e. if this were the price of the TURis consumables or lower price, TURis would become cost saving using the EAC values in the model.

For re-admissions we calculated the impact of using the data from the Fagerstrom 2011 paper for re-admissions (all causes). This had a significant impact on the results (Table 55 below). Using the EAC values in the model and including rates for re-admission all causes (in place of re-admission for clot retention) the model became cost saving -£319.62 for Olympus customers and -£229.27 for non-Olympus customers. This result must be treated with caution. Patients having transfusions due to bleeding may be included in re-admissions and therefore have been counted twice. The cost of re-admission is uncertain when all causes are included and the model is based on NHS Reference cost 2012-13 code 'LB20D – Infection or mechanical problems related to genitor-urinary prostheses, implants or graft, with interventions, with CC score 0-3. Non-elective short stay.' The results in Fagerstrom 2011 may not be representative of all the published studies where reporting is unclear.

4.6 Conclusions on the economic evidence

The key drivers in the sponsor's economic model are

1. a reduction in hospital LOS of 0.5 days for TURis compared with mTURP taken from the sponsor meta-analysis
2. the cost of a bed-day (linked with 1)
3. the consumables cost for mTURP.

The EAC meta-analysis has shown that the basis for the claimed reduction in LOS is a single publication leading to strong heterogeneity in the data. After removing this study the EAC meta-analysis found no significant difference in LOS. The sponsor estimated the cost of mTURP consumables to be 50% of the cost of TURis consumables. The EAC has obtained prices for generic consumables from the NHS supply chain and Olympus consumables (for customers with a loaned electrosurgery unit) from the sponsor's list price. The price of generic mTURP consumables is considerably lower than was assumed by the sponsor for non-Olympus customers. The price of Olympus consumables is higher than was assumed in the model. The case for TURis being cost saving compared with mTURP is supported for existing Olympus customers but not proven for non-Olympus customers using generic consumables. There is good evidence that TURis is associated with fewer complications (TUR syndrome and blood transfusions) than mTURP providing a clear clinical benefit. Cost savings associated with avoiding these complications is sufficient to balance the additional costs of the TURis consumables for existing Olympus customers using Olympus mTURP consumables.

Evidence on other potential clinical benefits (re-admissions) is less clear because of differences in reporting in the literature. Tentative calculations using the model show the potential for significant savings, but there is considerable uncertainty in the scenario.

Further data is needed to add to the weight of evidence on complications and re-admissions.

4.6.1 Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Table 53 below shows the cost difference between TURis and TURP after changing each input value in turn from sponsor value to EAC value as indicated. Negative results indicate that TURis is cost saving and positive results indicate that TURis incurs additional costs compared with TURP. For comparison the sponsor base case results are:

Existing Olympus customer - £133.63

Non-Olympus customer - £ 114.19

Table 53: model results reflecting changes to individual model inputs

Model variable	**Sponsor Value**	**EAC value**	**Model result with EAC value** **Result is negative if TURis is cost saving compared with mTURP**		**Comments**
			Existing Olympus customer	**Non- Olympus customer**	
TURis reduction in LOS	0.5 days	0 days	+ £24.97	+ £44.41	
Relative risk TUR syndrome	0.28	0.18	- £133.63	- £ 114.19	No change in results since model assumes no TUR syndrome in TURis arm

Model variable	Sponsor Value	EAC value	Model result with EAC value Result is negative if TURis is cost saving compared with mTURP		Comments
			Existing Olympus customer	Non- Olympus customer	
TUR risk in mTURP patients	1.1%	1.8%	-£145.20	-£125.79	
mTURP consumables cost	£80.57	£137.75 (Olympus customers) £56.84 (Third party consumables) + £10 electrosurgery unit cost	-£190.82	-£90.46	For Non-Olympus customers using third party consumables, assume electrosurgery unit capital cost of £10 per patient (Purchase cost of £10,000 over 7 years with 150 patients per year)

Model variable	Sponsor Value	EAC value	Model result with EAC value Result is negative if TURis is cost saving compared with mTURP		Comments
			Existing Olympus customer	Non- Olympus customer	
Cost of blood transfusion	£920.40	£329	-£105.25	-£85.80	EAC assumes 2.7 units RBC's @ £121.85/unit
Relative risk of blood transfusion in TURis	0.36	0.35	-£134.32	-£114.88	Sponsor result from meta-analysis was not statistically significant. EAC value from EAC meta-analysis p=0.0008

There is some uncertainty regarding the cost of transfusions. The EAC has used the same method for calculating the cost as was used by the sponsor in the model, but has corrected the resource use to include only red blood cells. The method does not include the staff costs and NHS costs of receiving and storing the blood products, preparing them and the giving set. This may therefore underestimate the cost. However the EAC considers marginal costing appropriate because any reduction in transfusions from using TURis would not reduce institutional overheads.The EAC ran the model including all of the changes in Table 53 above. The results are in Table 54 below.

Table 54: model results reflecting simultaneous changes to all model inputs

	mTURP	TURis	Difference
Olympus customers	£1196.60	£1183.99	-£12.60
Non-Olympus customers	£1125.69	£1203.44	+£77.75

Re-admissions (all causes) scenario

The EAC then modified the model so that the optional re-admission for clot retrieval was used to include re-admissions (all causes) based on Fagerstrom 2011. The rate of re-admissions mTURP was 16% and the RR for TURis was 0.31. The cost of re-admission was £2781. There is uncertainty regarding this cost when including all causes of re-admission. The results are in Table 55 below. The scenario remains cost saving for Olympus customers and non-Olympus customers in one-way sensitivity analysis when the rate of re-admissions for mTURP is 5% (Olympus customers -£108.55, non-Olympus customers -£18.19) and when the cost of re-admission is £915 (Olympus customers -£113.62 and non-Olympus customers -£23.26). **Table 55: model results reflecting the effect of re-admissions (all causes)**

	mTURP	TURis	Difference
Olympus customers	£1,641.56	£1,321.93	-£319.62
Non-Olympus customers	£1,570.65	£1,341.38	-£229.27

5 Conclusions

Remaining uncertainties include the difference in re-admissions due to complications and re-operations for incomplete resection.

The EAC's conclusions on the clinical submission are presented according to the sponsor's claims made in the scope in Section 3.10 of this report.

The EAC's conclusions on the economic submission are presented according to the sponsor's claims made in the scope in Table 56 below.

Table 56: EAC's conclusions on the economic submission

Healthcare system benefits:	EAC conclusion
A quicker procedure compared to monopolar TURP so more patients can be treated.	Procedures are not significantly shorter using TURis compared to mTURP. An EAC meta-analysis of five randomised studies found the difference in procedure time (TURis minus mTURP) to be -1.36 minutes (95% CI -3.69, 0.98) minutes. The result is not statistically significant and the size of the observed difference is small and unlikely to transfer to a real life resource saving.
Fewer complications during and after surgery resulting in lower re-admission rates.	**TUR syndrome** Exactly as in patient benefits, the RR of TUR syndrome is 0.18 (95% CI 0.05, 0.61) in favour of TURis based on meta-analysis of six randomised studies. ARR = -0.02 (95% CI -0.03, -0.01) NNT = 50 (95% CI 33, 100) TUR syndrome is an acute complication, occurring before discharge from hospital. **Clot retention** An EAC meta-analysis of five randomised trials indicates there is no statistically significant effect in favour of TURis: RR (TURis/mTURP) 0.54 (95% CI 0.26, 1.13) When clot retention occurs before discharge from hospital it is treated in the same hospital stay. When clot retention occurs after discharge from hospital this requires readmission for treatment. **Readmission due to haemorrhage** In an EAC meta-analysis of two randomised trials the RR of readmission due to haemorrhage (TURis/mTURP) is 0.29 (95% CI 0.10, 0.87, p = 0.03) in favour of TURis i.e. a statistically significant result since the confidence interval excludes the null value of 1. The absolute risk reduction is -0.04 (95% CI -0.07, -0.01) which represents a NNT of 25 (95% CI 14, 100) i.e. 25 patients would need to be treated with TURis to prevent one readmission due to haemorrhage. **Repeat procedure due to incomplete resection** Three studies provide data. In a fixed effect meta-analysis there is there is no statistically significant difference in the risk of repeat

	procedure due to incomplete resection between TURIs and mTURP: RR 0.76 (95% CI 0.42, 1.40, p = 0.38) **Urethral strictures and bladder neck contractures** In an EAC meta-analysis of data from 6 randomised studies there was no statistically significant difference in the risk of urethral stricture / bladder neck contracture between groups: RR 1.08 (95% CI 0.69, 1.68, p = 0.74). Overall re-admissions were reported in Fagerstrom 2011. In this study the rate of readmission was 5/98 cases (5.1%) in the TURis arm compared to 14/87 (16.1%) in the mTURP arm, p = 0.011.
Reduced costs associated with post-operative blood transfusion, healthcare-associated infection, shorter length of stay, reduced post-operative irrigation and no patient return electrode required.	The reduction in blood transfusions and TUR syndrome results in reduced costs for these elements. Since the reduced LOS is not supported by the evidence the overall outcome of the model is cost incurring if compared to the cost of generic consumables, driven by the additional costs at the TURis consumables. The result is cost saving if compared to use of Olympus consumables at list price. There is potential for further reduction of overall costs linked to re-admissions (all causes), but the evidence is unclear.
The use of saline irrigation fluid is cheaper and easier to access than glycine.	This is a minor element and was not included in the cost model.

6 Implications for research

The EAC has not identified clear areas where further comparative research would be warranted. There is strong evidence that TURis avoids the risk of TUR syndrome that is associated with mTURP and that TURis reduces the need for blood transfusion. This is likely to be sufficient to cast doubt on TURis and mTURP being equipoise. However better data on the rates of readmission to hospital by cause following TURis and following mTURP would enable further economic evaluation.

Appendix 1: EAC literature search strategies

The EAC designed the search strategies for different databases as follows.

Ovid MEDLINE(R) 1946 to March Week 3 2014

1 "Transurethral Resection of Prostate"/ and bipolar.tw. 153

2 ((Transurethral adj5 prostatectom*) and bipolar).tw. 20

3 (bipolar and prostat* and (transurethral adj5 resection)).tw. 149

4 (TURIS and prostat*).tw. 24

5 1 or 2 or 3 or 4 181

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 31, 2014>

1 ((Transurethral adj5 prostatectom*) and bipolar).tw. (1)

2 (bipolar and prostat* and (transurethral adj5 resection)).tw. (28)

3 (TURIS and prostat*).tw. (4)

4 1 or 2 or 3 (30)

Database: EMBASE <1947-Present>

1 ((Transurethral adj5 prostatectom*) and bipolar).tw. (28)
2 (bipolar and prostat* and (transurethral adj5 resection)).tw. (307)
3 (TURIS and prostat*).tw. (76)
4 transurethral resection/ and bipolar.tw. (371)
5 1 or 2 or 3 or 4 (421)

Cochrane Library

#1 ((Transurethral near/5 prostatectom*) and bipolar):ti,ab,kw (Word variations have been searched)
#2 (bipolar and prostat*) and (transurethral near/5 resection):ti,ab,kw (Word variations have been searched)
#3 MeSH descriptor: [Transurethral Resection of Prostate] this term only
#4 bipolar:ti,ab,kw (Word variations have been searched)
#5 #3 and #4
#6 (TURIS and prostat*):ti,ab,kw (Word variations have been searched)
#7 #1 or #2 or #5 or #6

HEED

"Transurethral resection" AND bipolar

ECONLit

" Transurethral resection" AND bipolar

Web of Science

# 4 262 #3 OR #2 OR #1 I
ndexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

# 3 34 TS=(TURIS AND prostat*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

# 2 244 TS=((bipolar and prostat*) AND (transurethral NEAR/5 resection))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

# 1 46 TS=((Transurethral NEAR/5 prostatectom*) AND (bipolar))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

National Technical Information Service (NTIS) database

Bipolar AND "transurethral resection"

NHS Evidence

Transurethral resection of prostate AND bipolar

Bipolar AND "transurethral resection"

Pubmed (last 6 months 'epub ahead of press')

Bipolar[All Fields] AND "transurethral resection"[All Fields] AND epub[All Fields]

ICTRP – not able to export to Reference Manager

Searched for: transurethral resection AND bipolar OR TURIS

Clinicaltrials.gov – not able to export to Reference Manager

Searched for: transurethral resection AND bipolar OR TURIS

MAUD FDA – not able to export to Reference Manager

Simple search for: transurethral resection AND bipolar OR TURIS

MHRA

Searched for: transurethral resection AND bipolar OR TURIS

EMA

Searched for: transurethral resection AND bipolar OR TURIS

Appendix 2: data from the randomised trial published in a Spanish-language paper

Tables 57 and 58 describe the Abascal Junquera 2006 randomised trial. Its data were used in EAC meta-analyses to determine whether the study is pivotal, but without translation to English by a proper agency so the data should be viewed with caution. In no analysis was the study pivotal.

Table 57 Source data for Abascal-Junquera randomised trial (not translated to English by a formal agency)

Patient population	Country	Age	Baseline IPSS	Baseline Qmax	Baseline prostate volume	Study design	Sample size
Inclusion criteria: Clinical diagnosis of symptomatic benign hyperplasia of the prostate, with prostate volume between 30 to 70cc by ultrasound. **Exclusion criteria:** Anticoagulants Neurogenic bladder Surgery for prostate adenocarcinoma, or suspected. Urinary catheter in place Patients on anti-platelet medication had it stopped one week before surgery	Spain March to December 2005	**TURis group:** Mean 69.5 years **mTURP group:** Mean 67.3 years	Not reported	Stated as mean flow: **TURis group:** 7.7 ml/s **mTURP group** 7.2 ml/s	**TURis group:** 39.5 (SD 9.8) cc **mTURP group** 42.7 (SD 11.6) cc	RCT comparing: TURis, with F26-30 resectoscope. Versus mTURP, ch26, 30 degrees Continuous irrigation with Glycine All procedures used SurgMaster generator and 250-280W cut, 50 W coagAll patients had a single dose of prophylactic antibiotic (gentamicina 3mg/kg) All patients had a urine culture the day before the procedure. **Follow-up:** Not known, none reported. **Surgeons:** 6 surgeons	45 patients **TURis group:** n = 24 **mTURP group:** n = 21 **Withdrawals:** Not known

Table 58: results of randomised study: Abascal Junquera 2006 (not translated to English by a formal agency)

Outcome	TURis (n = 24)	mTURP (n = 21)	p value	Comments
Procedure duration*	39.7 (SD 12) min	42.7 (SD 11) min	Not reported	
Volume of tissue resected	13 (SD 8.4) g	12.6 (SD 6.8) g	Not reported	
TUR syndrome*				
Decrease in serum Na	0.52 (SD 2.1) mg/dl	1.16 (SD 3) mg/dl	Not reported	
Or related outcome				
Need for blood transfusion*	0 patients	0 patients	Not reported	
Mean postoperative drop in Hb	3.48 g/dl (paper says "points")	3.32 g/dl	Not reported	Reported as no significant difference
Clot retention*				
Time to removal of catheter*	2.92 (SD 0.5) days	3.1 (SD 0.5)days	Not reported	Reported as no significant difference
Hospital stay*	3.63 (SD 0.5) days	3.67 (SD 0.5) days	Not reported	Reported as no significant difference
Readmission due to haemorrhage	Not reported	Not reported		
Functional outcomes	Not reported	Not reported		
Quality of life outcomes	Not reported	Not reported		
Other outcomes				
Urethral stricture / bladder neck contracture	Not reported	Not reported		
Surgeon rated cut capability	Cut capacity was considered notable-excellent in 90% of the patients in the TURis group vs 50% in the mTURP group (p=0,01);			Categories are poor, good, very good (notable), excellent
Surgeon rated adherence of fragments to electrode	adherence of fragments to electrode were considered abundant or very abundant in 0% of the TURis group vs 60% of the mTURP group (p=0,01);			Categories are none, scarce, moderate, abundant, very abundant.
Coagulation capability	Coagulation capability was excellent-notable in 25% of the TURis group vs 75% of the mTURP group (p=0,03).			Categories are poor, good, very good (notable), excellent
Bleeding	Bleeding was rated as scarce by 58% pof Bipolar group vs 61% of the monopolar group (p>0.05)			Categories unknown (very abundant – scarce)
visibility	Visibility was rated as good to very good by 88% of TURis group vs 90% of mTURP group ((p>0.05)			Categories unknown (excellent– scarce)
EAC comments on study quality Data extracted from English language abstract and tabulated data in the Spanish language, peer reviewed journal article. The "other outcomes" are from questionnaires to the 6 surgeons who completed the surgery. Not all have the questionnaire categories listed, or the complete results posted.				

Appendix 3: Summary table of all meta-analyses of randomised trials conducted by the EAC

Table 59: Summary table of all meta-analyses of randomised trials conducted by the EAC

Note: Rows 1-21 are EAC modifications of analyses presented by the sponsor. Rows 22-26 are additional analyses conducted by the EAC.

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
1.	TUR syndrome	Abascal 2006 Akman 2013 Chen 2010 Goh 2010 Michielsen 2010 Rose 2007	RR TURis/mTURP 0.28 (95% CI 0.08, 1.02). CI includes the null value. p = NS	We attempted to reproduce the sponsor's analysis using RevMan software. For three studies with zero events in both arms the RR was not estimable; these studies were excluded (Abascal 2006, Chen 2010, Rose 2007).	Akman 2013 Goh 2010 Michielsen 2010	Fixed effect model: RR 0.17 (95% CI 0.03, 0.94). Favours TURis, CI excludes the null value. p = 0.04 No heterogeneity detected
2.	TUR syndrome			Exclude 3 studies with zero events in both arms as above (Abascal 2006, Chen 2010, Rose 2007) Exclude 1 abstract (Goh 2010) Add 4 additional studies (Ho 2006, Chen 2009, Fagerstrom 2011, Geavlete 2011) We have not added available data from Michielsen 2007 because the lead author confirmed that the 2007 sample is duplicated in Michielsen 2010.	Akman 2013 Chen 2009 Fagerstrom Geavlete 2011 Ho 2006 Michielsen 2010	Fixed effect model: RR 0.18 (95% CI 0.05, 0.61). Favours TURis, CI excludes the null value p = 0.006 No heterogeneity detected ARR = -0.02 (95% CI -0.03, -0.01) NNT = 50 (95% CI 33, 100)

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
3.	TUR syndrome			As above, except include 1 abstract (Goh 2010)	Akman 2013 Chen 2009 Fagerstrom Geavlete 2011 Goh 2010 Ho 2006 Michielsen 2010	Fixed effect model: RR 0.17 (95% CI 0.05, 0.53). Favours TURis, CI excludes the null value. p = 0.002 No heterogeneity detected ARR = -0.02 (95% CI -0.03, -0.01) NNT = 50 (95% CI 33, 100)
4.	Blood transfusion	Akman 2013 Chen 2010 Fagerstrom Michielsen 2007	RR TURis/mTURP 0.52 (95% CI 0.26, 1.04) CI includes the null value p = NS	Add three studies (Chen 2009, Ho 2006, Geavlete 2011)	Akman 2013 Chen 2009 Chen 2010 Fagerstrom 2009, 2011 Geavlete 2011 Ho 2006 Michielsen 2007	Fixed effect model: RR 0.44 (95 CI 0.25, 0.78). Favours TURis, CI excludes the null value. p = 0.005 No heterogeneity detected ARR = -0.03 (95% CI -0.05, -0.01) NNT = 33 (95% CI 20, 100)

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
5.	Blood transfusion	The sponsor repeated the analysis above with removal of data from Michielsen 2007: Akman 2013 Chen 2010 Fagerstrom	RR 0.36 (95% CI 0.16, 0.80). Favours TURis, CI excludes the null value. No p value reported	Add three studies as above (Chen 2009, Geavlete 2011, Ho 2006). It is reasonable to exclude the data from Michielsen 2007 on the basis that more TURis procedures than monopolar procedures were performed by trainee urologists	Akman 2013 Chen 2009 Chen 2010 Fagerstrom 2009, 2011 Geavlete 2011 Ho 2006	Fixed effect model: RR 0.35 (95% CI 0.19, 0.64). Favours TURis, CI excludes the null value p = 0.0008 No heterogeneity detected. ARR = -0.05 (95% CI -0.07, -0.02) NNT = 20 (95% CI 14, 50) The effect of excluding the Michielsen 2007 study is to strengthen the effect in favour of TURis.
6.				Explore the effect of a random effect meta-analysis including the data from Michielsen 2007, where heterogeneity may be suspected due to junior surgeons' experience.	Akman 2013 Chen 2009 Chen 2010 Fagerstrom 2009, 2011 Geavlete 2011 Ho 2006 Michielsen 2007	Random effect model: RR 0.42 (95% CI 0.23, 0.77). Favours TURis, CI excludes the null value. No heterogeneity detected by the statistical method. The result of the random effects model is similar to the fixed effect analysis of the same data (Row 4).

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
7.	Clot retention	Akman 2013 Michielsen 2007	RR TURis/mTURP 0.63 (95% CI 0.21, 1.90) CI includes the null value. p = NS	Add three studies (Chen 2010, Geavlete 2011, Ho 2006)	Akman 2013 Chen 2010 Geavlete 2011 Ho 2006 Michielsen 2007	Fixed effect model: RR TURis/mTURP 0.54 (95% CI 0.26, 1.13) CI includes the null value. p = 0.10 No heterogeneity detected.
8.	Hospital stay	Akman 2013 Chen 2009 Michielsen 2010	Mean difference (TURis minus mTURP) -0.52 (95% CI -0.74, -0.30) days. Favours TURis, CI excludes the null value p = 0.0001	Add one study (Abascal-Junquera 2006)	Abascal-Junquera 2006 Akman 2013 Chen 2009 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -0.35 (95% CI -0.53, -0.18) days. Favours TURis, CI excludes the null value p < 0.0001 The effect of adding the Abascal-Junquera data is to reduce the difference in hospital stay between groups from 0.52 days to 0.35 days in favour of TURis. The Chen 2009 study introduces visible and significant heterogeneity (I^2 = 88%, p < 0.0001).

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
9.	Hospital stay			Use a random effects model due to visible and significant heterogeneity (Chen 2009)	Abascal-Junquera 2006 Akman 2013 Chen 2009 Michielsen 2010a, 2010b	Random effect model: Mean difference (TURis minus mTURP) -0.40 (95% CI -0.92, 0.12) days. CI includes the null value p = 0.13 In a random effects model the result is not statistically significant.
10.	Hospital stay			Remove the Chen 2009 study due to visible and significant heterogeneity and use a fixed effect model	Abascal-Junquera 2006 Akman 2013 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -0.12 (95% CI -0.32, 0.07) days. CI includes the null value p = 0.22 No heterogeneity evident With removal of the Chen 2009 data the result is not statistically significant.
11.	Hospital stay			Examine the effect of removing the data from the Spanish language paper (Abascal Junquera 2006)	Akman 2013 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -0.19 (95% CI -0.46, 0.07) days. CI includes the null value. p = 0.16 No heterogeneity evident The data from the Spanish paper do not have a profound influence on the result.

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
12.	Time to catheter removal	Akman 2013 Chen 2009 Michielsen 2010	Mean difference (TURis minus mTURP) -0.23 (95% CI -0.38, -0.08) days. Favours TURis, CI excludes the null value Heterogeneity evident	Correction of a data input error: Chen 2009 has a mean time of 2.5 days in the TURis arm (not 1.5 days)	Akman 2013 Chen 2009 Michielsen 2010	Fixed effect model: Mean difference (TURis minus mTURP) -0.15 (95% CI -0.30, -0.01) days Favours TURis, CI excludes the null value p = 0.04 Heterogeneity evident (I^2 = 79%, p = 0.009)
13.	Time to catheter removal			As above, plus: add one study (Abascal-Junquera 2006)	Abascal-Junquera 2006 Akman 2013 Chen 2009 Michielsen 2010	Fixed effect model: Mean difference -0.16 (95% CI -0.29, -0.03) days Favours TURis ,CI excludes the null value p = 0.02 Heterogeneity evident (I^2 = 68%, p = 0.02) The effect of adding the Abascal-Junquera data is small: it increases slightly the difference in time to catheter removal between groups from 0.15 days to 0.16 days in favour of TURis. The study by Chen 2009 appears to be the source of heterogeneity.

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
14.	Time to catheter removal			Use a random effects model due to heterogeneity (Chen 2009)	Abascal-Junquera 2006 Akman 2013 Chen 2009 Michielsen 2010	Random effect model: Mean difference (TURis minus mTURP) -0.24 (95% CI-0.50, 0.01]) days CI includes the null value. p = 0.06 In a random effect model the result is not statistically significant.
15.	Time to catheter removal			Remove the Chen 2009 study due heterogeneity and use a fixed effect model	Abascal-Junquera 2006 Akman 2013 Michielsen 2010	Fixed effect model: Mean difference (TURis minus mTURP) -0.11 (95% CI -0.25, 0.03) days. CI includes the null value. p = 0.11 No heterogeneity detected
16.	Time to catheter removal			Examine the effect of removing the Abascal-Junquera 2006 study	Akman 2013 Michielsen 2010	Fixed effect model: Mean difference (TURis minus mTURP) -0.09 (95% CI -0.25, 0.06). CI includes the null value. p = 0.24 No heterogeneity detected

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
17.	Procedure time	Akman 2013 Chen 2010 Fagerstrom Michielsen 2010 Michielsen 2007	Mean difference (TURis minus mTURP) 0.48 (95% CI -1.81, 2.77) minutes. CI includes the null value Heterogeneity evident	See below	See below	See below
18.	Procedure time	The sponsor repeated the analysis above with removal of data from Michielsen 2007: Akman 2013 Chen 2010 Fagerstrom Michielsen 2010	Mean difference (TURis minus mTURP) -1.68 (95% CI -4.18, 0.81) CI includes the null value. No heterogeneity detected	We agree with removal of data from Michielsen 2007, moreover because the sample is replicated in Michielsen 2010 Add three studies Abascal-Junquera 2006, Chen 2009, Ho 2006	Abascal-Junquera 2006 Akman 2013 Chen 2009 Chen 2010 Fagerstrom 2009, 2011 Ho 2006 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -2.15 (95% CI -4.31, 0.02) minutes. CI includes the null value. p = 0.05 Heterogeneity evident (I^2 = 53% p = 0.05) The heterogeneity appears to be caused by the Chen 2009 study.

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
19.	Procedure time			Use a random effects model due to heterogeneity (Chen 2009)	Abascal-Junquera 2006 Akman 2013 Chen 2009 Chen 2010 Fagerstrom 2009, 2011 Ho 2006 Michielsen 2010a, 2010b	Random effect model: Mean difference (TURis minus mTURP) -2.81 (95% CI -6.17, 0.55) minute. CI includes the null value p = 0.10
20.	Procedure time			Remove the Chen 2009 study due heterogeneity and use a fixed effect model	Abascal-Junquera 2006 Akman 2013 Chen 2010 Fagerstrom 2009, 2011 Ho 2006 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -1.53 (95% CI -3.74, 0.67) minutes. CI includes the null value. p = 0.17 No heterogeneity evident

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
21.	Procedure time			Examine the effect of removing the data from the Spanish-language paper (Abascal-Junquera 2006)	Akman 2013 Chen 2010 Fagerstrom 2009, 2011 Ho 2006 Michielsen 2010a, 2010b	Fixed effect model: Mean difference (TURis minus mTURP) -1.36 (95% CI -3.69, 0.98) minutes. CI includes the null value p = 0.26 No heterogeneity evident
22.	Re-admission due to haemorrhage	No meta-analysis in submission	No meta-analysis in submission	N/A	Fagerstrom 2011 Geavlete 2011 Rose 2007	Fixed effect model: RR (TURis/mTURP) 0.53 (95% CI 0.22, 1.35) CI includes the null value p = 0.03 No heterogeneity evident ARR = -0.04 (95% CI -0.07, -0.01) NNT = 25 (95% CI 14, 100)
23.	Re-admission due to haemorrhage			Exclude data from Rose 2007 to determine whether this study is pivotal	Fagerstrom 2011 Geavlete 2011	Fixed effect model: RR (TURis/mTURP) 0.29 (95% CI 0.10, 0.87) CI includes the null value p = 0.15 No heterogeneity evident

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
24.	Urethral stricture / bladder neck contracture (aggregated outcome)	No meta-analysis in submission	No meta-analysis in submission	N/A	Akman 2013 Chen 2010 Fagerstrom 2011 Geavlete 2011 Ho 2007 Michielsen 2011	Fixed effect model: RR (TURis/mTURP) 1.08 (95% CI 0.69, 1.68) CI includes the null value p = 0.74 No heterogeneity evident
25.	Urethral stricture	No meta-analysis in submission	No meta-analysis in submission	Using available disaggregated data	Chen 2010 Fagerstrom 2011 Geavlete 2011 Ho 2007 Michielsen 2011	Fixed effect model: RR (TURis/mTURP) 1.08 (95% CI 0.60, 1.96) CI includes the null value p = 0.79 No heterogeneity evident
26.	Bladder neck contracture	No meta-analysis in submission	No meta-analysis in submission	Using available disaggregated data	Chen 2010 Fagerstrom 2011 Geavlete 2011	Fixed effect model: RR (TURis/mTURP) 0.88 (95% CI 0.35, 2.20) CI includes the null value p = 0.79 No heterogeneity evident

Row	Outcome measure	Sponsor's included studies	Sponsor's result	EAC's modification	EAC's included studies	EAC's result
27.	Repeat procedure due to incomplete resection	No meta-analysis in submission	No meta-analysis in submission	N/A	Fagerstrom 2011 Geavlete 2011 Michielsen 2011	Fixed effect model: RR (TURis/mTURP) 0.76 (95% CI 0.42, 1.40) CI includes the null value p = 0.38 No heterogeneity evident

Appendix 4: EAC critique of the sponsor's economic model

The performed a critique of the sponsor's economic model based on Drummond 1996, cited by CRD 2008. This is shown in Table 60

Table 60 EAC critique of sponsor's economic model

Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	From the scope
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Decision tree
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Sponsor meta-analysis
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Fixed effects methods were used.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	Cost-consequences
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	n/a	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Except estimation of cost of mTURP consumables
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	

20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Acute episode only.
23. Was the discount rate stated?	Yes	3.5%
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	One-way and probabilistic sensitivity analysis were included.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Appendix 5: SNOMED-CT concepts

The EAC entered the terms 'benign prostatic hyperplasia' and 'transurethral resection of the prostate' on 03/06/14 on NPEx (http://www.snomedbrowser.com/) and the SNOFLAKE browser (http://www.snoflake.co.uk/). Table 61 presents the results.

Table 61 SNOMED CT concepts

Search term	Term	ConceptID	DescriptionType
Benign prostatic hyperplasia	Disorder of prostate	30281009	Preferred term
	Prostatic disorder	30281009	Synonym
	Disorder of prostate	30281009	Fully specified name
	Hyperplasia of prostate	433234005	Preferred term
	Hyperplasia of prostate (disorder)	433234005	Fully specified name
	Dysplasia of prostate	445068007	Preferred term
	Dysplasia of prostate (disorder)	445068007	Fully specified name
	Benign prostatic hyperplasia	266569009	Preferred term
	Hyperplasia of prostate	266569009	Synonym
	Prostatic hypertrophy	266569009	Synonym
	Benign myoma of prostate	266569009	Synonym
	BPH	266569009	Synonym
	Benign enlargement of prostate	266569009	Synonym
	Benign adenoma of prostate	266569009	Synonym
	Benign prostatic hypertrophy	266569009	Synonym
	Benign fibroma of prostate	266569009	Synonym
	Prostatic area hypertrophy	266569009	Synonym
	BEP – Benign enlargement of prostate	266569009	Synonym
	BPH – Benign prostatic hypertrophy	266569009	Synonym
	Nodular hyperplasia of prostate gland	266569009	Synonym
	Benign prostatic hyperplasia (disorder)	266569009	Fully specified name
	Benign localized hyperplasia of prostate	444808002	Preferred term
	Benign localized hyperplasia of prostate (disorder)	444808002	Fully specified name
	Benign prostatic hypertrophy with outflow obstruction	236646007	Preferred term
	Benign prostatic hypertrophy with outflow obstruction (disorder)	236646007	Fully specified name
	Benign prostatic hypertrophy without outflow obstruction	254902007	Preferred term
	Benign prostatic hypertrophy without outflow obstruction (disorder)	254902007	Fully specified name
	Prostatic hyperplasia of the lateral lobe	197959008	Preferred term
	Prostatic hyperplasia of the lateral lobe (disorder)	197959008	Fully specified name

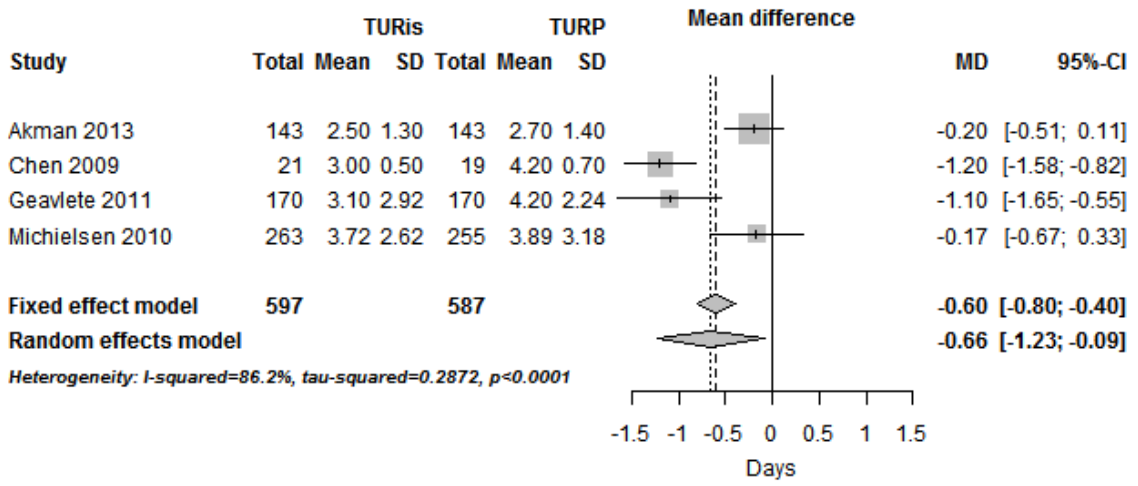
Search term	Term	ConceptID	DescriptionType
	Prostatic hyperplasia of the medial lobe	197960003	Preferred term
	Prostatic hyperplasia of the medial lobe (disorder)	197960003	Fully specified name
	Prostatic obstruction	4127004	Preferred term
	Prostatic obstruction (disorder)	4127004	Fully specified name
Transurethral resection of the prostate	Operation on prostate	741007	Preferred term
	Operation on prostate (procedure)	741007	Fully specified name
	Prostatectomy	90470006	Preferred term
	Prostate excision		Synonym
	Prostatectomy (procedure)		Fully specified name
	Transurethral prostatectomy (procedure)	90199006	Preferred term
	Loop prostatectomy	90199006	Synonym
	TUR of prostate	90199006	Synonym
	Endoscopic resection of prostate	90199006	Synonym
	Transurethral resection of prostate	90199006	Synonym
	TURP – Transurethral resection of prostate	90199006	Synonym
	Endoscopic prostatectomy	90199006	Synonym
	Transurethral prostatectomy (procedure)	90199006	Fully specified name
	Endoscopic resection of prostate using an electrotome	314202001	Preferred term
	TURP using an electrotome	314202001	Synonym
	Endoscopic resection of prostate using an electrotome (procedure)	314202001	Fully specified name
	Complete transurethral resection of prostate, including control of postoperative bleeding	87795007	Preferred term
	Complete transurethral resection of prostate, including control of postoperative bleeding (procedure)	87795007	Fully specified name
	Transurethral resection of prostate, first of two stages	68986004	Preferred term
	Transurethral resection of prostate, first of two stages (procedure)	68986004	Fully specified name

Appendix 6: EAC response to additional meta-analyses provided by the sponsor after the factual check

As discussed in section 3 the EAC identified an additional randomised study which the sponsor did not include in the submission (Geavlete 2011). This is a three-arm study comparing TURis versus mTURP versus TURis vaporisation procedure. Therefore only the first two arms are relevant to the scope. The study found hospital stay to be 3.1 (range 2-4) days in the TURis arm compared to 4.2 (range 3-6) days in the mTURP arm. The EAC reported this data in Table 29 but did not use the data in the meta-analysis of hospital stay because the data were not presented as mean (standard deviation). The EAC requested the standard deviations for hospital stay from the lead author but received no response.

Upon factual checking the first draft of the EAC report the sponsor provided the meta-analysis shown below in Figure 30.

Figure 30: Sponsor's meta-analysis of hospital stay



The sponsor has included the Geavlete 2011 study, by estimating the standard deviations as follows:

SD = (upper range limit – lowerrange limit)/(2*1.96)

Standard deviation for the TURis arm = (4-2)/(1.96*2) = 0.51

Standard deviation for the mTURP arm = (6-3)/(1.96*2) = 0.77

This method appears to be based on an assumption that hospital stay is normally distributed. We have our doubts about this as hospital stay has most often a right skewed distribution. The Cochrane Handbook advises caution in using methods to impute an unknown standard deviation from other statistics:

"Imputation techniques involve making assumptions about unknown statistics, and it is best to avoid using them wherever possible..... imputation may be reasonable for a small proportion of studies comprising a small proportion of the data if it enables them to be combined with other studies for which full data are available. Sensitivity analyses should be used to assess the impact of changing the assumptions made."

Taking this, Geavlete 2011 provides a substantial proportion of the studies (25%) and of the data (29%). We advise that the Geavlete 2011 data should be considered with caution. The results of meta-analyses of hospital stay are highly sensitive to the addition/exclusion of data from Chen 2009 and Geavlete 2011.

Another study reported hospital stay in a manner unsuitable for meta-analysis. Fagerstrom analysed TURis (n=98) versus mTURP (n=98) and found median hospital stay to be 51 hours (range 22 – 163 hours) and 52 hours (range 27 – 365) hours respectively. The EAC requested values for mean and standard deviation but the lead author did not provide the data.

A larger problem with the meta-analysis in Figure 30 is that there is substantial and visible heterogeneity across the studies. Figure 30 shows an I squared value of 86.2%, and a p value for heterogeneity of $p < 0.0001$. The heterogeneity is visible in the Forest plot, with two studies (Chen 2009 & Geavlete 2011) reporting similar results in favour of TURis and two (Akman 2013, Michielsen 2011) with confidence intervals including the null value of zero difference in hospital stay.

This heterogeneity raises the question of whether meta-analysis is the appropriate method to apply. It is not sufficient to select a random effects model in response to heterogeneity, and random effects models work well only with a larger number of studies (10 or more, Cochrane Handbook).

In summary the EAC's concerns with the sponsor's analysis are:

- Visible heterogeneity: meta-analysis may not be the best method to use
- Imputation of standard deviation (Geavlete 2011)
- The pooled estimate for the difference in hospital stay is small (< 1 day)
- None of the studies are from the UK, and decisions to discharge patients from hospital are likely to be influenced by different factors internationally

Table 63 summarises the hospital stay data from all identified randomised studies. Two studies found a statistically significant difference in hospital stay in favour of TURis. Five studies forund no statistically significant difference in favour of TURis, although of these one is based on a conference abstract data only (Goh 2010) and another on an English-language abstract from a Spanish language paper (Abascal-Junquera 2006).

Table 63 Summary of hospital stay data from randomised trials

Randomised study	n	Hospital stay (TURis)	Hospital stay (mTURP)	Difference	p	Country
Abascal-Junquera 2006	45	Mean 3.63 (SD 0.5) days	Mean 3.67 (SD 0.5) days	0.04 days	Not reported	Spain
Akman 2013	286	Mean 2.5 (SD 1.3) days	Mean 2.7 (SD 1.4) days	0.2 days	Not significant	Turkey
Chen 2009	40	Mean 3.0 (SD 0.5) days	Mean 4.2 (SD 0.7) days	1.2 days	p = 0.001	China
Fagerstrom 2011	185	Median 51 (range 22 – 163) hours	Median 52 (range 27 – 365) hours	1 hour	Not significant	Sweden
Geavlete 2011	340	Mean 3.1 (range 2 - 4) days	Mean 4.2 (range 27 – 365) hours	1.1 days	p = 0.001	Romania
Goh 2010	210	90 hours	103 hours	13 hours	p =0.06	Not known
Michielsen 2011	518	Mean 3.72 (SD 2.62) days	Mean 3.89 (SD 3.18) days	0.17 days	p = 0.773	Brussels

References

Abascal Junquera, J.M., Cecchini, R.L., Salvador, L.C., Martos, C.R., Celma, D.A., Morote, R.J., Abascal Junquera, J.M., Cecchini Rosell, L., Salvador Lacambra, C., Martos Calvo, R., Celma Domenech, A., & Morote Robles, J. 2006. [Bipolar versus monopolar transurethral resection of the prostate: peroperative analysis of the results]. [Spanish]. *Actas Urologicas Espanolas*, 30, (7) 661-666

Akman, T., Binbay, M., Tekinarslan, E., Tepeler, A., Akcay, M., Ozgor, F., Ugurlu, M., Muslumanoglu, A., Akman, T., Binbay, M., Tekinarslan, E., Tepeler, A., Akcay, M., Ozgor, F., Ugurlu, M., & Muslumanoglu, A. 2013. Effects of bipolar and monopolar transurethral resection of the prostate on urinary and erectile function: a prospective randomized comparative study. *BJU International*, 111, (1) 129-136

Bertolotto, F.N. 2009. Results of one thousand consecutive bipolar transurethral resection in saline system(TURis). *Journal of Urology*, Conference, (AUA) Annual

Centre for Reviews and Dissemination 2008. Systematic reviews: CRD's guidance for undertaking reviews in health care. *University of York*

Chen, Q., Zhang, L., Fan, Q.L., Zhou, J., Peng, Y.B., Wang, Z., Chen, Q., Zhang, L., Fan, Q.L., Zhou, J., Peng, Y.B., & Wang, Z. 2010. Bipolar transurethral resection in saline vs traditional monopolar resection of the prostate: results of a randomized trial with a 2-year follow-up. *BJU International*, 106, (9) 1339-1343

Chen, Q., Zhang, L., Liu, Y.J., Lu, J.D., Wang, G.M., Chen, Q., Zhang, L., Liu, Y.J., Lu, J.D., & Wang, G.M. 2009. Bipolar transurethral resection in saline system versus traditional monopolar resection system in treating large-volume benign prostatic hyperplasia. *Urologia Internationalis*, 83, (1) 55-59

Fagerstrom, T., Nyman, C.R., Hahn, R.G., Fagerstrom, T., Nyman, C.R., & Hahn, R.G. 2009. Bipolar transurethral resection of the prostate causes less bleeding than the monopolar technique: a single-centre randomized trial of 202 patients. *BJU International*, 105, (11) 1560-1564

Fagerstrom, T., Nyman, C.R., Hahn, R.G., Fagerstrom, T., Nyman, C.R., & Hahn, R.G. 2011. Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate. *Journal of Endourology*, 25, (6) 1043-1049

Fumado, L.P. 2011. Bipolar turp(TURIS): Selective symptomatic improvement after 1yr follow-up. *Journal of Endourology*, Conference, (var.pagings) November

Geavlete, B., Georgescu, D., Multescu, R., Stanescu, F., Jecu, M., Geavlete, P., Geavlete, B., Georgescu, D., Multescu, R., Stanescu, F., Jecu, M., & Geavlete, P. 2011. Bipolar plasma vaporization vs monopolar and bipolar TURP-A prospective, randomized, long-term comparison. *Urology*, 78, (4) 930-935

Giulianelli, R.A. 2012. Transurethral prostate resection monopolar versus plasmakinetics gyrus versus bipolar turis surgmaster scalpel: Single centre comparison study. *Urology*, Conference, (var.pagings) S73-S74

Goh, M.G. 2010. Bipolar versus monopolar transurethral Resection of the prostate (TURP) for benign prostatic obstruction: A randomised prospective trial comparing treatment efficacy and the incidence of transurethral resection (TUR) Syndrome. *Journal of Urology*, Conference, (var.pagings) e739

Goh, M.H.C. 2009. Bipolar versus monopolar transurethral resection of the prostate for benign prostatic obstruction: A randomised prospective trial with one year follow up. *BJU International*, Conference, (var.pagings)

Gulur, D.M.G. 2010a. Transurethral resection of the prostate for benign prostatic obstruction: A comparison of the Olympus bipolar and monopolar resectoscopes from the operation surgeon's perspective. *BJU International*, Conference, (var.pagings) June

Gulur, P.M.G. 2010b. Comparison between bipolar versus monopolar transurethral resection of the prostate: A randomised prospective trial. *European Urology, Supplements*, Conference, (var.pagings) 279

Gupta, N.A. 2010. Cost analysis of various procedures for surgical management of benign enlargement of prostate. *Journal of Urology*, Conference, (var.pagings) e811-e812

Ho, H., Yip, S.K., Cheng, C.W., Foo, K.T., Ho, H., Yip, S.K.H., Cheng, C.W.S., & Foo, K.T. 2006. Bipolar transurethral resection of prostate in saline: preliminary report on clinical efficacy and safety at 1 year. *Journal of Endourology*, 20, (4) 244-246

Ho, H.S., Yip, S.K., Lim, K.B., Fook, S., Foo, K.T., Cheng, C.W., Ho, H.S.S., Yip, S.K.H., Lim, K.B., Fook, S., Foo, K.T., & Cheng, C.W.S. 2007. A prospective randomized study comparing monopolar and bipolar transurethral resection of prostate using transurethral resection in saline (TURIS) system. *European Urology*, 52, (2) 517-522

Jun Hyun, H.Y.S. 2012. Comparative analysis of the efficacy and safty of conventional transurethral resection (TUR) of prostate, transurethral resection of prostate in saline (TURIS) and TURIS-vaporization for treatment of BPH; single surgeon experience. *International Journal of Urology*, Conference, (var.pagings) August

Lee, Y.T., Ryu, Y.W., Lee, D.M., Park, S.W., Yum, S.H., Han, J.H., Lee, Y.T., Ryu, Y.W., Lee, D.M., Park, S.W., Yum, S.H., & Han, J.H. 2011. Comparative Analysis of the Efficacy and Safety of Conventional Transurethral Resection of the Prostate, Transurethral Resection of the Prostate in Saline (TURIS), and TURIS-Plasma Vaporization for the Treatment of Benign Prostatic Hyperplasia: A Pilot Study. *Korean Journal of Urology*, 52, (11) 763-768

Lourenco T, 'Dow J, abi G, everill M, ickard R, & rmstrong N 2008. Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement. *Health Technol Assess*, 12, (35)

Michielsen, D.P., Coomans, D., Braeckman, J.G., Umbrain, V., Michielsen, D.P.J., Coomans, D., Braeckman, J.G., & Umbrain, V. 2010a. Bipolar transurethral resection in saline: the solution to avoid hyponatraemia and transurethral resection syndrome. *Scandinavian Journal of Urology & Nephrology*, 44, (4) 228-235

Michielsen, D.P., Coomans, D., Michielsen, D.P.J., & Coomans, D. 2010b. Urethral strictures and bipolar transurethral resection in saline of the prostate: fact or fiction? *Journal of Endourology*, 24, (8) 1333-1337

Michielsen, D.P., Coomans, D., Peeters, I., Braeckman, J.G., Michielsen, D.P., Coomans, D., Peeters, I., & Braeckman, J.G. 2010c. Conventional monopolar resection or bipolar resection in saline for the management of large (>60 g) benign prostatic hyperplasia: an evaluation of morbidity. *Minimally Invasive Therapy & Allied Technologies: Mitat*, 19, (4) 207-213

Michielsen, D.P., Coomans, D., Van, L.C., Braeckman, J.G., Michielsen, D.P.J., Coomans, D., Van Lersberghe, C., & Braeckman, J.G. 2011. Comparison of the haemostatic properties of conventional monopolar and bipolar transurethral resection of the prostate in patients on oral anticoagulants. *Archives of Medical Science*, 7, (5) 858-863

Michielsen, D.P., Debacker, T., De, B., V, Van, L.C., Kaufman, L., Braeckman, J.G., Amy, J.J., Keuppens, F.I., Michielsen, D.P.J., Debacker, T., De Boe, V., Van Lersberghe, C., Kaufman, L., Braeckman, J.G., Amy, J.J., & Keuppens, F.I. 2007. Bipolar transurethral resection in saline--an alternative surgical treatment for bladder outlet obstruction? *Journal of Urology*, 178, (5) 2035-2039

Petkov, T.S., I 2011. Transurethral resection of prostate in saline (TURis) versus standard monopolar transurethral resection of prostate. *European Urology, Supplements*, Conference, (var.pagings) 583

Puppo, P., Bertolotto, F., Introini, C., Germinale, F., Timossi, L., Naselli, A., Puppo, P., Bertolotto, F., Introini, C., Germinale, F., Timossi, L., & Naselli, A. 2009. Bipolar transurethral resection in saline (TURis): outcome and complication rates after the first 1000 cases. *Journal of Endourology*, 23, (7) 1145-1149

Rose, A., Suttor, S., Goebell, P.J., Rossi, R., Rubben, H., Rose, A., Suttor, S., Goebell, P.J., Rossi, R., & Rubben, H. 2007. [Transurethral resection of bladder tumors and prostate enlargement in physiological saline solution (TURIS). A prospective study]. [German]. *Urologe (Ausg*, A). 46, (9) 1148-1150

Shum, C.F., Mukherjee, A., Teo, C.P., Shum, C.F., Mukherjee, A., & Teo, C.P.C. 2014. Catheter-free discharge on first postoperative day after bipolar transurethral resection of prostate: Clinical outcomes of 100 cases. *International Journal of Urology*, 21, (3) 313-318

Sugihara, T., Yasunaga, H., Horiguchi, H., Nakamura, M., Nishimatsu, H., Kume, H., Ohe, K., Matsuda, S., Homma, Y., Sugihara, T., Yasunaga, H., Horiguchi, H., Nakamura, M., Nishimatsu, H., Kume, H., Ohe, K., Matsuda, S., & Homma, Y. 2012. In-hospital outcomes and cost assessment between bipolar versus monopolar transurethral resection of the prostate. *Journal of Endourology*, 26, (8) 1053-1058

Varney, S.J. & Guest, J.F. 2003. The annual cost of blood transfusions in the UK. *Transfus.Med.*, 13, (4) 205-218 available from: PM:12880391

Document cover sheet

Assessment report: MT217 PLASMA assessment report update

EAC team: Cedar (Laura Knight, Susan Peirce and Helen Morgan)

Project lead(s): Laura Knight

Information specialists: Helen Morgan and Simone Willis

Clinical evidence reviewer: Laura Knight and Helen Morgan

Economic evidence reviewer: Susan Peirce

EAC sign-off: Grace Carolan-Rees

Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
0.1	Authoring	Laura Knight	06/06/2020	
0.1	Authoring and evidence QA	Helen Morgan	23/06/2020	
1.0	First draft to NICE	Laura Knight	24/06/2020	24/06/2020
1.1	Review by NICE	Chris Pomfrett	25/06/2020	
1.2	Address comments by NICE	Laura Knight	26/06/2020	
1.3	Final review	Grace Carolan-Rees	01/07/2020	
2.0	Second draft to NICE	Laura Knight	01/07/2020	01/07/2020
2.1	Addressing company comments following fact check	Helen Morgan and Laura Knight	08/07/2020	
3.0	Third draft to NICE	Laura Knight	08/07/2020	08/07/2020
3.1	Additions following pre-meet	Laura Knight and Susan Peirce	14/07/2020	
4.0	Fourth draft to NICE	Laura Knight	15/07/2020	16/07/2020
4.1	Update costings post-MTAC – change models to	Susan Peirce	07/09/2020	

	65% 2nd electrode use, add threshold values			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT217 The PLASMA system for transurethral resection of the prostate

External Assessment Centre update report

Produced by: Cedar

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Date completed: 16/07/2020

Contains confidential information: Yes

Number of attached appendices: 2

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AE	Adverse event
AR	Assessment report
ARU	Assessment report update
BPH	Benign prostatic hyperplasia
bTURP	Bipolar transurethral resection of prostate
EAC	External Assessment Centre
IPSS	International Prostate Symptom Score
IPSS QoL	International Prostate Symptom Score Quality of Life
LOS	Length of Stay
LUTS	Lower urinary tract symptoms
MTEP	Medical Technologies Evaluation Programme
mTURP	Monopolar transurethral resection of prostate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVR	Postvoid residual volume
Q_{max}	Maximum urinary flow rate
QoL	Quality of Life
RBC	Red Blood Cell
RCT	Randomised controlled trial
SD	Standard deviation
TURP	Transurethral resection of prostate

Executive summary

Clinical evidence

New clinical evidence was submitted by the company for the purpose of this assessment report update (ARU). However, following a review of the new evidence submitted and an updated search from the previous assessment report, only two new studies, with three publications, were identified by the EAC and are included in this report. One study included is split over two publications, one reporting short-term follow-up and one reporting long-term follow-up results.

One study is an RCT conducted in Japan and one is a non-randomised comparative study conducted in Turkey. As none of these were conducted within the UK/NHS setting the results cannot be readily generalised to this setting.

The quality of the included studies was moderate to high with most to all outcomes, all participants and interventions being relevant to the scope. However, all were conducted in countries outside of the UK.

Economic cost model

The original model submitted from the company was a de novo model as no published evidence relevant to this device and indication was available at that time. No new relevant economic evidence has been found since publication of the original assessment report (Cleves et al. 2014). Please refer to (Cleves et al. 2014) for an in-depth evaluation of the cost model. Costs related to the procedure, device and the comparator were updated based on values from the company, NHS supply chain and NHS tariffs (2018/19).

As the evidence available in this update does not refer to a UK/NHS setting, it should be used with caution. However, the economic models would suggest the adoption of the PLASMA system could be cost saving to the NHS, especially for current Olympus technology owners.

N.B The manufacturer changed the name of the system from TURis to PLASMA in 2017. They indicated that all references to 'TURis' should be replaced with 'PLASMA'. Clinical experts indicated that the name change should be made clear in any update of guidance as 'TURis' is still commonly used. For the purpose of this report, only PLASMA will be used.

1 Decision problem

The company has not proposed any variation to the decision problem specified in the scope.

Table 1: Decision problem and scope details

Decision problem	Scope	EAC comment
Population	Adults with lower urinary tract symptoms (LUTS) presumed secondary to benign prostatic hyperplasia (BPH), in whom TURP is indicated	None
Intervention	TURP using the PLASMA system (formerly known as TURis)	None
Comparator(s)	• TURP using a monopolar system • TURP using other bipolar systems	None
Outcomes	The outcome measures to consider include: • Hospital length of stay • Procedural blood loss and blood transfusion requirement • Time of removal of urinary catheter post-operatively • TUR syndrome • Re-admittance for repeat procedures • Duration of surgical procedure • Healthcare associated infection • Relief of symptoms associated with BPH (IPSS) • Maximum flow rates (Qmax) • Residual urine volumes • Benign prostatic hyperplasia impact index (BPHII)	None

	• Reduction in prostate volume • Quality of life measures, e.g. International Prostate Symptom Score Quality of Life (IPSS-QOL) • Device-related adverse events • Procedural complication rate during and after surgery	
Cost analysis	Cost models should consider 2 scenarios for the adoption of the PLASMA system: • Hospitals which currently have an Olympus ESG-400 generator • Hospitals which currently do not have an Olympus ESG-400 generator. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include the length of stay, use in a day case scenario, and the incidence of adverse events, such as TUR syndrome and urethral stricture.	None
Subgroups	• Individuals with prosthetic lower limbs • Individuals with a cardiac pacemaker	None
Special considerations, including those related to equality	It has been suggested that men aged 80 years and over, especially those with frail health and comorbidity, have been found to have an increased risk of morbidity following TURP, though effectiveness of the intervention is not affected.	None
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact **No**	None

	on daily living, compared with people without that protected characteristic? Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality? **No** Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance? **No**	
Any other special considerations	See cost analysis. PLASMA requires the use of an Olympus ESG-400 generator. Some hospitals who currently perform monopolar TURP and use other bipolar TURP systems produced by Olympus may already own an ESG-400 generator and avoid this cost. Resection is performed using loop electrodes. Haemostasis is performed using roller electrodes. Use of a hybrid technique with PLASMA button electrodes for haemostasis has been reported.	None

2 Overview of the technology

The PLASMA system (previously TURis, Olympus Medical) is a bipolar electrosurgery system designed for use when surgical intervention is indicated for prostatic enlargement. It first received a CE mark in April 2012 as a class IIb device for electrosurgery and endoscopic applications. The company has confirmed no changes have been made to the technology following the name change and that the CE mark is still in date as of July 2020.

The PLASMA system consists of an Olympus generator, a resectoscope, which incorporates the PLASMA active working element and electrode, a telescope, an inner and outer sheath, a light guide cable, and a saline cable. The active and return electrode are contained within the resectoscope at the site of the operation, eliminating the need for a patient return electrode because PLASMA uses saline irrigation fluid to conduct electrical current within the resectoscope. The surgeon uses an endoscopic image to guide the electrode assembly through the urethra to the prostate. The electrode is then used to cut and coagulate prostate tissue and saline is used to flush the bladder free of resected prostate tissue and blood. Electrodes are available in different sizes and shapes (described as loop, button and roller) for cutting or coagulation and to take into account surgeon choice. For resection, a loop is used to repeatedly cut out small chippings to create a wide channel through the prostate and a roller or button may be used to achieve haemostasis. The prostatic chippings are flushed out before inserting a urethral urinary catheter at the end of the procedure.

3 Clinical context

Current treatment options for benign prostatic hyperplasia when conservative management options have been unsuccessful or are not appropriate in the NICE guideline on lower urinary tract symptoms (CG97) include:

- Monopolar or bipolar transurethral resection of the prostate (TURP)
- Transurethral vapourisation of the prostate (TUVP)
- Holmium laser enucleation of the prostate (HoLEP; at centres specialising in the technique or with mentorship arrangements in place)
- Transurethral incision of the prostate (TUIP; only in prostates smaller than 30 g)
- Open prostatectomy (only in prostates larger than 80 g).

Surgery for managing voiding LUTS presumed secondary to BPE, should only be consider offering botulinum toxin injection into the prostate as part of a

randomised controlled trial. If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering laser vaporisation techniques, bipolar TUVP or monopolar or bipolar transurethral vaporisation resection of the prostate (TUVRP) as part of a randomised controlled trial that compares these techniques with TURP.

Minimally invasive treatments such as transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), high-intensity focused ultrasound (HIFU), transurethral ethanol ablation of the prostate (TEAP) and laser coagulation are not recommended by NICE for people with LUTS.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company conducted update searches of PubMed, in approximately April 2019 and February 2020, search details were not provided. From the 2019 update search, 5 published studies were selected as relevant and 8 were excluded after full-text review; from the 2020 update search a further 3 studies were selected as relevant and 5 were excluded after full-text review; study selection details are provided in appendix A.

NICE and the EAC conducted update searches since those conducted for original AR to ensure that all relevant, recently published literature was identified for this guidance update

In April 2019 NICE conducted update searches based on the original EAC searches with the inclusion of additional terms to capture the name change of the technology from TURis to PLASMA. The update searches were conducted on 11th April 2019 in the following databases: Medline, including In-Process and Epub Ahead of Print (Ovid), EMBASE (Ovid), Cochrane Database of Systematic Reviews, CENTRAL, DARE, EconLit, HTA (CRD), NHS EED (CRD). Searches were also conducted for ongoing trials in Clinical Trials.gov, ISRCTN, WHO International Clinical Trials Registry Platform. Database records were imported into Endnote and duplicates removed, 521 records were identified (including 2 presented by the manufacturer). A researcher from the EAC reviewed all 521 records identified by the searches, 8 were selected as being relevant for full review. A second researcher reviewed the 8 selected studies to confirm relevance and 2 (with 3 publications) were included.

Further update searches were conducted by the EAC on 9th June 2020 in the following databases: Medline ALL (Ovid), EMBASE (Ovid), Cochrane Database of Systematic Reviews, CENTRAL, HTA (CRD). Searches were

also conducted for ongoing trials in Clinical Trials.gov, WHO International Clinical Trials Registry Platform. Also, the MHRA's medical device alerts and field safety notices and the MAUDE database were searched for adverse events. This update search identified a further 101 records. These were reviewed by a researcher at the EAC where 13 were selected for a full text review. From these no further studies were selected for inclusion in this update. The Medline (Ovid) search strategy used in the update searches is presented in appendix A.

4.2 *Included and excluded studies*

The studies selected by the company are listed in table 2 together with the EAC's selection decision. The EAC identified 2 studies, neither of which were selected by the company for full-text review, that were deemed relevant to the scope of this guidance update and have been included in Table 3.

Table 2: Studies selected by the company

Study	EAC Decision
Alexander (2019)	**Excluded** - Cochrane systematic review, the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted. Also the intervention was B-TURP and not specifically PLASMA, therefore the results of Alexander (2019) cannot be directly applied to the effectiveness of PLASMA.
Al-Rawashdah (2017)	**Excluded** – used Gyrus PK Super-Pulse Generator (Olympus Winter and Ibe GmbH, Hamburg, Germany) for B-TURP
Huang (2019)	**Excluded** – systematic review and network analysis, the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted. Also one of the included interventions was B-TURP and not specifically PLASMA, therefore the results of Huang (2019) cannot be directly applied to the effectiveness of PLASMA.
Kumar (2019)	**Excluded** – 36 month outcomes of Kumar (2013), this was excluded by the EAC in the original AR as the intervention was Gyrus ACMI plasmakinetic system.
Mullhaupt 2019)	**Excluded** - Not identified by the EAC as not bipolar TURP.
Sinanoglu (2014)	**Excluded** – used Gyrus Plasmakinetic System
Treharne (2018)	**Excluded** – systematic review of company's original submission and included additional RCT Komura (2015), the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted. Komura (2015) has been included by the EAC.
Wang (2015)	**Excluded –** meta-analysis of RCTs of plasmakinetic resection of prostate (PKRP), the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted, also there are insufficient details to determine if the included studies are all PLASMA.

Table 3: Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Komura et al (2014 and 2015) Japan	Randomised Controlled Trial (UMIN 000010801) January 2008-April 2010 All treatments were performed by a single well-experienced urologist. Both procedures were performed using a 26F resectoscope. **Intervention:** Bipolar TURP using PLASMA system. The generator was set at 300 W for cutting and 120 W for coagulation. The irrigation fluid used was 3 L normal saline (0.9%). **Comparator:** Monopolar TURP. The generator was set at 120 W and 60 W for cutting and coagulation, respectively, 4% mannitol	Bipolar TURP n=69 (n=62 analysed) mean age 69.8 (5.8) years Monopolar TURP n=67 (n=63 analysed), mean age 67.9 (5.4) years Inclusion criteria: • Symptomatic benign prostatic hyperplasia (BPH) Exclusion criteria: • Suspected prostate cancer • Bladder Calculus • Previous prostate surgery • Those taking 5α-reductase inhibitor preoperative medication	• Operation time • Decline of sodium level • Haemoglobin levels • Clot retention • Catheterization time • Adverse events • Efficacy (36 month follow up)	Sample size calculation based on operation time (120 patients to provide 90% power to detect effect six of 0.6 point) Randomisation performed according to Consolidated Standards of Reporting Trials guidelines

	solution with 1% ethanol was used for irrigation. **Follow-up:** 1, 3, 6 months and every 3 months thereafter until 36 months. **Funding:** Not reported **Status:** Published ●			
Karadeniz et al (2016) Turkey	Prospective Observational Study (non randomised comparative study). NCT02681471 December 2013 – April 2015 Operations were performed by experienced urology staff. **Intervention:** Bipolar TURP performed using a 24 Fr PLASMA (OLYMPUS) resectoscope and irrigation fluid	Fifty-two patients who underwent TURP were assessed for eligibility. Two were excluded due to blood sampling errors. Bipolar TURP n = 25, mean age 67.8 (8.6) years Monopolar TURP n = 25, mean age 68.5 (8.2) years Inclusion criteria: • Aged between 50 and 90 years • Physical status of American Society of Anaesthesiology (ASA) Class II or III Exclusion criteria: • Severe heart failure	• Operation duration • Perioperative Serum Sodium levels • Perioperative Haemoglobin levels ●	

	containing 0.9% sodium chloride **Comparator:** Monopolar TURP performed using a 24 Fr Karl Storz resectoscope and irrigation fluid containing 5% mannitol. **Follow-up:** None **Funding:** Departmental sources only **Status:** Published ●	• Respiratory failure • Electrolyte imbalance due to neoplasms • Diarrhoea • Vomiting • Bleeding diathesis ●		

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

All studies included were comparative in design; one an RCT (Komura, 2014 and 15) and another a prospective comparative design (Karadeniz, 2016). For full details see Table 3.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

Komura, 2014 and 2015 used appropriate randomisation techniques with no significant differences between groups at baseline. Outcome assessors were blinded to treatment allocation, therefore reducing the risk of bias in outcome reporting. However, due to the nature of the trial the surgeons and patients were not fully blinded to the treatment allocation. Karadeniz (2016) did not allocate participants randomly to each group. However, the baseline characteristics did not significantly differ between groups suggesting no risk of bias. All were fully published studies with good sample sizes.

For full details of the critical appraisals of each study please see Appendix B.

5.3 *Results from the evidence base*

Table 4 provides a breakdown of the clinical results for all included evidence. Results from Komura (2015) are not included in this table as they are identical to those already included for Komura (2014).

Table 4: Clinical results of evidence review

Study	Hospitalisation duration and catheterisation time	Operative time (mean (SD))	Volume of resected tissue (g)	Procedural blood loss rate (mL/min) and requirement for blood transfusion	Serum Sodium levels (mEq/L)	Postoperative haemoglobin level (g/dL)	IPSS	Maximum urinary flow rate (Q_{max} (mL/s)) and postvoid residual volume (PVR (mL))	Quality of life (QoL)
Komura (2014 and 2015)	Catheterisation time (mean hours) was significantly longer in the mTURP group (35.8) compared to the PLASMA group (20.6), p=0.042 Hospitalisation time (mean days) was significantly higher in the mTURP group (3.4) compared to the TURis group (2.5),	Operation time was significantly higher in the PLASMA group = 79.5 mins, mTURP = 68.4 mins , p=0.048)	No difference in resected tissue, p=0.957.	Not reported	Perioperative decline of serum sodium levels was significantly higher in the mTURP group,3.6(4.3) compared to PLASMA, 0.5(0.9), p<0.001	Perioperative decline of haemoglobin levels was 1.5 g/dL in both groups	Scores decreased in both groups between each time point. These did not differ significantly between groups at any time point. Preoperative: • mTURP: 22.2 (5.5) • PLASM	Q_{max} scores increased in both groups between baseline and 3 months and were comparable at 36 months. These did not differ significantly between groups at any time point. Preoperative: • mTURP:	Scores decreased in both groups between each time point. These did not differ significantly between groups at any time point. Preoperative: • mTURP: 5.2 (1.0) • PLASMA: 5.2 (0.7)

	p=0.045						A: 23.7 (5.8) , p=0.178 3 month post-op: • mTURP: 6.1 (4.4) • PLASMA: 7.7 (6.0), p=0.112 36 month post-op: • mTURP: 4.2 (2.4) • PLASMA: 5.2 (4.0), p=0.107	7.1 (3.3) • PLASMA: 6.4 (2.2), p=0.171 3 month post-op: • mTURP: 19.3 (7.8) • PLASMA: 16.7 (7.4), p=0.065 36 month post-op: • mTURP: 18.6 (6.5) • PLASMA: 16.8 (5.6), p=0.121	3 month post-op: • mTURP: 2.3 (1.7) • TURis: 2.6 (1.7), p=0.275 36 month follow-up: • mTURP: 1.7 (1.7) • PLASMA: 2.3 (1.8), p=0.087
Karadeniz (2016)	Not reported	Operation time as comparable between mTURP (72 +/- 30.9) and PLASMA (73 +/- 16)	PLASMA = 47.5 (13.8) mTURP = 49.2 (29.8)	Not reported	Perioperative Na+ values were significantly lower in the mTURP group compared with	Perioperative Hb levels did not differ significantly between mTURP and PLASMA at 1st measurement (13.5 and	Not reported	Not reported	Not reported

			p>0.05		PLASMA at both 1st measurements (136.9 and 141.8 respectively) and 2nd measurements (132.68 and 140.76 respectively), p<0.001	12.32 respectively) and 2nd measurement (13.6 and 12.33)			

6 Adverse events

Adverse events (AEs) were reported in all included studies. All AEs were rated using the Clavien Dindo classification system and are listed in Table 5 by Clavien Dindo Grade. No field safety notices or medical device alerts were identified by the EAC. The MAUDE (FDA) database was also searched, no adverse events were identified but 23 products problems none of which appear to have caused patient harm.

Table 5: Adverse events

	Clavien Dindo classification system					
Study	**Grade I**	**Grade II**	**Grade IIIa**	**Grade IIIb**	**Grade IV**	**Grade V**
Komura et al (2014 and 2015)	• Nine patients (14.5%) in the mTURP group and 3 (4.8%) in the PLASMA group reported UTIs	• Perioperative transfusions were needed in 4 (7%) of the mTURP group and 1 (1.6%) of the PLASMA group	• Seven patients (11.3%) in the monopolar group vs 1(1.6%) in the TURIS experienced clot retention • Two patients in both groups reported acute urinary retention following the procedures • Urethral stricture rate at 36 month follow-up was 4/61 (6.6%) patients in the in the mTURP group and 12/63 (19%) in the PLASMA group (p=0.022)	None reported	• One patient presented dyspnea immediately after treatment with PLASMA and was diagnosed with worsening of chronic heart failure caused by excess preload from fluid absorption	None reported

Karadeniz et al (2016)	None reported	• Two patients in the mTURP group required a blood transfusion (Grade II)	None reported	None reported	• TUR syndrome was diagnosed in two patients (8% incidence) in the mTURP group (Grade III)	None reported

7 Interpretation of the clinical evidence

Results from the evidence suggests PLASMA could be beneficial to patients with LUTS secondary to BPH within the NHS. Catheterisation and hospitalisation times could be reduced when using PLASMA compared to mTURP. However, urological outcomes such as Q_{max} and PVR and QoL measures did not differ between TURP groups immediately after surgery or during longer-term follow-up. Haematology outcomes such as decline in haemoglobin and sodium levels was either comparable between groups or worse in the PLASMA group immediately after surgery. Based on the evidence the benefit to patients would come primarily from the reduced length of hospital stay and catheterisation time.

7.1 *Integration into the NHS*

None of the included studies were conducted within a UK and/or NHS setting, therefore the results are not generalizable to an NHS setting based on this alone.

Whilst clinical experts contacted as part of this update process suggested that bipolar TURP is now the standard of care, there is no clinical evidence available at this time to support this. If this is the case however, then minimal training would be required for staff to implement and safely use the PLASMA system.

7.2 *Ongoing studies*

No ongoing studies have been identified

8 Economic evidence

8.1 *Published economic evidence*

No new economic evidence was identified during the updated literature search. For a detailed evaluation of the available economic evidence please refer to Cleves et al, 2014.

8.2 *Company de novo cost analysis*

The manufacturer provided an executable Excel model of a simple decision tree. This compared bipolar transurethral resection of the prostate (TURP) using PLASMA against monopolar TURP in men with lower urinary tract symptoms (LUTS). The treatments were assumed to be of equal clinical efficacy (resection weight or radicality) and differences in costs were therefore related to the technology costs, incidence of adverse events, length of hospital stay and readmission rates.

The manufacturer conducted a meta-analysis to calculate values to inform their model for TUR syndrome, blood transfusions and clot retention. Clot retention and reoperations were provided as model options. The EAC made some changes to the original values due to differences in interpretation of the clinical evidence.

Multiple versions of the cost model were used in the final guidance (MTG23) representing a number of different possible scenarios (NICE 2015b). At the initial meeting of the Medical Technologies Advisory Committee (MTAC) additional modelling was requested to include the effect of length of hospital stay and all-cause readmissions.

Costs were considered separately for hospitals that already owned an Olympus generator and those that did not. Following the MTAC meeting the initial base cases were adapted to include a reduction in length of hospital stay (LOS) of 0.19 days for PLASMA. Scenarios included an additional reduction in all-cause readmission rate of 11% for PLASMA.

There were therefore 6 separate Excel models (

Table **6**), although the initial 2 base cases, without a difference in LOS, were not used in the MTG23 recommendations. Sensitivity analysis comprised a combination of the best and worst case values for length of stay and readmission rates.

Capital costs of the PLASMA and monopolar generators were not considered in the sponsor's models. Hospitals that have an Olympus generator for PLASMA and for monopolar are assumed to have these on loan from the company. The generator for the non-Olympus monopolar comparator is

assumed to already be owned by the hospital. Hospitals that already use Olympus generators would need to purchase reusable working elements and saline tubes to use the PLASMA system. Whereas hospitals without an Olympus generator would require additional accessories. The EAC added £10 to the cost of each monopolar procedure for non-Olympus hospitals, to account for the purchase cost of the generator.

The cost of the procedure is not included in the model, except for the cost of electrosurgical consumables. Patients receive either monopolar TURP or bipolar PLASMA TURP. They have a length of stay (LOS), risk of blood transfusion and risk of readmission that varies dependent on the treatment pathway, but all other costs are considered equal. The time horizon of the model includes these short term complications (during the hospital stay) and the risk of a readmission. (The time scale for readmissions is not known, but expected to be within a few months of the TURP.)

As monopolar and PLASMA TURP were considered to be of equal clinical efficacy, the key clinical parameters are the elimination of TUR syndrome, and reductions in blood transfusions and all-cause readmissions. TUR syndrome is the absorption of fluid due to the use of glycine solution during monopolar TURP. It is a rare, but serious, complication and requires an average of 2 days stay in high dependency unit (HDU) plus 2 days on a general ward (NICE 2015a). Additional treatment costs for TUR syndrome were not included in the model so this is probably an underestimate of the true cost.

Table 6: MTG23 model results (negative results are cost saving for PLASMA)

	Olympus customers			Non-Olympus customers		
	mTURP	**PLASMA**	**Difference**	**mTURP**	**PLASMA**	**Difference**
Initial base case¥	[redacted]	[redacted]	-£12.60	[redacted]	[redacted]	£77.75
Reduction in LOS	[redacted]	[redacted]	-£70.55	[redacted]	[redacted]	£19.80
Reduction in LOS and readmissions	[redacted]	[redacted]	-£375.02	[redacted]	[redacted]	-£284.66

¥ Not used in guidance recommendations

Table 6 shows the summary results from the final EAC-adapted models as used in MTG23. In the guidance the difference in LOS was included in the base case and so PLASMA was considered to be mildly cost-incurring (approximately £20 per procedure) if adopted by hospitals that previously used non-Olympus generators for monopolar TURP. In all other cases,

PLASMA was considered likely to be cost-saving by up to £375 (NICE 2015b). Key drivers of the final cost outcomes were:

- cost of monopolar consumables
- reduction in length of stay for PLASMA
- cost of a bed day
- reduction in readmission rates for PLASMA.

The PLASMA system uses saline as part of the electrosurgery conduction pathway, thus creating a plasma. The plasma produces localised vaporisation, which cuts and coagulates the tissue. The PLASMA loop electrode cuts away pieces of prostate tissue that can be used for analysis. The button electrode produces total vaporisation of the tissue and may be considered as bipolar transurethral vaporisation of the prostate (TUVP) procedure. Bipolar TUVP is only recommended for use as part of a randomised controlled trial (RCT) according to existing clinical guidance (CG97, NICE 2015a). The PLASMA system (including the button electrode) was included in the scope of the original NICE evaluation. However, use of the button electrode was excluded by the manufacturer and the EAC from the clinical and cost evidence.

This report updates the model parameters and costs where new data is available. We have not modelled PLASMA vaporisation using the PLASMAbutton electrode due to advice from clinical experts and the manufacturer (see below).

8.3 *Current validity of model*

The assumptions from the original models (as finally submitted for guidance) are summarised as:

1. There is no difference in the efficacy of PLASMA and mTURP
2. The capital cost of an mTURP generator is not considered (already owned)
3. The cost of an Olympus generator is not considered (generator is supplied free of charge as part of a contract to purchase PLASMA consumables)
4. PLASMA and mTURP electrodes are single use
5. Patients experiencing intra-operative bleeding require a blood transfusion
6. There is no difference between mTURP and PLASMA in terms of:
    - procedure time
    - strictures and contractures
    - readmissions due to haemorrhage
    - time to catheter removal
    - rate of repeat procedures due to incomplete resection

The EAC has contacted 3 clinical experts and the manufacturer and asked them to comment on whether the assumptions and parameters used in the original model remain valid for the update or whether there have been any changes.

Two clinical experts indicated that there had been an increase in the use of bipolar TURP. In their experience most units provided this and it was standard of care in some places. One clinical expert reported the European Association of Urology guidelines (Gravas et al. 2019) that indicate that bipolar and monopolar TURP are recommended for prostates of 30-80ml. The change to bipolar since the publication of MTG23 includes other bipolar manufacturers than Olympus. Olympus has indicated that 114 NHS centres are using PLASMA in 2020, compared to 61 in 2015 (England, Scotland and Wales). A third clinical expert indicated that bipolar should be the 'gold standard' for electrosurgical TURP, however other manufacturers had been slow to develop reliable bipolar devices, so hospitals with these manufacturers as standard would also be slow to change to bipolar.

There was no suggestion that assumptions on the cost of generators or single-use electrodes were invalid (assumptions 2-4).

Three clinical experts indicated that blood transfusion rates and/or volumes may be lower now. Two clinical experts indicated that the haemoglobin threshold for initiating transfusion had decreased from 80 g/L to 70 g/L or were restricted to patients who were symptomatic due to blood loss. Two clinical experts indicated that transfusion rates were very low, probably lower than the 5.8% used for monopolar TURP in the original model. Another indicated that 2.7 units of red blood cells (RBC) used in the model seemed high, and suggested that 1-2 units was more likely.

One clinical expert indicated that there was recent evidence to suggest that bipolar TURP is associated with higher rates of strictures and/or contractures than monopolar.

There is an overall indication that PLASMA TURP is associated with better haemostasis than monopolar (based on lower blood transfusion rates and an increase in use of coagulating electrodes, see below). Therefore, a lower rate of admissions for haemorrhage would be expected for PLASMA TURP.

In the original model, mTURP LOS was 3.3 days with a reduction of 0.19 days for PLASMA. The national average length of stay for endoscopic prostate resection is now 2 days according to NHS Hospital Episode Statistics (HES, M65.3 'Endoscopic resection of prostate NEC') (NHS Digital 2019). This is an average that includes multiple surgical modalities (but not laser resection,

which has a separate code), and both monopolar and bipolar TURP. This reduction from 3.3 to 2 days may be due to:

- an increase in the use of bipolar TURP.
- an increase in the use of other recent technologies for treating benign prostatic hyperplasia (NICE 2016).
- changes in peri-procedural practice that have contributed to this.

Two clinical experts indicated that bipolar TURP may now be offered as a day-case as standard of care for some patients, such as low-risk patients, with prostates <80ml, who are capable of managing their own catheter. There was no suggestion that monopolar TURP would be offered as a day case.

Reference cost data for 2018-19 indicates 11,211 elective finished consultant episodes (FCEs) for LB25F 'Transurethral Prostate Resection Procedures (CC Score 0-2)' (average unit cost of £3,029, NHS Improvement 2019). There were 1,115 day case FCEs for this healthcare resource group (HRG, average unit cost of £1,972) representing approximately 9% of the total number of elective procedures. In England there is a Best Practice Tariff for this HRG to incentivise conducting procedures as a day case. The tariff for 2019-20 is £2,152 for standard LOS and £2,370 for day case (NHS Improvement 2019).

The PLASMA button electrodes produce tissue vaporisation via a plasma effect as an alternative to resection using a loop electrode. All three clinical experts and the manufacturer indicated that they consider this to be a separate procedure to PLASMA TURP. The evidence base is distinct and the clinical outcome values in the TURP model should not be transferred into a model of PLASMA TUVP virus monopolar TURP. Previously the model assumed that 22% of PLASMA resections also included the use of a roller electrode for haemostasis. All three clinical experts and the manufacturer indicated that the use of the button electrode for haemostasis after loop resection is now relatively common. Two clinical experts indicated that they use the PLASMA button electrode for haemostasis following resection with a loop electrode. The suggestion is that this produces better haemostasis, therefore a lower risk of transfusion and higher chance of treatment as a day case. One clinical expert stated that they suspected that many of these cases also included some vaporisation of prostate tissue, and should therefore be considered a hybrid procedure.

8.4 *Updated input parameters*

The parameters and costs in the model taken from national indices such as Hospital Episode Statistics (HES) (NHS Digital 2019) and NHS National reference costs (NHS Improvement 2019) have been updated to the most

recently available data. Due to the use of Patient Level Costing, NHS Reference Costs for 2018-19 no longer includes values for length of stay or excess bed day costs. It does include HDU bed day costs of £883 compared to £619 in the guidance (XC07Z, "Adult CC, 0 organs supported"). To estimate an updated cost for a ward bed day we use the NHS Reference costs for 2017-18. This publication did include length of stay (2 days) and excess bed day costs (£358) for LB25F. The increase in HRG tariff payment for LB25F has increased from £216 in 2018-19 to £235 in 2019-20. This increase of 8.8% was applied to the 2017-18 Reference Cost for LB25F excess bed day, to get a value of £389 for 2018-19.

The manufacturer conducted a literature search in 2019 and listed 2 meta-analyses (MA) (Treharne et al. 2018;Wang et al. 2015), 2 RCTs (Al-Rawashdah et al. 2017;Kumar et al. 2019) and 1 observational study (Sinanoglu et al. 2014) published since the MTG23 review. At initial review these do not appear to change much of the evidence base. One MA is a journal report of the manufacturer's submission with one additional RCT (Treharne, Crowe, Booth, & Ihara 2018). One RCT (Al-Rawashdah, Pastore, Al Salhi, Fuschi, Petrozza, Maurizi, Illiano, Costantini, Palleschi, & Carbone 2017) and the observational study (Sinanoglu, et al. 2014) use the Gyrus PK system rather than the Olympus PLASMA. According to the original Briefing Note for MTG23 these should not be considered equivalent devices.

One clinical expert has also provided a list of 10 references, although they note that these may not all be within scope. NICE conducted an updated literature review in 2019. This returned 101 results published since the search date for MTG23. The EAC scanned these for recent systematic reviews and meta analyses and for UK based studies, but no additional ones were identified.

There is no explicit data to demonstrate that the length of stay for monopolar TURP has changed. The EAC has retained the 3.3 day stay for monopolar, and compared this to a 2 day stay for PLASMA TURP in the base case. A separate scenario of a further reduction in LOS of 1 bed day for PLASMA TURP is presented to estimate savings for moving to day case surgery. However this is likely to underestimate the true savings of this. The day case cost of £1057 in NHS reference costs cannot be used in these models. NHS reference costs include the full cost of the FCE, including procedures and inpatient aftercare, which have not been modelled in MTG23. A further scenario in which both monopolar and PLASMA modalities incur a 2 day stay is also presented.

Following advice from clinical experts the EAC has reduced the number of RBC units for a blood transfusion from 2.7 to 2.

Two clinical experts suggested a value of 50% of PLASMA procedures using a second coagulating electrode. A third indicated that they use the button electrode on all cases. The manufacturer provided a mean value of 1.65 electrodes per procedure, or 65% of procedures using 2 electrodes. This is based on total sales data for all PLASMA resection procedures. We have changed the value from the original models from 22% to 65%, and also assessed the effect of changing this to 0%. The manufacturer indicated that a mix of roller and button electrodes were used for haemostasis and suggested a 50:50 split. The button electrodes are more expensive than the roller electrodes [redacted].

One clinical expert stated that they considered a reduction in readmissions of 11% for PLASMA TURP to be very unlikely. However, no other value was suggested.

Originally readmission was costed at £2,781, using the non-elective short stay HRG, LB20D – "Infection or Mechanical Problems Related to Genito-Urinary Prostheses, Implants or Grafts, with Interventions, with CC Score 0-3" (NHS Improvement 2013, Total - HRGs). In 2018-19 the same HRG was costed at £689 (NHS Improvement 2019). In both data sets the number of long stays massively outnumber the short stays, and it is unclear why the short stay HRG was considered to be most appropriate for this outcome. Whereas the short stay cost has decreased markedly since 2013, the long stay cost has increased from £1,602 to £2,222.

The original and updated model inputs are given in Tables 7 and 8 below:

Table 7. Updated model inputs

Row / variable	Original value	Source	New value	Source
LOS	3.3 days	Mean of 2 RCTs (Akman, 2013; Michielsen 2011)	Same	
Reduction in LOS for PLASMA	0.19 days	EAC's meta-analysis of two studies	1.3 days	HES 2018-19 (M65.3)
Cost per inpatient day (general ward)	£305	NHS reference costs 2012-13, LB25F	£389	NHS reference costs 2017-18, NHS Improvement 2018 and 2019, LB25F
Cost per inpatient day (HDU)	£619	NHS reference costs 2012-13, XC07Z	£883	NHS reference costs 2018-19 XC07Z
Cost per unit RBC	[redacted]	NHSBT Price list 2014-15	[redacted]	NHSBT Price List 2019-20
Mean blood transfusion volume	2.7 units	Varney et al. 2003	2 units	Clinical expert
Cost of blood transfusion	£329.00	Calculation	£266.88	Calculation
Cost of readmission	£2781	NHS reference costs 2012-13 LB20D	£689	NHS reference costs 2018-19 LB20D

Table 8: Base case inputs – Original and updated

Variable	Original value	Source	Updated value	Source
PLASMA telescope cost	[redacted]	Manufacturer	[redacted]	Manufacturer
PLASMA light guide cable	[redacted]	Manufacturer	[redacted]	Manufacturer
PLASMA inner sheath	[redacted]	Manufacturer	[redacted]	Manufacturer
PLASMA outer sheath	[redacted]	Manufacturer	[redacted]	Manufacturer
PLASMA working element	[redacted]	Manufacturer	[redacted]	Manufacturer
PLASMA saline cable	[redacted]	Manufacturer	[redacted]	Manufacturer
Total capital cost for PLASMA – non-Olympus customer	[redacted]	3x telescope, 3x light guide cable, 3x inner sheath, 3x outer sheath, 3x working element, 3x saline cable.	[redacted]	3x telescope, 3x light guide cable, 3x inner sheath, 3x outer sheath, 3x working element, 3x saline cable.
Total capital cost for PLASMA – existing Olympus customer	[redacted]	3x working element, 3x saline cable.	[redacted]	3x working element, 3x saline cable.
Lifespan for PLASMA capital equipment	7 years	Range selected to capture variability in the care taken of equipment.	Unchanged	
Discount rate for costs	3.5%	MTEP methods guide; HM Treasury Green Book	Unchanged	

The £10 per procedure cost for non-Olympus monopolar generators was calculated from an estimate of £10,000 for the generator (average of several generator costs), divided over 150 patients per year for 7 years (actual value calculated was £9.52). Additionally, we could only identify a match for the generic return electrode in the current NHS Supply Chain. Values for loop and rollerball electrodes were very different to those quoted in the original assessment report and varied considerably. We have not used new NHS Supply Chain data for the monopolar consumables, but have used the NHS cost Inflation Index (NHSCII) inflation index (Curtis and Burns 2019) to calculate the increase in these consumable costs based solely on inflation. From 2014-15 to 2018-19 this is an overall increase of 6.06%. This means that total monopolar consumables for non-Olympus customers increases from [redacted] to [redacted] Updated values for the Olympus monopolar consumables were provided by the manufacturer

Table 9: Consumables costs – Original and updated values

Variable	Original value	Source	Updated value	Source
Loop electrode for mTURP: Olympus owners	[redacted]	Manufacturer	[redacted]	Manufacturer
Roller electrode for mTURP: Olympus owners	[redacted]	Manufacturer	[redacted]	Manufacturer
Return electrode for mTURP: Olympus owners	[redacted]	Manufacturer	[redacted]	Manufacturer
Total consumables for mTURP: Olympus owners	[redacted]	Calculation	[redacted]	Calculation
Loop electrode for mTURP: non-Olympus owners	[redacted]	NHS Supply Chain	Not used separately	
Roller/ball electrode for mTURP: non-Olympus owners	[redacted]	NHS Supply Chain	Not used separately	
Return electrode for mTURP: non-Olympus owners	[redacted]	NHS Supply Chain	Not used separately	NHS Supply Chain
Cost of non-Olympus generator per procedure (150 procedures/year for 7 years)	£10.00	*Unknown*	Not used separately	
Total consumables for mTURP: non-Olympus owners	[redacted]	Calculation	[redacted]	Uprated using NHSCII
PLASMA electrode small loop cost	[redacted]	Manufacturer (£1520/12)	[redacted]	Manufacturer (£1665/12)
PLASMA electrode medium loop cost	[redacted]	Manufacturer (£1520/12)	[redacted]	Manufacturer (£1665/12)
PLASMA electrode roller cost	[redacted]	Manufacturer (£1880/12)	[redacted]	Manufacturer
PLASMAButton cost	NA	NA	[redacted]	Manufacturer
Proportion of PLASMA procedures using additional roller electrode	22%	Manufacturer	65%	Manufacturer

8.5 *Results from updated changes*

For the base case model, PLASMA is cost-saving by £459 per procedure for hospitals owning Olympus generators and by £343 for hospitals owning non-Olympus generators (Table 10).

Table 10: Base case as per MTG23

Olympus owners	Original (-0.19 day)		Updated (-1.3 day)	
	TURP	PLASMA	TURP	PLASMA
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£1283.70	£778.00
Per proc	£1,196.60	£1,126.04	£1510.32	**£1,051.42**
Difference	**-£70.56**		**-£458.91**	
Non-Olympus owners	**Original (-0.19 day)**		**Updated (-1.3 day)**	
	TURP	PLASMA	TURP	PLASMA
Capital		[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£1283.70	£778.00
Per proc	£1,125.69	£1,145.49	£1415.86	**£1,073.02**
Difference	**£19.80**		**-£342.84**	

MTG23 included a scenario where an 11% reduction in all-cause readmissions rate was included for PLASMA, based on a single RCT (16% versus 5%, Fagerström et al. 2011). One clinical expert cast doubt on the size of this difference, however we do not have additional data to update this. The cost of readmission as originally modelled (HRG LB20D) has decreased significantly from £2,781 to £689 since the original cost modelling. However, due to the large difference in readmission rates this is still the most significant cost driver for adverse events (approximately £75 lower per procedure for PLASMA). The cost of an additional LOS for TUR syndrome is much larger (£2,544), but the incidence is very low (1.8% for monopolar TURP) so that overall impact on the model is slight (approximately £46 difference). The combination of reduced LOS and reduced readmission rate indicates that PLASMA is substantially cost saving with respect to monopolar TURP: between £418 and £534 per procedure (Table 11).

Table 11: Cost savings for PLASMA with reduction in LOS and all-cause readmissions

Olympus owners	Original		Updated	
	TURP	PLASMA	TURP	PLASMA
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£500.09	£149.96	£172.20	£40.91
LOS	£1,006.50	£948.55	£1,283.70	£778.00
Per proc	£1,644.34	£1,269.32	£1,621.25	£1,086.91
Difference	-£375.02		-£534.34	
Non-Olympus owners	Original		Updated	
	TURP	PLASMA	TURP	PLASMA
Capital		[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£500.09	£149.96	£172.20	£40.91
LOS	£1,006.50	£948.55	£1,283.70	£778.00
Per proc	£1,573.43	£1,288.77	£1,526.79	£1,108.38
Difference	-£284.66		-£418.41	

Several variations to the base case were modelled as independent scenarios to individually examine the effect of:

1. mTURP and PLASMA both have a LOS of 2 days (with 65% second electrodes)
2. mTURP has a LOS of 3.3 days, PLASMA has a LOS of 1 day (day case, with 65% second electrodes)
3. 0% of procedures use a second electrode (with 1.3 days difference in LOS)
4. 65% of procedures use a second electrode (with 1.3 days difference in LOS)
5. 22% of procedures use a second electrode (with 1.3 days difference in LOS)

One bed day is £389, and the changes in LOS have simple effects on the outcome. For 0% use of 2nd electrodes the PLASMA consumable costs reduce by [redacted], and for 22% they decrease by [redacted]. In all scenarios PLASMA remains cost saving with respect to mTURP, except for providers currently using non-Olympus equipment if there is no saving in LOS (Table 12). In this case the additional cost of consumables and of transferring to Olympus generators is not outweighed by the reductions in TUR syndrome and blood transfusion. This scenario would still be slightly cost-incurring (+£29) if the reduction in readmissions was included. LOS is the biggest driver of cost savings for the use of PLASMA.

Table 12: Scenario variations to the base case

Scenario	Olympus			Non-Olympus		
	mTURP	PLASMA	Difference	mTURP	PLASMA	Difference
1. 2 day LOS	£1,004.62	£1,051.42	-£46.79	£910.16	£1,073.02	+£162.86
2. PLASMA day case	£1,510.32	£662.42	-£847.91	£1,415.86	£684.02	-£731.84
3. 0% 2nd electrode	£1,510.32	£932.71	-£577.61	£1,415.86	£954.31	-£461.55
4. 65% 2nd electrode	£1,510.32	£1,051.42	-£458.91	£1,415.86	£1,073.02	-£342.84
5. 22% 2nd electrode	£1,510.32	£972.89	-£537.43	£1,415.86	£994.49	-£421.37

The reduction in LOS at which PLASMA becomes cost-saving compared to mTURP was explored using a simple threshold analysis. This was done for both 65% and 22% use of second electrodes. In most cases treatment using PLASMA is cost-saving if LOS is reduced by less than half a day (Table 13). Where providers are already using Olympus and only 22% of cases use 2nd electrodes, the difference in consumable costs between mTURP and PLASMA is small, and outweighed by the savings due to reduced complications. Therefore PLASMA remains cost-saving even if LOS is very slightly increased in comparison to mTURP.

Table 13: LOS reductions at which PLASMA becomes cost-saving

Scenario	Olympus	Non-Olympus
65% 2nd electrode use	-0.1 days	-0.4 days
22% 2nd electrode use	+0.1 days	-0.2 days

9 Conclusions

9.1 *Conclusions from the clinical evidence*

The evidence included had low to moderate risk of bias. The main concern was that one study (Komura et al, 2014 and 2015) did not state whether ITT analysis had been conducted. If not this could seriously impact the results. However, all outcomes, populations and interventions and comparators included were relevant to the scope. No evidence was included in relation to subgroups mentioned in the scope or with other bipolar TURP systems as the comparator.

The evidence suggests that PLASMA could be beneficial to patients in relation to hospitalisation and catheterisation time. However, it appears to be

comparable with mTURP for urological outcomes such as Q_{max} and PVR and worse for post-op haematology outcomes such as decline in sodium and haemoglobin levels. Adverse events however occurred much less within the PLASMA group apart from in one study where urethral strictures occurred more in the PLASMA group. This could result in higher costs associated with PLASMA such as readmissions, follow-up surgery and further post-care. However, one clinical expert stated that the incidence of urethral stricture following bTURP is in practice extremely rare.

There is a significant gap in the evidence as none of the included studies were conducted in an UK/NHS setting. This makes the results much less generalisable to this setting and so must be used with caution.

9.2 *Conclusions from the economic evidence*

There is significant uncertainty regarding the continued relevance of the comparison between PLASMA as a novel intervention and monopolar TURP as the standard of care comparator. Information from clinical experts and the manufacturer suggest that bipolar TURP is now widely adopted, and that non-adopters are likely to follow as existing equipment is replaced. An appropriate alternative comparator for the PLASMA system may be either different bipolar systems or alternative technologies used for treating BPH. Additionally, the emergence of bipolar TUVP and a potential 'hybrid' technique utilising elements of resection and vaporisation may confound the development of clear guidelines for one technique over another. Given the large number of technologies now in use in this area a revision of Clinical Guidelines (NICE 2015a) may be needed to encompass recent developments. There was consensus between clinical experts and the manufacturer that sole use of the PLASMA Button electrode for vaporisation of the prostate should not be treated as equivalent to PLASMA resection and should probably be considered for separate guidance development.

There is also increasing uncertainty regarding the continued appropriateness of incidence rates used in the original guidance (NICE 2015b). The significant reduction in average LOS reported in HES and Reference Cost datasets since the original guidance may be the result of increased use of bipolar TURP. Alternatively it could suggest more general changes in peri and post-surgical care that would affect the model structure. Patients are likely to have expectations of early mobilisation post-surgery, and may be part of programmes such as Enhanced Recovery After Surgery (ERAS, (NHS Digital 2019b). In addition, a Best Practice Tariff for day case indicates a drive towards further reductions in average LOS. Early discharge must not be pursued at the cost of increased readmissions, however NHS readmission data has not been fully published for 5 years (NHS Digital 2019a). Alternatively, more in depth methods using routinely collected data may be

able to determine more reliable up-to-date estimates for UK LOS and readmissions. Blood transfusions and TUR syndrome should also be updated, but these adverse events have a much smaller impact on the cost model.

There has probably been an increase in the use of second PLASMA electrodes (either roller or button) to achieve better haemostasis after a loop resection since the guidance was published. However, we have little explicit data for the size of this increase. The increase to 65% use of a second electrode increases the cost of the PLASMA consumables per procedure. However, in most cases this is outweighed by the saving in bed days.

10 Summary of the combined clinical and economic sections

The clinical evidence included, whilst of moderate to good quality, is lacking in number. The comparative studies produced mixed results with some suggesting PLASMA is beneficial, some showing it to be comparable to mTURP and some showing PLASMA to be worse. However, the economic models clearly suggest that PLASMA could be cost saving to the NHS, especially for current Olympus owners.

11 Implications for research

Both clinical and economic evidence conducted in the UK is vital to know whether this technology should be implemented within the NHS.

12 References.

Abdallah, M. M. and Badreldin, M. O. 2014. A short-term evaluation of the safety and the efficacy of bipolar transurethral resection of the prostate in patients with a large prostate (>90 g). Arab Journal of Urology 12(4), pp. 251-255.

Cleves A, Morgan H, Poole R, Carolan-Rees G. 2014. The TURis system for transurethral resection of the prostate: 3. Assessment Report. In: The TURis system for transurethral resection of the prostate: supporting information. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/mtg23/documents/supporting-documentation.

Curtis, L. & Burns, A. 2018, *Unit Costs of Health and Social Care 2018*, Personal Social Services Research Unit. Available from: https://kar.kent.ac.uk/70995/ (accessed 13/02/2020).

Fagerström, T., Nyman, C.R., & Hahn, R.G. 2011. Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate. *Journal of Endourology*, 25, (6) 1043-1049.

Gravas, S., Cornu, S., Gacci, M., Gratzke, C., Herrmann, T., Mamoulakis, C., Rieken, M., Speakman, M., & Tikkinen, K. 2019, *EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)*, European Association of Urology.

Karadeniz, M. S. et al. 2016. Bipolar versus monopolar resection of benign prostate hyperplasia: a comparison of plasma electrolytes, hemoglobin and TUR syndrome. SpringerPlus 5(1), p. 1739.

Komura, K. et al. 2015. Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. BJU international 115(4), pp. 644-652.

Komura, K. et al. 2014. Could transurethral resection of the prostate using the TURis system take over conventional monopolar transurethral resection of the prostate? A randomized controlled trial and midterm results. Urology 84(2), pp. 405-411.

Michielsen, D.P., Coomans, D., Van, L.C., & Braeckman, J.G. 2011. Comparison of the haemostatic properties of conventional monopolar and bipolar transurethral resection of the prostate in patients on oral anticoagulants. *Archives of Medical Science*, 7, (5) 858-863.

NHS Digital. (2019) Hospital Admitted Patient Care Activity, 2018-19: procedures and interventions. 19-09-2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

NHS Digital. Emergency readmissions published for first time in five years. 21-03-2019a. Available from: https://digital.nhs.uk/news-and-events/latest-news/emergency-readmissions-published-for-first-time-in-five-years (accessed 03/06/2019).

NHS Digital. Enhanced recovery. 2019b. Available from: https://www.nhs.uk/conditions/enhanced-recovery/#

NHS Improvement 2013, *National schedule of reference costs 2012/13*. Available from : https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013

NHS Improvement 2018a, *Annex A: The national prices and national tariff workbook (2018-19)*. Available from: https://improvement.nhs.uk/resources/developing-the-national-tariff/#past

NHS Improvement 2018b, *National schedule of reference costs 2017/18*. Available from: https://improvement.nhs.uk/resources/reference-costs/

NHS Improvement 2019a, *Annex A: The national prices and national tariff workbook (2019-20)*. Available from: https://improvement.nhs.uk/resources/national-tariff/

NHS Improvement 2019b, *National schedule of reference costs 2018/19*. Available from: https://improvement.nhs.uk/resources/national-cost-collection/

NICE 2015a, *Lower urinary tract symptoms in men: management. Clinical guideline (CG97)*. Available from: https://www.nice.org.uk/guidance/cg97

NICE 2015b, *The PLASMA system for transurethral resection of the prostate: Medical technologies guidance (MTG23)*. Available fom: https://www.nice.org.uk/guidance/mtg23

NICE 2016, *GreenLight XPS for treating benign prostatic hyperplasia: medical technologies guidance (MTG29)*. Available from: https://www.nice.org.uk/guidance/mtg29

Sinanoglu, O., Ekici, S., Balci, M.C., Hazar, A.I., & Nuhoglu, B. 2014. Comparison of plasmakinetic transurethral resection of the prostate with monopolar transurethral resection of the prostate in terms of urethral stricture rates in patients with comorbidities. *Prostate international*, 2, (3) 121-126

Treharne, C., Crowe, L., Booth, D., & Ihara, Z. 2018. Economic value of the transurethral resection in saline system for treatment of benign prostatic hyperplasia in England and Wales: systematic review, meta-analysis, and cost-consequence model. *European Urology Focus*, 4, (2) 270-279

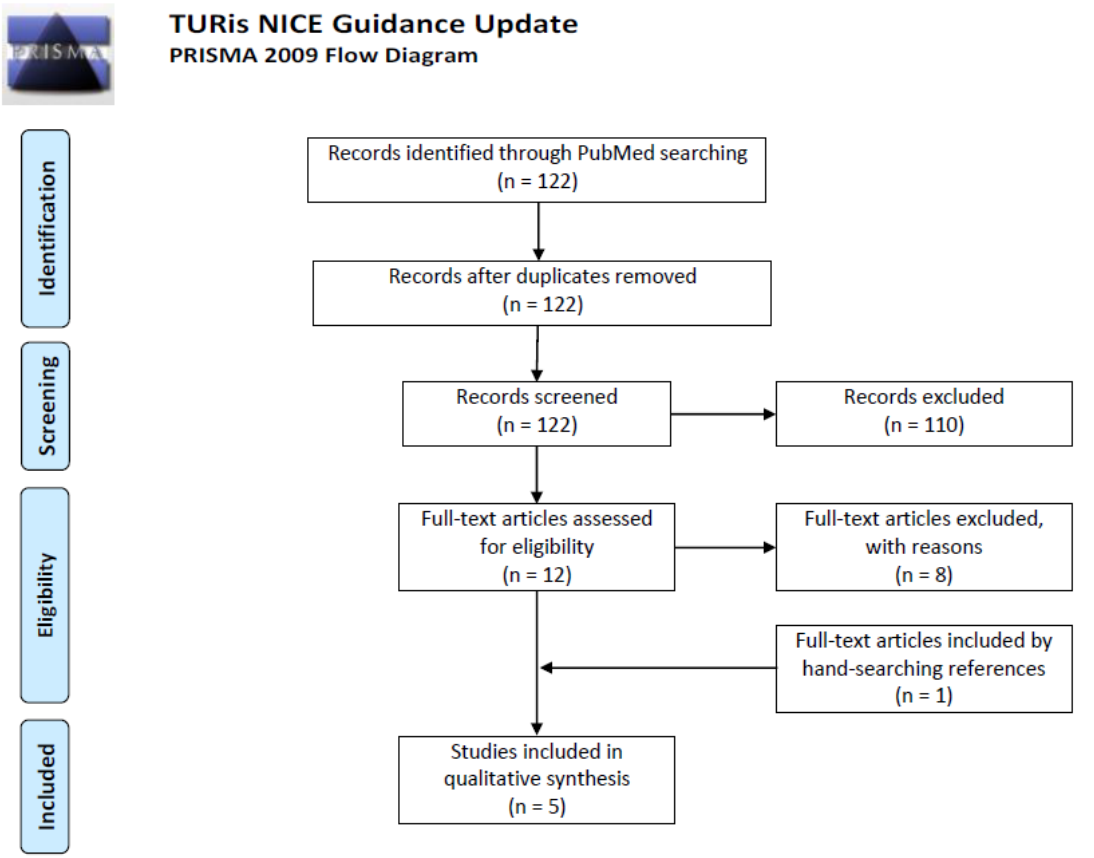
Wang, K., Li, Y., Teng, J.F., Zhou, H.Y., Xu, D.F., & Fan, Y. 2015. Transurethral plasmakinetic resection of the prostate is a reliable minimal invasive technique for benign prostate hyperplasia: a meta-analysis of randomized controlled trials. *Asian Journal of Andrology*, 17, (1) 135

13 Appendices

Appendix A – Search strategy and PRISMA Flow Diagram
Appendix B - Critical appraisals

Appendix A - Search Strategy and PRISMA Flow Diagram

Company evidence selection (2019 update search)



Reasons for full-text-exclusion:

Braeckman, J. and L. Denis (2017). "Management of BPH then 2000 and now 2016 - From BPH to BPO." Asian J Urol **4**(3): 138-147: **Review on the history of BPH, no up-to-date clinical data**

da Silva, R. D., et al. (2015). "Bipolar energy in the treatment of benign prostatic hyperplasia: a current systematic review of the literature." Can J Urol 22 Suppl 1: 30-44: **Review without meta-analysis, impossible to interpret without context**

He, L. Y., et al. (2016). "The effect of immediate surgical bipolar plasmakinetic transurethral resection of the prostate on prostatic hyperplasia with acute urinary retention." Asian J Androl **18**(1): 134-139: **Only within PK-TURP-comparison, no comparison to M-TURP**

Hu, Y., et al. (2016). "Five-Year Follow-Up Study of Transurethral Plasmakinetic Resection of the Prostate for Benign Prostatic Hyperplasia." J Endourol **30**(1): 97-101: **No Comparison to M-TURP**

Li, S., et al. (2015). "Plasmakinetic resection technology for the treatment of benign prostatic hyperplasia: evidence from a systematic review and meta-analysis." Sci Rep 5: 12002: **Review without meta-analysis, impossible to interpret without context**

Pham, R., et al. (2016). "How I do it: Same day discharge for transurethral resection of prostate using Olympus PlasmaButton and PlasmaLoop." Can J Urol **23**(5): 8491-8494: **No comparison to M-TURP**

Smith, C., et al. (2017). "Comparison of Traditional and Emerging Surgical Therapies for Lower Urinary Tract Symptoms in Men: A Review." Cardiovasc Intervent Radiol **40**(8): 1176-1184: **Review on the history of BPH-treatment techniques, no up-to-date clinical data**

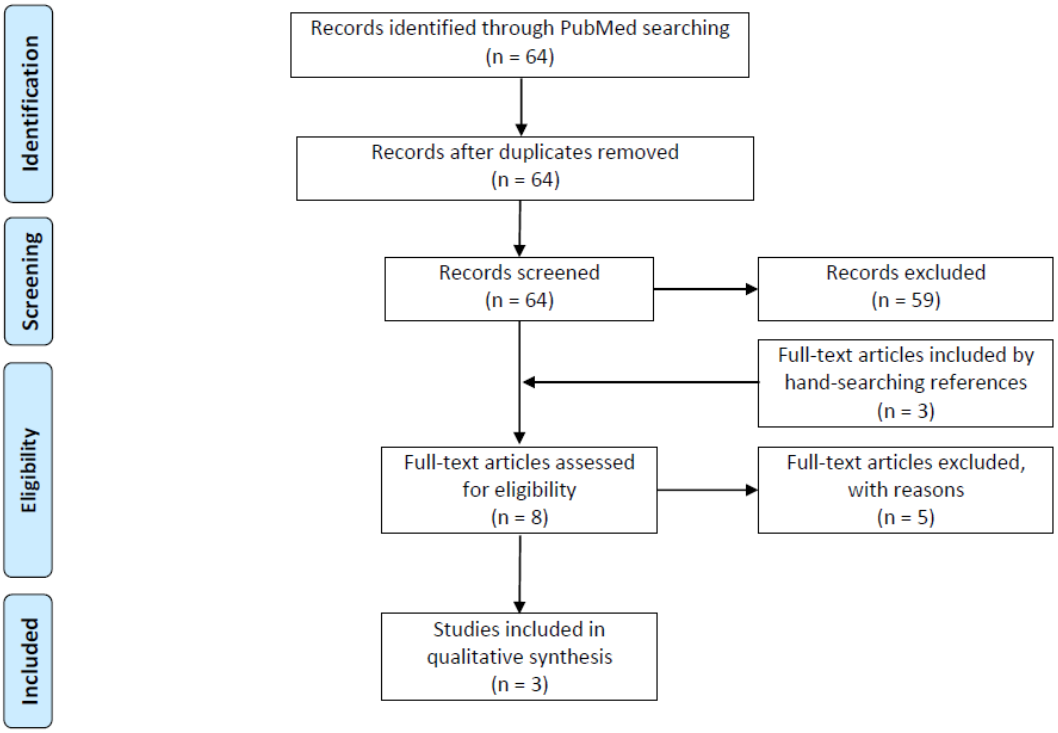
Ulchaker, J. C. and M. S. Martinson (2018). "Cost-effectiveness analysis of six therapies for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia." Clinicoecon Outcomes Res **10**: 29-43: **No differentiation between M-TURP and B-TURP**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Company evidence selection (2020 update search)

OLYMPUS

TURis NICE Guidance Update
PRISMA 2009 Flow Diagram



Reasons for full-text-exclusion:

Brown, A. D., et al. (2019). "Minimally Invasive Treatment for Benign Prostatic Hyperplasia: Economic Evaluation from a Standardized Hospital Case Costing System." Cardiovascular and interventional radiology **42**(4): 520-527. **Reason for exclusion:** No differentiation between mTURP and bTURP

Davis, N. F., et al. (2019). "Medical therapy versus transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic enlargement (BPE): a cost minimisation analysis." World journal of urology **37**(5): 873-878. **Reason for exclusion:** No explanation for choice of CMA – no clinical data for the therapies was provided, there are reasonable concerns that the outcomes are actually not equal and hence the assumption faulty.

DeWitt-Foy, M. E., et al. (2019). "Cost Comparison of Benign Prostatic Hyperplasia Treatment Options." Current urology reports **20**(8): 45-45. Reason for exclusion: No differentiation between monopolar and bipolar TURP

Miernik, A., et al. (2019). "Endoscopic enucleation of the prostate." Der Urologe. Ausg. A **58**(4): 437-450. **Reason for exclusion:** This is not a clinical trial, but a further education program

Rieken, M., et al. (2019). "Surgical treatment of benign prostatic hyperplasia-resection, vaporization or enucleation?" Der Urologe. Ausg. A 58(3): 263-270. **Reason for exclusion:** Review without data synthesis/meta analysis

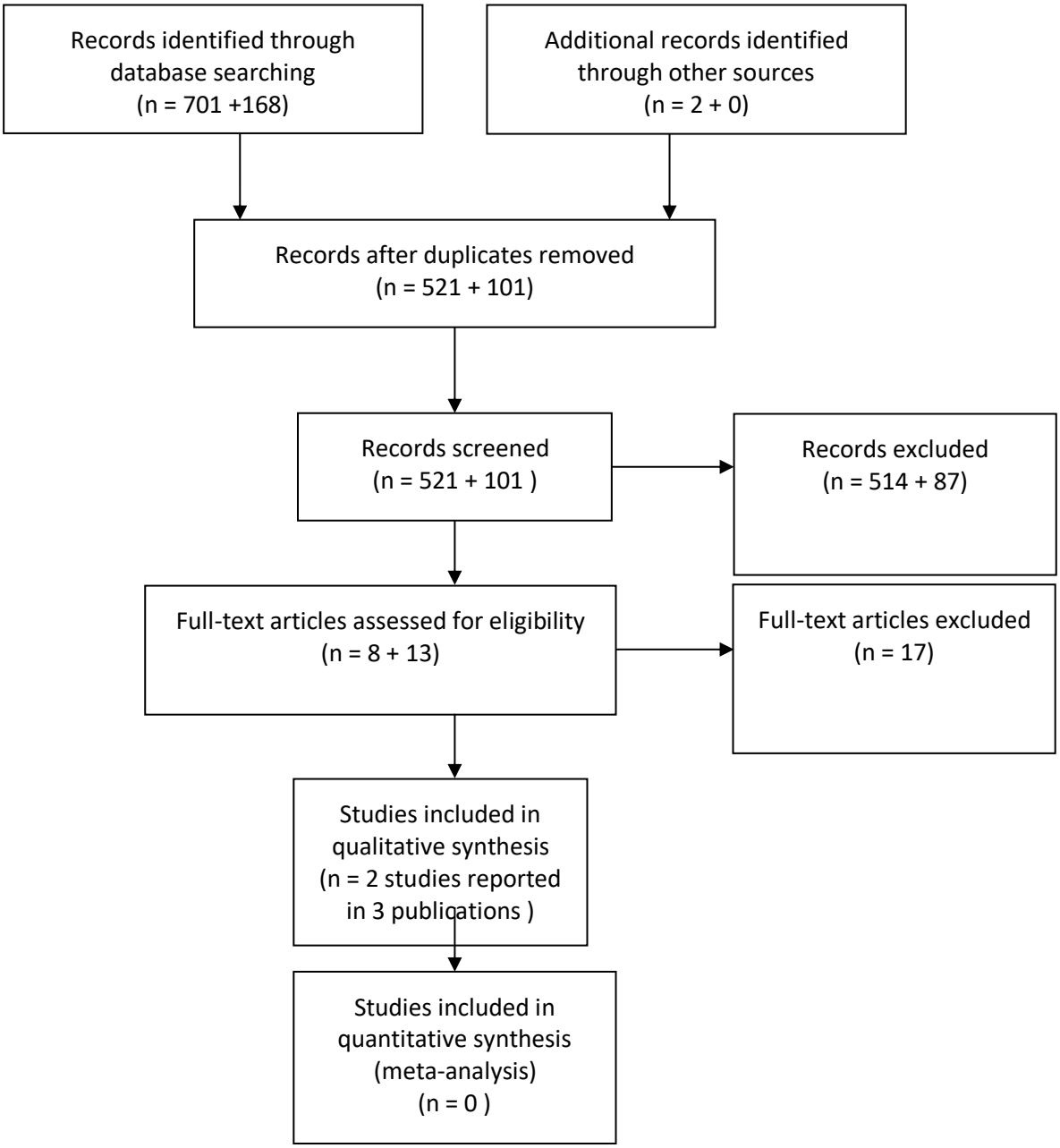
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Medline search strategy used in update searches by EAC and NICE

1 "Transurethral Resection of Prostate"/ and bipolar.tw.
2 ((Transurethral adj5 prostatectom*) and bipolar).tw.
3 (bipolar and prostat* and (transurethral adj5 resection)).tw.
4 (TURIS and prostat*).tw.
5 (PLASMA and TURIS).tw.

6 ((PLASMA or TURIS) and olympus).tw.
7 (PLASMA and bipolar and (transurethral or resection* or enucleat* or prostat* or BPH)).tw.
8 or/1-7
9 animals/ not humans/
10 8 not 9
11 limit 10 to yr="2014 -Current"

PRISMA Flow diagram*



*Values are split into search for the initial evidence update review plus the updated search for this ARU

Appendix B: Critical Appraisals

Quality assessment of included controlled trial assessed by the Cochrane Risk of Bias tool (Sterne et al. 2019)

Risk of Bias Domain	Komura et al (2014 and 2015)
Bias arising from the randomization process	Some concerns
Bias due to deviations from intended interventions	Some concerns
Bias due to missing outcome data	Low
Bias in measurement of the outcome	Low
Bias in selection of the reported result	Low
Overall risk of bias	**Some concerns**

Quality assessment of included non-randomised comparative study assessed by the Joanna Briggs Institute Checklist for Quasi-Experimental Studies

Karadeniz et al (2016)	Yes	No	Unclear	N/A
Is it clear in the study what is the 'cause' and what is the 'effect'(i.e. there is no confusion about which variable comes first)?	✓			
Were the participants included in any comparisons similar?	✓			
Were the participants included in any comparisons receivingsimilar treatment/care, other than the exposure or interventionof interest?	✓			
Was there a control group?	✓			
Were there multiple measurements of the outcome both preand post the intervention/exposure?	✓			
Was follow up complete and if not, were differences betweengroups in terms of their follow up adequately described andanalyzed?	✓			

Were the outcomes of participants included in any comparisonsmeasured in the same way?	✓			
Were outcomes measured in a reliable way?	✓			
Was appropriate statistical analysis used?	✓			
Comments	Other than non-randomised no significant issues identified, baseline characteristics were similar.			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report update overview

MT217 The PLASMA system for transurethral resection of the prostate

(update of MTG23 The TURis system for transurethral resection of the prostate)

This assessment report update overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) assessment report update (ARU). **It should be noted that this document was prepared using information in v3.0 of the ARU which has been updated in subsequent versions of the ARU.** The assessment report update overview includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence, the EAC assessment report and the EAC assessment report update. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its updated recommendations on the technology.

Key issues for consideration by the Committee are described in section 5, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and has been redacted before publication. This information is highlighted [redacted]. This overview also contains:

- Appendix A: Sources of evidence

Comments from professional bodies and patient organisations are collated in the accompanying review decision.

1 The technology

The PLASMA system (formerly called TURis, Olympus Medical) is a bipolar electrosurgery system for use when surgical intervention for lower urinary tract symptoms (LUTS), presumed secondary to benign prostatic hyperplasia, is indicated. The PLASMA system consists of the ESG-400 Olympus generator (including power cable and trolley); the resectoscope which incorporates the active working element, PRO 12º 4 mm telescope, PRO inner sheath, PRO 26FR outer sheath, and electrodes; a light guide cable; and ESG-400 SALINE cable. Only loop electrodes in the PLASMA system are indicated for resection.

The surgeon uses the active working element to position a loop electrode to conduct resection. The electrode is the only single-use element of the system. The electrode carries the current from the resectoscope, delivers it to the tissue and completes the circuit using conductive irrigation fluid (saline). Loop electrodes are used to cut tissue. Loop electrodes are available in different sizes and angles to accommodate different anatomies and morphologies; the choice is made by the surgeon and the electrodes are easily changed during the procedure. As with other electrosurgical devices, the PLASMA generator has two pedals controlling power settings for cutting and coagulation (including haemostasis). Roller electrodes are used after resection for haemostasis. Use of a hybrid technique with button electrodes for haemostasis has been reported.

The PLASMA system first received a CE mark in April 2012 as a class IIb device for electrosurgery and endoscopic applications.

1.1 Disease or condition

The PLASMA system is intended for use in the treatment of benign prostatic hyperplasia. The NICE guideline on lower urinary tract symptoms defines benign prostatic hyperplasia as histopathologically confirmed hyperplastic change (i.e. abnormality or changes at the cell level) in the prostate. About half of men with BPH will develop benign prostatic enlargement (BPE), which refers to an increase in size of prostate gland.

1.2 Patient group

The prevalence of BPH increases with age. BPH affects about 1 in 3 men over the age of 50. An analysis of the UK General Practice Research Database found that lower urinary tract symptoms suggestive of BPH are present in 3.5% of men in their 40s and in 35% in their 80s (Logie et al. 2001). LUTS secondary to BPH include poor flow, frequent micturition, urgency, and nocturia. Untreated, BPH can result in urinary tract infection (UTI), acute or chronic urinary retention, and obstructive renal failure. Although LUTS secondary to BPH do not usually cause severe illness, they have a negative impact on quality of life which potentially can include reduced sexual function.

1.3 Current management

Current treatment options for benign prostatic hyperplasia when conservative management options have been unsuccessful or are not appropriate in the NICE guideline on lower urinary tract symptoms include:

- monopolar or bipolar transurethral resection of the prostate (TURP).
- transurethral vaporisation of the prostate (TUVP).
- holmium laser enucleation of the prostate (HoLEP; at centres specialising in the technique or with mentorship arrangements in place).
- transurethral incision of the prostate (TUIP; only in prostates smaller than 30 g).
- open prostatectomy (only in prostates larger than 80 g).

Minimally invasive treatments such as transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), high-intensity focused ultrasound (HIFU), transurethral ethanol ablation of the prostate (TEAP) and laser coagulation are not recommended by NICE for people with lower urinary tract obstructive symptoms.

NICE CG97 Lower urinary tract symptoms in men: management (2010 updated in 2015) recommended monopolar or bipolar TURP but had the following caveat:

> "1.5.7 If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering laser vaporisation techniques, bipolar TUVP or monopolar or bipolar transurethral vaporisation resection of the prostate (TUVRP) as part of a randomised controlled trial that compares these techniques with TURP. [2010]"

NICE medical technologies guidance has been published on the following technologies:

- The TURis system for transurethral resection of the prostate (MTG23) is being updated with this guidance.
- The UroLift prostatic urethral lift system (MTG26) which is recommended as an alternative day-case treatment option for LUTS caused by BPH in men aged 50 years and older, who have a prostate of less than 100 ml without an obstructing middle lobe. It is a reversible procedure that can be done in a day-surgery unit. The Urolift guidance (MTG26) is scheduled for a standard review.
- The GreenLight XPS laser (MTG29) which is recommended for treating benign prostatic hyperplasia in non-high-risk patients, and can also be done as a day-case procedure.
- Rezum for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia (MTG49) is a steam (water vapour) ablation technology performed as a day case procedure.

2 Company claimed benefits and the decision problem

The benefits to patients claimed by the company compared to monopolar TURP are:

- Reduced risk of transurethral resection (TUR) syndrome through the use of saline irrigation fluid instead of glycine.
- Reduced risk of post-operative blood transfusion due to intraoperative bleeding.
- A shorter surgical procedure leading to fewer intra and post-operative complications and a lower level of hospitalisation.
- Earlier catheter removal time for improved patient comfort.

The benefits to the healthcare system claimed by the company are:

- A quicker procedure compared to monopolar TURP so more patients can be treated.
- Fewer complications during and after surgery resulting in lower re-admission rates.
- Reduced costs associated with post-operative blood transfusion, healthcare-associated infection, shorter length of stay, reduced post-operative irrigation and no patient return electrode required.
- The use of saline irrigation fluid is cheaper and easier to access than glycine.

The EAC did not have any comments regarding the decision problem and scope details.

3 The evidence

All published evidence includes the former name for the technology (TURis). New evidence not covered in MTG23 was considered by the EAC. A search was conducted by NICE information services as part of the guidance review process (and included in the published guidance review decision) on 11 April 2019 and yielded 521 records (details in ARU). After review, 2 studies (reported in 3 publications) were selected by the EAC. An update search was conducted on 9 June 2020 and no further studies were included. The search strategies are given in appendix A of the ARU. One study was subsequently excluded because it was conducted with the Gyrus system, not TURis. The company performed update searches of Pubmed in April 2019 and February 2020.

3.1 Summary of evidence of clinical benefit

The rationale for selecting studies by the EAC is given in table 2 of the ARU.

Table 1: Summary of studies

Study	Type of publication	Type of study	Comment
Studies included by both EAC and company			
Karadeniz et al (2016)	Full paper	Prospective Observational Study (non randomised comparative study).	Bipolar TURP n = 25, mean age 67.8 (8.6) years Monopolar TURP n = 25, mean age 68.5 (8.2) years
Komura et al (2014 and 2015)	Full papers	Randomised Controlled Trial	Bipolar TURP n=69 (n=62 analysed) mean age 69.8 (5.8) years Monopolar TURP n=67 (n=63 analysed), mean age 67.9 (5.4) years

Studies in company submission excluded by EAC			
Alexander (2019)	Full paper	Cochrane systematic review	Only primary studies included. Study was bipolar TURP but not identified as PLASMA
Al-Rawashdah et al (2017)	Full paper	Randomised controlled trial	The Gyrus PK super pulse generator (Olympus) was used for bipolar TURP. The Gyrus system was considered out of scope in the original EAC assessment for MTG23
Huang (2019)	Abstract	Systematic review and network analysis	Only primary studies included. Bipolar TURP but studies not identified as PLASMA

Kumar (2019)	Full paper		36 month outcomes of Kumar (2013) this was excluded by the EAC in the original AR as the intervention was Gyrus ACMI plasmakinetic system.
Mullhaupt (2019)	Full paper	Post hoc analysis of RCT	Not identified by the EAC as not bipolar TURP.
Sinanoglu (2014)	Full paper	Retrospective audit	Used Gyrus Plasmakinetic System
Treharne (2018)	Full paper	Systematic review	Systematic review of company's original submission and included additional RCT Komura (2015), the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted. Komura (2015) has been included by the EAC.
Wang (2015)	Full paper	Meta analysis	Meta-analysis of RCTs of plasmakinetic resection of prostate (PKRP), the EAC chose only to select primary studies for inclusion to avoid double counting and to ensure all relevant data was extracted, also there are insufficient details to determine if the included studies are all PLASMA.

Studies not in submission included by EAC			
None			

The manufacturer conducted a literature search in 2019 and listed 2 meta-analyses (MA) (Treharne et al 2018;Wang et al 2015), 2 RCTs (Al-Rawashdah et al 2017;Kumar et al 2019) and 1 observational study (Sinanoglu et al 2014) published since the MTG23 review. The EAC considered these citations did not change the evidence base. One MA is a journal report of the manufacturer's submission with one additional RCT (Treharne et al 2018). One RCT (Al-Rawashdah et al 2017) and the observational study (Sinanoglu et al. 2014) use the Gyrus PK system rather than the Olympus PLASMA. According to the original Briefing Note for MTG23 these should not be considered equivalent devices.

When preparing the guidance review decision, NICE conducted an updated literature review in 2019. This returned 101 results published since the search date for MTG23. The EAC scanned these for recent systematic reviews and meta analyses and for UK based studies, but no additional s were identified.

Table 2. Pivotal studies:

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Komura (2014 and 2015) Japan	Bipolar TURP n=69 (n=62 analysed) mean age 69.8 (5.8) years Monopolar TURP n=67 (n=63 analysed), mean age 67.9 (5.4) years	TURis bipolar TURP Monopolar TURP	Operation time Decline of sodium level Haemoglobin levels Clot retention Catheterization time Adverse events Efficacy (36 month follow up)	**See ARU table 3.** Hospitalisation time (mean days) was significantly higher in the mTURP group (3.4) compared to the TURis group (2.5), p=0.045. Operation time was significantly higher in the PLASMA group = 79.5 mins, mTURP = 68.4 mins , p=0.048) Perioperative decline of	11	Not reported	Sample size calculation based on operation time (120 patients to provide 90% power to detect effect six of 0.6 point) Randomisation performed according to Consolidated Standards of Reporting Trials guidelines. Appropriate randomisation techniques with no significant differences between groups at baseline. Outcome assessors were blinded to treatment allocation, therefore reducing the risk of bias in outcome reporting. However, due to the nature of the trial the surgeons and patients were not fully

				serum sodium levels was significantly higher in the mTURP group,3.6(4.3) compared to PLASMA, 0.5(0.9), p<0.001			blinded to the treatment allocation.
Karadeniz (2016) Turkey	Bipolar TURP n = 25, mean age 67.8 (8.6) years Monopolar TURP n = 25, mean age 68.5 (8.2) years	TURis bipolar TURP Monopolar TURP	Operation duration Perioperative Serum Sodium levels Perioperative Haemoglobin levels	Operation time was comparable between mTURP (72 +/- 30.9) and PLASMA (73 +/- 16). Perioperative Na+ values were significantly lower in the mTURP group compared with PLASMA at both 1st measurements (136.9 and 141.8 respectively)			Did not allocate participants randomly to each group. However, the baseline characteristics did not significantly differ between groups suggesting no risk of bias.

				and 2nd measurements (132.68 and 140.76 respectively), p<0.001. Perioperative Hb levels did not differ significantly between mTURP and PLASMA at 1st measurement (13.5 and 12.32 respectively) and 2nd measurement (13.6 and 12.33).			
Abbreviations used: TURP = transurethral resection of the prostate; mTURP = monopolar transurethral resection of the prostate; TURis = original name for the PLASMA system.							

The EAC considered that the evidence suggests PLASMA could be beneficial to patients with LUTS secondary to BPH within the NHS. Catheterisation and hospitalisation times could be reduced when using PLASMA compared to mTURP. However, urological outcomes such as Qmax and PVR and QoL measures did not differ between TURP groups immediately after surgery or during longer-term follow-up. Haematology outcomes such as decline in haemoglobin and sodium levels was either comparable between groups or worse in the PLASMA group immediately after surgery. Based on the evidence the benefit to patients would come primarily from the reduced length of hospital stay and catheterisation time.

The EAC considered that none of the included studies were conducted within a UK and/or NHS setting, therefore the results are not generalizable to an NHS setting based on this alone.

The EAC commented that whilst clinical experts contacted as part of this update process suggested that bipolar TURP is now the standard of care, there is no clinical evidence available at this time to support this. If this is the case however, then minimal training would be required for staff to implement and safely use the PLASMA system.

An expert has indicated to NICE that monopolar TURP is still used in the NHS, especially for larger prostates.

The incidence of TUR syndrome associated with monopolar TURP using glycine irrigation is eliminated using saline irrigation with the PLASMA system (e.g. Karadeniz et al 2016).

The incidence of urethral strictures was increased with bipolar TURP compared with monopolar TURP in two studies:

> Komura et al (2014 and 2015) reported that the urethral stricture rate at 36 month follow-up was 4/61 (6.6%) patients in the mTURP group and 12/63 (19%) in the PLASMA group (p=0.022).

An expert has indicated to NICE that there are several options to treat urethral strictures including urethroplasty.

3.2 Summary of economic evidence

No new economic evidence was identified during the updated literature search. For a detailed evaluation of the available economic evidence please refer to the original assessment report (Cleves et al, 2014).

De novo analysis

To produce MTG23, the manufacturer provided an executable Excel model of a simple decision tree. This compared bipolar transurethral resection of the prostate (TURP) using PLASMA against monopolar TURP in men with lower urinary tract symptoms (LUTS). The treatments were assumed to be of equal clinical efficacy (resection weight or radicality) and differences in costs were therefore related to the technology costs, incidence of adverse events, length of hospital stay and readmission rates. Please see the ARU for details of the EAC considerations of the current validity of the model.

For the update of MTG23 the EAC has contacted 3 clinical experts and the manufacturer. They were asked to comment on whether the assumptions and parameters used in the original model remain valid for the update or whether there have been any changes.

Two clinical experts indicated that most TURP procedures now use bipolar electrosurgery devices as standard of care. The manufacturer has indicated that 100 NHS centres are using PLASMA in 2019, compared to 61 in 2015 (England, Scotland and Wales). A third clinical expert indicated that bipolar should be the 'gold standard' for electrosurgical TURP, however other manufacturers had been slow to develop reliable bipolar devices, so hospitals with these manufacturers as standard would also be slow to change to bipolar.

Three clinical experts indicated that blood transfusion rates and/or volumes may be lower now. Two clinical experts indicated that the haemoglobin threshold for initiating transfusion had decreased from 80 g/L to 70 g/L or

were restricted to patients who were symptomatic due to blood loss. Two clinical experts indicated that transfusion rates were very low, probably lower than the 5.8% used for monopolar TURP in the original model. Another indicated that 2.7 units of red blood cells (RBC) used in the model seemed high, and suggested that 1-2 units was more likely.

One clinical expert indicated that there was recent evidence to suggest that bipolar TURP is associated with higher rates of strictures and/or contractures than monopolar.

There is an overall indication that PLASMA TURP is associated with better haemostasis than monopolar (based on lower blood transfusion rates and an increase in use of coagulating electrodes, see below). Therefore, a lower rate of admissions for haemorrhage would be expected for PLASMA TURP.

The PLASMA button electrodes produce tissue vaporisation via a plasma effect as an alternative to resection using a loop electrode. All three clinical experts and the manufacturer indicated that they consider this to be a separate procedure to PLASMA TURP. The evidence base is distinct and the clinical outcome values in the TURP model should not be transferred into a model of PLASMA TUVP virus monopolar TURP. Previously the model assumed that 22% of PLASMA resections also included the use of a roller electrode for haemostasis. All three clinical experts and the manufacturer indicated that the use of the button electrode for haemostasis after loop resection is now relatively common. Two clinical experts indicated that they use the PLASMA button electrode for haemostasis following resection with a loop electrode. The suggestion is that this produces better haemostasis, therefore a lower risk of transfusion and higher chance of treatment as a day case. One clinical expert stated that they suspected that many of these cases also included some vaporisation of prostate tissue, and should therefore be considered a hybrid procedure.

Model parameters

Costs and resource use

Please refer to the ARU for details on updated costs and resource use.

Results from updated changes.

The initial base case, without length of stay (LOS) difference, is replicated here to demonstrate the effect of the increased use of 2 electrodes for PLASMA procedures. Where the LOS was considered to be equal for the two treatment arms, PLASMA originally saved £12.61 per procedure for Olympus owners and cost £77.75 for non-Olympus owners. The larger proportion of procedures using 2 electrodes has substantially increased the cost of consumables for PLASMA from £161 to £257 (Table 9). This means that if PLASMA does not lead to a reduction in LOS and/or readmissions it is cost-incurring both for hospitals that use Olympus generators (£47) and those using non-Olympus generators (£163).

Table 3: Updated base case without Length of Stay (LOS) difference

Olympus owners	**Original**		**Updated**	
	TURP	**PLASMA**	**TURP**	**PLASMA**
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£1,006.50	£778.00	£778.00
Per procedure	£1,196.60	£1,183.99	£1004.62	£1051.42
Difference	**-£12.61**		**£46.79**	
Non-Olympus owners	**Original**		**Updated**	
	TURP	**PLASMA**	**TURP**	**PLASMA**
Capital	-	[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£1,006.50	£778.00	£778.00
Per procedure	£1,125.69	£1,203.44	£910.16	£1,073.02
Difference	**£77.75**		**£162.86**	

The base case as presented in MTG23 included a 0.19-day reduction in LOS for PLASMA procedures. The average LOS for endoscopic TUR procedures

has reduced from 3.3 to 2 days. Although this data does not capture device use, this reduction may be due to an increase in the use of several recent technologies for treating benign prostatic hyperplasia that may tend to reduce LOS (NICE 2016). There may also be other simultaneous changes in per-procedure practice that have contributed to this.

The EAC considers it is likely that bipolar TURP is appropriate for use as a day case procedure and therefore the EAC have modelled a reduction of 1 day in the LOS for PLASMA. A reduction in the cost of 1 bed day does not capture the full saving between a 2 day stay and a day case, however, not all patients receiving PLASMA will be suitable for day case treatments. Without more detailed data, this provides a first approximation of the cost difference if a reduction in LOS is achieved with PLASMA. This table shows that the saving in bed day costs outweighs the increase in consumable costs, so that PLASMA is cost saving by £342 per procedure for hospitals owning Olympus generators and by £226 for hospitals owning non-Olympus generators.

An expert has advised NICE that patients treated with PLASMA as a day case will need to be discharged with a catheter in place.

Table 4: Base case as per MTG23, including LOS difference

Olympus owners	Original (-0.19 day)		Updated (-1 day)	
	TURP	PLASMA	TURP	PLASMA
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£778.00	£389.00
Per proc	£1,196.60	£1,126.04	£1004.62	£664.42
Difference	**-£70.56**		**-£342.21**	
Non-Olympus owners	**Original (-0.19 day)**		**Updated (-1 day)**	
	TURP	PLASMA	TURP	PLASMA
Capital		[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£778.00	£389.00
Per proc	£1,125.69	£1,145.49	£910.16	£683.89
Difference	**£19.80**		**-£226.27**	

MTG23 included a scenario where an 11% reduction in all-cause readmissions rate was included for PLASMA, based on a single RCT (Fagerström et al. 2011). One clinical expert cast doubt on the size of this difference, however we do not have additional data to update this [redacted] However, due to the large difference in readmission rate (16% versus 5%) this is still the most significant cost driver for adverse events (approximately £75 lower per procedure for PLASMA). The cost of an additional [redacted] but the incidence is very low (1.8% for monopolar TURP) so that overall impact on the model is slight (approximately £46 difference). The combination of reduced LOS and reduced readmission rate indicates that PLASMA is substantially cost saving with respect to monopolar TURP: between £302 and £418 per procedure (Table 11). However, this result should be treated with caution due to the significant uncertainty regarding any difference in readmission rates.

Table 5: Cost savings for PLASMA with reduction in LOS and all-cause readmissions

Olympus owners	Original (-0.19 day)		Updated (-1 day)	
	TURP	PLASMA	TURP	PLASMA
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£500.09	£149.96	£172.20	£40.91
LOS	£1,006.50	£948.55	£778.00	£389.00
Per proc	£1,644.34	£1,269.32	£1,115.55	£697.91
Difference	**-£375.02**		**-£417.64**	
Non-Olympus owners	**Original (-0.19 day)**		**Updated (-1 day)**	
	TURP	**PLASMA**	**TURP**	**PLASMA**
Capital		[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£500.09	£149.96	£172.20	£40.91
LOS	£1,006.50	£948.55	£778.00	£389.00
Per proc	£1,573.43	£1,288.77	£1,021.09	£719.38
Difference	**-£284.66**		**-£301.71**	

The company noted during a fact check of the ARU that the assumption of reduced length of stay had been applied equally to PLASMA and monopolar TURP. The EAC provided an additional scenario where the reduced length of stay was only calculated for PLASMA (table 6). Given the updated inputs to the model to reflect a LOS of 3.3 days for monopolar TURP compared to 2 days for PLASMA, PLASMA appears to be cost saving by £459 for Olympus owners and £343 for non-Olympic owners.

Table 6: Cost savings for PLASMA with 2 days length of stay and monopolar TURP with 3.3 days length of stay

Olympus owners	Original (-0.19 day)		Updated (-1.3 day)	
	TURP	PLASMA	TURP	PLASMA
Capital	-	[redacted]	-	[redacted]
Consumables	£137.75	[redacted]	£165.35	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£1283.70	£778.00
Per proc	£1,196.60	£1,126.04	£1510.32	£1051.42
Difference	-£70.56		-£458.90	
Non-Olympus owners	Original (-0.19 day)		Updated (-1.3 day)	
	TURP	PLASMA	TURP	PLASMA
Capital		[redacted]		[redacted]
Consumables	£66.84	[redacted]	£70.89	[redacted]
Complications	£52.35	£6.68	£61.27	£5.42
LOS	£1,006.50	£948.55	£1283.70	£778.00
Per proc	£1,125.69	£1,145.49	£1415.86	£1073.02
Difference	£19.80		-£342.84	

4 Ongoing research

The company and the External Assessment Centre are not aware of any ongoing research on PLASMA.

5 Issues for consideration by the Committee

The title of the guidance should be changed to indicate the new name for the technology. The title may also need to indicate that the guidance is only for resection and not vaporisation of the prostate.

Clinical evidence

It was noted by an EAC expert that there were reports of increased numbers of incidents of urethral strictures with bipolar techniques. Is there evidence for

an increased incidence of urethral strictures, and is this of clinical relevance considering the therapy required for treatment of urethral stricture?

Cost evidence

The EAC has presented an update to the original cost model and new cost scenarios reflecting differences in length of stay and all cause readmissions. The committee should consider which scenario is most appropriate.

6 Authors

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NICE Medical Technologies Evaluation Programme, July 2020

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report update:

- Knight L, Peirce S, Morgan H. MT217 PLASMA assessment report update July 2020.

B Submissions from the following sponsors:

- Olympus 17/4/19 and 25/2/20.

C Related NICE guidance

Lower urinary tract symptoms in men: management. NICE clinical guideline 97 (2010, updated 2015). Available from www.nice.org.uk/guidance/CG97

D References

Abdallah, M. M. and M. O. Badreldin (2014) A short-term evaluation of the safety and the efficacy of bipolar transurethral resection of the prostate in patients with a large prostate (>90 g). Arab Journal of Urology 12(4): 251-255.

Al-Rawashdah, S. F., et al. (2017) Prospective randomized study comparing monopolar with bipolar transurethral resection of prostate in benign prostatic obstruction: 36-month outcomes. World Journal of Urology 35(10): 1595-1601.

Alexander, C., et al. (2019) Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction (Review) Cochrane Database Syst Rev, 12, CD009629.

Huang, S-W, et al. (2019) Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis. BMJ (Clinical research ed.) 367: l5919-l5919.

Karadeniz, M. S., et al. (2016) Bipolar versus monopolar resection of benign

prostate hyperplasia: a comparison of plasma electrolytes, hemoglobin and TUR syndrome. SpringerPlus 5(1): 1739.

Komura, K., et al. (2014) Could transurethral resection of the prostate using the TURis system take over conventional monopolar transurethral resection of the prostate? A randomized controlled trial and midterm results. Urology 84(2): 405-411.

Komura, K., et al. (2015) Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. BJU International 115(4): 644-652.

Kumar, B., et al. (2019) Urethral stricture after bipolar transurethral resection of prostate-truth vs hype: a randomized controlled trial. Indian Journal of Urology 35(1): 41-47.

Müllhaupt, G., et al. (2019) In-hospital cost analysis of prostatic artery embolization compared with transurethral resection of the prostate: post hoc analysis of a randomized controlled trial. BJU international 123(6): 1055-1060.

Sinanoglu O, et al. (2014) Comparison of plasmakinetic transurethral resection of the prostate with monopolar transurethral resection of the prostate in terms of urethral stricture rates in patients with comorbidities. Prostate Int. 2(3):121-6.

Treharne C., et al (2018) Economic Value of the Transurethral Resection in Saline System for Treatment of Benign Prostatic Hyperplasia in England and Wales: Systematic Review, Meta-analysis, and Cost-Consequence Model. Meta-Analysis. Eur. Urol, Focus 4(2):270-279.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

The PLASMA system for transurethral resection of the prostate

1 Technology

1.1 Description of the technology

The PLASMA system (formerly called TURis, Olympus Medical) is a bipolar electrosurgery system for use when surgical intervention for lower urinary tract symptoms (LUTS), presumed secondary to benign prostatic hyperplasia, is indicated. The PLASMA system consists of the ESG-400 Olympus generator (including power cable and trolley); the resectoscope which incorporates the active working element, PRO 12º 4 mm telescope, PRO inner sheath, PRO 26FR outer sheath, and electrodes; a light guide cable; and ESG-400 saline cable. Only the loop electrode in the PLASMA system is indicated for resection.

The surgeon uses the active working element to position the loop electrode in order to conduct resection. The electrode is the only single-use element of the system. The electrode carries the current from the resectoscope, delivers it to the tissue and completes the circuit using conductive irrigation fluid (saline). The loop electrode is used to cut tissue. Roller electrodes are used after resection for haemostasis. Loop electrodes are available in different sizes and angles to accommodate different anatomies and morphologies; the choice is made by the surgeon.

1.2 Relevant diseases and conditions

The PLASMA system is intended for use in the treatment of benign prostatic hyperplasia.

The NICE guideline on lower urinary tract symptoms defines benign prostatic hyperplasia as histopathologically confirmed hyperplastic change (i.e. abnormality or changes at the cell level) in the prostate. About half of men with BPH will develop benign prostatic enlargement (BPE), which refers to an increase in size of prostate gland.

The prevalence of BPH increases with age. BPH affects about 1 in 3 men over the age of 50. An analysis of the UK General Practice Research Database found that lower urinary tract symptoms suggestive of BPH are present in 3.5% of men in their 40s and in 35% in their 80s (Logie et al. 2001). LUTS secondary to BPH include poor flow, frequent micturition, urgency, and nocturia. Untreated, BPH can result in urinary tract infection (UTI), acute or chronic urinary retention, and obstructive renal failure. Although LUTS secondary to BPH do not usually cause severe illness, they have a negative impact on quality of life which potentially can include reduced sexual function.

1.3 Current management

Current treatment options for benign prostatic hyperplasia when conservative management options have been unsuccessful or are not appropriate in the NICE guideline on lower urinary tract symptoms include:

• monopolar or bipolar transurethral resection of the prostate (TURP)

• transurethral vapourisation of the prostate (TUVP)

• holmium laser enucleation of the prostate (HoLEP; at centres specialising in the technique or with mentorship arrangements in place)

• transurethral incision of the prostate (TUIP; only in prostates smaller than 30 g)

• open prostatectomy (only in prostates larger than 80 g).

Minimally invasive treatments such as transurethral needle ablation (TUNA), transurethral microwave thermotherapy (TUMT), high-intensity focused ultrasound (HIFU), transurethral ethanol ablation of the prostate (TEAP) and

laser coagulation are not recommended by NICE for people with lower urinary tract obstructive symptoms.

NICE medical technologies guidance has been published on the following technologies:

- The TURis system for transurethral resection of the prostate (MTG 23) is being updated with this guidance.

- The UroLift prostatic urethral lift system (MTG 26) which is recommended as an alternative day-case treatment option for LUTS caused by BPH in men aged 50 years and older, who have a prostate of less than 100 ml without an obstructing middle lobe. This can be done in a day-surgery unit.

- The GreenLight XPS (MTG 29) which is recommended for treating benign prostatic hyperplasia in non-high-risk patients, and can also be done as a day-case procedure.

NICE has published interventional procedures guidance on transurethral water vapour ablation (IPG 625) and water jet ablation (IPG 629) for lower urinary tract symptoms caused by benign prostatic hyperplasia. The IPG 625 recommends that transurethral water vapour ablation can be used with standard arrangements for clinical governance, consent and audit.

1.4 Regulatory status

The PLASMA system first received a CE mark in April 2012 as a class IIb device for electrosurgery and endoscopic applications.

1.5 Claimed benefits

The benefits to patients claimed by the company compared to monopolar TURP are:

- Reduced risk of transurethral resection (TUR) syndrome through the use of saline irrigation fluid instead of glycine.
- Reduced risk of post-operative blood transfusion due to intraoperative bleeding.

- A shorter surgical procedure leading to fewer intra and post-operative complications and a lower level of hospitalisation.
- Earlier catheter removal time for improved patient comfort.

The benefits to the healthcare system claimed by the company are:

- A quicker procedure compared to monopolar TURP so more patients can be treated.
- Fewer complications during and after surgery resulting in lower re-admission rates.
- Reduced costs associated with post-operative blood transfusion, healthcare-associated infection, shorter length of stay, reduced post-operative irrigation and no patient return electrode required.
- The use of saline irrigation fluid is cheaper and easier to access than glycine.

2 Decision problem

Population	Adults with lower urinary tract symptoms (LUTS) presumed secondary to benign prostatic hyperplasia (BPH), in whom TURP is indicated
Intervention	TURP using the PLASMA system (formerly known as TURis)
Comparator(s)	• TURP using a monopolar system • TURP using other bipolar systems
Outcomes	The outcome measures to consider include: • Hospital length of stay • Procedural blood loss and blood transfusion requirement • Time of removal of urinary catheter post-operatively • TUR syndrome • Re-admittance for repeat procedures • Duration of surgical procedure • Healthcare associated infection • Relief of symptoms associated with BPH (IPSS) • Maximum flow rates (Qmax) • Residual urine volumes • Benign prostatic hyperplasia impact index (BPHII) • Reduction in prostate volume

	• Quality of life measures, e.g. International Prostate Symptom Score Quality of Life (IPSS-QOL) • Device-related adverse events • Procedural complication rate during and after surgery	
Cost analysis	Cost models should consider 2 scenarios for the adoption of the PLASMA system: - Hospitals which currently have an Olympus ESG-400 generator - Hospitals which currently do not have an Olympus ESG-400 generator. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include the length of stay, use in a day case scenario, and the incidence of adverse events, such as TUR syndrome and urethral stricture.	
Subgroups to be considered	• Individuals with prosthetic lower limbs • Individuals with a cardiac pacemaker	
Special considerations, including those related to equality	It has been suggested that men aged 80 years and over, especially those with frail health and comorbidity, have been found to have an increased risk of morbidity following TURP, though effectiveness of the intervention is not affected.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	See cost analysis. PLASMA requires the use of an Olympus ESG-400 generator. Some hospitals who currently perform monopolar TURP and use other bipolar TURP systems produced by Olympus may already own an ESG-400 generator and avoid this cost. Resection is performed using loop electrodes. Haemostasis is performed using roller electrodes. Use of a hybrid technique with PLASMA button electrodes for haemostasis has been reported.	

3 Related NICE guidance

Published

- NICE clinical guideline 97 (2010) Lower urinary tract symptoms in men: management
- NICE interventional procedure guidance 629 (2018) Transurethral water jet ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia
- NICE interventional procedure guidance 625 (2018) Transurethral water vapour ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia
- NICE medical technology guidance 29 (2016) GreenLight XPS for treating benign prostatic hyperplasia
- NICE medical technology guidance 26 (2015) Urolift for treating lower urinary symptoms of benign prostatic hyperplasia
- NICE medical technology guidance 23 (2015) The TURis system for transurethral resection of the prostate

In development

NICE is developing the following guidance:

- Rezum for treating benign prostatic hyperplasia. NICE medical technology guidance. Publication expected April 2020.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association for Perioperative Practice
- British Association of Day Surgery
- British Association of Urological Surgeons
- British Urological Group (BUG)
- British Uro-oncology Group

- PSA Prostate Cancer Support Association
- Royal College of Anaesthetists
- Royal College of Surgeons of England
- The Association for Perioperative Practice
- The College of Operating Department Practitioners

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Bladder and Bowel UK
- Bladder Health UK
- Everyman
- Men's Health Forum (MHF)
- Orchid - Fighting Male Cancer
- Prostate Cancer UK
- Prostate Help Association (PHA)
- Tackle Prostate Cancer
- Urology User Group Coalition

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of MTG23: The TURis system for transurethral resection of the prostate

This guidance was issued in February 2015.

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However, the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders. NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance.

1. Review decision

Schedule a standard update of the guidance into the MTEP work programme, bringing the topic back to the committee to review the new evidence, the potential for bipolar TURP to be the standard of care, and the implications for costs based on reduced length of stay.

2. Original objective of guidance

To assess the case for adoption of TURis system for transurethral resection of the prostate.

3. Current guidance

1.1 The case for adopting the transurethral resection in saline (TURis) system for resection of the prostate is supported by the evidence. Using bipolar diathermy with TURis instead of a monopolar system avoids the risk of transurethral resection syndrome and reduces the need for blood transfusion. It may also reduce the length of hospital stay and hospital readmissions.

1.2 Using the transurethral resection in saline (TURis) system instead of monopolar transurethral resection of the prostate (TURP) results in an

estimated saving of £71 per patient for hospitals that already use an Olympus monopolar system and an estimated additional cost of £20 per patient for other hospitals. However, there is some evidence of a reduction in readmissions with the TURis system compared with monopolar TURP. If this evidence is included, using the TURis system results in an estimated saving of £375 per patient for hospitals that already use an Olympus monopolar system and an estimated saving of £285 per patient for other hospitals.

4. Rationale

The TURis system has been renamed to PLASMA. There is new literature, including reports on the clinical efficacy and long-term outcomes of using the technology. Although overall, the clinical pathway is unchanged, it has been suggested by experts that bipolar TURP is now the standard of care. The costs of the technology, length of stay, and costs of the care pathway have changed.

5. New evidence

The search strategy from the original assessment report was re-run with additional fields to include the new name PLASMA. References from March 2014 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below.

5.1 Technology availability and changes

The technology is still available but has been renamed from TURis to PLASMA. The CE mark is unchanged. The cost of the technology has increased.

5.2 Clinical practice

The NICE pathway is Lower urinary tract symptoms in men

The clinical pathway is unchanged in terms of diagnosis and therapeutic options. Since the publication of MTG23 TURis, MTEP have produced MTG26 Urolift and MTG29 Greenlight that are alternative therapies for the same population and considered by the same pathway. NICE QS45 Lower urinary tract symptoms in men gives criteria for assessing the efficacy of clinical procedures that may be applied to any surgical intervention.

NICE CG97 Lower urinary tract symptoms in men: management (2010) recommended monopolar or bipolar TURP but had the following caveat:

> *"1.5.7 If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering laser vaporisation techniques, bipolar TUVP or monopolar or bipolar transurethral vaporisation resection of the prostate (TUVRP) as part of a randomised controlled trial that compares these techniques with TURP. [2010]"*

CG97 Lower urinary tract symptoms in men: management covers the surgical options but does not make specific recommendations on named technologies. The EAC costing report (2019) suggests that an update of CG97 should be considered.

3 clinical experts, who have had direct use of the technology, responded to NICE. 1 expert stated, "since the original guideline, there has been widespread uptake of bipolar TURP." The EAC suggests that bipolar therapy has become the standard of care in the NHS.

It was noted by an EAC expert that there were reports of increased numbers of incidents of urethral strictures with bipolar techniques. Papers studying the incidence of urethral strictures were included in the literature review.

5.3 NICE facilitated research

There were no research recommendations in the guidance.

5.4 New studies

The updated literature search identified 6 studies that were reviewed by the EAC.

Abdallah et al (2014) evaluated the efficacy and safety of bipolar transurethral resection of the prostate (TURP) using the TURis system in 40 patients with a large prostate (>90g) who were considered at risk for monopolar TURP. Grade I complications in the first month after TURP included haematuria with or without blood clot retention in 3 patients and urinary tract infection in 3 patients. Grade II complications included 1 patient who developed hypertension and signs of volume overload. Two patients required a blood transfusion after TURP. Follow-up indicated that at 9 months and 11 months respectively, 2 patients reported lower urinary tract obstructive symptoms with recurrent attacks of UTI, investigations showed a bulbar urethral stricture which was managed endoscopically in both patients. The study was conducted in Egypt.

Komura et al (2014) conducted a randomised trial in 136 patients to assess whether bipolar TURP (n=69) using the TURis system demonstrated comparable efficacy and safety with monopolar TURP (n=67). Mean operative times were longer in the TURis group compared with the monopolar group (p=0.048) and resected prostatic tissue and resection radicality were similar between the groups. No patient was diagnosed with TUR syndrome. By 3 months after treatment no patient complained of persistent incontinence. All follow-up variables were significantly improved at 3 months post treatment and improvements were maintained through 36 months follow-up for both groups. The study was conducted in Japan.

Komura et al (2015) is a study reporting the safety outcomes in 136 patients randomised to undergo monopolar TURP or bipolar TURP using the TURis system (Komura et al 2014). No significant difference was reported in reduction of haemoglobin and haematocrit levels or in peri-operative transfusion rates. Clot retention occurred significantly more often in the monopolar TURP group (p=0.044). Two monopolar TURP patients required transurethral coagulation 2 days after treatment as opposed to none from the TURis group. Two patients in each group reported acute urinary retention following removal of indwelling catheter. At 36 months follow up, a significantly higher rate of urethral stricture in the TURis group was reported (p=0.022). Caution should be used when reviewing and interpreting the results from the two Komura publications as they are both reporting on the same population. There are some differences in outcomes reported with longer follow-up data in Komura et al 2015. The study was conducted in Japan.

Karadeniz et al (2016) is a prospective, non-randomised study comparing bipolar TURP using the TURis system and monopolar TURP in 52 patients scheduled for elective TURP. Volume of irrigation fluid used in bipolar TURP was 27,080±16,240ml compared with 25,360±13,443ml in monopolar TURP. Resected prostatic tissue weight was 47.5±13.8g in the bipolar group compared with 49.2±29.8g in the monopolar group (p>0.05). Operation duration did not differ significantly between the groups (p>0.05). The study was conducted in Turkey.

Al-Rawashdah et al (2017) is a randomised trial in 497 patients comparing operative and functional outcomes in patients undergoing monopolar (n=246) or bipolar (n=251) TURP with a mean follow up of 63.2 months (36-98.4). The Gyrus PK super pulse generator (Olympus) was used for bipolar TURP. The Gyrus system was considered out of scope in the original EAC assessment for MTG23 but was included by the EAC in this review. Mean operative time in the bipolar arm was 68.3 mins versus 76.72 mins in the monopolar arm (not statistically significant, p=0.093). Mean length of hospitalisation was 3.27 days in the bipolar arm and 3.57 days in the monopolar arm (p=0.049).

Haemoglobin level drop in the bipolar arm was 1.63g/dl (1.44-1.82) compared with 2.34g/dl (2.12-2.55) in the monopolar TURP arm (p <0.0001). Mean fall in postoperative serum sodium concentration was 2.21 mEq/l in the bipolar group versus 6.12 mEq/l in the monopolar group (p<0.001). The 3-, 12-, 24- and 36-month follow up showed significant and equal improvements in LUTS related to benign prostate obstruction in the two treatment groups. The incidence of TUR syndrome was 2.78% in the monopolar group compared with 0% in the bipolar group (p=0.001), blood transfusion rate was 1.99% in the monopolar versus 0% in the bipolar group (p=0.013) and the rate of urethral strictures was 2.78% in the monopolar group versus 0.4% in the bipolar group (p=0.002). The study was conducted in Italy.

Kumar et al (2019) is a randomised controlled, single blind study in 80 patients comparing monopolar (n=40) and bipolar (n=40) TURP. Mean operative time, post-operative catheterisation and duration of hospital stay did not differ significantly between the groups. No patient in the monopolar arm developed stricture urethra at 12 months versus 3 case in the bipolar group (p=0.2). No patient in either group required blood transfusion or re-operation or developed TUR syndrome. Subgroup analysis indicated that there was a significant reduction in mean International Prostate Symptom Score (IPSS) and a significant increase in maximum urinary flow rate (Qmax) at 12 months compared to preoperative values for all patients in the failed medical management subgroup of both monopolar (n=25) and bipolar (n=29) groups (p<0.0001). Mean improvement in the IPSS score and Qmax from baseline to 3 month, 6 months and 12 months was similar between the subgroups. The study was conducted in India.

5.5 Cost update

The EAC ran the original models with new parameters. All parameters had changed. The cost for the components of TURis had all increased. The base case using no difference in length of stay showed that TURis is now cost-incurring rather than cost-saving.

EAC costing report table 1: Updated base case without length of stay difference

Olympus owners	Original		Updated	
	TURP	TURis	TURP	TURis
Capital	-	£9.68	-	£10.28
Consumables	£137.75	£161.13	£149.75	£250.67
Complications	£52.35	£6.68	£53.32	£5.42
Length of Stay	£1,006.50	£1,006.50	£716.00	£716.00
Per procedure	£1,196.60	£1,183.99	£919.07	£982.37
Difference	**-£12.61**		**£63.31**	
Non-Olympus owners	**Original**		**Updated**	
	TURP	**TURis**	**TURP**	**TURis**
Capital	-	£29.13		£31.22
Consumables	£66.84	£161.13	£68.86	£250.67
Complications	£52.35	£6.68	£53.32	£5.42
Length of Stay	£1,006.50	£1,006.50	£716.00	£716.00
Per procedure	£1,125.69	£1,203.44	£838.18	£1,003.31
Difference	**£77.75**		**£165.13**	

The original base case included a 0.19-day reduction in length of stay for TURis. The EAC considers that the average length of stay for endoscopic procedures has reduced to 2 days for TURis, a reduction of 1 day compared to TURP. With this change, TURis becomes cost saving. The EAC considers that there is uncertainty regarding the continued appropriateness of incidence rates of readmissions, blood transfusions, strictures and contractures used in the original guidance which may have an impact on cost savings.

EAC costing report table 2: Base case as per MTG23, including length of stay difference

Olympus owners	**Original (-0.19 day)**		**Updated (-1 day)**	
	TURP	**TURis**	**TURP**	**TURis**
Capital	-	£9.68	-	£10.28
Consumables	£137.75	£161.13	£149.75	£250.67
Complications	£52.35	£6.68	£53.32	£5.42
Length of Stay	£1,006.50	£948.55	£716.00	£358.00
Per procedure	£1,196.60	£1,126.04	£919.07	£624.37
Difference	**-£70.56**		**-£294.69**	
Non-Olympus owners	**Original (-0.19 day)**		**Updated (-1 day)**	
	TURP	**TURis**	**TURP**	**TURis**
Capital		£29.13		£31.22
Consumables	£66.84	£161.13	£68.86	£250.67
Complications	£52.35	£6.68	£53.32	£5.42
Length of Stay	£1,006.50	£948.55	£716.00	£358.00
Per procedure	£1,125.69	£1,145.49	£838.18	£645.31
Difference	**£19.80**		**-£192.87**	

6. Summary of new information and implications for review

The technology has been renamed from TURis to PLASMA. Since all the evidence was on TURis, this name is retained in this report, including the citations. The CE mark is unchanged. The cost of the technology has increased. New evidence supports the clinical efficacy of PLASMA with reductions in the incidence of TUR syndrome and blood loss. The technology

is cost saving if a reduction in length of stay is assumed and the unit already owns an Olympus generator. The reduction in length of stay would require use of TURis as a day case procedure.

7. Implications for other guidance producing programmes

Once the Medical Technology Guidance has been updated, the TURis system may be considered in an update of lower urinary tract symptoms in men: management (CG97).

8. Implementation

Data from the company indicates that the uptake of TURis has increased since the publication of guidance (figure 1 derived from tabular data provided by the company).

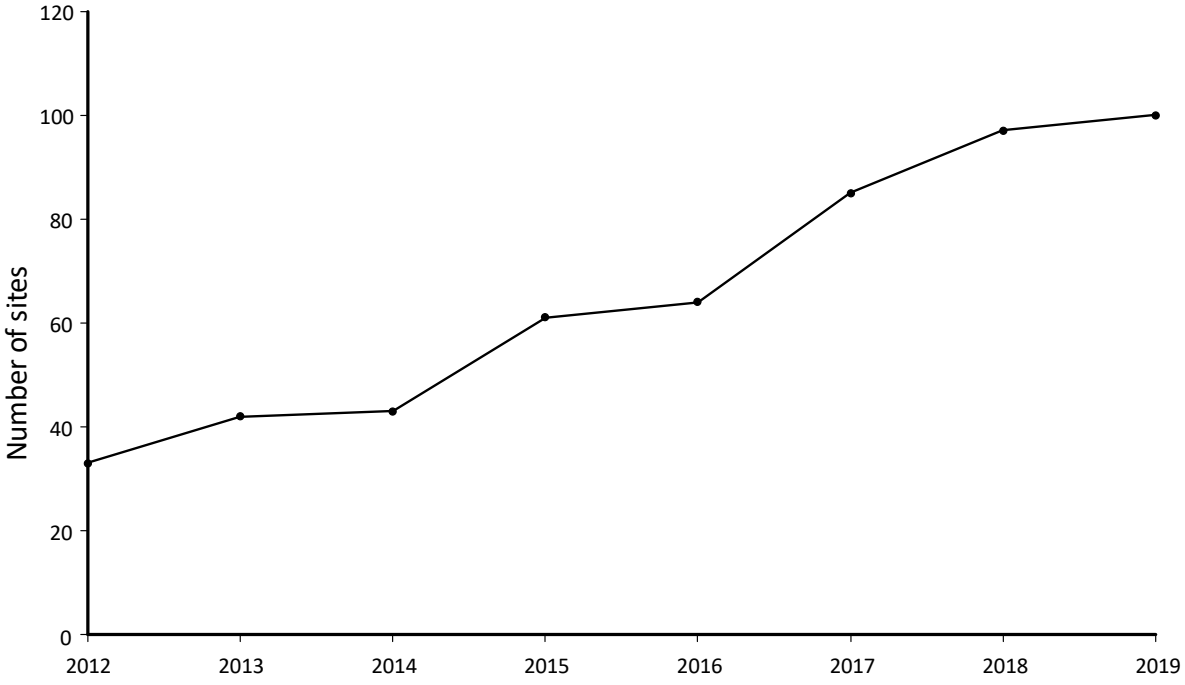

Figure 1. Uptake data from the company

Data from the NICE adoption and impact team suggest that the number of inpatient episodes for endoscopic resection of the prostate has fallen. This will include bipolar and monopolar techniques. The technical lead suggests this may be because of alternative therapies e.g. bipolar vaporisation, MTG29 Greenlight, and MTG26 Urolift.

9. Equality issues

No equality issues were identified in MTG23

An equality issue was raised at consultation:

> Men aged 80 years and over, especially those with frail health and comorbidity, have been found to have an increased risk of morbidity following TURP*, though effectiveness of the intervention is not affected. * References:(1) Living status in patients over 85 of age after TUVRP, Aihua Li, Y. Zhang, H.H. Lu, B.H. Zhang, researchgate.net (Article in the Aging Male, August 2013, source: PubMed) (2) Pathological analysis on transurethral enucleation resection of the prostate-related prostate surgical capsule, Shiping Wei, Fan Cheng, Weiming Yu, Wideochir Inne Tech Maloinwazyjne. 2019 Apr: 14(2): 255-261 (3) Is transurethral resection of the prostate safe and effective in the over 80 year old, R.D. Brierly, A.H. Mostafid, D. Kontothanassis et. al, Ann. R. Coll. Surg. England, Jan. 2001, 83(1): 50-53 (4) Risk of acute myocardial infarction after TURP in the elderly - NCBI, C de Lucia. 2013

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Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	Yes
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

IPG 14 Transurethral electrovaporisation of the prostate gave normal arrangements recommendations in October 2003.

CG 97 Lower urinary tract symptoms in men: management was updated in 2015.

In progress

None.

References

Abdallah, M. M. and M. O. Badreldin (2014) A short-term evaluation of the safety and the efficacy of bipolar transurethral resection of the prostate in patients with a large prostate (>90 g). Arab Journal of Urology 12(4): 251-255.

Al-Rawashdah, S. F., et al. (2017) Prospective randomized study comparing monopolar with bipolar transurethral resection of prostate in benign prostatic obstruction: 36-month outcomes. World Journal of Urology 35(10): 1595-1601.

Karadeniz, M. S., et al. (2016) Bipolar versus monopolar resection of benign prostate hyperplasia: a comparison of plasma electrolytes, hemoglobin and TUR syndrome. SpringerPlus 5(1): 1739.

Komura, K., et al. (2015) Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. BJU International 115(4): 644-652.

Komura, K., et al. (2014) Could transurethral resection of the prostate using the TURis system take over conventional monopolar transurethral resection of the prostate? A randomized controlled trial and midterm results. Urology 84(2): 405-411.

Kumar, B., et al. (2019) Urethral stricture after bipolar transurethral resection of prostate-truth vs hype: a randomized controlled trial. Indian Journal of Urology 35(1): 41-47.

National Institute for Health and Care Excellence
Medical Technologies Evaluation Programme

Review of MTG23 The TURis system for transurethral resection of the prostate

Consultation Comments table

There were 21 consultation comments from 3 consultees (committee member, company contact and registered society). The comments are reproduced in full.

Table 1

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
1	3 British Association of Urological Surgeons (BAUS)	1 & 8	The clinical environment surrounding Transurethral Resection of Prostate (TURP) is changing. (1) There is a greater drive towards daycase surgery, in certain situations discharging patients home with non-irrigated 3 way catheters. (2) TURis has gained popularity over the past 5-7 years, with a 2.5 fold rise in availability within UK urology units over this time. However, there has also been an increase in the number of alternative treatment options available, including transurethral steam vapourisation / water ablation, Urolift, prostate artery embolisation and prostate enucleation and vapourisation, by means of various energy sources. (3) As a consequence, there has been a general decline in the numbers of patients undergoing BPH outflow surgery by means of conventional monopolar TURP.	Thank you for your comment. NICE are grateful for information regarding changes in the clinical options, including alternative technologies. This information will be included in the update of guidance. Separate guidance (MTG26) has been produced by NICE describing Urolift.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
2	3 BAUS	1.1	The current case for adoption of TURis is based on (1) Avoidance of TUR syndrome (2) Reduced need for transfusion (3) Potential reduction in hospital length of stay and complications.	Thank you for your comment.
3	3 BAUS	1.2	There has been a previous assertion of reduced costs to the NHS of £71 per case (in units already using the Olympus system) or marginally increased cost £20 (in those that do not) with further estimated cost reductions arising from reduced lengths of stay and unplanned readmission rates (£375 vs £285). However, as has been noted, there has been an increase in the cost of this technology, and although the new overall costing take into account newer data on LOS and complications, the financial gain is less apparent. It is also unclear whether these calculations have taken in to account other apparent cost differences, such as the higher cost of saline irrigant compared with glycine.	Thank you for your comment. All relevant costs will be taken into consideration during the update of guidance.
4	2 Olympus Medical	3	The exclusion of the 'Wang et al. 2015' is unexpected and we request a rationale for why they were not considered. The endpoints in the study are consistent with the variables in the model and should be included.	Thank you for your comment. The study was considered by the external assessment centre but they reported that it did not add additional information (cost report). On further review, NICE have noted that a named technology was not identified in the methods section. In the discussion (p.138) the Gyrus system is mentioned, which was out of scope for MTG23.
5	2 Olympus Medical	3	We have no record of providing the 65% figure for the use of a second electrode to NICE, however, upon examination of the figure seems to represent the total ratios of electrodes for all procedures (e.g. bladder cancer management) which would not adequately	Thank you for your comment. The purpose of the consultation is to reach a decision regarding whether the guidance is to be updated.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			represent the situation for PLASMA and we do currently not see any rationale to change the key assumptions from the former review, as there is a risk that using the value of 65% would be a significant overestimate of consumable costs – as electrodes can be used for various indications including Hysteroscopy and any sales data should also consider this as well as customer's back stock. Therefore, the original 22% figure is the most accurate estimate available for the number of electrodes specifically used in resection (as these assumptions were originally considered). We acknowledge the new estimates from the clinical expert in the evaluation (50%), nonetheless, we would suggest that the original figure is still maintained at the original (22%).	This information will be evaluated during the guidance update to reflect NHS costs.
6	3 BAUS	4	This MTEP is specific for Olympus TURis (recently renamed PLASMA), but there has to be acknowledgement that other saline resection technologies are available from competing manufacturers, including Storz and the Mediplus, to name two. Each has subtle differences in their design, primarily in the design of the return electrode, but the principle that plasma energy is used to dissect and coagulate tissue is similar. Whether such design differences will have an impact on the outcome variables above, notably stricture rates, is uncertain. To date there have been no studies directly comparing one device against another and nor are their likely to be any in the future. To demonstrate subtle differences would require large numbers of patients to be studied based on the infrequent occurrence of these complications.	Thank you for your comment. Medical technology guidance is only on one technology, in this case PLASMA (formerly called TURis), compared with the standard of care in the NHS. The update will include new evidence that is relevant to the technology
7	3 BAUS	4	There has been a suggestion that with the uprise in the uptake of bipolar TURP and the decline in the popularity of monopolar TURP that TURis should become the new standard of care, with its reduced rates of transfusion and TUR syndrome. Caution is required with the implementation of this statement, as	Thank you for your comment. NICE will ensure that the current standard of care in the NHS is described in the update of guidance.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			monopolar TURP still remains a valid procedure for small, uncomplicated TURPs with a comprehensive historical evidence base supporting it use. Care needs to be exercised in the wording to ensure that although Bipolar TURP is becoming the new standard of care, this presently does not mean that it is the standard of care over and above monopolar TURP as well as all other treatment modalities. Nor should this assertion be restricted to a single manufacturer, unless there is compelling data to prove otherwise.	
8	3 BAUS	4	As a consequence of the perceived advantages of saline resection, there has been a tendency amongst urologists to preferentially use bipolar resection for the larger, potentially more difficult prostates, in which TUR syndrome and transfusion are more likely to occur, reserving monopolar TURP for the smaller, uncomplicated TURPs. Care needs to be taken to ensure that this selection bias is factored into any future non-randomised comparisons that take place.	Thank you for your comment. NICE will consider any potential for selection bias in evidence included in the update of guidance.
9	3 BAUS	4	Care is also necessary to ensure that bipolar and monopolar resection, as a technique are clearly differentiated from transurethral vapourisation and transurethral enucleation of prostate, regardless of energy source. These are clearly distinct techniques by comparison, with quite distinct evidence bases.	Thank you for your comment. NICE will include new evidence relevant to the technology and comparators that were defined in the original scope.
10	3 BAUS	4	There is no doubt that TURis and bipolar TURP has a significant role to play in the surgical management of bladder outflow obstruction due to BPH. However, tere is a prescient need for high quality long-term comprehensive outcome data to be collated from patients undergoing bladder outflow surgery, regardless of treatment modality and taking into account selection biases that may arise, as one technique may well be better suited to a particular set of circumstances than another. BAUS is in a well-placed position to provide this, through its established audit programme and based on it historical track record in doing so.	Thank you for your comment. The need for further research will be considered during the update of guidance.

Review of MTG23 The TURis system for transurethral resection of the prostate

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
11	2 Olympus Medical	5.2	We agree that the LUTS CG97 require updating to reflect bipolar as the current standard of care	Thank you for your comment.
12	3 BAUS	5.2	Since the publication of NICE CG97 Lower urinary tract symptoms in men: management (2010) there has been a suggestion of an increased incidence of urethral strictures with TURis.	Thank you for your comment. The incidence of adverse events will be considered in the update of guidance.
13	3 BAUS	5.4	With the additional publication of 6 studies since the original MGT23 guidelines were published, there is no doubt about the efficacy of Bipolar TURP (TURis) compared with monopolar TURP, but the stricture rate data is conflicting, with some smaller series showing higher rates with TURis and other series, including a large randomised series of 497 patients favouring bipolar (GYRUS) resection. Transfusions rates and TUR syndrome rates are lower with saline resection. Overall, the rates of all of these complications are generally, however, low or unseen in many of these series (0-2.8%) for both monopolar and bipolar resection and grade 2-3, at worst. These low rates highlight the fact that large cohorts and patient series are required to accurately quantify them and to enable reasonable costing forecasts to be made for complications and readmission rates alone. Some complications, such as stricture disease may be associated with delayed presentation and be costly in the long term if recurrent in nature, and this emphasised the need for accurate long-term follow up for these rare events.	Thank you for your comment. The Gyrus technology is not the same as PLASMA/TURis and is out of scope for assessment in MTG23. The incidence of adverse events will be considered in the update of guidance.
14	2 Olympus Medical	5.5	We strongly disagree with the base-case assumption of zero difference in LOS between mTURP and PLASMA as taken from the expert opinion. Base-case LOS reduction should still be -0.19 days in favour of PLASMA as agreed in the original guidance. ***(5.15 – MTG23 – Feb 2015)***	Thank you for your comment. The purpose of this consultation is to consider the review proposal to perform a standard update of guidance.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			Therefore, we suggest the following scenarios for the comparison of mTURP and PLASMA: • Base-case LOS-reduction of -0.19 days and reduction in readmissions • Base-case LOS-reduction of -0.19 days and no reduction in readmissions • LOS-reduction of 1 day and reduction in readmissions LOS-reduction of 1 day and no reduction in readmissions	These scenarios will be considered during the update.
15	2 Olympus Medical	5.5	The current evaluation does not account for differences in the incidence of clot retention following treatment with mTURP compared to PLASMA, is that correct? We strongly promote the consideration of clot retention, since it has been part of the original guidance and there is additional conclusive evidence for this endpoint, as reported in Abdallah et al. 2014 & Komura et al. 2015.	Thank you for your comment. The review report produced by the external assessment centre was to inform decision making by NICE on whether an update of MTG23 was required. The purpose of this consultation is to consider the review proposal to perform a standard update of guidance. Any new evidence relevant to clinical outcomes will be considered in the update of guidance.
16	2 Olympus Medical	5.5	We suggest a more transparent summary of the complication costs by disclosing each cost component separately. This is referring to Table 5 & 6 (supporting document), which, compared to the values for complications in Table 7, do not include the costs of readmission, but state only differences in LOS. Thereby the descriptions of the tables should also be modified.	Thank you for your comment. The purpose of this consultation is to consider the review proposal to perform a standard update of guidance. The descriptions of the tables will be different to the review proposal in the updated guidance.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
17	2 Olympus Medical	5.5	Section 5.5 states “The EAC considers that the average length of stay for endoscopic procedures has reduced to 2 days for TURis, a reduction of 1 day compared to TURP”. Should this instead read “The EAC considers that the average length of stay for endoscopic procedures has reduced to 2 days for TURP and a reduction of 1 day is achievable with TURis”? We notice that within the costing tables below, the length of stay figure for TURP in the updated scenario is shown as 2 days and a 1 day reduction for TURis is taken from there. Based on the above, we disagree with the reduction in average length of stay for monopolar TURP from 3.3 days (original guidance) to 2 days. The EAC’s source of the original 3.3 day figure is taken from clinical evidence. This is the mean of two RCTs; Akman 2013 (2.7 days) and Michielsen (3.89 days). To our knowledge, there has not been any substantial further evidence to suggest that the average length of stay for monopolar TURP has reduced to 2 days. Furthermore, the average length of stay for TURP as taken from HES data 2012-2013 (13. M65.3 Endoscopic resection of prostate NEC (50). Range: ±25%.) is also reported as 3.3 days, this is cited in the original guidance. We believe this to be representative of monopolar TURP as this was the standard of care at the time and thus validates the figure taken from clinical evidence. In addition, a recent randomized trial of 496 patients identified in the updated literature search, Al-Rawashdah et al (2017), reported a mean length of stay in the monopolar TURP arm of 3.57 days. This is consistent with the previously reported evidence. The newly proposed average length of stay for monopolar TURP figure of 2 days is taken from recent	Thank you for your comment. The purpose of this consultation is to consider the review proposal recommendation, which is to perform a standard update of guidance. The evidence for length of stay in the NHS will be considered when the guidance is updated.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			HES and NHS Reference Costs data (HES 2017-18 M65.3, NHS reference costs 2017-18 LB25F). In section 5.2, the EAC refer to bipolar TURP now being standard of care. With this in mind, the HES and reference cost data for length of stay will be made up of a significant proportion of bipolar users and thus is not representative of monopolar TURP length of stay. Whilst this demonstrates the effective implementation to date of the original NICE guidance MTG23 since its publication, it is not relevant to use this as a starting point for length of stay reduction as we would effectively be comparing PLASMA to a mixture of monopolar and bipolar users. The recommendations in the guidance are for the adoption of PLASMA due to its improved cost-effectiveness and clinical outcomes compared to monopolar TURP and thus we recommend that the figure of 3.3 days, calculated from the RCTs and used in the original guidance be retained. We then propose the updated cost tables recalculated with this change.	
18	1 Committee Member	6	Page 8, line 3- first word ‘day’ should be ‘stay’	Thank you for your comment. This error has been corrected,
19	2 Olympus Medical	6	Following on from comments 6, Section 6 reports “The reduction in length of day [stay] would require use of TURis as a day case procedure.” We disagree with this comment as this would only be the case where the length of stay for monopolar TURP is 2 days. As demonstrated above, this unlikely to be the case.	Thank you for your comment. The revised parameters of the model will be considered when the guidance is updated.
20	1 Committee Member	8	First paragraph, first sentence should be: “The evidence suggests that TURis remains a clinical and cost effective treatment option for benign prostate	Thank you for your comment.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			hyperplasia." The second sentence should be: "However, there is uncertainty regarding…"	The report from the external assessment centre is an independent academic work outside the NICE style guidelines.
21	1 Committee Member	9	Suggest adding the following sentence: Elderly men especially those with frail health and comorbidity have been found to have an increased risk of morbidity following TURP*, though effectiveness of the intervention is not affected. * References: (1) Living status in patients over 85 of age after TUVRP, Aihua Li, Y. Zhang, H.H. Lu, B.H. Zhang, researchgate.net (Article in the Aging Male, August 2013, source: PubMed) (2) Pathological analysis on transurethral enucleation resection of the prostate-related prostate surgical capsule, Shiping Wei, Fan Cheng, Weiming Yu, Wideochir Inne Tech Maloinwazyjne. 2019 Apr: 14(2): 255-261 (3) Is transurethral resection of the prostate safe and effective in the over 80 year old, R.D. Brierly, A.H. Mostafid, D. Kontothanassis et. al, Ann. R. Coll. Surg. England, Jan. 2001, 83(1): 50-53 (4) Risk of acute myocardial infarction after TURP in the elderly - NCBI, C de Lucia. 2013	Thank you for your comment. This information has been added to the review decision document.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Information request from the sponsor for Medical Technologies Guidance Update of MT211 (MTG23) The TURis system for transurethral resection of the prostate

Update of MT211(MTG23) The TURis system for transurethral resection of the prostate

The original guidance was issued in February 2015.

The review decision for this guidance was issued in December 2019.

Company update

1. **Changes in the technology: MTG23 was on the TURis system, consisting of an Olympus generator and a resectoscope, which incorporates the TURis active working element and electrode, a telescope, an inner and outer sheath, a light guide cable and a saline cable.**

    a. Is the technology still available to the NHS in the UK?

    Yes

    b. If the technology has changed, what it the latest current version and when was this model first marketed in the UK? **Please provide technical specifications which show the differences.**

    The technology itself has not changed, but the branding has been changed from TURis to PLASMA.

    c. Does the new model perform the same function and use the same mode of action as the technology in MTG23?

    Not applicable, the technology has not changed

    d. Does the new model have a new CE mark?

    Not applicable, the technology has not changed

e. Has the cost of the technology changed since the original guidance? Please give details (this can be kept commercial-in-confidence).

The prices have slightly increased since the original guidance. The main driver has been inflation over this period. Please see below the original prices versus current prices. We request that this is kept **commercial-in-confidence.**

Is the company aware of any new clinical evidence on the use of TURis, available since the original evaluation and Guidance Review (i.e. after March 2019)?

If new evidence is available, please give brief details, a reference for published evidence or a title and one line description for unpublished evidence – please complete a form in appendix 1 for each piece of unpublished evidence.

We have performed a systematic literature review, searching NCBI PubMed. Please find the detailed PRISMA flow diagram in Appendix 2. The search identified the following three (published) sources researching clinical and / or economic outcomes of B-TURP compared to M-TURP:

Alexander, C., et al. (2019). „Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction (Review)" Cochrane Database Syst Rev, 12, CD009629.

- Cochrane systematic review, included 59 randomized controlled trials (RCTs) comparing M-TURP to B-TURP
- n= 8924 participants
- **Endpoints**: Urological Symptoms (IPSS at 12 months), HRQoL, Post-surgical complications

Results: Significant reduction of TUR syndrome (RR 0.17, 95% CI 0.09 to 0.30; participants = 6745; RCTs = 44; I^2 = 0%); No difference in urinary incontinence at 12 months (RR 0.20, 95% CI 0.01 to 4.06; participants = 751; RCTs = 4; I^2 = 0%); Significant reduction in blood transfusions (RR 0.42, 95% CI 0.30 to 0.59; participants = 5727; RCTs = 38; IP = 0%); No differences in rates of re-TURP (RR 1.02, 95% CI 0.44 to 2.40; participants = 652; RCTs = 6; IP = 0%).
Limitations: Methodological limitations in studies, regarding selection bias, performance bias and reporting bias

Huang, S.-W., et al. (2019). "Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis." BMJ (Clinical research ed.) **367**: l5919-l5919.

- Systematic review and network meta-analysis of RCTs, comprising of 109 trials
- n=613-4639 participants (bTURP & mTURP comparison)
- **Endpoints:** Functional outcomes, perioperative parameters, post-operative complications, longterm complications

Results: Compared to mTURP, bTURP showed significantly less blood transfusions (0.42 network OR; 95%CI=0.28-0.61), significantly less clot retention (0.29 network OR; 95%CI=0.12-0.68), significantly shorter hospital stay (-10.05% network mean difference; 95%CI=15.96-4.15), and a non-significant difference in recurrence, urethral stricture, and recatheterisation
Limitations: Model limitations (network meta analysis); No statement of actual length of stay

Müllhaupt, G., et al. (2019). "In-hospital cost analysis of prostatic artery embolization compared with transurethral resection of the prostate: post hoc analysis of a randomized controlled trial." BJU international **123**(6): 1055-1060.

- Post-hoc analysis of an RCT comparing prostatic artery embolization (PAE) and transurethral resection of the prostate (monopolar TURP)
- n=99 (48 PAE; 51 mTURP)
- **Endpoints:** Length of stay, Costs

Results: Mean duration of hospital stay was 4.2 days (SD 1.7)*. Mean costs for inpatient stay were 5405€ (SD 2280€) for TURP, mean costs for the surgical procedure were 3617€ (SD 2280€) for TURP, amounting to total in-hospital costs of 9137€ (SD 3301€)

Limitations: No comparison to bTURP; however, LOS could be used for mTURP.

* Please see additional comments linked to monopolar TURP length of stay in section 5 (Additional Information), comment 2.

2. **Is the company aware of any adoption or usage data (such as audit) from the NHS or elsewhere?** Please give details where possible, this can be kept commercial-in-confidence as required.

We are unaware of any adoption data from within the NHS, however we are able to provide sales data indicating how many hospitals began using PLASMA in each financial year since 2012. *Please note however that this data includes all PLASMA resection procedures (eg. TURP, bladder cancer management, hysteroscopic resection) and may not represent the situation for TURP alone.*

Financial Year	Number of New Adopters
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

We request that this list is kept **commercial-in-confidence**.

3. **Does the company have a list of NHS users?** If so, could you please append a list to this submission, this can be kept commercial-in-confidence as required.

A list of current NHS users is provided in Appendix 3. This list is taken from sales data and details all NHS hospitals that have purchased PLASMA electrodes since April 2017. A three year time horizon has been selected as PLASMA electrodes typically have a three year shelf life.

[redacted]

We request that this list is kept **commercial-in-confidence**.

4. Has the technology added new indications or is now used in new applications not covered by the original guidance? If so, please give details.

No

5. **Additional information**

Any other relevant information supporting the use of the technology.

Following the recent consultation for MTG23, we would like the following points to be considered as part of the full guidance review. Points 1 and 2 correspond to the 'Cost Update' section of the 'TURis review proposal paper' (section 5.5).

1. We strongly disagree with the base-case assumption of zero difference in LOS between mTURP and PLASMA as taken from the expert opinion.

   Base-case LOS reduction should still be -0.19 days in favour of PLASMA as agreed in the original guidance. (MTG23, Section 5.15 – Feb 2015)

   Therefore, we suggest the following scenarios for the comparison of mTURP and PLASMA:

   - Base-case LOS-reduction of -0.19 days and reduction in readmissions
   - Base-case LOS-reduction of -0.19 days and no reduction in readmissions
   - LOS-reduction of 1 day and reduction in readmissions
   - LOS-reduction of 1 day and no reduction in readmissions

2. Within the costing tables, the length of stay figure for TURP in the updated scenario is shown as 2 days and a 1 day reduction for TURis is taken from there.

Based on the above, we disagree with the reduction in average length of stay for monopolar TURP from 3.3 days (original guidance) to 2 days. The EAC's source of the original 3.3 day figure is taken from clinical evidence. This is the mean of two RCTs; Akman 2013 (2.7 days) and Michielsen (3.89 days). To our knowledge, there has not been any substantial further evidence to suggest that the average length of stay for monopolar TURP has reduced to 2 days. Furthermore, the average length of stay for TURP as taken from HES data 2012-2013 (13. M65.3 Endoscopic resection of prostate NEC (50). Range: ±25%.) is also reported as 3.3 days, this is cited in the original guidance. We believe this to be representative of monopolar TURP as this was the standard of care at the time and thus validates the figure taken from clinical evidence. In addition, a recent randomized trial of 496 patients identified in the 2019 updated literature search, Al-Rawashdah et al (2017), reported a mean length of stay in the monopolar TURP arm of 3.57 days. This is consistent with the previously reported evidence.

The newly proposed average length of stay for monopolar TURP figure of 2 days is taken from recent HES and NHS Reference Costs data (HES 2017-18 M65.3, NHS reference costs 2017-18 LB25F). In section 5.2, the EAC refer to bipolar TURP now being standard of care. With this in mind, the HES and reference cost data for length of stay will be made up of a significant proportion of bipolar users and thus is not representative of monopolar TURP length of stay. Whilst this demonstrates the effective implementation to date of the original NICE guidance MTG23 since its publication, it is not relevant to use this as a starting point for length of stay reduction as we would effectively be comparing PLASMA to a mixture of monopolar and bipolar users. The recommendations in the guidance are for the adoption of PLASMA due to its improved cost-effectiveness and clinical outcomes compared to monopolar TURP and thus we recommend that the figure of 3.3 days, calculated from the RCTs and used in the original guidance be retained. We then propose the updated cost tables be recalculated with this change.

3. Section 4 TURis review proposal supporting document refers to the use of a second electrode during PLASMA resection. We suggest to use the 22% figure as taken from the original guidance, since this reflects the latest available clinical evidence. We have no record of providing the 65% figure referenced in section 4. Upon examination, the figure appears to represent the ratio of electrodes sold to the number of procedures completed, according to our sales data. However, this data includes all PLASMA resection procedures (eg. TURP, bladder cancer management, hysteroscopic resection) and this would not adequately represent the situation for TURP alone. There is a risk that using the value of 65% would significantly overestimate consumable costs as electrodes can be used for various indications, as described above. In addition, sales data would include customers' existing unused stock on shelves. Therefore, the original 22% figure remains the most accurate available number of additional electrodes specifically used in prostate resection.

Declaration:

Company representative: Graham Popham

Position: Head of Market Access date: 25/02/2020

Appendix 1

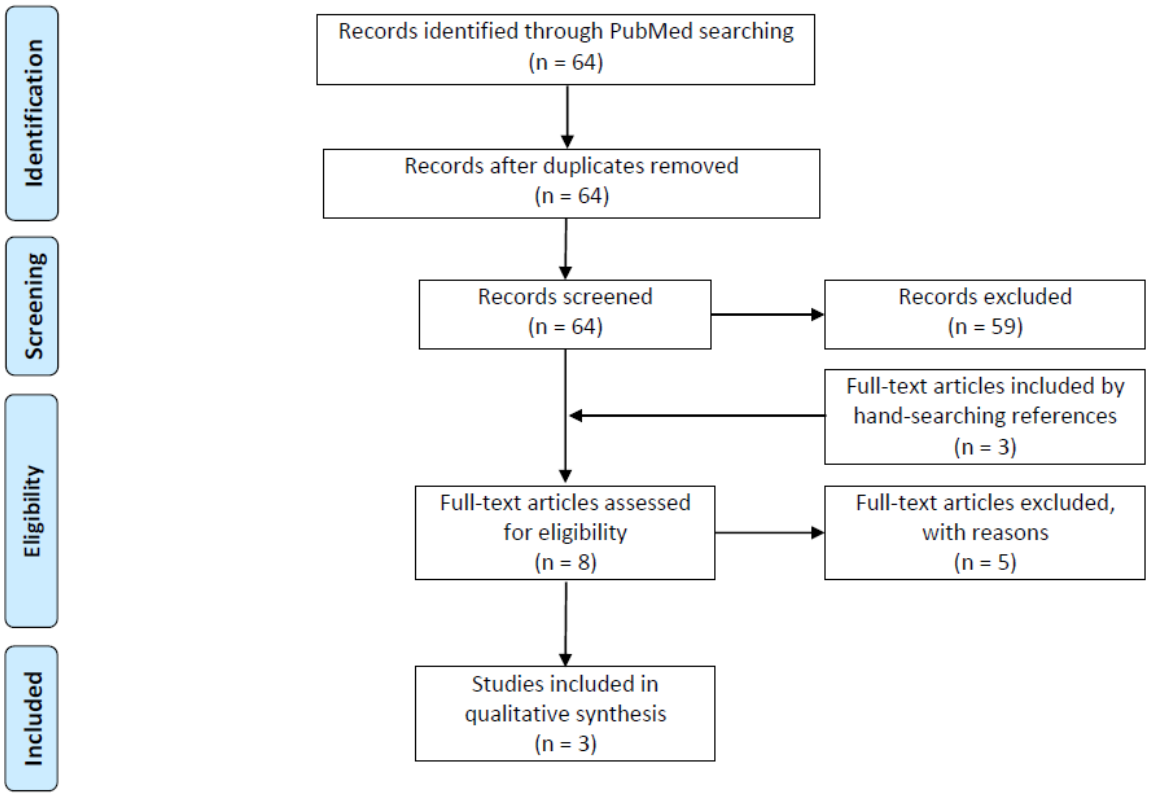
Unpublished study details	
Should this study be seen as: publicly available, academic-in-confidence, commercial-in-confidence? Is there a planned publication date?	
Study details [e.g. Trial code if registered as a clinical trial, authors, title, details of funding]	
Design [e.g. was it randomised, was there a control group or comparator technology, was it a post-marketing study]	
Assigned interventions [how was the technology used, how often]	
Participants [how many people were in the study, how were they selected, which indication did they have, which setting were they in e.g. hospital, GP etc]	
Follow-up period	
Primary outcome [what was the main symptom or parameter measuring the effect of the technology]	
Secondary outcome(s) [any other symptoms, parameters measured]	
Key results – efficacy	
Key results – safety [were there any side effects or adverse events]	
Information source [e.g. webpage or link to details of the study, if available]	
Any other comments	

For more information about how we process your data please see our privacy notice.

Appendix 2

OLYMPUS

TURis NICE Guidance Update
PRISMA 2009 Flow Diagram



Reasons for full-text-exclusion:

Brown, A. D., et al. (2019). "Minimally Invasive Treatment for Benign Prostatic Hyperplasia: Economic Evaluation from a Standardized Hospital Case Costing System." Cardiovascular and interventional radiology **42**(4): 520-527. **Reason for exclusion:** No differentiation between mTURP and bTURP

Davis, N. F., et al. (2019). "Medical therapy versus transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic enlargement (BPE): a cost minimisation analysis." World journal of urology **37**(5): 873-878. **Reason for exclusion:** No explanation for choice of CMA – no clinical data for the therapies was provided, there are reasonable concerns that the outcomes are actually not equal and hence the assumption faulty.

DeWitt-Foy, M. E., et al. (2019). "Cost Comparison of Benign Prostatic Hyperplasia Treatment Options." Current urology reports **20**(8): 45-45. Reason for exclusion: No differentiation between monopolar and bipolar TURP

Miernik, A., et al. (2019). "Endoscopic enucleation of the prostate." Der Urologe. Ausg. A **58**(4): 437-450. **Reason for exclusion:** This is not a clinical trial, but a further education program

Rieken, M., et al. (2019). "Surgical treatment of benign prostatic hyperplasia-resection, vaporization or enucleation?" Der Urologe. Ausg. A 58(3): 263-270. **Reason for exclusion:** Review without data synthesis/meta analysis

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 3

List of current NHS users

National Institute for Health and Care Excellence

Guidance Review Expert Advice

MTG23 TURIS Collated Expert Advice Questionnaires

Expert contact details and declarations of interest:

Expert #1	Marios Hadjipavlou, Senior Urology Registrar, Guy's & St Thomas NHS Foundation Trust
	DOI: Nothing declared
Expert #2	James Andrew Thomas, Consultant Urologist, Cwn Taff Morganwg University LHB
	DOI: Nothing declared
Expert #3	Nikesh Thiruchelvam, Consultant Urologist, Cambridge University NHS Trust
	Educational fees from Neotract (Urolift)

1	NICE would like your Expert Advice on this product/ technology provided it remains in your area of specialist work and knowledge – even if you have not seen or used it. We need the views of specialists in relevant disciplines about its benefits for patients and the NHS, and about its use in the current care pathway. With this in mind, is this a technology which is relevant to your area of practice or expertise? Yes ☐ No ☐ If you answered "no" to this question, please answer no further questions, but return the form to medtech@nice.org.uk.	Expert #1: Yes Expert #2 Yes Expert #3 Yes

YOUR PERSONAL EXPERIENCE (IF ANY) WITH THIS TECHNOLOGY

2	Please indicate your experience with this technology a) I have had direct involvement with its use Yes ☐ No ☐ b) I have referred patients for its use Yes ☐ No ☐ c) I manage patients on whom it is used in another part of their care pathway Yes ☐ No ☐ d) would like to use this technology but it is not currently available to me Yes ☐ No ☐ Any comments?	Expert #1: a) Yes b) Yes c) Yes d) Yes I have used the TURis resection system in previous hospitals during my training. As well as for TURP, I have used this for transurethral bladder neck incision as well as for bladder tumour resection. I do not currently use TURis as my current Trust has a contract for bipolar diathermy with a different company.
		Expert #2 a) Yes b) c) d)
		Expert #3 a) No b) No c) No d) No
3	Have you been involved in any kind of research on this technology since MTG23 was evaluated February 2015 Yes ☐ No ☐	Expert #1: No
		Expert #2 No
		Expert #3 No

THIS PRODUCT (TECHNOLOGY) USE IN THE NHS		
4	a) Is this technology available to you in your NHS practice? Yes ☐ No ☐ b) Do you use this technology in your NHS practice? Yes ☐ No ☐ If the technology is available and you don't use it, could you briefly explain why?	Expert #1: a) No b) No Expert #2 a) Yes b) Yes Expert #3 a) Yes b) Yes
5	Do you know if the technology is used elsewhere in the NHS (e.g. in primary care, secondary care or for different clinical indications)? Please describe the 'clinical scenario' (or scenarios) where this technology is being used:	Expert #1: Yes, the technology is being used in secondary care in several urology departments in the NHS and privately. The TURis system is primarily used for transurethral prostate resection in patients with bladder outflow obstruction due to benign prostate hyperplasia or prostate cancer. Such patients can present with urinary retention, lower urinary tract symptoms, recurrent urinary tract infections, bladder stones or recurrent haematuria. The system can also be used to perform bladder neck incision in patients with smaller prostates that do not require resection. It may also be used for enucleation or vaporisation of prostatic tissue. TURis can also be used for transurethral resection of bladder tumours.

		Expert #2 No
		Expert #3 No

VERSIONS

6	Are you aware of different versions of this technology being used?	Expert #1: Similar bipolar resection systems are available by other companies such as Karl Storz and Richard Wolf.
		Expert #2 Yes
		Expert #3 Yes, there are a number of bipolar TURP systems. I am not aware of any differences in their use and I am not aware of any trials comparing the different systems
7	"Competing products": Are you aware of any other products which have been introduced with the same purpose as this one?	Expert #1: Karl Storz Bipolar Resectoscope System Richard Wolf 'Shark' Bipolar Resectoscope System
		Expert #2 Yes
		Expert #3 There are many new minimally-invasive options for benign prostatic enlargement but they are not comparable

NEW EVIDENCE AVAILABLE SINCE MTG23 (February 2015)

8	Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.	Expert #1: Komura et al. BJU Int. 2015 Apr;115(4):644-52 Bozzini et al. Actas Urol Esp. 2017 Jun;41(5):309-315 Mertziotis et al. Adv Urol. 2015;2015:251879 Kawamura et al. Tokai J Exp Clin Med. 2015 Dec 20;40(4):132-6 Liem et al. Urol Oncol. 2018 Jul;36(7):338.e1-338.e11 Giulianelli et al. Arch Ital Urol Androl. 2017 Oct 3;89(3):232-235. Skinner et al. Can Urol Assoc J. 2017 Jun;11(6):194-198. Ozer et al. Cent European J Urol. 2015;68(3):284-8. Tan et al. Investig Clin Urol. 2017 May;58(3):186-191. Giulianelli et al. Urology. 2015 Aug;86(2):407-13. N.B. Note that in some of the above studies, it is unclear whether the bipolar system used was TURis by Olympus. Also, in some studies, the system may have been used for procedures other than transurethral resection of prostate (e.g. transurethral vaporisation of prostate, resection of bladder tumour, etc)
		Expert #2 Yes, can give specific details
		Expert #3 No

FACILITIES, TRAINING AND FUNCTIONING		
9	Are you aware of any particular facilities or infrastructure which has been required to be in place for the safe and effective use of this technology?	Expert #1: There is no specific infrastructure required for the use of this technology, other than that expected in a fully functioning operating theatre accommodating for urological surgery.

		Expert #2 No
		Expert #3 No, easy to implement as it is very similar to existing monopolar TURP
10	Has any special training been required to use this technology safely and effectively?	Expert #1: The user would need to be competent at transurethral resection of prostate. No special training is required for transition from a monopolar system to a bipolar system such as TURis.
		Expert #2 No
		Expert #3 No, as above
11	Functioning of the technology How useful would NICE guidance on this particular technology be to you or there NHS colleagues? Please comment on any issues you are aware of relating to the functioning, reliability and maintenance of this technology.	Expert #1: I am not aware of any issues relating to this technology.
		Expert #2 Nil
		Expert #3 Nil

COSTS		
12	Please provide any comments on the current cost of this technology. In particular, please comment on cost savings or successful NHS business cases you are aware of.	Expert #1: I am not familiar with the financial aspects of this technology.

		Expert #2 No comment
		Expert #3
13	Have there been any significant changes the care pathway since the guidance was published (such as changes in the comparator or availability of alternative (competing) technologies)? Do you have any explanatory comments on why?.	Expert #1: I am not aware of any changes in care pathways at my Trust or other Trusts as a result of the published NICE guidance.
		Expert #2 No
		Expert #3 Since the original guideline, there has been widespread uptake of bipolar TURP

GENERAL ADVICE BASED ON YOUR SPECIALIST KNOWLEDGE		
14	Is there controversy about any aspect of this technology or about the care pathway?	Expert #1: None
		Expert #2 No
		Expert #3 Yes, as shown by GIRFT, there should be greater UK provision of day case TURP (which is aided by bipolar TURP)
15	Have there been any significant changes in the clinical pathway since this guidance was published? Would any changes impact on the position of TURis in the care pathway?	Expert #1 There is evidence for a reduced risk of transurethral resection syndrome, reduced need for blood transfusion and possibly a reduced length of stay associated with using bipolar diathermy rather than monopolar diathermy. In recent years, this has led to a move towards bipolar systems being used in most urology units for transurethral prostate resection. In my

		opinion, this move has been towards bipolar diathermy technology in general, and not specifically to the TURis system by Olympus. It is difficult to determine whether the move towards TURis or other bipolar systems can be attributed to the NICE guidance, and to what degree this would have been.
		Expert #2 No
		Expert #3 No
16	Do you know of the level of use of TURis in local clinical practice? What is TURis being used for?	Expert #1: Transurethral prostate resection/vaporisation/enucleation; bladder neck incision/resection; transurethral bladder tumour resection.
		Expert #2 Yes – TURP, TUVP and TURBT
		Expert #3 Not aware of regional use.
17	Has the published NICE guidance on this technology proved useful to you and your colleagues?	Expert #1 The NICE guidance has helped to consolidate the evidence for moving from a monopolar to using a bipolar system for transurethral prostate resection. This has also strengthened the belief amongst most UK urologists that bipolar transurethral prostate resection is the gold standard. In my opinion, the conclusions from this guidance are transferable to other bipolar resection systems other than TURis.
		Expert #2 No
		Expert #3

		No
18	Do you know of any groups of patients who have specifically benefitted in relation to the use of the technology?	Expert #1: Patients with bladder outflow obstruction (lower urinary tract symptoms or urinary retention) due to benign disease (benign prostate hyperplasia) or malignancy (prostate cancer). Patients with suspected or known bladder cancer requiring bladder tumour resection also potentially benefit from TURis.
		Expert #2 BPH and bladder cancer patinets
		Expert #3 Yes, patients with male lower urinary tract symptoms or urinary retention
19	Do you think the care pathway or evidence has changed such that an update would result in a different recommendation?	Expert #1: I believe this would be unlikely.
		Expert #2: No
		Expert #3: No

DECLARATIONS OF INTEREST BY EXPERT ADVISERS

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure in the previous 12 months or likely to exist in the future. Please use the "Conflicts of Interest for Expert Advisers" policy (attached below) as a guide when declaring any conflicts of interest. Expert Advisers should seek advice if required from the Programme Director

20	Do you or a member of your family have a personal financial interest? The main examples are as follows:	Expert #1: a) No

20.1	**a) Consultancy, directorships, position in or work in the commercial healthcare sector** attracting regular or occasional payments or benefits in kind	☐ **YES**	☐ **NO**	b) No c) No d) No e) No f) No g) No h) No
	b) Clinicians receiving payment from the commercial sector for undertaking a procedure while giving advice on that procedure to NICE	☐ **YES**	☐ **NO**	
	c) Any **Fee-paid work** commissioned by the commercial healthcare sector for which the individual receives payment or financial benefit in kind	☐ **YES**	☐ **NO**	
	d) Any **Shareholdings** in the commercial healthcare sector held by the individual	☐ **YES**	☐ **NO**	
	e) A **financial interest in a company's product** that is, or may become, a competitor to the product under consideration	☐ **YES**	☐ **NO**	Expert #2 a) No b) No c) No d) No e) No f) No g) No h) No
	f) Expenses and hospitality provided by the commercial healthcare sector beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐ **YES**	☐ **NO**	
	g) Funds which include investments in the commercial healthcare sector that are held in a portfolio where the individual has the ability to instruct as to the composition of the fund	☐ **YES**	☐ **NO**	
	h) Do you have a **personal non-financial** interest in the matter under consideration, for example; • Expressed a clear opinion reached as a conclusion of a research project or in a published statement, • Been an author on a document submitted as an evidence publication to a NICE advisory committee • Hold office in a professional organisation, charity or advocacy group with a direct interest in the topic • Have any other reputational risks in relation to the topic.	☐ **YES**	☐ **NO**	Expert #3 a) Yes b) No c) Yes d) No e) No f) No g) No h) No
	If you have answered YES to any of the above statements please describe, in sufficient detail, the nature of the conflict(s) below.			

20.2	Do you have a non-personal interest? These involve payment or other benefits to a department or organisation in which the individual is employed but not received personally. The main examples are as follows: **a)** A **grant** from a company for the running of a unit or department where the individual is employed ☐ **YES** ☐ **NO** **b)** A **grant** or **fellowship** or other payment to sponsor a post or member of staff in the unit where the individual is employed ☐ **YES** ☐ **NO** **c)**The commissioning of research or other work by, or advice from, staff who work in a unit where the individual is employed ☐ **YES** ☐ **NO** **d)** Contracts with, or grants from, NICE ☐ **YES** ☐ **NO** If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.	Expert #1: a) No b) No c) No d) No Expert #2 a) No b) No c) No d) No Expert #3 a) No b) No c) No d) No

20.3	Do you or your organisation or department have any links with, or funding from the tobacco industry? Yes ☐ No ☐ If you have answered **YES** to the above statement please describe the nature of the conflict(s) below.	Expert #1: No Expert #2 No Expert #3 No

NICE National Institute for Health and Care Excellence

Medical technology guidance (MTG)

Expert questionnaire

Technology name & indication: The PLASMA system (formerly called TURis, Olympus Medical) a bipolar electrosurgery system

Your information

Name:	Professor Ian Pearce
Job title:	Consultant Urological Surgeon and Andrologist
Organisation:	Manchester Royal Infirmary
Email address:	**Click here to enter text.**
Professional organisation or society membership/affiliation:	**British Association of Urological Surgeons**

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on this technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. You advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website in a collated expert advice document as part of the process of public consultation on the draft guidance. Any interests declared will also be published in registers that NICE holds.

For more information about how we process your data please see our privacy notice.

X☐ I give my consent for the information in this questionnaire to be used and published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the technology and/or your experience

1	Please describe your level of experience with the technology, for example: – Are you familiar with the technology? – Have you used it? – Are you currently using it? – Have you been involved in any research or development on this technology? – Do you know how widely used this technology is in the NHS?	I am familiar with the technique, having been involved in previous NICE assessments. I have used and lectured on the technique (un-sponsored0 Whilst I have used it in the past, I currently use it only on a sporadic basis. This technique is widely employed within the NHS and private health care settings
2	Has the technology been superseded or replaced?	The technology has not been directly superseded but newer techniques have been introduced, namely Urolift and Rezum. In addition HoLEP is also available and performs the same task

Current management

3	How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?	In reality, this technology is a minor improvement to existing technology of monopolar TURP
4	Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?	Newer, more novel approaches do exist, Urolift and Rezum, but these offer a similar patient end point via a different mechanism of action Urolift technology involves the use of surgical implants to physically push the obstructing prostatic lobes away from the centre, thus creating a larger lumen through which urine can pass. No tissue is resected, the complication rate is minimal and hospital stay shorter. Rezum is an alternative technology involving the direct injection of steam into the prostate tissue resulting in prostatic tissue death over time and relief of obstruction

Potential patient benefits

5	What do you consider to be the potential benefits to patients from using this technology?	The main benefits are that the learning curve is extremely short since the operative technique is virtually the same as for a standard monopolar TURP. The other advantage is that when units replace their diathermy machines for TURP, adopting a machine sufficient for TURiS results in increased cost effectiveness. Serious complicatio9ns secondary to fluid absorption eg : TUR sundrome are drastically reduced if not almost eliminated by TURiS
6	Are there any groups of people who would particularly benefit from this technology?	Patients with already low serum sodium and those with large vascular prostates
7	Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Only the reduction in serious complications secondary to irrigation absorption eg TUR syndrome, cardiotoxicity. These complications are rare (<1%) even for standard monopolar TURP. Blood transfusion rates are lower and hospital stay is reduced

Potential system impact

8	What do you consider to be the potential benefits to the health or care system from using this technology?	Reduced complications Shorter hospital stay Shorter operation time
9	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?	Likely to cost less in the long run

10	What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?	There are no resource implications other than the need to naturally replace diathermy units as and when required
11	Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?	No
12	Are you aware of any safety concerns or regulatory issues surrounding this technology?	No

General advice

13	Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.	NA

Other considerations

14	Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population ?	Most patients suitable for TURP should be suitable. In the region of 25,000 per year in the UK
15	Would this technology replace or be an addition to the current standard of care?	It would eventually replace standard monopolar TURP but these numbers would be reduced by the other novel therapies such as Urolift, Rezum and prostate artery embolization,)PAE)
16	Are there any issues with the usability or practical aspects of the technology?	No

17	Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?	No
18	Are you aware of any further evidence for the technology that is not included in this briefing?	No
19	Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.	No
20	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Comparison of outcomes with Rezum, Urolift and PAE

Declarations of interests

Please state any potential conflicts of interest relevant to the technology (or competitor technologies) which you are advising, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Non-financial professional	Editor of Journal of Clinical Urology	**2012**	**Current**
Non-financial professional	Trustee of BAUS	**2015**	**Current**
Choose an item.			

X☐ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Ian Pearce**
Dated:	**20/03/2020**

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Update Report factual check

MT217/MTG23 The PLASMA system for transurethral resection of the prostate

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Cedar EAC to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **3 July 2020** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report update.

1 July 2020

1.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Updated base case assumption of zero difference in length of stay (LOS) between monopolar TURP (mTURP) and PLASMA	Base-case LOS reduction should be, as a minimum, -0.19 days in favour of PLASMA as agreed in the original guidance. (MTG23, Section 5.15 – Feb 2015). There is a suggestion that the 2019 HES data LOS for TURP (2 days) indicates that the length of stay reduction from monopolar TURP to PLASMA TURP is greater, given the significant adoption of bipolar TURP / PLASMA TURP. With this in mind, we suggest that the cost model scenarios for the comparison of mTURP and PLASMA be updated to the following: • Base-case LOS-reduction of -0.19 days and reduction in readmissions • Base-case LOS-reduction of -0.19 days and no reduction in readmissions • LOS-reduction of 1 day and reduction in readmissions • LOS-reduction of 1 day and no reduction in readmissions	We are not aware of any clinical evidence indicating that the difference in LOS between mTURP and PLASMA has changed to zero, this is only the view of the clinical expert.	We have provided an update with this scenario. However, the health economist who completed the economics for this update is on leave and so we have not included this update in the report, but as a separate document for now. This may be included at a later date following their review.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response

Change of LOS value for mTURP from 3.3 days to 2 days	We recommend that the figure of 3.3 days, calculated as the mean of two RCTs; Akman 2013 (2.7 days) and Michielsen (3.89 days) and used in the original guidance be retained. We then propose the updated cost tables be recalculated with this change.	The EAC's source of the original 3.3 day figure for mTURP LOS is taken from clinical evidence. To our knowledge, there has not been any substantial further evidence to suggest that the average length of stay for monopolar TURP has reduced to 2 days. A recent randomized trial of 496 patients identified in the 2019 updated literature search, Al-Rawashdah et al (2017), reported a mean length of stay in the monopolar TURP arm of 3.57 days. This is consistent with the previously reported evidence. Furthermore, the average length of stay for TURP prior to the original guidance being published, as taken from HES data 2012-2013 (13. M65.3 Endoscopic resection of prostate NEC (50). Range: ±25%.) is also reported as 3.3 days (this is cited in the original guidance). We believe this to be representative of monopolar TURP as this was the standard of care at the time and thus validates the figure taken from clinical evidence. The newly proposed average length of stay for monopolar TURP figure of 2	We have provided an update with this scenario. However, the health economist who completed the economics for this update is on leave and so we have not included this update in the report, but as a separate document for now. This may be included at a later date following their review and input. However, as there is no clear clinical evidence to suggest that bipolar TURP is now standard of care, and the HES would most likely reflect 18/19 figures, there is still the assumption that monopolar TURP would be the predominant procedure for resection and that 2 days would refer to this procedure. This will need to be discussed further with our health economist for this project.

		days is taken from recent NHS Hospital Episode Statistics data (HES, M65.3 'Endoscopic resection of prostate NEC') (NHS Digital 2019). Two clinical experts refer to bipolar TURP now being standard of care. With this in mind, the HES data for length of stay will be made up of a significant proportion of bipolar TURP / PALSMA users and thus is not representative of monopolar TURP length of stay alone. Whilst this may demonstrate the effective implementation to date of the original NICE guidance MTG23 since its publication, it is not relevant to use this as a starting point monopolar length of stay as we would effectively be comparing PLASMA to a mixture of monopolar and bipolar users. The purpose of this guidance, as stated in the scope, is to compare PLASMA with monopolar TURP and thus we recommend retaining 3.3 days LOS for mTURP as indicated in the literature.	

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Updated proportion of PLASMA procedures using additional roller electrode from 22% to 65%	We propose the original figure of 22%	We suggest to use the 22% figure as taken from the original guidance since this reflects the latest available clinical evidence. We have no record of providing the 65% figure. Upon examination, the figure appears to represent the ratio of electrodes sold to the number of procedures completed, according to our sales data. However, this data includes all PLASMA resection procedures (eg. TURP, bladder cancer management, hysteroscopic resection) and this would not adequately represent the situation for TURP alone. There is a risk that using the value of 65% would significantly overestimate consumable costs as electrodes can be used for various indications (as described above). In addition, sales data would include customers' existing unused stock on shelves. Therefore, the original 22% figure remains the most accurate available number of additional electrodes specifically used in prostate resection.	

4.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated both that no new clinical evidence was submitted by the company for the purpose of this assessment report update (ARU) and that the company did not update their search strategy for the purpose of this assessment report (AR) update.	Olympus completed two searches for additional evidence and we propose that these be reviewed for inclusion. A summary of the clinical evidence found and a copy of the search strategy from April 2019 can be found in Appendix 1. A summary of the clinical evidence found and a copy of the search strategy from February 2020 can be found in Appendix 2.	Two searches for new clinical evidence were completed, one in the company information request submitted April 2019 and one in the company information request submitted in February 2020. The search strategy for each was also supplied. Both can be found in the appendix	Our apologies, there was miscommunication during the process. The EAC have now reviewed the submitted evidence and amended the ARU report accordingly, specifically with an additional table (table 2 – note tables have been re-numbered)

5.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
In the “Decision problem and scope details” section, TURP using a monopolar system and TURP using other bipolar systems are listed as comparators	Only TURP using a monopolar system should be listed as the comparator	The only comparator listed in the original guidance scope was TURP using a monopolar system. Olympus did not propose any variation to the decision problem specified in the scope.	This was specified by NICE and not the EAC.

6.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Within the section "Current Validity of the Model", it is stated that the manufacturer has indicated that 100 NHS centres are using PLASMA in 2019, compared to 61 in 2015 (England, Scotland and Wales).	The number of new adopters of PLASMA in each financial is as follows: **Financial Year Number of New Adopters** [redacted] A list of current NHS users is provided in Appendix 3. This list is taken from sales data and details all NHS hospitals that have purchased PLASMA electrodes since April 2017. A three year time horizon has been selected as PLASMA electrodes typically have a three year shelf life. According to the sales data, it would appear that [redacted] hospitals have discontinued use during this time period. The limitations of the data mean that we cannot distinguish between hospitals that have truly discontinued use and those that have changed the way in which they procure the consumables eg. consolidated Trust purchasing. Equally, as above, this data also includes all PLASMA resection procedures (eg. TURP, bladder cancer management, hysteroscopic resection) and may not represent the situation for TURP alone.	An update to the number of adopters and list of centres using PLASMA was provided in the company information update submitted in February 2020.	Apologies, this was not provided to the EAC beforehand. Number of centers has been updated from the list in Appendix 3.

7.

Appendix 1

Our systematically performed literature review searching NCBI PubMed identified the following five (published) sources researching clinical and or economic outcomes of B-TURP compared to M-TURP:

Meta-Analyses:

Treharne, C., et al. (2018). "Economic Value of the Transurethral Resection in Saline System for Treatment of Benign Prostatic Hyperplasia in England and Wales: Systematic Review, Meta-analysis, and Cost-Consequence Model." Eur Urol Focus **4**(2): 270-279.

- Fixed effects meta-analysis, comprising of 25 publications
- n=928-1625 (n=459-804 patients received M-TURP and n=469-821 patients received B-TURP using TURis)
- **Endpoints**: Post-surgery complications, costs

Results: Significantly shorter LOS in TURis group (2,87 vs. 3,43 days; p<0,0001); significantly less TUR syndromes (0 vs. 13; p=0,006); significantly less blood transfusions (14 vs. 40; p=0,0003); significantly less clot retention (11 vs. 26; p=0,0161); potential cost savings of -21% in TURis for Olympus centres and -13% for non-Olympus centres
Limitations: Fixed-effects instead of random-effects model

Wang, K., et al. (2015). "Transurethral plasmakinetic resection of the prostate is a reliable minimal invasive technique for benign prostate hyperplasia: a meta-analysis of randomized controlled trials." Asian J Androl 17(1): 135-142.

- Meta-analysis comparing TURP and PKRP, comprising of 18 studies
- n=24-193 patients (n=24-136 patients received TURP, n=24-193 patients received PKRP)
- **Endpoints:** IPSS, Qmax, operative time, LOS, catheterization time, post-surgery complications, etc.

Results: Significantly higher Qmax in PKRP-patients (mean diff. -0,85; p=0,002), significantly shorter operation time (mean diff. 7,38 min; p<0,00001), significantly shorter catheterisation time (mean diff. 1,43 days; p<0,00001), significantly shorter hospital stay (mean diff. 0,67; p=0,04), significantly lower risk (risk difference; p) in PKRP-patients for transfusions (0,02; p=0,01), TUR syndrome (0,02; p=0,006) and clot retention (5,23; p=0,0003), all other endpoints were non-significant
Limitations: No obvious

RCTs:

Kumar, B. N., et al. (2019). "Urethral stricture after bipolar transurethral resection of prostate - truth vs hype: A randomized controlled trial." Indian J Urol **35**(1): 41-47.

- Single-blinded, randomised controlled trial
- n=85 patients (n=43 patients received M-TURP using Storz Autocon II 400 generator and n=42 patients received B-TURP using TURis + UES-40 SurgMaster generator)
- **Endpoints**: IPSS, Qmax, operative time, LOS, post-surgery compications

Results: Patients receiving M-TURP showed significantly lower IPSS at 3 months follow-up (10,2 vs. 11,4; p=0,01); all other endpoints were not significant
Limitations: Relatively high amount of patients with chronic kidney disease in B-TURP arm (7,5% vs. 0%)

Al-Rawashdah, S. F., et al. (2017). "Prospective randomized study comparing monopolar with bipolar transurethral resection of prostate in benign prostatic obstruction: 36-month outcomes." World J Urol **35**(10): 1595-1601.

- Randomised controlled trial, no information on blinding
- n=497 patients (n=251 patients received M-TURP using Storz resectoscope and Erbe generator; n=246 patients received B-TURP using Storz resectoscope and Gyrus PK Super-Pulse Generator)
- **Endpoints**: IPSS, IPSS QoL, Qmax, operative time, length of stay (LOS), post-surgery complications

Results: Significantly lower LOS in B-TURP (3,27 vs. 3,57; p=0,049) as well as significantly less TUR syndrome events (0 vs. 7; p=0,001) and blood transfusions (0 vs. 5; p=0,013); all other endpoints were not significant
Limitations: Two different surgeons, each treating only one group; partially incomplete follow-up

Retrospective study design:

Sinanoglu, O., et al. (2014). "Comparison of plasmakinetic transurethral resection of the prostate with monopolar transurethral resection of the prostate in terms of urethral stricture rates in patients with comorbidities." Prostate Int 2(3): 121-126.

- Bi-centric retrospective analysis
- n=317 patients (n=154 received M-TURP using Storz resectoscope and n=163 received PK-TURP, using Gyrus Plasmakinetic System)
- **Endpoints:** IPSS, Qmax, operative time, LOS, post-surgery complications

Results: Patients with B-TURP showed significantly higher IPSS after surgery (25,6 vs. 19,3; p<0,001) and significantly lower IPSS after 12 months follow-up (8,3 vs. 10; p<0,001); patients receiving B-TURP also showed more stricture urethras (17/163 vs. 6/154); patients receiving M-TURP had more blood transfusions (4 vs.0).
Limitations: The authors raise issues of a selection bias regarding the prostate volumes and comorbidities of the patients, which were significantly higher in B-TURP
Please find attached the PRISMA diagram in Appendix I.

No unpublished sources could be identified.

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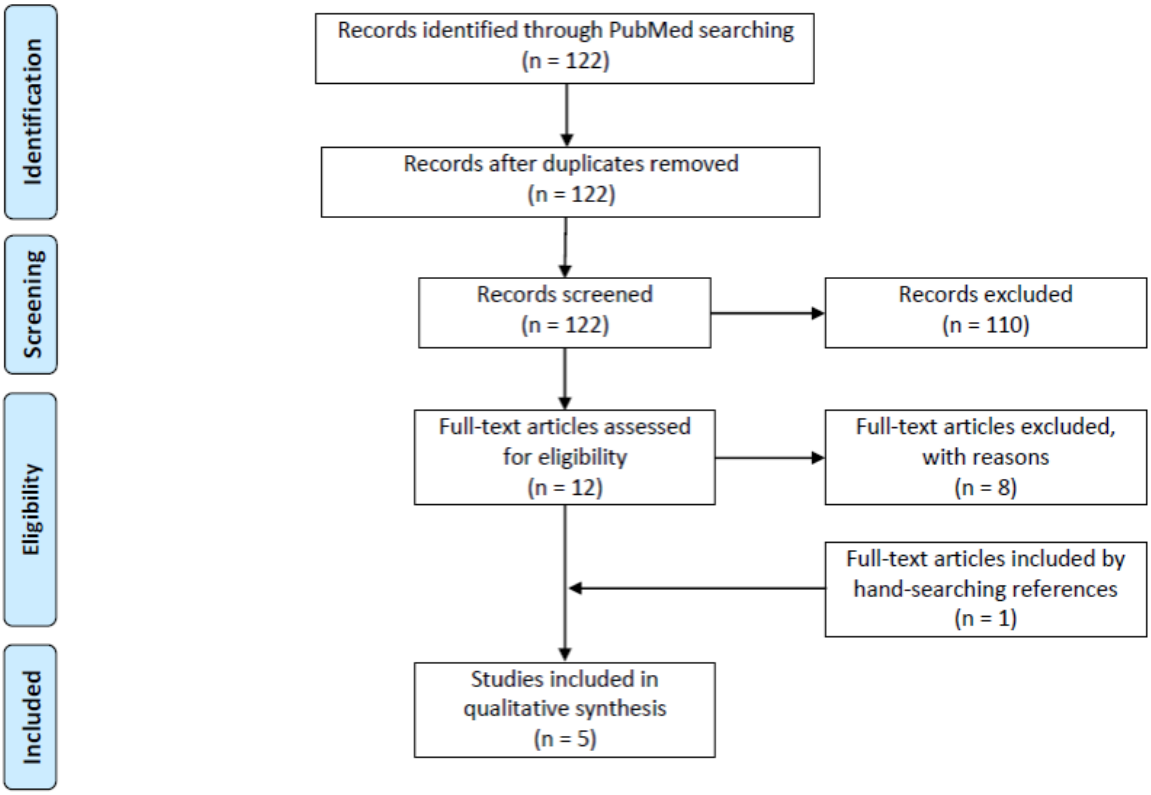
PRISMA 2009 Flow Diagram



Reasons for full-text-exclusion:

Braeckman, J. and L. Denis (2017). "Management of BPH then 2000 and now 2016 - From BPH to BPO." Asian J Urol **4**(3): 138-147: **Review on the history of BPH, no up-to-date clinical data**

da Silva, R. D., et al. (2015). "Bipolar energy in the treatment of benign prostatic hyperplasia: a current systematic review of the literature." Can J Urol 22 Suppl 1: 30-44: **Review without meta-analysis, impossible to interpret without context**

He, L. Y., et al. (2016). "The effect of immediate surgical bipolar plasmakinetic transurethral resection of the prostate on prostatic hyperplasia with acute urinary retention." Asian J Androl **18**(1): 134-139: **Only within PK-TURP-comparison, no comparison to M-TURP**

Hu, Y., et al. (2016). "Five-Year Follow-Up Study of Transurethral Plasmakinetic Resection of the Prostate for Benign Prostatic Hyperplasia." J Endourol **30**(1): 97-101: **No Comparison to M-TURP**

Li, S., et al. (2015). "Plasmakinetic resection technology for the treatment of benign prostatic hyperplasia: evidence from a systematic review and meta-analysis." Sci Rep 5: 12002: **Review without meta-analysis, impossible to interpret without context**

Pham, R., et al. (2016). "How I do it: Same day discharge for transurethral resection of prostate using Olympus PlasmaButton and PlasmaLoop." Can J Urol **23**(5): 8491-8494: **No comparison to M-TURP**

Smith, C., et al. (2017). "Comparison of Traditional and Emerging Surgical Therapies for Lower Urinary Tract Symptoms in Men: A Review." Cardiovasc Intervent Radiol **40**(8): 1176-1184: **Review on the history of BPH-treatment techniques, no up-to-date clinical data**

Ulchaker, J. C. and M. S. Martinson (2018). "Cost-effectiveness analysis of six therapies for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia." Clinicoecon Outcomes Res **10**: 29-43: **No differentiation between M-TURP and B-TURP**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2

We have performed a systematic literature review, searching NCBI PubMed. Please find the detailed PRISMA flow diagram at the end. The search identified the following three (published) sources researching clinical and / or economic outcomes of B-TURP compared to M-TURP:

Alexander, C., et al. (2019). „Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction (Review)" Cochrane Database Syst Rev, 12, CD009629.

- ➢ Cochrane systematic review, included 59 randomized controlled trials (RCTs) comparing M-TURP to B-TURP
- ➢ n= 8924 participants
- ➢ **Endpoints**: Urological Symptoms (IPSS at 12 months), HRQoL, Post-surgical complications

Results: Significant reduction of TUR syndrome (RR 0.17, 95% CI 0.09 to 0.30; participants = 6745; RCTs = 44; I^2 = 0%); No difference in urinary incontinence at 12 months (RR 0.20, 95% CI 0.01 to 4.06; participants = 751; RCTs = 4; I^2 = 0%); Significant reduction in blood transfusions (RR 0.42, 95% CI 0.30 to 0.59; participants = 5727; RCTs = 38; IP = 0%); No differences in rates of re-TURP (RR 1.02, 95% CI 0.44 to 2.40; participants = 652; RCTs = 6; IP = 0%).
Limitations: Methodological limitations in studies, regarding selection bias, performance bias and reporting bias

Huang, S.-W., et al. (2019). "Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis." BMJ (Clinical research ed.) **367**: l5919-l5919.

- ➢ Systematic review and network meta-analysis of RCTs, comprising of 109 trials
- ➢ n=613-4639 participants (bTURP & mTURP comparison)
- ➢ **Endpoints:** Functional outcomes, perioperative parameters, post-operative complications, longterm complications

Results: Compared to mTURP, bTURP showed significantly less blood transfusions (0.42 network OR; 95%CI=0.28-0.61), significantly less clot retention (0.29 network OR; 95%CI=0.12-0.68), significantly shorter hospital stay (-10.05% network mean difference; 95%CI=15.96-4.15), and a non-significant difference in recurrence, urethral stricture, and recatheterisation
Limitations: Model limitations (network meta analysis); No statement of actual length of stay

Müllhaupt, G., et al. (2019). "In-hospital cost analysis of prostatic artery embolization compared with transurethral resection of the prostate: post hoc analysis of a randomized controlled trial." BJU international **123**(6): 1055-1060.

- ➢ Post-hoc analysis of an RCT comparing prostatic artery embolization (PAE) and transurethral resection of the prostate (monopolar TURP)
- ➢ n=99 (48 PAE; 51 mTURP)

- **Endpoints:** Length of stay, Costs

Results: Mean duration of hospital stay was 4.2 days (SD 1.7)*. Mean costs for inpatient stay were 5405€ (SD 2280€) for TURP, mean costs for the surgical procedure were 3617€ (SD 2280€) for TURP, amounting to total in-hospital costs of 9137€ (SD 3301€)

Limitations: No comparison to bTURP; however, LOS could be used for mTURP.

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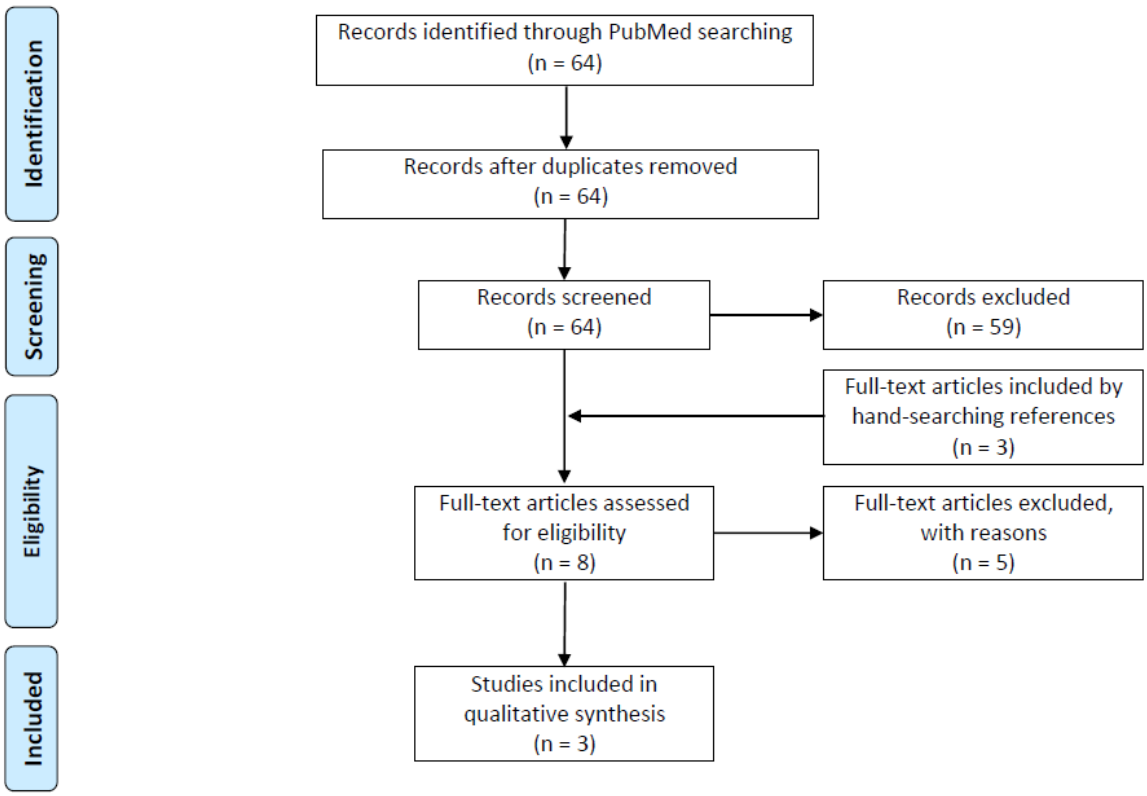
PRISMA 2009 Flow Diagram



Reasons for full-text-exclusion:

Brown, A. D., et al. (2019). "Minimally Invasive Treatment for Benign Prostatic Hyperplasia: Economic Evaluation from a Standardized Hospital Case Costing System." Cardiovascular and interventional radiology **42**(4): 520-527. **Reason for exclusion:** No differentiation between mTURP and bTURP

Davis, N. F., et al. (2019). "Medical therapy versus transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic enlargement (BPE): a cost minimisation analysis." World journal of urology **37**(5): 873-878. **Reason for exclusion:** No explanation for choice of CMA – no clinical data for the therapies was provided, there are reasonable concerns that the outcomes are actually not equal and hence the assumption faulty.

DeWitt-Foy, M. E., et al. (2019). "Cost Comparison of Benign Prostatic Hyperplasia Treatment Options." Current urology reports **20**(8): 45-45. Reason for exclusion: No differentiation between monopolar and bipolar TURP

Miernik, A., et al. (2019). "Endoscopic enucleation of the prostate." Der Urologe. Ausg. A **58**(4): 437-450. **Reason for exclusion:** This is not a clinical trial, but a further education program

Rieken, M., et al. (2019). "Surgical treatment of benign prostatic hyperplasia-resection, vaporization or enucleation?" Der Urologe. Ausg. A 58(3): 263-270. **Reason for exclusion:** Review without data synthesis/meta analysis

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 3

List of current NHS users

[redacted]