NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT565 Optilume for recurrent bulbar urethral strictures

Supporting documentation – Committee papers

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

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **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.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
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.

Upon request of the NICE Medical Technology Appraisal Committee lead team meeting on 07/03/2022, the EAC produced an alternative base case which can be found in Appendix G.

Document cover sheet

Assessment report: Optilume

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EAC sign-off: Dr Rhys Morris

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0.2	Tailored template to subject	MB	23/12/21	
0.3	Clinical context complete	MB	18/01/2022	
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0.5	RoB tables added	MB	23/01/2022	
0.6	Implement suggested changes to draft	MB	24/01/2022	
0.7	Economics sections added	MB	26/01/2022	
1.0	Draft assessment report to NICE	MB	27/01/2022	

1.1	Draft assessment post-NICE review	MB	01/02/2022	
1.2	Results section finalised with updated tables	MB	02/02/2022	
1.3	Clinical evidence review and outcomes tables finalised	MB	06/02/2022	
1.4	Integration into the NHS finalised	MB	07/02/2022	
1.5	Glossary added	MB	07/02/2022	
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1.7	Clean final report for Director (RM) sign-off	MB/RM	08/02/2022	
1.8	Formatting finalised	MB	09/02/2022	
1.9	Economics Section Added, all appendices added. All changes accepted	SO'C	09/02/2022	
2.0	Final report to NICE	MB	09/02/2022	
3.0	Post-fact check	MB	15/02/2022	
4.0	Post-MTAC economic appendix added	MB/MD	05/04/2022	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance
GID-MT565 Optilume for recurrent bulbar urethral strictures
External Assessment Centre report

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Contains confidential information: Yes

Number of attached appendices: 7

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

None

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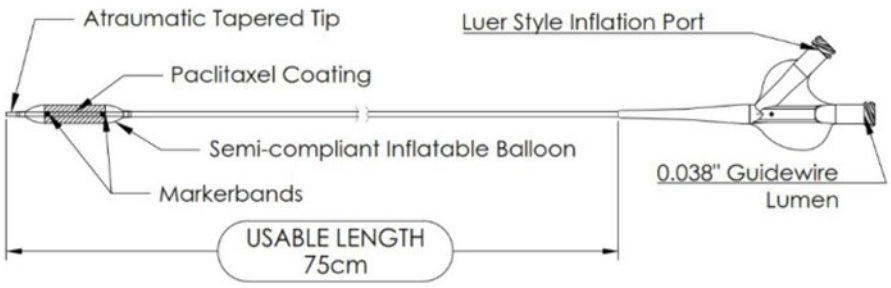

Figure 1. Optilume Drug Coated Balloon design (taken from company instructions for use)

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.

Any ‘commercial in confidence’ information in the submission document should be underlined and highlighted in turquoise.

Any ‘academic in confidence’ information in the report is underlined and highlighted in yellow.

Contents

1 **Glossary**

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Term	Definition
Adenocarcinoma	A malignant tumour originating in glandular epithelium
Aetiology	The cause of a disease or abnormal condition
Alanine Aminotransferase	An enzyme which promotes transfer of an amino group from glutamic acid to pyruvic acid and which when present in abnormally high levels in the blood is a diagnostic indication of liver disease or damage
Anastomosis	The union of parts or branches (as of streams, blood vessels, or leaf veins) so as to intercommunicate or interconnect
Armamentarium	A collection of resources available or utilised for an undertaking or field of activity, especially: the equipment, methods, and pharmaceuticals used in medicine
Asymptomatic	Having or showing no symptoms of disease
Atraumatically	Of a medical or surgical procedure causing minimal tissue injury
Balanitis Xerotica Obliterans	A chronic, progressive, scarring, inflammatory skin condition, also known as Lichen Sclerosus
Benign Prostatic Hyperplasia	Enlargement of the prostate gland caused by a benign overgrowth of chiefly glandular tissue that occurs especially in men over 50 years old and that tends to obstruct urination by constricting the urethra
Brachytherapy	Radiotherapy in which the source of radiation is placed (as by implantation) in or close to the area being treated
Bronchiectasis	A chronic dilatation of bronchi or bronchioles
Bulbar Urethra	An anatomical region of the penis which lies between penoscrotal junction and membranous urethra which includes the external urethral sphincter. The bulbar urethra is divided into the proximal, middle and distal bulbar urethra.

Circumferential	The external boundary or surface of a figure or object
Corpus spongiosum	The median longitudinal column of erectile tissue of the penis that contains the urethra and is ventral to the two corpora cavernosa
Cystoscope/cystoscopy	A rigid endoscope for inspecting and passing instruments into the urethra and bladder
Cystourethrography	Radiography for the purpose of preparing a cystourethrogram, an X-ray study of the urinary bladder and urethra made after injection of these organs with a contrast medium
Dysuria	Difficult or painful discharge of urine
Epithelium	A membranous cellular tissue that covers a free surface or lines a tube or cavity of an animal body and serves especially to enclose and protect the other parts of the body, to produce secretions and excretions, and to function in assimilation
Extravasation	To pass by infiltration or effusion from a proper vessel or channel (such as a blood vessel) into surrounding tissue
Fossa navicularis	Dilatation of the urethra at the most distal portion of the urethra (penile/pendulous urethra) near the urethral meatus.
Haematuria	The presence of blood or blood cells in the urine
Heterogeneity	The quality or state of consisting of dissimilar or diverse elements
Hypospadias	An abnormality of the penis in which the urethra opens on the under surface
Iatrogenic	Induced inadvertently by a physician or surgeon or by medical treatment or diagnostic procedures
Idiopathic	Arising spontaneously or from an obscure or unknown cause
Immunosuppressed	A suppressed immune response

Lichen Sclerosus	A chronic skin disease that is characterized by the eruption of flat white hardened papules with central hair follicles often having black keratotic plugs
Meatotomy	Incision of the urethral meatus (a natural body passage) especially to enlarge it
Myelosuppression	Suppression of the bone marrow's production of blood cells and platelets
Neurogenic bladder	Bladder problems due to disease or injury of the central nervous system or peripheral nerves involved in the control of urination
Neurotoxicity	Toxic to the nerves or nervous tissue
Paclitaxel	An antineoplastic drug $C_{47}H_{51}NO_{14}$ originally derived from the bark of the Pacific yew but now typically derived as a semisynthetic product of the English yew and used to treat ovarian cancer
Penile	Of, relating to, or affecting the penis
Phalloplasty	Plastic surgery of the penis or scrotum
Pharmacokinetic	The characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion
Prophylactic	Guarding from or preventing the spread or occurrence of disease or infection
Prostatectomy	Surgical removal or resection of the prostate gland
Prostatic	Of the prostate, a gland surrounding the neck of the bladder in male mammals and releasing a fluid component of semen
Restenosis	The reoccurrence of stenosis in a blood vessel or heart valve after it has been treated with apparent success
Self-catheterisation	The use of or introduction of a catheter individually
Ultrasonography	The diagnostic use of ultrasound and especially a non-invasive technique involving the formation of a two-dimensional image used for the examination and

	measurement of internal body structures and the detection of bodily abnormalities
Urethra	The canal that in most mammals carries off the urine from the bladder and in the male serves also as a passageway for semen
Urethrography	Radiography of the urethra after injection of a radiopaque substance
Urethrotomy	Surgical incision into the urethra especially for the relief of stricture
Urethroplasty	Plastic surgery of the urethra
Urethroscope	An instrument for viewing the interior of the urethra
Uroflowmetry	Timed measurement of the rate of urination, used to diagnose conditions that result in slow urinary output

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1 Abbreviations

Term	Definition
AUA	American Urological Association
BPH	Benign Prostatic Hyperplasia
BOO	Bladder Outlet Obstruction
BXO	Balanitis Xerotica Obliterans
CE	Conformity European Certification
CI	Confidence interval
CRD	Central Registration Depository
CDSR	Cochrane Database & Systematic Reviews
CKD	Chronic Kidney Disease
CUA	Canadian Urological Association
DARE	Database of Abstracts of Reviews of Effects
DCB	Drug-coated Balloon
DHSC	Department of Health and Social Care
DVIU	Direct Vision Internal Urethrotomy
EAC	External Assessment Centre
EAU	European Association of Urology
EEC	European Economic Community
EED	European Evaluation Database
EPA	Excision and Primary Anastomosis
EU	European Union
FDA	Food and Drug Administration
FSN	Field Safety Notice
ICTRP	International Clinical Trials Registry Platform
IIEF	International Index of Erectile Function
INHTA	International Network of Health Technology Assessment
IPSS	International Prostate Symptom Score
IPSS QoL	International Prostate Symptom Score – Quality of Life
ISD	Intrinsic Sphincter Deficiency
ITT	Intention-to-treat
IQR	Interquartile range
LS	Lichen Sclerosis
LUTS	Lower Urinary Tract Symptoms
MAUDE	Manufacturer and User Facility Device Experience
MDA	Medical Devices Agency
MeSH	Medical Subject Heading
MHRA	Medicines & Healthcare products Regulatory Agency
MIB	MedTech Innovation Briefing
MTAC	Medical Technologies Advisory Committee
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PIFU	Patient-initiated follow-up
PROM	Patient-reported Outcome Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVR	Post-Void Residual
Qmax	Maximum Flow Rate
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
ROBUST	Re-Establishing Flow via Drug Coated Balloon for the Treatment of Urethral Stricture Disease
SAE	Serious Adverse Event
SD	Standard deviation
SHIM	Sexual Health Inventory for Men
tEPA	Transecting Excision and Primary Anastomosis
USS-PROM	Urethral Stricture Surgery Patient Reported Outcome Measure
VAS	Visual analogue scale
Vs	Versus

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Executive summary

Optilume® Urethral Drug-Coated Balloon (Optilume DCB) is a CE marked medical device incorporating an inflatable balloon passed over a guidewire through the urethra of the penis. Under direct vision, the balloon is placed along the length of a urethral stricture. The balloon has a proprietary circumferential coating of the anti-fibrotic and anti-proliferative pharmaceutical Paclitaxel. When the balloon is in-situ across the stricture and inflated, the paclitaxel adheres to the luminal wall of the urethra and acts to prevent new tissue growth and reduce scar formation – a common cause of urethral stricture disease recurrence. Through a decreased stricture recurrence, Optilume is proposed to improve lower urinary tract symptoms commonly experienced by men with urethral strictures.

Current treatment options for urethral strictures include first-line endoscopic management (DVIU/dilatation), and open surgery urethroplasty. However, failure rates are high with endoscopic management but many patients choose not to undergo open surgery. Following a stricture recurrence, treatment options are limited, often requiring frequent repeat endoscopic procedures. Optilume is proposed as an alternative treatment to further endoscopic procedures for men ≥18 years with recurrent anterior urethral strictures. The claimed benefits of Optilume include a rapid and sustained improvement in urinary symptoms and the need for retreatment with either endoscopic procedures or the costly open surgery urethroplasty.

The current clinical evidence for Optilume DCB device consists of three North American studies; ROBUST I, II and III. All three are multicentre trials, but comparative evidence is limited to the randomised ROBUST III trial which compares Optilume to standard care (DVIU/dilatation) in the treatment of urethral strictures. ROBUST I is the only study with outcomes beyond 1-year.

Successful treatment of a urethral stricture can be measured by several methods; subjectively by assessing the patients' symptoms, or more objectively by the clinician through assessment of the anatomical success and freedom from repeat intervention. In the ROBUST trials, all clinically significant outcomes were improved rapidly in patients treated with Optilume, and supported by unpublished 4-year data. In ROBUST III, Optilume improved symptoms immediately for all outcomes and up to 1-year follow up compared with standard care. Conversely, initial improvements in symptoms in the control group were short-lived and started to deteriorate rapidly, with a higher stricture recurrence rate.

The economic model was structured appropriately, and used the best available source of evidence, ROBUST III, a comparative RCT with 1 year outcomes. The key clinical parameter for the model is the recurrence of stricture, and the subsequent retreatment with either a repeat of the initial procedure, or with urethroplasty. The model becomes cost saving when sufficient retreatments are avoided to compensate for the increased cost of the Optilume procedure compared with standard

endoscopic methods. There are some additional cost savings related to reduced time in a health state with recurrent stricture, and a reduction in procedure related adverse events, however these are minor and depend on several assumptions.

The EAC made only one substantial change to the base case model, which was to assume all Optilume procedures took place in a day case setting, and none were carried out as an outpatient procedure. The EAC also undertook additional modelling to explore the impact of an extended time horizon and alternative clinical inputs.

The amended model resulted in a cost saving of £1,877 per person with recurrent stricture treated with Optilume compared to standard endoscopic management, at 5 years. The model remained cost saving for all scenarios at 5 and 10 years, however the magnitude of the result was dependant on the inputs used to define stricture recurrence.

The EACs assessment of the current evidence base and feedback from clinical experts using the Optilume device indicate that Optilume is a clinically effective and safe treatment that is likely to be cost saving. Optilume therefore has a place in NHS therapy for the treatment of urethral strictures. However, it is important to note that the evidence is limited to men aged ≥18 years with a recurrent bulbar urethral stricture who have previously undergone a failed endoscopic procedure and this may limit the generalisability of the evidence both in terms of the population and the potential place for Optilume in the clinical pathway.

1 Decision problem

The company have proposed some variations to the decision problem in the scope, the main changes being to the population (Table 1).

The scope included men with bulbar urethral strictures and the company are proposing this is changed to patients with anterior urethral strictures. In an early discussion with Cedar, the company advised that Optilume is indicated in any type of anterior urethral stricture [see correspondence log], however the EAC note that there is limited clinical evidence for the use of Optilume in strictures other than those in the bulbar region. The term ‘anterior urethral strictures’ includes penile strictures and there is currently extremely limited evidence for the use of Optilume in penile strictures. In addition, according to clinical experts, patients with penile strictures typically do not respond well to endoscopic management such as dilatation, and are usually offered urethroplasty which is much more effective in these stricture types. Clinical experts therefore agreed that they would not consider Optilume as a treatment option in penile strictures as the standard of care is to perform urethroplasty. All clinical experts recommended that the indication for Optilume be changed to ‘Bulbar urethral strictures’ only, as outlined in the scope [see correspondence log]. The EAC agreed with these clinical expert recommendations.

The company has proposed the addition of 'bothersome urinary symptoms' to population. The EAC consider this is appropriate as urethral strictures cause lower urinary tract symptoms (LUTS), and where bothersome, are likely to require treatment.

The company states that Optilume can be used for single, tandem or diffuse anterior urethral strictures. Although not a variation from the scope, the EAC discussed this with clinical experts who agreed that they would use Optilume in tandem or diffuse urethral strictures, providing the balloon will stretch the length of the stricture(s). One clinical expert commented that the terminology 'tandem' and 'diffuse' are terminology not commonly used amongst urological clinicians but define two discreet strictures, or one long stricture, respectively.

The company have added self-catheterisation as an outcome when considering time to treatment failure. In discussion with clinical experts with experience of using Optilume, catheterisation post-treatment was not commonplace therefore the EAC do not agree with the addition of self-catheterisation as an outcome.

Table 1: Decision problem scope

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	Men 18 years of age and over with recurrent bulbar urethral strictures equal to or less than 3 cm in length.	Men ≥18 years of age with bothersome urinary symptoms associated with recurrent urethral stricture disease for a single, tandem or diffuse anterior urethral stricture of ≤3 cm in length	Rationale for addition of 'bothersome urinary symptoms' is valid as per Optilume company indications for use (pg.4). The terms 'tandem' and 'diffuse' are terminology not used in clinical practice, but would still be treated using Optilume according to clinical experts. As discussed throughout the report, there is insufficient evidence for the use of Optilume in anterior urethral strictures as the evidence base is limited in all but bulbar urethral strictures. The EAC has amended the population to Men ≥18 years of age with bothersome urinary symptoms associated with recurrent bulbar urethral stricture of ≤3 cm in length.

Intervention	Optilume®		

Comparator(s)	• Urethral dilatation
	  ○ S-Curve Dilators
	  ○ Rigid rod (metal or plastic) dilatation
	• Urethrotomy (Steel blade mounted on a urethroscope)
	• Urethroplasty		

Outcomes	The outcome measures to consider include: • Stricture free rate • Rate of reintervention procedures • Time to treatment failure (time until additional stricture treatment is required) • Qmax (Peak flow rate) as measured by uroflowmetry • International Prostate Symptom Score • Post-void residual (PVR) urine volume • Device-related adverse events	The outcome measures to consider include: • Stricture free rate • Rate of reintervention procedures • Time to treatment failure (time to additional stricture, including self-catheterisation) • Qmax (Peak Flow Rate) as measured by uroflowmetry • International Prostate Symptom Score • Post-voice residual (PVR) urine volume • Device-related adverse events	Change to scope outcomes to include self-catheterisation when considering time to treatment failure. As self-catheterisation was not considered a relevant outcome by the clinical experts, the EAC do not agree with the addition of self-catheterisation to the scope.
Cost analysis	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.		
Subgroups	None identified		
Special considerations,	Optilume® is intended for men with recurrent bulbar		

including issues related to equality	urethral strictures. These can be caused by injury to the penis, surgery or infection. Some people may not identify as men but have a penis. Urethral strictures become more common in people over 55. Sex, gender reassignment and age are protected characteristics under the Equality Act (2010).		

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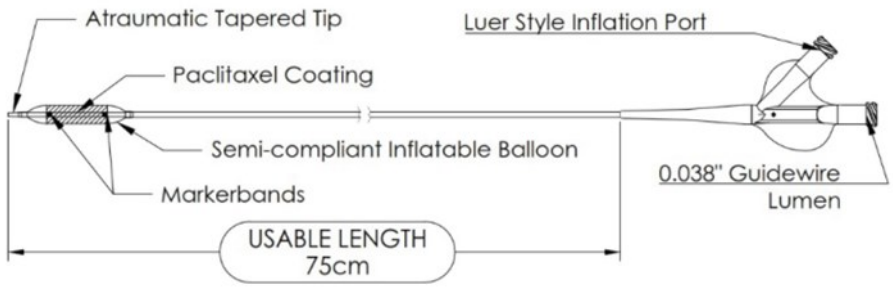
2 Overview of the technology

Optilume urethral drug-coated balloon (Optilume DCB; Urotronic, Plymouth, MN) is the first drug-coated balloon developed for the management of urethral stricture disease in adult males ≥18 years. The Optilume DCB is contraindicated for use in people with known hypersensitivity to paclitaxel or structurally related compounds, and lesions that cannot be crossed with a 0.038" guidewire. Clinical experts agreed that it would not be used in those with a known hypersensitivity to paclitaxel, but also stated it would not be used in people who were immunosuppressed.

Optilume is designed to be used as a dilatation balloon for a single, tandem or diffuse anterior urethral stricture of ≤3 cm in length. Although the terms 'tandem' and 'diffuse' are not commonly used in UK clinical practice, clinical experts noted that they would use the Optilume DCB for two discreet strictures.

The device is a 0.038-inch (0.97 mm) guidewire and flexible cystoscope compatible over-the-wire catheter, with a dual lumen design and a tapered atraumatic tip (Figure 1). The Optilume DCB is passed over a guidewire under direct vision and placed in position along the length of the stricture using the two radiopaque marker bands that indicate the working length of the balloon. The distal end of the catheter has a semi-compliant inflatable balloon which is inflated using normal saline/water with a pressure inflation device provided by the company for a minimum of 5 minutes to mechanically dilate the urethral stricture designed for immediate symptomatic relief. Once adequate inflation time and urethral dilatation have been achieved, the balloon can be deflated, removed, and safely disposed of. A catheter may be placed at the discretion of the clinician and can be administered post-operatively although clinical experts suggest this is not standard practice in the NHS.

Figure 1: Optilume Drug Coated Balloon design (taken from company instructions for use)



The innovative aspects that the Optilume device incorporates is the proprietary circumferential coating of 3.5 µg/mm^2 of the active pharmaceutical paclitaxel along

the working length of the balloon body. The paclitaxel is an antifibrotic and antiproliferative drug which acts to prevent new tissue growth and reduce scar formation and is already used as a coating in minimally invasive vascular applications to prevent restenosis.

The Optilume DCB device is available in six sizes; two lengths and three diameters (Table 2).

Table 2: Optilume Drug Coated Balloon dimensions

Diameter (Fr/mm)	Length (mm)	Paclitaxel dose (mg)
18.0/6.0	30	2
18.0/6.0	50	3.3
24.0/8.0	30	2.6
24.0/8.0	50	4.4
30.0/10.0	30	3.3
30.0/10.0	50	5.5

Optilume DCB is a Class III, CE marked (CE 1434) device. The company submitted the necessary regulatory requirements for the device, including CE certification and declaration of conformity to medical directive (93/42/EEC) and these have been checked and confirmed by the EAC. Since the original launch of Optilume DCB, the company state that there have been no changes or refinements to device functionality.

3 Clinical Context

Urethral strictures result from an abnormal circumferential scarring in the epithelium and underlying corpus spongiosum of the urethra, to varying degrees, causing progressive narrowing of the urethral lumen. The origins of this fibrosis may be due to intrinsic conditions but commonly occur in response to damage or infection. Regardless, all strictures involve some injury to the epithelium, and during the subsequent healing process, fibrosis and scarring of the vascular corpus spongiosum occurs (Simsek et al. 2018). Urethral stricture disease has several different aetiologies; iatrogenic, idiopathic, inflammatory or traumatic causes. The most frequent is iatrogenic resulting from urethral manipulations, related to placing of indwelling catheters, transurethral manipulation, surgery for hypospadias, prostatectomy and brachytherapy. Strictures can also occur due to trauma associated with pelvic fractures, and in approximately 60% of patients the function of the distal sphincter mechanism and hence continence depends on the integrity of the bladder neck. The least prevalent cause in the UK is infection, including untreated gonorrhoea and chlamydia, Balanitis Xerotica Obliterans (BXO) and Lichen Sclerosus (Lumen et al. 2009).

The incidence of urethral strictures is relatively common, but differs based on worldwide populations, geography and income. Prevalence increases with age, rising from around 20 per 100,000 in their 50s, to over 100 per 100,000 for men over 65. Urethral stricture disease accounted for 17,000 hospital admissions in 2016-2017 in the UK, with management of strictures equating to an NHS cost of £18 million in the 12-month period (Bugeja et al., 2021).

Patients with urethral strictures present with lower urinary tract symptoms (LUTS). The majority of patients with strictures experience moderate complications such as bother from lower urinary tract voiding symptoms, recurrent urinary tract infection and the need for repeat urethral procedures (Santucci, Joyce, and Wise 2007). Left untreated, strictures can lead to serious complications such as recurrent urinary tract infections, urinary retention and eventual renal impairment (Bugeja et al. 2020).

The EAC identified a number of potentially relevant guidelines including NICE Guidance for the management of LUTS in men (NICE CG97). Additional guidance is available from European Association of Urology (REF), the American Urological Association (REF) and the Canadian Urological Association (REF). Where relevant, specific recommendations are discussed in this section and Table 3 summarises the potentially relevant recommendations from the EAU and NICE CG97. Potentially relevant recommendations from the CUA and AUA can be found in Appendix B.

The diagnosis of urethral stricture and determination of stricture aetiology and measurement requires a full patient history to document the onset and severity of obstructive and storage-related voiding symptoms. In the UK, diagnosis of strictures in patients presenting with LUTS often depends upon the facilities at the treating centre. Uroflowmetry is widely used in the assessment of the urethral stricture and retrograde urethrography is also used to provide information on stricture location and length. Cystoscopy is also commonly used as it can show the location and degree of stricture, but if the stricture cannot be passed, limited information can be obtained. Therefore, ultrasonography can also be helpful in assessing the stricture length and degree of spongiofibrosis and scarring.

Clinical experts noted that patient age would have an impact on whether they considered the presence of a urethral stricture to be the reason for LUTS. The experts noted for example that in a young patient with LUTS, a urethral stricture would be one of the most likely diagnostic priorities. However, in an elderly patient with LUTS, a urethral stricture would not necessarily be the first diagnostic assumption. Instead, the patient would perhaps undergo investigations for benign prostatic hyperplasia (BPH), and managed using the appropriate care pathway [see EAC correspondence log].

Following appropriate clinical assessment and diagnosis of a urethral stricture, when considering management options for a patient, many factors need to be considered including:

- Stricture length, aetiology, location, number of strictures
- Timing of previous interventions
- Symptom severity and the presence of complications
- Patient factors including co-morbidities, contraindications and patient preference
- Age and general well-being of the patient
- Impact of management on quality of life
- The expertise available to the patient

Current treatment options for urethral stricture include urethral dilatation, direct visual internal urethrotomy (DVIU) and urethroplasty. Choice of treatment is considered as part of a multi-disciplinary team, with first-line treatment of strictures shorter than 3 cm in length being managed with either of two endoscopic procedures; urethral dilatation or urethrotomy, unless the patient has a contraindication or would prefer to undergo urethroplasty.

Urethral dilatation – An endoscopic procedure carried out by a urologist and performed under local or general anesthesia with or without sedation and cystoscopy. Dilatation involves the sequential dilatation of a stricture with a balloon, filiform and followers, urethral sounds, or self-dilatation with catheters. A standard non-drug coated balloon dilatation may also be available. A stricture that narrows again following dilatation often requires repeated dilatation and/or direct visual internal urethrotomy.

Direct Visual Internal Urethrotomy (DVIU) – An endoscopic procedure carried out by a urologist and performed under general anaesthesia using a cold or hot-knife transurethral incision to release the stricture tissue. Like urethral dilatation, urethrotomy may be offered as a first line therapy. However, patients with longer strictures (>2 cm), multiple, penile or distal strictures typically do not respond well to repeat incisions and are usually offered urethroplasty as it is more effective for treating such stricture types.

Urethroplasty - A highly-invasive open surgical procedure done under general anaesthesia by specialist urologists in a limited number of tertiary UK centres. Urethroplasty is the ‘gold standard’ curative treatment option for patients with urethral strictures, with a higher success rate in resolving urethral strictures with no further treatment needed, compared with the existing standard endoscopic treatments aforementioned. However, urethroplasty takes an average of two to three hours operative time, followed by a 1-2-night hospital stay, post-operative catheterisation for 2-3 weeks during a 2-6-week recovery period at home (Shen et

al., 2021). A cheek or lower lip buccal mucosal graft may also be required for augmentation and as noted by one clinical expert, if grafting were needed, it would be done as part of the initial urethroplasty.

Men undergoing urethroplasty in the UK have often had several previous endoscopic urethral stricture treatments often due to a chronic stricture state. These patients may also require self-catheterisation and repeat treatments of the same stricture. Recurrence rates for both current endoscopic procedures vary considerably between 8-77% after DVIU and 36-92% after dilatation, but lead to progressively worse outcomes over time, with an almost 100% failure rate after three treatments (Al Taweel and Seyam 2015; Heyns et al., 1998).

The number of urethral dilatation and/or urethrotomy treatments performed in a patient with a urethral stricture before urethroplasty varies and is dependent upon the local facilities available and the patient's preference. Thus, resource utilisation and costs associated with carrying out multiple procedures prior to urethroplasty make for a prolonged, often repetitive, and burdensome issue for both the patient and healthcare service.

Optilume is a proposed addition to the treatment options for bulbar urethral strictures in men who have undergone ≥1 prior endoscopic procedures which have failed. The indication for Optilume is not to replace any of the currently available treatments but to add to the existing armamentarium in an effort to delay or prevent the need for the more invasive urethroplasty surgery.

Procedures using Optilume DCB take approximately 20-25 minutes according to a clinical expert using Optilume in the UK. According to the company, the technology can be used by trained consultants in urology, urology trainees, and urology nurse specialists and would be indicated in the treatment of patients presenting with anterior urethral strictures ≤3cm as a standalone treatment, or as an adjunctive therapy to existing endoscopic management of urethral strictures. The EAC note that the technology should not be used in penile strictures. This is supported by the clinical experts who commented that they would not use Optilume in penile strictures as open surgery is much more effective for these patients. Additionally, European Association of Urology (EAU) guidelines recommend against the use of DVIU and urethral stents for penile strictures. Instead, the EAC guidelines recommends offering men with penile urethral stricture disease, augmentation urethroplasty by either single-stage or staged approach, taking into consideration previous interventions and stricture characteristics. The American Urological Association (AUA) also recommend initial treatment of meatal of fossa navicularis strictures (penile strictures) with either dilatation or meatotomy.

The company state that the procedure can be performed in an outpatient setting under local anaesthesia or conscious sedation, removing the requirement for

inpatient stay, general anaesthesia and theatre time. The company made the EAC aware that there is one clinician in the UK using the device in an outpatient setting under local anaesthesia Clinical experts however were not convinced that outpatient care using Optilume was feasible. They raised several concerns such as the discomfort to the patient. One clinical expert noted that due to the degree of precision required, the patient must remain still for approximately 7 minutes, which experts felt was unrealistic and would be unlikely to be tolerated by the patient. Another expert added that sedation cannot be done in an outpatient setting. One expert noted that sedation of a patient with I.V. sedation allows them to sleep through the procedure; making it not only more comfortable for the patient, but easier for the procedure to be performed. Therefore, in treating patients with Optilume, experts would use general anaesthesia or local anaesthesia with sedation to ensure the patient is comfortable, avoiding the risk of compromising the precision of the procedure. Two experts treating a small number of patients with Optilume in the NHS noted that the recovery time was a couple of hours, and most patients woke from sedation with no side effects reported. Post-operatively, experts noted that catheterisation was not necessary but that the bladder should be emptied prior to discharge. The company also recommend that due to the potential genotoxicity of paclitaxel, men should have protected sex for 30 days post-treatment, and those with sexual partners of childbearing age should use a condom for at least 90 days post-treatment to avoid possible drug transmission and teratogenic risk.

Both the AUA and CUA recommend that surgeons should offer urethroplasty rather than repeated endoscopic management following failed dilatation or direct visual internal urethrotomy (DVIU) for recurrent anterior urethral strictures as the short-term outcomes are comparable, but recurrence rate for urethroplasty is lower than endoscopic management (16% Vs 28%) (Rourke et al, 2020.,Pickard et al. 2020., Wessells et al, 2016). However, in the NHS the decision of whether to continue using endoscopic management or to refer a patient to surgery for urethroplasty is usually a multidisciplinary decision taking into consideration the wishes of the patient. In the experience of the clinical experts, it was noted that when given the choice, patients often choose to avoid or postpone open surgery (urethroplasty), and instead prefer to undergo endoscopic procedures in the knowledge that there is a chance of recurrence. Additionally, endoscopic procedures are low risk and can often be performed close to home by community/general urologists. Due to the specialist nature of urethroplasty and limited number of surgeons trained in urethroplasty in the UK, waiting time for this surgery can be long. Clinical experts reported that the coronavirus pandemic has further exacerbated this problem, with waiting lists now up to two years long according to one clinical expert. Optilume however can be performed by a general urologist and may therefore reduce waiting lists for patients requiring treatment.

During discussion with clinical experts, the EAC queried whether experts would consider re-treating a stricture recurrence with another Optilume device. One expert stated that they would use it again but the decision would be based upon timeframe of stricture recurrence. Several experts agreed that they would see no issue with considering Optilume for re-treatment of a recurrent stricture, but as there is no rigid pathway, the choice is likely to be patient driven. There is limited evidence for repeat Optilume in the ROBUST trials as discussed in section 5.3.

Table 3: Potentially relevant guideline recommendations for urethral strictures

Guideline	Potentially Relevant Recommendations
NICE Clinical Guidance (CG97) (Updated 06/2015)	**Diagnosis/Initial management** • At initial assessment, offer men with LUTS an assessment of their general medical history to identify possible causes of LUTS, and associated comorbidities. Review current medication, including herbal and over-the-counter medicines, to identify drugs that may be contributing to the problem.
EAU (Lumen et al., 2021)	**Aetiology and prevention** • Advise safe sexual practices, recognise symptoms of sexually transmitted infection and provide access to prompt investigation and treatment for men with urethritis. • Avoid unnecessary urethral catheterisation • Do not routinely perform urethrotomy when there is no pre-existent urethral stricture **Physical examination** • Use a validated patient reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease. • Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease • Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease • Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery • Combine retrograde urethrography with voiding cystourethrography to assess (nearly)- obliterative strictures, stenoses and pelvic fracture urethral injuries

Guideline	Potentially Relevant Recommendations
	• Perform cystourethroscopy as an adjunct to imaging if further information is required • Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required. **Disease management in males** • Do not intervene in patients with asymptomatic incidental (>16 Fr) strictures • Do not use direct vision internal urethrotomy (DVIU) for penile strictures • Do not use DVIU/dilatation as solitary treatment for long (> 2cm) segment strictures • Perform DVIU/dilatation for a primary, single, short (<2 cm) and non-obliterative stricture at the bulbar urethra • Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty • Use either “hot” or “cold knife” techniques to perform DVIU depending on operator experience and resources • Use visually controlled dilatation in preference to blind dilatation • Do not perform repetitive (> 2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option • Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/direct vision internal urethrotomy if urethroplasty is not a viable option • Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture • Do not use permanent urethral stents • Do not use urethral stents for penile strictures • Use a temporary stent for recurrent bulbar strictures after direct vision internal urethrotomy to prolong time to next recurrence only if urethroplasty is not a viable option • Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics

Guideline	Potentially Relevant Recommendations
	• Offer an interval of at least four to six months before proceeding to the second stage of the procedure provided that outcome of the first stage is satisfactory • Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively • Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings • Do not use genital skin in augmentation penile urethroplasty in men with Lichen Sclerosus-related strictures. • Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with lichen Sclerosus-related strictures. • Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures • Use transecting excision and primary anastomosis (tEPA) for short posttraumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis • Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury • Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA) • Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment • Do not perform endoscopic treatment for an obliterative stenosis • Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis • Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment • Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion **Disease management in transgender patients** • Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty

Guideline	Potentially Relevant Recommendations
	• Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent **Peri-operative care of urethral surgery** • Do not perform urethroplasty within three months of any form of urethral manipulation • Administer intra-operative prophylactic regimen with antibiotics at time of urethral surgery • Use PROM questionnaires to assess subjective outcomes and patient satisfaction • Use validated questionnaires to evaluate sexual function after urethral stricture surgeries

Special considerations, including issues related to equality

Optilume is intended for men with recurrent bulbar urethral strictures. These can be caused by injury to the penis, surgery or infection. In discussion with clinical experts, it was noted that Optilume would not be indicated in patients with lichen sclerosis or Balanitis Xerotica Obliterans (BXO) as such dense scarring tissue is not suitable for Optilume. A second expert added that this very dense scarring stricture makes dilatation with a balloon very difficult, and therefore would not consider using Optilume in BXO patients as urethrotomy would be more suitable. Patients with BXO would need the infection treated prior to using Optilume for the stricture and according to one clinical expert, were likely not included in the ROBUST trial due to the risk of sepsis if left untreated. The company also state in their device instructions for use that safety and effectiveness data have not been established during the clinical study of Optilume to support the treatment of strictures in patients with BXO. This proposed change to indications is not thought to impact the use of Optilume in the UK due to the rarity of infection-related urethral strictures in the UK.

Clinical experts also commented that patients with trauma-induced strictures probably would not be candidates for Optilume either, but these patients would be discussed in a multi-disciplinary meeting.

Patients with contraindications or hypersensitivity to paclitaxel would not be candidates for the Optilume DCB. One clinical expert noted that patients with immunosuppression would also be unlikely to receive treatment with Optilume.

Sex, gender reassignment and age are protected characteristics under the Equality Act (2010) and the EAC considered the use of Optilume in these groups individually below.

The company noted in their special considerations that some people may not identify as men but have a penis. The EAC questioned the use of Optilume in trans men who have undergone female to male gender reassignment, specifically in patients post-phalloplasty. The company advised that the stricture rate for this population is quite high, but the device has not been studied in this population yet. The company were also optimistic about the devices potential use in this subpopulation in the future. The EAC believe that this may be a potential equalities issue as Optilume may not be a suitable treatment option for the treatment of trans men as there is currently no evidence in this population and it is unclear whether the current evidence is generalisable.

Urethral strictures become more common in people over 55. The EAC did not identify any equalities issues relating to Optilume generalisability in the population aged ≥55 years.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company conducted a broad search over a very wide time period from the 1st January 1900 to the 3rd December 2021. The search was not limited to humans and was conducted during years when Optilume would not have been available in addition to years when it would be available. The concepts used to search for evidence included the population, intervention, comparator and outcomes: urethral stricture, drug coated balloons, standard endoscopic treatments or urethroplasty and the outcome of stricture recurrence. They searched for evidence for efficacy and safety.

The company ran searches in Medline (PubMed) and searched two clinical trial registration databases. Adverse events were searched for in the MHRA's medical device alerts and field safety notices, and the FDA MAUDE database using the product name between 1st January 1900 and 9th December 2021. When searching Medline, they utilised MeSH headings and free text terms for the population concept and free text terms for the population, intervention, comparator and outcome concepts. The search results were filtered for 'Clinical Trial' and 'Randomised Controlled Trial'. The search in the two clinical trial databases (US National Library of Medicine Registry and EU Clinical Trials Register) was run using 'Urethral Stricture' as a very broad key word. The searches in both Medline and the clinical trial registration databases resulted in 2,796 records of which 2,628 were removed by an unspecified automation tool. As the searches were broad and only run in one database and 2 clinical trial registration databases and

pre-selection was performed using an unspecified automation tool, the EAC were not confident all relevant literature had been obtained and therefore conducted their own systematic searches. Details of the company and EAC searches are provided in appendix A.

The inclusion and exclusion criteria applied by the company are summarised in Table 4. The company included all studies that reported outcomes after endoscopic single arm treatment or open surgical single arm treatment for male urethral stricture patients. The EAC also considered randomised clinical trials, cohort studies and comparative case series for relevant information. They restricted inclusion to studies available in English.

Table 4: Company study selection criteria

Inclusion and exclusion criteria:
Inclusions: • Male urethral stricture • Outcomes after endoscopic treatment, single arm • Outcomes after open surgical treatment (urethroplasty), single arm • Randomised comparative studies Exclusions: • Preclinical/animal studies • In-vitro studies • Paediatric studies • Case reports or early experimental techniques • Editorials, commentary, technology assessments • Posterior or membranous strictures • Hypospadias repair, meatal/glans stricture repair • Studies of adjunct therapies (e.g. steroids, mitomycin C) • Diagnostic assessments • Female strictures • Cost effectiveness or other non-recurrence outcome measures • Clean intermittent catheterisation or home dilatation • Study protocol or design discussion • Non-comparable population (e.g. length >5cm, urethral dislocation)

The EAC literature searches identified 43 records through database searching. The company submission included 17 studies, one journal article in press, a published abstract. The company also provided the EAC with an additional unpublished trial report and an additional abstract due for publication in March 2022, totaling 21 papers. After duplicates were removed, 54 records were screened independently by title and abstract in accordance with the scope by two EAC researchers. Of these, 35 records were excluded by title and abstract sifting as they were outside of the scope, leaving 19 full-text articles assessed for

eligibility. Full texts were retrieved and reviewed again by two researchers, and disagreements on inclusion were discussed until a consensus was reached. Four of the full-text articles were excluded; 3 narrative reviews and 1 with no mention of Optilume. This left 15 records included in the evidence base; 4 full-text peer-reviewed publications (DeLong et al., 2022; Elliott et al., 2021a; Mann et al., 2021; Virasoro et al., 2020) one unpublished trial report (Elliott et al., 2022a), and 10 abstracts (Chee et al., 2021; Elliott et al., 2022b; Elliott et al., 2021b; Elliott et al., 2021c; Elliott et al., 2020; Elliott et al., 2019; Justin et al., 2021; Pichardo et al., 2019; Virasoro et al., 2021; Wang et al., 2019).

A full study flow diagram outlining the number of studies identified by the EAC and excluded at each stage can be found in Appendix A.

4.2 *Included and Excluded Studies*

There were four publications (DeLong et al., 2022; Elliott et al., 2021a; Mann et al., 2021; Virasoro et al., 2020), one unpublished trial report (Elliott et al., 2022a) and 10 abstracts (Chee et al., 2021; Elliott et al., 2022b; Elliott et al., 2021b; Elliott et al., 2021c; Elliott et al., 2020; Elliott et al., 2019; Justin et al., 2021; Pichardo et al., 2019; Virasoro et al., 2021; Wang et al., 2019) included in the evidence base. All publications and abstracts related to three studies (ROBUST I, ROBUST II and ROBUST III) which were considered relevant to the decision problem. Two of these (DeLong et al., 2022, Elliott et al., 2021a) had not been published at the time of the company submission but were included as unpublished evidence and provided as part of their submission. Both studies have since been published and the peer-reviewed publications are used in this assessment report. Results from the unpublished trial report (Elliott et al., 2022a) were also used where relevant. Mann et al., 2021 was the only study referenced in a previous NICE product (MIB241), a multicentre, single-arm, prospective open-label study investigating the safety and efficacy of Optilume.

Of the 21 studies included by the company, 14 of the studies were excluded by the EAC as they did not include the use of the Optilume device; eight because the technology concerned Urethrotomy (Azab et al., 2020; Cecen et al., 2014; Guo et al., 2010; Heyns et al., 1998; Isen et al., 2015; Pansadoro et al., 1996; Santucci et al., 2010; Steenkamp et al., 1997); four concerned urethroplasty (Aldaqadossi et al., 2014; Elkady et al., 2019; Erickson et al., 2014; Hoy et al., 2013); 1 used an alternative stent to Optilume (Jordan et al., 2013); and 1 compared urethrotomy to urethroplasty without the inclusion of Optilume (Pickard et al., 2020). These are presented separately in Table 5.

In addition, 9 abstracts relating to ROBUST I, II and III were identified by the EAC, one of which (Chee et al., 2021) had not been included in the company submission. The company also provided one abstract (Elliott et al., 2022b) not yet published. A list of abstracts can be found in Appendix B.

Table 5: Studies selected by the EAC as the evidence base

Publication	Included in Company Submission	Included in EAC Assessment Report	EAC Comment
Aldaqadossi et al., 2014	✓	X	Prospective randomised study into urethroplasty techniques only, with no use of Optilume and so is outside scope of MTG
Azab et al., 2020	✓	X	Prospective comparative study comparing Amplatz renal dilator Vs. visual internal urethrotomy, with no use of Optilume and so is outside scope of MTG
Cecen et al., 2014	✓	X	Prospective randomised study into urethrotomy techniques only, with no use of Optilume and so is outside scope of MTG
DeLong et al., 2022	✓	✓	Manuscript submitted by company. Not identified during EAC literature search. Publication became available early 2022. This study has 1-year outcomes from ROBUST II
Elkady et al., 2019	✓	X	Prospective randomised study into urethroplasty techniques, with no use of Optilume and so is outside scope of MTG
Elliott et al., 2021a	✓	✓	One-year results for ROBUST III. Abstract submitted by company (Elliott et al., 2021b), but during assessment report process, study was published and is used in the evidence base.
Elliott et al., 2022a (Unpublished)	✓	✓	Unpublished 4-year report on ROBUST I data submitted during assessment report process.
Erickson et al., 2014	✓	X	Study into urethroplasty techniques for urethral strictures only, with no use of Optilume and so is outside scope of MTG
Guo et al., 2010	✓	X	Study into transurethral thulium laser urethrotomy for urethral strictures, with no use of Optilume and so outside the scope
Heyns et al., 1998	✓	X	Prospective study comparing dilatation Vs. internal urethrotomy, with no use of Optilume and so is outside the scope
Hoy et al., 2013	✓	X	Prospective cohort study into dorsal onlay augmented anastomosis, with no use of Optilume and so is outside the scope
Isen et al., 2015	✓	X	Prospective nonrandomised trial into DVIU using endoscopic scissors, with no use of Optilume and so out of scope

Publication	Included in Company Submission	Included in EAC Assessment Report	EAC Comment
Jordan et al., 2013	✓	X	Randomised trial with catheter diversion or a memokath stent. No use of Optilume and so out of scope
Mann et al., 2021	✓	✓	Two-year results for ROBUST I
Pansadoro et al., 1996	✓	X	Old study into urethrotomy for urethral strictures with no relevance to Optilume, and so out of scope.
Pickard et al., 2020	✓	X	OPEN randomised controlled trial into Urethoplasty versus endoscopic urethrotomy. No use of Optilume and so out of scope
Santucci et al., 2010	✓	X	Retrospective review of DVIU for urethral strictures, with no use of Optilume and so out of scope
Steenkamp et al., 1997	✓	X	Old randomised trial comparing urethrotomy with dilatation. No use of Optilume and so out of scope.
Virasoro et al., 2020	✓	✓	1-year results from ROBUST I

A summary of the included publications is presented in Table 6, Table 7 and Table 8 below. It should be noted that the traffic light system used in tables 6-8 relates only to whether the study can be considered applicable to the decision problem as outlined in the scope. While it briefly highlights some of the potential limitations and areas for concern it is not a quality appraisal. Critical appraisal of all the included studies is reported in section 5 and appendix C.

Table 6-8: Studies selected by the EAC as the evidence base

Table 6: ROBUST I

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
One-year outcomes				
Virasoro et al. (2020) **Location:** U.S **Setting:** Four Latin American centres (2 Panama, 2 Dominican Republic) **Design**: Multicentre, single arm, prospective, open-label trial Results also reported in the following abstracts: • Elliott et al., 2019 • Pichardo et al., 2019 • Wang et al., 2019	**Intervention:** Optilume DCB **Comparator:** None – Single arm **Sample size:** 53 **Inclusion criteria:** • Men ≥18 years with a single bulbar urethral stricture <12Fr and ≤2.0 cm long on urethrogram • Undergone 1-4 prior endoscopic treatments • IPSS ≥13 • Qmax <10 ml/sec • Significant symptoms of stricture such as frequency or urination, dysuria, urgency, haematuria, slow flow,	**Patient demographics (n=53):** • Age (years): ○ Mean±SD: 50.7±15.47 ○ Range: 22.0-81.0 ○ Median: 50.0 • Race, n (%) ○ Hispanic or Latino: 44 (83.0%) ○ Black or African: 8 (15.1%) ○ Other: 1 (1.9%) • Anatomic location, n (%): ○ Bulbar: 53/53 100% • Stricture aetiology, n (%): ○ Iatrogenic: 24 (45.3%) ○ Idiopathic: 2 (3.8%)	**Primary efficacy endpoint:** One-year anatomic success without retreatment, regardless of symptoms or flow rate. Failure was defined as anatomic failure or retreatment; additionally, any subject who exited the study prior to cystoscopic evaluation with IPSS ≥11 was considered a failure. **Primary safety endpoint:** Rate of treatment-related urinary SAEs, defined as urethral fistula formation, de novo urinary retention >14 days post-treatment, de novo stress incontinence (>1 pad/day) at 90 days post-treatment, or urethral rupture. **Secondary endpoints:** • IPSS • IIEF (Overall satisfaction) • Qmax	Partially meets scope criteria as includes Optilume but no comparator. However, participants were ineligible if their stricture was ≥2.0 cm versus ≤3.0 cm scope. Freedom from repeat intervention not reported in one-year outcomes. Single arm with no comparator with standard of care. Bulbar strictures only which matches scope but not company indication. Participants were pre-treated with a combination of uncoated balloon and/or DVIU. This is not standard of care. No statistical analysis of data, just descriptive statistics.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
(Amber)	feeling of incomplete emptying, recurrent UTIs **Exclusion criteria:** • Strictures greater than 2.0 cm long • Prior urethroplasty • Radical prostatectomy • Lichen Sclerosus • Penile prosthesis • Artificial Urinary sphincter • Pelvic Radiation • Urinary stone passage in previous 6 months • CKD or serum creatinine >2 mg/dL • Intradetrusor onabotulinum toxin A injection within 12 months of study entry • Neurogenic bladder • Bladder or prostate cancer in previous 5 years • Active non-genitourinary cancer **Randomisation:** Non-randomised	○ Traumatic: 27 (50.9%) • Stricture measurements, Mean±SD ○ Stricture length (mm): 9.00±5.20 ○ Urethral diameter at stricture (mm): 2.47±1.97 ○ Urethral diameter at area healthy tissue (mm): 10.2±3.62 • Pre-treatment: ○ Uncoated balloon: 31 (59%) ○ DVIU: 8 (15%) ○ Uncoated balloon + DVIU: 14 (26%) • Number of previous endoscopic treatments, n (%) ○ 1: 30 (57%) ○ 2: 13 (25%) ○ 3: 8 (15%) ○ 4: 2 (4%) (Amber)	• PVR • Conc. Paclitaxel in the blood, urine, and semen • VAS pain score (Amber)	No information on consecutive recruitment, so possibility of sampling bias. No PROMs measured at one-year outcomes. All outcomes measured but incomplete inclusion of patients. A total of 58 DCB procedures were performed for 53 participants; including 5 re-treatments with Optilume DCB.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Procedure: Strictures pre-treated with an uncoated balloon and/or DVIU until lumen diameter increased by 50%. Balloon inflated to the rated burst pressure and held for ≥5 minutes. **Statistical analysis:** Baseline characteristics and the primary safety endpoint use descriptive analysis **Status:** Published **Funding:** Urotronic, Inc (Company) **Conflicts of interest:** Dr. Elliott, Dr. Virasoro, and Dr. DeLong serve as consultants for Urotronic. ● (Amber)			
Two-year outcomes				

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
Mann et al., 2021 **Location:** U.S **Setting:** Four Latin American centres (2 Panama, 2 Dominican Republic) **Design**: Multicentre, single arm, prospective, open-label trial Results also reported in Elliott et al., 2020 (abstract) ● (Amber)	As reported in Virasoro et al., 2020	As reported in Virasoro et al., 2020	**Primary efficacy endpoint:** ≥50% improvement in IPSS compared to baseline in the absence of retreatment. **Primary safety endpoint:** Rate of treatment-related urinary SAEs, defined as urethral fistula formation, de novo urinary retention >14 days post-treatment, de novo stress incontinence (>1 pad/day), or urethral rupture. **Secondary endpoints**: • Improvements in LUTS based on USS-PROM • IIEF (Overall satisfaction) • Qmax • PVR ● (Amber)	Study follows on from Virasoro et al., 2020 Partially meets scope criteria as includes Optilume but no comparator. However, participants were ineligible if their stricture was ≥2.0 cm versus ≤3.0 cm scope. Freedom from repeat intervention not reported in two-year outcomes. Single arm with no comparator to standard of care. Patient cohort had mostly undergone 1 or two endoscopic procedures which may not be representative of typical patients requiring Optilume. Change in primary outcome from one-year anatomic success without retreatment, regardless of symptoms or flow rate, to 50% improvement in IPSS compared to baseline in the absence of retreatment. This was due to cystoscopy was not conducted at follow-up after 1 year and therefore the emphasized endpoint was improvement in subjective symptoms.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
				Anatomic success not measured at 2-year outcome.
Four-year outcomes				
Elliott et al., 2022a (unpublished) **Location:** U.S **Setting:** Four Latin American centres **Design**: Multicentre, single arm, non-randomised, prospective, open-label trial Results also reported in the following abstracts: • Chee et al., 2021 • Elliott et al., 2021c	As reported in Virasoro et al., 2020	As reported in Virasoro et al., 2020	**Primary efficacy endpoint:** Improvement in International Prostate Symptoms score (IPSS) at 90 days. **Primary safety endpoint:** Rate of treatment-related serious complications. The treatment related serious complications include the following: • urethral fistula formation • de novo urinary retention lasting >14 consecutive days post-treatment • unresolved de novo stress incontinence (>1 pad/day) at 90 days post-treatment or earlier • urethra rupture or burst	Partially meets scope criteria as includes Optilume but no comparator. However, participants were ineligible if their stricture was ≥2.0 cm versus ≤3.0 cm scope. Single arm with no comparator to standard of care. Patient cohort had mostly undergone 1 or two endoscopic procedures which may not be representative of typical patients requiring Optilume.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
(Amber)			**Secondary endpoints:** • Stricture recurrence rate at 6 months • Improvement in USS-PROM • Change in IIEF • Repeat treatment rate • Change in Qmax at 3m and 6m • Paclitaxel content in blood, urine and semen • Stress Urinary Incontinence at <90 days and >90 days • VAS pain score (Amber)	

Table 7: ROBUST II

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
1-year outcomes				

DeLong et al., 2022
 	
Location: U.S
 	
Setting: Five American centres
 	
Design: Prospective, multicentre, non-randomised, open-label study
 	
🟡 (Amber)
	Intervention: Optilume DCB
	
	Comparator: None – single arm
	
	Sample size: 16
	
	Inclusion criteria:
	• Adult men with a single anterior urethral stricture ≤3 cm in length with lumen diameter <12 F
	• ≥2 prior endoscopic treatments of the stricture
	• Bothersome LUTS
	• IPSS ≥13
	• Qmax <15 mL/sec
	
	Exclusion criteria:
	• Prior urethroplasty
	• Radical prostatectomy
		Patient demographics (n=16):
		
		• Age, years (Mean±SD): 63.8±15.7
		• Stricture aetiology, n (%):
		  ○ Iatrogenic: 2 (12.5)
		  ○ Idiopathic: 11 (68.8)
		  ○ Traumatic: 3 (18.8)
		• Anatomic location:
		  ○ Bulbar: 100%
		• Stricture measurements (Mean±SD):
		  ○ Length, cm: 2.1±0.7
		  ○ Urethral diameter at stricture, mm: 2.3±0.9
		  ○ Urethral diameter distal to stricture, mm: 10.5±5.2
		• Number of prior dilatations (Mean±SD): 4.1±4.9
		• Procedure type, n (%)
		  ○ Direct DCB dilatation: 10 (62.5)
			Primary safety endpoint: Rate of treatment-related serious complications at 90 days, defined as a composite of formation of fistula, new strictures requiring intervention, unresolved de novo stress urinary incontinence requiring >1 pad/day, and urethral rupture. Any change in sexual function was evaluated using the "overall satisfaction" domain of the International Index of Erectile Function (IIEF).
			
			Efficacy endpoints:
			• Anatomic success at 6 months (defined as the ability to pass a 16F flexible cystoscope through the treatment site)
			• IPSS
			• USS-PROM
			• Qmax
			• Freedom from repeat intervention
			• VAS pain score
			
			🟡 (Amber)
				Small case series of just 16 patients with only 9 available for 1 year follow up. Possible sampling bias due to no information on consecutive recruitment. Demographics of participants limited to just age and baseline characteristics, and no information on investigational sites beyond country of investigational sites.
				
				Partially meets scope criteria as includes Optilume but no comparator. However, participants were only eligible if they had ≥2 prior endoscopic procedures which does not fit with where the Optilume device would be considered by clinicians (≥1 prior endoscopic treatment).

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	• Pelvic radiation • Artificial urinary sphincter • Urethral stent • Stricture dilatation or incision within 6 weeks • Lichen Sclerosus diagnosis • Urinary stone passage within 6 weeks • Chronic renal failure • Neurogenic bladder • History of carcinoma of bladder or prostate within the last 5 years **Procedure:** Baseline retrograde urethrogram performed to inform balloon size. Balloon inflated as per physician's discretion to rated burst pressure for ≥5 minutes. Strictures were dilated directly with the Optilume DCB or pre-dilated with an uncoated balloon, rigid rod, or DVIU. **Statistical analysis:** Intent-to treat analysis performed for all endpoints.	○ Pre-dilatation with uncoated balloon or DVIU: 6 (37.5) ○ Direct DCB dilatation with post-dilatation: 0 (0%) ● (Green)		Lack of a control arm with a small sample size. Exclusion criteria was restrictive. 37.5% of participants were pre-dilated. This is not standard of care and if Optilume were to be used in the NHS, patients would not be pre-dilated. 7 patients lost to follow-up, leaving just 9 participants. 2 of which were re-treatment with Optilume.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Descriptive statistics were used for data summaries. 2-sided students t test used for significance of improvements. **Status:** Published **Funding:** Urotronic, Inc (company) **Conflicts of interest:** The study was sponsored and funded by Urotronic, Inc. ● (Amber)			

Table 8: ROBUST III

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
1-year outcomes				

Elliott et al., 2021a
 	
Location: United States (21) Canada (1)
 	
Setting:
 	
Design: Multicentre, randomised, single-blind controlled trial
 	
Results also reported in the following abstracts. Only data from the full text was extracted:
• Elliott et al., 2021b
• Justin et al., 2021
• Virasoro et al., 2021
 	
● (Green)
	Intervention: Optilume DCB
	
	Comparator: Standard endoscopic care (DVIU/dilatation)
	
	Sample size: 127
	Optilume DCB: n=79
	Standard care: n=48
	
	15 additional subjects non-randomised to a PK arm
	
	Inclusion criteria:
	• Adult men with anterior strictures ≤12F and ≤3cm in length
	• ≥2 prior endoscopic treatments
	• IPSS ≥11
	• Qmax <15 mL/sec
		Patient demographics:
		
		Standard of care | Optilume DCB (p-value)
		• Age, years (mean±SD): 60.6±16.0 | 58.7±15.5 (p=0.500)
		• Race (%)
		  ○ White: 81.3 | 83.3
		  ○ Black or African American: 12.5 | 11.5
		  ○ Other: 6.3 | 5.1
		• BMI: 28.9±6.9 | 30.5±6.7 (p=0.206)
		• Stricture aetiology (%) (p=0.566)
		  ○ Iatrogenic: 34 | 26.9
		  ○ Idiopathic: 46.8 | 53.8
		  ○ Inflammatory: 4.3 | 1.3
		  ○ Traumatic: 14.9 | 17.9
			Primary efficacy endpoint:
			Anatomic success, defined as the proportion of participants in whom a 16F flexible cystoscope or 14F catheter could pass atraumatically at 6 months.
			
			Primary safety endpoint:
			Freedom from a composite of serious device- or procedure-related events, including urethral fistula, unresolved de novo stress urinary incontinence or urethral rupture through 3 months.
			
			Efficacy outcomes:
			• Average Qmax
			• IPSS
			• IPSS QoL
			• IIEF
			  Freedom from repeat intervention
			● (Green)
				Patients unblinded after 6 months which could bias some secondary outcomes, for instance in the crossover at 6 months.
				
				Primary outcome missing for 7 control and 12 DCB participants.
				
				Pre-dilatation in Optilume DCB arm likely to favour successful efficacy endpoint.
				Outcomes not statistically measured, just descriptive statistics used.
				
				USS-PROM not a reported outcome.
				
				VAS pain score not an outcome for ROBUST III.

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments

	Exclusion criteria:
	• Previous urethroplasty
	• Hypospadias repair
	• Lichen Sclerosus
	• Unresolved confounding aetiologies (e.g. bladder neck contracture, neurogenic bladder, BPH)
	
	Randomisation: 2:1 allocation of treatment Vs. control. Stratified by prior pelvic radiotherapy (yes/no) and number of prior endoscopic treatments (<5 Vs ≥5).
	
	Procedure:
	Intervention group - Strictures pre-treated with an uncoated balloon or DVIU to ≥20F. Inflation of DCB to rated burst pressure for ≥5 minutes.
		• Anatomic location (%) (p=0.319)
		  ○ Bulbar: 95.7 | 89.9
		  ○ Penile: 4.3 | 10.1
		• Stricture measurements
		  ○ Length (cm): 1.72±0.73 | 1.63±0.76 (p=0.528)
		  ○ Diameter (mm): 2.33±0.88 | 2.46±0.96 (p=0.470)
		• Prior Dilatation
		  ○ Mean: 4.3±7.5 | 3.2±1.73 (p=0.321)
		  ○ Median: 3.0 | 3.0
		  ○ Proportion with ≥5 (%): 20.8 | 16.5 (p=0.636)
		
		● (Green)		

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Control group – Serial dilatation with urethral sounds, DVIU, balloon dilatation or a combination. For the additional paclitaxel cohort (15), samples of plasma, semen and urine were taken at baseline and various time point post-procedure through 6 months. **Statistical analysis:** For the primary endpoint, a two-sample continuity corrected Chi-square test at the two-sided 0.05 alpha level. Log-rank test for comparison of freedom from repeat intervention. Subject characteristics were evaluated with the Fishers exact test for categorical measures and unpaired t-test for continuous measures.			

Study design and setting	Design and intervention(s)	Participant information	Outcomes	EAC comments
	Descriptive statistics were used to summarise all outcome measures. **Funding:** Urotronic, Inc. (Company) **Conflicts of interest:** SPE: Boston Scientific, Percuvision; SC: Paladin, Acerus Pharma, Coloplast, SMSNA/Boston Scientific; MJE: Coloplast, Medtronic; AS: AUUA; RN: Boston Scientific; AM: Coloplast, Boston Scientific; CO: Exilixis Corp. ● (Green)			

Abbreviations used in tables 6-8: CKD: Chronic Kidney Disease; DCB: Drug-coated balloon; DVIU: Direct Vision Internal Urethrotomy; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; LUTS: Lower Urinary Tract Symptoms; PK: Pharmacokinetic; PROM: Patient-reported outcome measure; PVR: Post-void residual urine volume; Qmax: Maximum flow rate; QoL: Quality of Life; SAEs: Severe Adverse Events; SD: Standard deviation; VAS: Visual Analog Scale

5 Clinical evidence review

Overview of methodologies of all included studies

A total of 12 publications (Chee et al., 2021; DeLong et al., 2022; Elliott et al., 2021a; Elliott et al., 2021b; Elliott et al., 2020; Elliott et al., 2019; Justin et al., 2021; Mann et al., 2021; Pichardo et al., 2019; Virasoro et al., 2020; Virasoro et al., 2021; Wang et al., 2019) were eligible for inclusion in this review which reported results from a total of 3 studies (ROBUST I, ROBUST II and ROBUST III). In addition, the company provided one unpublished trial report (Elliott et al. 2022a – unpublished) which reported both baseline data and long-term follow-up results from ROBUST I. The types of available evidence are listed in Table 9.

All 12 publications identified were related to the three ROBUST studies; ROBUST I, II and III. Four of the studies were peer reviewed, published journal articles (DeLong et al., 2022; Elliott at al., 2021a; Mann et al., 2021 Virasoro et al., 2020;) and one is an unpublished trial report (Elliott et al. 2022a). Two publications reported results from ROBUST I (Virasoro et al., 2020; Mann et al., 2021) and one unpublished trial report provided by the company reported both baseline data and long-term follow-up results from ROBUST I (Elliott et al., 2022a). One publication reported results from ROBUST II (Delong et al., 2022) and one publication reported results from ROBUST III (Elliott et al., 2021a).

ROBUST III (Elliott et al., 2021a) is a randomised control trial comparing Optilume with standard care, and ROBUST I (Elliott et al., 2022; Mann et al., 2021; Virasoro et al., 2020) and ROBUST II (Delong et al., 2022) are single arm, non-comparative open label studies. All three ROBUST studies were industry sponsored by the company (Urotronic Inc.).

Table 9: Study types included

Type of evidence	References
Peer reviewed, published journal article – randomised trial	Elliott at al., 2021a
Peer reviewed, published journal article – cohort study	Virasoro et al., 2020; Mann et al., 2021; DeLong et al., 2022
Conference abstracts and/or posters	Chee et al., 2021; Elliott et al., 2022b; Elliott et al., 2021b; Elliott et al., 2021c; Elliott et al., 2020; Elliott et al., 2019; Justin et al., 2021; Pichardo et al., 2019; Virasoro et al., 2021; Wang et al., 2019
Clinical study reports	Elliott et al. 2022a (Unpublished)

Company web reports	None

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

ROBUST I

Formal quality appraisal was completed for the ROBUST I study collectively rather than for each individual publication as the methodology remained the same throughout. Each of the quality appraisals can be found in Appendix C, however some limitations are discussed below.

The ROBUST I study was a multicentre, single-arm, prospective, open-label small case series of 53 patients across four Latin American centres in the Dominican Republic (2) and Panama (2). As the study was single-arm, there was no comparator or control group. Collective appraisal of studies reporting ROBUST I outcomes identified some concerns around incomplete inclusion of participants and consecutive recruitment. This leads to less reliability of the findings than if both these aspects had been met (Virasoro et al., 2020; Mann et al., 2021; Elliott et al., 2022a).

Strict eligibility criteria were applied during recruitment to include men ≥18 years, with a single bulbar urethral stricture <12 Fr and ≤2.0 cm long. All strictures were identified using a urethrogram. A total of 85 participants were screened and 53 patients enrolled and treated with Optilume. Patients were included if they had undergone 1-4 prior endoscopic treatments, however the EAC identified a discrepancy in the number of patients enrolled as having 3 or 4 prior interventions at one-year outcomes versus 4-year outcomes. There was also incomplete inclusion of all participants as 7 and 10 patient baseline measurements were missing for the Qmax and PVR respectively.

The primary outcome measure for ROBUST I as reported on ClinicalTrials.gov is the rate of treatment related serious complications (90-days post-procedure). The reported secondary outcome measure is stricture recurrence rate (90-days post-procedure) by improvement in IPSS. The primary safety endpoint at 1-year in Virasoro et al., 2020 was defined as the rate of treatment-related urinary severe adverse events (SAEs). The efficacy endpoint in Virasoro et al., 2020 was defined as one-year anatomic success without retreatment, regardless of symptoms or flow rate. The primary safety endpoint in Mann et al., 2021 was serious urinary adverse events. The primary efficacy endpoint in Mann et al., 2021 was defined as ≥50% improvement in IPSS at 24 months compared to baseline in the absence of retreatment (Mann et al., 2021). Similarly, in the unpublished 4-year report (Elliott et al., 2022a), the primary safety endpoint is the rate of treatment-related serious complications at 3 months post-treatment. The primary efficacy endpoint in the 4-

year report (Elliott et al., 2022a) was defined as the [redacted] In discussion with the company, they justified the change in emphasis of outcomes across the studies, noting that anatomic success was chosen as the efficacy endpoint at 1-year as this is the 'gold standard' for measuring success post-urethroplasty. Since cystoscopy was not conducted at later timepoints, the emphasized endpoint was improvement in subjective symptoms without repeat intervention. The EAC are satisfied that this is not a change in primary outcomes, but just an emphasis on the available data and most appropriate measure at the timepoint being reported.

Paclitaxel concentration and VAS pain scores were evaluated at early timepoints and reported in the one year manuscript. Two-year outcomes also looked at USS-PROMs which was not an outcome measured in the one-year outcome paper (Virasoro et al., 2020).

In discussion with the company, the EAC questioned whether the three-year ROBUST I results would be reported in a separate publication. The company advised that this was in progress but would not be published in time for the assessment report. Although the results are available in the four-year report (Elliott et al., 2022a), the EAC notes potential publication bias as the outcomes may have influenced the decision to publish. There was however an abstract for 3-year ROBUST I results with a primacy efficacy endpoint as the proportion of participants with 50% improvement in the IPSS at 3 years, in line with 2-year results (Elliott et al., 2021c). The full 3-year publication is due for publication in 2022.

The EAC also identified some concerns regarding adverse event data as there is limited information provided in the published papers. Virasoro et al., 2020 reported 52 adverse events, with 49% categorised, but the other 51% were not reported. Similarly, in the two-year outcomes (Mann et al., 2021), 71 adverse events were reported; 44% of which were categorised by event type and the rest were unknown. However, in the unpublished report (Elliott et al., 2021a), all adverse events were accounted for and categorised.

The EAC also noted that the outcomes in the unpublished 4-year ROBUST I report were different to those reported in Virasoro et al., 2020 and Mann et al., 2021 publications. In the unpublished report (Elliott et al., 2022a), this is explained to be due to the change of protocol between both Rev C and Rev D, and Rev D and Rev F to align with the statistical analysis plan (SAP). In this, authors explain that the following significant changes to the protocol were made: Allow bladder neck contracture; rearrange the order of endpoints; and the additional exclusion criteria of 'Patients with a suprapubic catheter' was added.

The Optilume device is intended to be used directly without pre-dilatation, however patients in ROBUST I were pre-dilated and if pre-dilatation did not yield the stricture, DVIU was recommended prior to application of the Optilume DCB. It should be noted that it is unclear whether outcomes may differ for the 26% of participants who received a combination of pre-dilation types. Neither study reported on how the difference in predilatation between participants affected stricture recurrence.

ROBUST I is a small non-comparative case series with issues around recruitment and therefore the findings lack reliability.

ROBUST II

Delong et al. 2022a reported on the 1-year outcomes of the ROBUST study – a prospective, multicentre, non-randomised, open-label study of just 16 patients. Each of the patients were men aged ≥18 years with bothersome LUTS, with a single anterior urethral stricture ≤3cm in length, having ≥2 prior endoscopic treatments. Each of the recruited participants had a baseline urethrogram to inform balloon size, however this is not standard of care and in the company's instructions for use for Optilume, pre-dilatation is not recommended.

Demographics of patients were limited and no breakdown of results per investigational site involved in the study, of which there were 5. Similarly, to ROBUST I, there was limited information on consecutive recruitment, although all baseline measurements were included for all 16 patients. Seven patients were lost to follow-up at one-year due to treatment failures (3), consent withdrawal (1), incomplete follow-up (2), and retreatment with Optilume (1), leaving just 9 patients available at for follow-up at 12-months. There was limited information on consecutive recruitment and so potential sampling bias introduced. Of all the three studies, ROBUST II included a detailed grading of adverse events.

Overall, DeLong et al., 2022a is a very small case series with no comparator and issues around recruitment, therefore the findings lack reliability.

ROBUST III

The ROBUST III study (Elliott et al., 2021a) is a multicentre, single-blind, randomised controlled trial of the safety and efficacy of the Optilume device for treatment of anterior urethral strictures.

The sample size was 127 randomised patients; 48 in the control group and 79 in the Optilume arm. An additional 15 non-randomised subjects were enrolled for paclitaxel pharmacokinetic assessments. Patients were eligible if they were an adult male with an anterior stricture ≤12Fr and ≤3 cm in length, with ≥2 prior endoscopic treatments, an IPSS score ≥11 and Qmax <15 ml/sec. Patient demographics between groups were not statistically different, but the two groups

were not treated equally and so the EAC questions whether these results are applicable to a typical patient population.

The study was single-blinded with patients randomised in a 2:1 ratio via a centralized electronic system and stratified by prior pelvic radiotherapy and number of prior endoscopic treatments, but the choice of stratified groups was not explained. Total patients stratified to either pelvic radiotherapy or ≥5 prior endoscopic procedures for the control and intervention groups are 16/48 (33%) and 22/79 (27%) respectively. There is also no information on the concealment of allocation and an imbalance in the eventual treatment allocation between the two groups (Control: 48, Optilume: 79). Therefore, the EAC judge the randomisation process to be at a high risk of bias.

Patients randomised to the intervention arm were blinded to treatment assignment through 6-months post-treatment, after which point they were unblinded and given the choice to cross-over to the Optilume group. Participants wanting to cross over to the Optilume group could only do so if stricture recurrence was confirmed via recurrent symptoms, decreased flow, and stricture diameter was <12Fr as measured by retrograde urethrogram. Although it was not made clear when the patients were told they could cross over. All endpoints were assessed utilizing intent-to-treat methodology, where all subjects randomised to control were assessed in the control group. Those undergoing repeat intervention, including cross-over to receive Optilume after confirmed strictured recurrence, were considered failures for categorical endpoints or assigned the worst observed value for continuous endpoints for timepoints after the intervention. This unblinding could have biased some secondary outcomes at follow-up including the IIEF and PROMs scoring. Additionally, the study was single-blinded and so surgeons and investigators were not blinded to the type of treatment and therefore the interpretation of cystoscopic findings and data assessment may be subject to ascertainment bias. The EAC deem the risk of bias from the effect of assignment on interventions to be low.

The study also had incomplete inclusion of participants. At 12-months, 42 of the 47 patients were followed up, with most outcomes measured; with the exception of the International Index of Erectile Function (IIEF) as just 13 results were recorded and no explanation of why this was the case. The primary efficacy outcome was anatomical success at 6-months, with a Kaplan-Meier estimates of freedom from repeat intervention through 1-year. Overall, the EAC deem the risk of bias from missing outcome data to be low.

The statistical analysis plan was not reported for ROBUST III in the paper, and it is not clear if this plan was finalised before the outcome data were available for analysis. There were two primary outcomes stated for efficacy and safety: stricture free rate (6 months) and rate of major device or procedure-related complications

(3 months). The only outcome measure to be measured statistically was the stricture free rate, and all other outcome measures were reported instead using descriptive statistics. There were some concerns about the risk of bias in selection of the reported result.

Overall, the EAC judge the Elliott et al., 2021a study to be at high risk of bias due to domain one for the randomisation process being high risk (Table 10).

Full details of critical appraisals using the Joanna Briggs Institute (JBI) critical appraisal checklist for case series studies are reported in Appendix C.

Table 10: Risk of bias results for ROBUST III

Risk of Bias Domain	ROBUST III (Elliott et al., 2021)
Bias arising from the randomisation process	High
Bias due to deviations from intended interventions	Low
Bias due to missing outcome data	Low
Bias in measurement of the outcome	Low
Bias in selection of the reported result	Some Concerns
Overall risk of bias	**High**

5.1 *Results from the evidence base*

A summary of the 12-month outcome data from all three ROBUST trials can be found Table 19. The table also includes any 4-year outcome data from ROBUST I.

5.1.1 Anatomical success

Anatomical success was defined using a urethral lumen test (ULT) to assess the ability to pass a flexible cystoscope into the bladder (≥16 Fr) or the ability to pass a 14Fr catheter atraumatically through the stricture and are summarised in Table 11.

ROBUST I

One-year efficacy endpoint for ROBUST I was defined as anatomic success based on a Urethral Lumen Test (ULT), regardless of symptoms or flow rate. A ULT was defined as the ability to pass a flexible cystoscope (≥16 Fr) into the bladder or the ability to pass a 14Fr catheter atraumatically. The Optilume device is intended to be used directly without pre-dilatation, however patients in ROBUST I were pre-dilated and if pre-dilatation did not yield the stricture,

DVIU was recommended prior to application of the Optilume DCB. The included patients were pre-dilated with an uncoated balloon (59%), DVIU (15%) or a combination of the two (26%) to minimize the risk of double exposure to the drug coating.

Anatomic success was measured at 6 and 12 months, achieving success in 32/46 (70%) of participants at 12-months, with 14 failures (30%); 12 of which occurred within 6-months of the procedure. Failure was defined as a failed ULT (n=7), retreatment (n=5), or exit with an IPSS≥11 but no cystoscopy performed (n=2).

ROBUST II

Anatomic success in the ROBUST II trial was defined as the ability to pass a 16Fr flexible cystoscope through the treatment site.

Of the 13 participants who completed the 6-month follow-up cystoscopy, 2 were considered failures. Two additional participants were considered failures due to recurrence of their stricture requiring repeat treatment prior to the 6-month visit (1 re-treated with Optilume DCB and 1 Urethroplasty). The remaining 73.3% (11/15) participants treated with Optilume demonstrated anatomic success through to 6-months but was not reported at 12-months.

ROBUST III

Anatomic success in ROBUST III was defined as the ability to pass a 16Fr flexible cystoscope or a 14Fr catheter through the treated area. At 6-months, the Optilume group achieved a significantly higher success rate (74.6%) than the dilatation/DVIU control group (26.8%). However, cystoscopy outcomes were missing in 12 and 7 patients respectively. This resulted in a difference of 44.4% using multiple imputation [p<0.001]. The treatment effect was consistent across some specific clinical subgroups, including participants with ≥5 Vs ≤5 prior endoscopic treatments and stricture length ≥2 Vs ≤ 2 cm. The paper also included a forest plot demonstrating anatomical success favouring Optilume over control for all subgroups, however some subgroups were too small for definitive comparison, including aetiology, stricture location, and previous dilatation.

Table 11: Anatomical success results

Anatomical Success						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	N/A	32/46 (70%)			
ROBUST II	Optilume	N/A	11/15 (73.3%)*	N/R	N/R	N/R
ROBUST III	Optilume	N/A	50/67 (74.6%)*	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/A	11/41 (26.8%)*	N/R	N/R	N/R

*6 months

5.1.2 Stricture Free Outcomes

Stricture free outcomes were reported in all three ROBUST trials as Freedom from repeat intervention, but ROBUST I also defined stricture free outcome using an International Prostate Symptom Score ≤11 and Urethral Lumen Test and results are reported in Table 12.

Freedom from Repeat Intervention

Freedom from repeat intervention was defined as retreatment with the Optilume DCB or exit due to treatment failure. Each of the three trials reported freedom from repeat intervention and are summarised in Table 12.

ROBUST I

Freedom from repeat intervention was not reported in the ROBUST I publications with one- or two-year outcomes (Virasoro., 2020, Mann et al., 2021) but was reported in the unpublished 4-year report.

After 12-months, there were 48 evaluable participants, and of those, 40 (83%) were free from repeat intervention; 38/47 (81%) at 2 years; 33/43 (77%) at 3 years, [redacted]

ROBUST II

A total of 4 participants received repeat treatment, resulting in a rate of freedom from repeat treatment of 73.3% (11/15). Of the 4 requiring repeat intervention; 2 were re-treated with the Optilume DCB, and 2 participants underwent urethroplasty. No further information was reported on the outcome or success of the re-treated patients.

ROBUST III

Freedom from repeat intervention was one of the key secondary endpoints in ROBUST III and was reported to be significantly higher in the Optilume DCB group compared to control at 1-year (83.2% Vs 21.7%, p<0.0001).

Table 12: Stricture Free Outcomes

Stricture Free Outcome measured by Freedom from Repeat Intervention						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	N/A	(40/48) 83%	(38/47) 81%	(33/43) 77%	[redacted]
ROBUST II	Optilume	N/A	11/15 (73.3%)	N/R	N/R	N/R
ROBUST III	Optilume	N/A	83%	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/A	22%	N/R	N/R	N/R
Stricture Free Outcome measured by IPSS ≤11						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	N/A	79%	66%	[redacted]	[redacted]
ROBUST II	Optilume	N/A	N/R	N/R	N/R	N/R
ROBUST III	Optilume	N/A	N/R	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/A	N/R	N/R	N/R	N/R
Stricture Free Outcome measured by ULT						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	N/A	77%	N/R	N/R	N/R
ROBUST II	Optilume	N/R	N/R	N/R	N/R	N/R
ROBUST III	Optilume	N/R	N/R	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/R	N/R	N/R	N/R	N/R

5.1.3 International Prostate Symptom Score (IPSS), IPSS Quality of Life (QoL) and IPSS Responder Rate

The International Prostate Symptom Score (IPSS) & IPSS Quality of Life questionnaires are validated screening tools with 7 questions to screen for, rapidly diagnose, track the symptoms of, and suggest management of the lower urinary tract symptoms of Benign Prostatic Hyperplasia (BPH). Scores range from 0-7 as mildly symptomatic, 8-19 as moderately symptomatic, and 20-35 as severely symptomatic. Results for IPSS, IPSS QoL and IPSS responder for the ROBUST trials can be found in Table 13.

ROBUST I

IPSS was a secondary endpoint of ROBUST I. [redacted] 51 participants had an IPSS score available at 90 days post-procedure at an average of 6.1±7.63 compared to 25.2±4.46 at baseline (n=53). [redacted] changing from 4.9±0.86 at baseline [redacted]

ROBUST II

IPSS was an efficacy endpoint of ROBUST II. The average IPSS decreased dramatically from 18.4±4.9 (n=16) at baseline to 7.2±5.3 at 30 days (n=16); with symptoms remaining similar up to the 1-year follow-up (6.0±6.1) (n=9) [p<0.001]. IPSS Quality of Life (IPSS QoL) also improved from 4.4±1.3 at baseline, to 1.5±1.5 at 30 days to 1.4±1.5 at 1 year [p<0.001].

ROBUST III

IPSS and IPSS QoL were additional outcomes in ROBUST III. Both the Optilume and control groups demonstrated a substantial improvement in IPSS from baseline to 30 days; Optilume: 22.0±6.8 (n=79) to 7.6±5.7 (n=78); Control: 22.8±7.0 (n=47) to 9.5±7.4 (n=47). However, the control groups IPSS started to deteriorate by 3 months, returning to 19.9±7.5 (n=42) at 1-year. Optilume demonstrated a sustained improvement in IPSS through to 1-year: 9.0±7.1 (n=67).

A similar result was found with the IPSS QoL outcome as patients in both groups shown a rapid improvement in score at 30 days from baseline; Optilume: 4.5±1.3 (n=79) to 1.7±1.4 (n=78); Control: 4.7±1.2 (n=47) to 2.0±1.6 (47). However, the control group deteriorated from 2.0±1.6 (n=47) at 30 days, to 4.0±1.3 (n=42) at 1-year, whereas Optilume demonstrated a sustained improvement in IPSS QoL at 1-year 1.9±1.5 (n=67).

The IPSS responder rate was reported in all three ROBUST trials, however the definition used differed. In ROBUST I and II, the number of participants who experienced an improvement in IPSS score ≥50% compared to baseline without repeat treatment were reported as IPSS responder. In both studies, participants who were re-treated with Optilume DCB or identified as an exit due to treatment failure were considered to have had no improvement from baseline and were a 'non-responder'. [redacted]

ROBUST I

IPSS responder rate was not reported in one- or two-year outcome papers (Virasoro et al., 2020; Mann et al., 2021), but is reported in the 4-year report.

At 90-days post-procedure, of the 51 evaluable patients; the responder rate was 84% (43/51) with a failure rate of 16% (8/51). [redacted]

ROBUST II

The IPSS responder rate in ROBUST II was 75% (12/16) at 30 days, decreasing to 61.5% (8/13) at 1 year with no comparator.

ROBUST III

IPSS responder rate was not reported in the published ROBUST III trial outcomes (Elliott et al., 2021a), but upon request to the company, was submitted as academic in confidence data. [redacted]

[redacted]

Table 13: International Prostate Symptom Score (IPSS) and IPSS Quality of Life (QoL) results

IPSS Symptom Score – mean and standard deviation						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	25.2±4.46 (53)	4.9±5.63 (42)	*6.9±7.66 (38)	*5.5±6.90 (33)	[redacted]
ROBUST II	Optilume	18.4±4.9 (16)	6.0±6.1 (9)	N/R	N/R	N/R
ROBUST III	Optilume	22.0±6.8 (79)	9.0±7.1 (67)	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	22.8±7.0 (47)	19.9±7.5 (42)	N/R	N/R	N/R
IPSS Quality of Life – mean and standard deviation						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	4.9±0.86 (53)	0.8±1.06 (42)	*0.9±1.47 (38)	*0.7±1.19 (33)	[redacted]
ROBUST II	Optilume	4.4±1.3 (16)	1.4±1.5 (9)	N/R	N/R	N/R
ROBUST III	Optilume	4.5±1.3 (79)	1.9±1.5 (67)	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	4.7±1.2 (47)	4.0±1.3 (42)	N/R	N/R	N/R
IPSS Responder Rate						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	N/A	37/48 (77%)	68%	67%	[redacted]
ROBUST II	Optilume	N/A	8/13 (61.5%)	N/R	N/R	N/R

IPSS Symptom Score – mean and standard deviation						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST III	Optilume	[redacted]	[redacted]	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	[redacted]	[redacted]	N/R	N/R	N/R

**Compared to the baseline value, p<0.0001*

5.1.4 International Index of Erectile Function (IIEF)

International Index of Erectile Dysfunction (IIEF) is a validated questionnaire for evaluating the effect of a treatment on sexual function. IIEF is composed of 15 items investigating 5 dimensions; Erectile function, Orgasmic function, Sexual Desire, Intercourse Satisfaction and Overall Satisfaction. For all domains, a higher score indicates less dysfunction. Results for IIEF in the ROBUST trials can be found in Table 14.

ROBUST I

In ROBUST I, participants were asked to refrain from sexual intercourse until 30 days post-procedure in the study. Therefore, the relevant comparison of IIEF scores is at baseline, 30 days and beyond. Authors reported two of the 5 dimensions in their outcomes; erectile function and overall satisfaction. [redacted] Similarly, with the overall satisfaction dimension, there was a mild improvement from baseline to one-year: (6.5±2.62) (n=53) to 7.8±2.62 (n=42) respectively. [redacted]

ROBUST II

ROBUST II reported just the 'overall satisfaction' domain of the IIEF, with an average score improving from 6.7±2.9 at baseline (n=16) to 7.3±2.8 at 1 year (n=9) [p=0.596].

ROBUST III

ROBUST III reported no change in overall satisfaction and erectile function at baseline through to one-year as measured by the IIEF in either the Optilume: 5.8±2.9 (n=72) to 6.9±3.0 (n=59); or control group: 6.0±3.2 (n=46) to 5.8±2.7 (n=13).

Table 14: International Index of Erectile Function (IIEF) results

Index of Erectile Function (IIEF) Overall satisfaction – mean & standard deviation						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	6.5±2.62 (53)	8.1±2.5 (40)	7.6±2.5 (38)	8.2±2.2 (33)	[redacted]
ROBUST II	Optilume	6.7±2.9 (16)	7.3±2.8 (9)	N/R	N/R	N/R
ROBUST III	Optilume	5.8±2.9 (72)	6.9±3.0 (59)	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	6.0±3.2 (46)	5.8±2.7 (13)	N/R	N/R	N/R

5.1.5 Maximum Flow Rate (Qmax)

Maximum flow rate (Qmax) is defined as the peak or maximum flow rate. The Qmax is used to assess a patient for bladder outlet obstruction (BOO) and provide some insight as to the degree of obstruction in the male patient with suspected BPH. Results for Qmax outcomes in the ROBUST trials can be found in Table 15.

ROBUST I

Maximum flow rate (Qmax) was a secondary outcome for the ROBUST I trial. Mean Qmax (mL/sec) improved from 5.0±2.56 (n=46) at baseline to 23.6±12.63 (n=51) at 14 days, and a sustained improvement upon baseline through to 30 days (24.2±14.15). After 30 days, there was a gradual decrease at all time points through to [redacted]

ROBUST II

Qmax was an efficacy endpoint in ROBUST II. The baseline Qmax was 6.9±3.7 mL/sec (n=16), increasing at each time point to 20.8±9.1 mL/sec (n=9) at 1-year [p<0.001] – an improvement of 201.4%. Peak flow at 1 year was higher than the 15 mL/sec typically used to define patients free from clinically significant stricture recurrence.

ROBUST III

Qmax was an additional outcome used in ROBUST III. Both groups showed a significant increase in Qmax from baseline to 30 days. Optilume increased from 7.6±3.4 (n=78) to 18.3±9.1 (n=75), and the control group from 7.4±3.5 (n=47) to 15.8±8.5 (n=44). However, by the 3-month visit, the Qmax of the control group started to deteriorate, falling to 7.6±4.0 (n=41) at 1-year, versus 15.5±9.0 (n=65) for the Optilume group.

Table 15: Maximum Flow Rate (Qmax) results

Maximum Flow Rate (Qmax) – mean & SD						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	5.0±2.56 (46)	19.5±9.96 (42)	*17.5±10.4 (38)	*15.1±8.3 (33)	[redacted]
ROBUST II	Optilume	6.9±3.7 (16)	20.8±9.1 (9)			
ROBUST III	Optilume	7.6±3.4 (78)	15.5±9.0 (65)			

Maximum Flow Rate (Qmax) – mean & SD						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
	Standard endoscopic care (DVIU/dilatation)	7.4±3.5 (47)	7.6±4.0 (41)			

5.1.6 Post-void Residual (PVR)

Post-void residual is defined as the quantity of urine that remains in the bladder after urinating. Results for PVR in the ROBUST trials can be found in Table 16.

ROBUST I

Post-void residual (PVR) was a secondary endpoint in ROBUST I. At baseline the PVR was 141.4±105.05 (n=43), improving to a mean of 32.7±33.06 (n=49) at 14 days, with a sustained improvement through to 1-year (26.79±33.10). After 1-year, the PVR started to deteriorate to [redacted]

ROBUST II

PVR was an efficacy outcome in ROBUST II, improving from 187.1±227.1 mL (n=16) at baseline to a mean of 79.3 mL, 59.5 mL and 66.4 mL at 3 months, 6 months and 1 year respectively, although the decrease was not statistically significant [p=0.134].

ROBUST III

The PVR in ROBUST III at baseline was 109.8±116.9 mL (n=77) and 133.8±155.1 mL (n=47) for the Optilume and control groups respectively. Both groups improved at the 30-day visit with means of 75.6 and 79.1, but the control group started to deteriorate, and at 1-year had a worse PVR than at baseline (181.5±201.7). By comparison, the Optilume group had a temporary deterioration in the mean at 3 months (103.4), improving to a mean of 73.1 at 6 months, but deteriorating once again by the 1-year outcome (94.6±121.8).

Table 16: Post-void Residual (PVR) results

Post-Void Residual (PVR) Results						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	141.4±105.05 (43)	26.79±33.10 (42)	*45.5±49.5 (38)	*50.2±62.5 (33)	[redacted]
ROBUST II	Optilume	187.1±227.1 (16)	66.4±57.5 (9)	N/R	N/R	N/R
ROBUST III	Optilume	109.8±116.9 (77)	94.6±121.8 (66)	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	181.5±201.7 (42)	109.8±116.9 (77)	N/R	N/R	N/R

5.1.7 Urethral Stricture Surgery-Patient Reported Outcome Measure (USS-PROM)

The USS-PROM score is a patient-reported outcome measure used to quantify changes in voiding symptoms and health-related quality of life following urethral stricture surgery. A lower score indicates lesser symptoms (0 is asymptomatic and 24 is the most symptomatic). Results for USS-PROM outcomes in the ROBUST trials can be found in Table 17.

ROBUST I

USS-PROM was a secondary outcome in ROBUST I. There was a durable improvement from baseline (15.9±4.69) through to [redacted]

ROBUST II

USS-PROM was an efficacy endpoint in ROBUST II and demonstrated an improvement from baseline (10.8±3.4, n=16) to 1-year (4.3±4.0, n=8) [p<0.001].

Table 17: Urethral Stricture Surgery-Patient Reported Outcome Measure (USS-PROM) results

Urethral Stricture Surgery-Patient Reported Outcome Measure (USS-PROM)						
Study	**Treatment**	**Baseline**	**1 Year**	**2 year**	**3 Year**	**4 Year**
ROBUST I	Optilume	15.9±4.69 (53)	1.4±1.78 (40)	3.6±5.8 (38)	[redacted]	[redacted]
ROBUST II	Optilume	10.8±3.4 (16)	4.3±4.0 (8)	N/R	N/R	N/R
ROBUST III	Optilume	N/R	N/R	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/R	N/R	N/R	N/R	N/R

5.1.8 Visual Analog Scale (VAS) pain score

The Visual Analog Scale (VAS) is a standardised questionnaire taken pre-and post-procedure to evaluate the pain experienced by participants. The lower the score, the less pain experienced by the subject (0-10). Results for IIEF in the ROBUST trials can be found in Table 18.

ROBUST I

VAS pain score was a secondary endpoint in ROBUST I. Most patients experienced only minor pre-procedure pain associated with their stricture disease, with a mean VAS score of 2.9±2.87 (n=53). Post-procedure there was a slight decrease (2.6±2.5), falling to a mean of 0.6±0.98 (n=51) and 0.9±1.87 (n=51) at 14 days and 30 days respectively. This decrease in VAS score indicates participants experienced much less pain when compared to baseline or pre-procedure. VAS pain score was not reported after 30 days.

ROBUST II

VAS pain score in the ROBUST II trial was 1.7±2.3 at baseline, 2.0±2.0 at treatment; 1.1±1.2 at Foley catheter removal, and decreased to 0.3±0.6 at 30 days.

ROBUST III

VAS pain scores were similar at baseline for the Optilume (1.6±2.2) and control groups (1.9±2.3), and both increased post-procedure at pre-discharge to 2.5±2.2 and 2.1±2.2 respectively. At 30 days, pain was substantially lower than at baseline, however the control group experienced less pain than the Optilume group.

Table 18: Visual Analog Scale (VAS) pain score results

Visual Analog Scale (VAS) pain score results – mean & standard deviation					
Study	**Treatment**	**Baseline**	**Post-procedure**	**14 days**	**30 days**
ROBUST I	Optilume	2.9±2.87 (53)	2.6±2.5 (53)	0.6±0.96 (51)	0.9±1.87 (51)
ROBUST II	Optilume	1.7±2.3 (16)	N/R	N/R	0.3±0.6 (9)
ROBUST III	Optilume	1.6±2.2 (78)	2.5±2.2 (77)	N/R	0.6±1.0 (78)

Visual Analog Scale (VAS) pain score results – mean & standard deviation					
Study	**Treatment**	**Baseline**	**Post-procedure**	**14 days**	**30 days**
	Standard endoscopic care (DVIU/dilatation)	1.9±2.3 (47)	2.1±2.2 (47)	N/R	0.2±0.6 (47)

5.2 *Paclitaxel safety results*

One of the innovative aspects of the Optilume device is the paclitaxel coated balloon. It has been observed that during infusion studies of paclitaxel in treating cancer participants, there have been adverse reactions and drug-related side effects including neurotoxicity and myelosuppression (Virasoro et al., 2020) and this may lead to queries around the safety of paclitaxel use with Optilume. While there are some data published, this is limited currently. The company provided some additional confidential data which has been included in addendum document.

Although there have been drug related side effects and adverse reaction when using paclitaxel to treat cancer, the concentration of paclitaxel delivered locally during the Optilume DCB procedure is much lower than a single dose of systemic chemotherapy provided to cancer patients. Result from the ROBUST I study reported that the urine concentration immediately post-procedure in ROBUST I was about six times lower than in chemotherapy patients, and dropped significantly by five days. Serum levels were also very low in pharmacokinetic studies of the drug by the company in both ROBUST I and III trials, demonstrating an elimination profile as expected.

The EAC are aware of the recent MHRA safety concerns regarding the ongoing use of paclitaxel drug coated balloons and implantable drug eluting stents in peripheral artery disease. This has been considered by the EAC, but as the paclitaxel concentration in Optilume is lower than in these devices and primarily localised to the urethra, the EAC is not concerned with respect to safety.

ROBUST I

The concentration of paclitaxel in the urine, blood and semen were a secondary endpoint in the ROBUST I trial. Mean urinary paclitaxel concentration was 184.3±179.1 ng/ ml immediately post-procedure (n=52) and 2.6±4.8 ng/mL at five days (n=21) (Virasoro et al., 2020). Plasma paclitaxel concentration was very low, as it was near the limit of quantification immediately post-procedure (low=0.1 ng/ml) (Virasoro et al., 2020). Semen paclitaxel concentration, measured in 31 participants, was low (2.5±2.9 ng/mL) at 14 days and 1.0±1.6 at 30 days post procedure (Virasoro et al., 2020).

ROBUST II

Pharmacokinetic, biochemical and serological tests were not reported in the ROBUST II trial.

ROBUST III

ROBUST III (Elliott et al., 2021a) included a nonrandomised arm of 15 participants for paclitaxel pharmacokinetic assessments, including samples of plasma, semen and urine taken at baseline and various time points post-procedure through 6-months. Systemic exposure to paclitaxel was minimal, with average plasma concentration rising above the limit of quantification at 1-hour post-procedure (0.12 ng/mL) and 3 hours (0.11 ng/mL).

Average paclitaxel concentration in the urine was highest immediately post-procedure (414.4 ng/mL) and decreased to 13.8 ng/mL at Foley removal. At 30-days post-procedure, the paclitaxel was below the limit of quantification (Elliott et al., 2021a).

The paclitaxel concentration in semen was not reported at baseline, but was 2.99 ng/mL at 30 days, 0.48 ng/mL at 3 months and 0.12 ng/mL at 6 months, and was detectable in 9/15 (60%), 5/13 (39%), and just 1/12 (8.3%) of participants respectively (Elliott et al., 2021a).

5.3 Overall results

5.3.1 Anatomical Success

One of the methods used in all three ROBUST trials to measure the success of urethral stricture treatment was the anatomical success. This was defined across all studies using a flexible cystoscope of ≥15Fr in diameter or a 14Fr catheter through the treatment site atraumatically.

The Optilume DCB was shown to be consistently effective in achieving a high rate of anatomical success across the ROBUST studies; 70% (32/46) at 12-months in ROBUST I; and 73.3% (11/15) and 74.6% (50/67) at 6-months for both ROBUST II and III respectively. By comparison, the control group in ROBUST III had a success rate of 26.8% (11/41), which was a statistically significant difference versus the Optilume group [p<0.001]. In ROBUST III there were also 8 participants with a penile stricture, 5 of which (62.5%) demonstrated anatomical success at 6-month follow up.

5.3.2 Stricture Free Outcomes

When considering stricture free outcome by freedom from repeat intervention, in ROBUST III there was a significant difference at 12-months; 83.2% Vs 21.7% for the Optilume and control groups respectively (p<0.0001). A similar rate of 73.3% (11/15) was found in ROBUST II, and 81% (38/47) in ROBUST I at 12-months, with only a slight decrease to [redacted]

ROBUST I was the only study to define being stricture free using two additional parameters; IPSS ≤11 and ULT success. However, irrespective of the method of measuring the stricture free rate, similar results were found; 79% at 1 year, [redacted] using IPSS ≤11 and 77% using ULT at 1-year follow-up.

Despite the definition of being stricture free being variable, Optilume successfully prevented strictures in ≥70% participants in all ROBUST studies for all definitions even through to 4-year outcomes.

5.3.3 International Prostate Symptom Score (IPSS), IPSS Quality of Life (QoL) and IPSS Responder Rate outcomes

In ROBUST I, IPSS demonstrated a baseline average categorised as severely symptomatic, changing to mildly symptomatic post-procedure [redacted]

ROBUST II, IPSS, IPSS QoL were both reported to be significantly improved post-procedure versus baseline, with a sustained improvement in symptoms through to the one-year follow-up [p<0.001]. IPSS responder rate was similar to ROBUST I at

75% (12/16) at 30 days post-procedure, but deteriorated slightly at the 1-year follow up to 61.5% (8/13).

Similar to ROBUST I and II outcomes, IPSS, IPSS QoL, IPSS responder rate in ROBUST III all significantly improved post-procedure. [redacted]

Despite the aforementioned difference in defining IPSS responder rate in ROBUST III, results tended to be very similar regardless, and demonstrate a significant improvement in all outcomes using IPSS, with a [redacted]

5.3.4 International Index of Erectile Function (IIEF)

When considering the overall satisfaction domain of the IIEF in the ROBUST trials, all studies found a slight improvement post-procedure through to one-year outcomes, but none demonstrated a significant improvement. The control group in ROBUST III demonstrated an insignificant decrease at 1-year follow-up. The erectile function domain was reported on in ROBUST I and found a similar non-significant trend. Overall, Optilume was not found to have a negative impact upon either domains of the IIEF through to 4-years.

5.3.5 Maximum Flow Rate (Qmax)

The maximum flow rate (Qmax) was found to dramatically improve post-procedure from baseline in all ROBUST trials, with a demonstrable improvement through to 4-years in ROBUST I. The control group in ROBUST III also demonstrated a significant increase post-procedure, but unlike the Optilume group, Qmax in this group rapidly deteriorated back to baseline at 1-year follow up.

5.3.6 Post-void Residual (PVR)

Similar to Qmax, PVR improved dramatically from baseline to post-procedure in all ROBUST trials. In ROBUST I at 1-year follow up there had been some deterioration but was still improved upon baseline, and kept much the same through to the 4-year follow-up [$p<0.0001$]. The control group in ROBUST III demonstrated a similar improvement to the Optilume group post-procedure at the 30-day visit, but did not sustain the improvement like the Optilume group, but deteriorated by 1-year to a worse PVR than before the procedure.

5.3.7 Urethral Stricture Surgery-Patient Reported Outcome Measure (USS-PROM)

The USS-PROM reported in both ROBUST I and II was found to decrease at the 1-year follow-up compared to baseline. This indicated an improvement in the

patients voiding symptoms and quality of life post-procedure. There is however no comparator as ROBUST III did not report upon USS-PROM scores.

5.3.8 Visual Analog Scale (VAS) pain score

Patients in ROBUST II experienced a slight increase in pain during treatment, this decreased to levels below baseline at Foley catheter removal and substantially increased to an almost pain free level at 30 days. Peri-operative pain was not reported in ROBUST I or III, but participants experienced a slight decrease in their VAS pain score post-procedure, followed by a subsequent improvement through to 30-days. Participants in the control group of ROBUST III demonstrated a greater decrease in VAS pain score at 30-days than those in the Optilume group, but neither were significant compared to baseline.

Table 19: Summary Results for all outcomes

Anatomical Success				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	N/A	32/46 (70%)	N/R
ROBUST II	Optilume	N/A	11/15 (73.3%)*	N/R
ROBUST III	Optilume	N/A	50/67 (74.6%)*	N/R
	Standard endoscopic care (DVIU/dilatation)	N/A	11/41 (26.8%)*	N/R
Stricture Free Outcome measured by Freedom from Repeat Intervention				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	N/A	(40/48) 83%	[redacted]
ROBUST II	Optilume	N/A	11/15 (73.3%)	N/R
ROBUST III	Optilume	N/A	83%	N/R
	Standard endoscopic care (DVIU/dilatation)	N/A	22%	N/R
Stricture Free Outcome measured by IPSS ≤11				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	N/A	79%	[redacted]
Stricture Free Outcome measured by ULT				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	N/A	77%	N/R
IPSS Symptom Score – mean and standard deviation				

Study	Treatment	Baseline	1 Year	4 Year
ROBUST I	Optilume	25.2±4.46 (53)	4.9±5.63 (42)	[redacted]
ROBUST II	Optilume	18.4±4.9 (16)	6.0±6.1 (9)	N/R
ROBUST III	Optilume	22.0±6.8 (79)	9.0±7.1 (67)	N/R
	Standard endoscopic care (DVIU/dilatation)	22.8±7.0 (47)	19.9±7.5 (42)	N/R

IPSS Quality of Life – mean and standard deviation

Study	Treatment	Baseline	1 Year	4 Year
ROBUST I	Optilume	4.9±0.86 (53)	0.8±1.06 (42)	[redacted]
ROBUST II	Optilume	4.4±1.3 (16)	1.4±1.5 (9)	N/R
ROBUST III	Optilume	4.5±1.3 (79)	1.9±1.5 (67)	N/R
	Standard endoscopic care (DVIU/dilatation)	4.7±1.2 (47)	4.0±1.3 (42)	N/R

IPSS Responder Rate

Study	Treatment	Baseline	1 Year	4 Year
ROBUST I	Optilume	N/A	37/48 (77%)	[redacted]
ROBUST II	Optilume	N/A	8/13 (61.5%)	N/R
ROBUST III	Optilume	[redacted]	[redacted]	N/R
	Standard endoscopic care (DVIU/dilatation)	[redacted]	[redacted]	N/R

International Index of Erectile Function (IIEF) Overall satisfaction - mean & standard deviation

Study	Treatment	Baseline	1 Year	4 Year

ROBUST I	Optilume	6.5±2.62 (53)	8.1±2.5 (40)	[redacted]
ROBUST II	Optilume	6.7±2.9 (16)	7.3±2.8 (9)	N/R
ROBUST III	Optilume	5.8±2.9 (72)	6.9±3.0 (59)	N/R
	Standard endoscopic care (DVIU/dilatation)	6.0±3.2 (46)	5.8±2.7 (13)	N/R

International Index of Erectile Function (IIEF) Erectile function - mean & standard deviation				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	[redacted]	[redacted]	[redacted]
ROBUST II	Optilume	N/R	N/R	N/R
ROBUST III	Optilume	N/R	N/R	N/R
	Standard endoscopic care (DVIU/dilatation)	N/R	N/R	N/R

Maximum Flow Rate (Qmax) – mean & standard deviation				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	5.0±2.56 (46)	19.5±9.96 (42)	[redacted]
ROBUST II	Optilume	6.9±3.7 (16)	20.8±9.1 (9)	N/R
ROBUST III	Optilume	7.6±3.4 (78)	15.5±9.0 (65)	N/R
	Standard endoscopic care (DVIU/dilatation)	7.4±3.5 (47)	7.6±4.0 (41)	N/R

Post-Void Residual (PVR) – mean and standard deviation				
Study	**Treatment**	**Baseline**	**1 Year**	**4 Year**
ROBUST I	Optilume	141.4±105.05 (43)	26.79±33.10 (42)	[redacted]

ROBUST II	Optilume	187.1±227.1 (16)	66.4±57.5 (9)	N/R
ROBUST III	Optilume	109.8±116.9 (77)	94.6±121.8 (66)	N/R
	Standard endoscopic care (DVIU/dilatation)	181.5±201.7 (42)	109.8±116.9 (77)	N/R

Urethral Stricture Surgery-Patient Reported Outcome Measure (USS-PROM) – mean and standard deviation

Study	Treatment	Baseline	1 Year	4 Year
ROBUST I	Optilume	15.9±4.69 (53)	1.4±1.78 (40)	[redacted]
ROBUST II	Optilume	10.8±3.4 (16)	4.3±4.0 (8)	N/R

Visual Analog Scale (VAS) pain score results – mean & standard deviation

Study	Treatment	Baseline	Post-procedure	14 days	30 days
ROBUST I	Optilume	2.9±2.87 (53)	2.6±2.5 (53)	0.6±0.96 (51)	0.9±1.87 (51)
ROBUST II	Optilume	1.7±2.3 (16)	N/R	N/R	0.3±0.6 (9)
ROBUST III	Optilume	1.6±2.2 (78)	2.5±2.2 (77)	N/R	0.6±1.0 (78)
	Standard endoscopic care (DVIU/dilatation)	1.9±2.3 (47)	2.1±2.2 (47)	N/R	0.2±0.6 (47)

6 Adverse events

The company submission included searches of MHRA and FDA MAUDE databases for any reports of device related adverse events. The EAC conducted similar searches.

Adverse events were reported in all of the included studies, with varying degree of detail. The most commonly reported adverse events in the literature were urinary tract infection (UTI) and acute urinary retention. Table 20 provides a summary of the adverse events reported in the literature.

ROBUST I

For the ROBUST I study, a total of 80 'any adverse events' were identified through to 4-years; 74 of which were non-serious adverse events, and 6 were SAEs from 5 participants reported in Table 20 below. However, all SAEs reported were not related to the device or the procedure and all resolved. Most events were common post-urinary intervention adverse events such as UTI (15%), fever (7.5%), or LUTS. Adverse events were generally treated with oral pain relievers, antibiotics or insertion of a Foley catheter. There were a total of 14/80 treatment-related adverse events; 10 procedure related, and 4 device related (Table 20).

There were 4 device deficiencies up until the time of the 4-year report, none of which resulted in an AE; Optilume DCB burst during inflation (2/4), Optilume DCB started to leak after inflation (1/4), and slow deflation of balloon (1/4). Three of the four deficiencies required a 2nd Optilume DCB balloon to be inserted. There were no deaths reported in the ROBUST I study as of October 19th, 2021.

ROBUST II

ROBUST II included a detailed report of the adverse events found during the study up until 1-year post-procedure with each event graded according to Clavien-Dindo grade I-III. The study reported no serious treatment related complications at 90 days post-procedure, but a total of 21 adverse events in 10 participants at 1-year follow up. 2 of the adverse events were device-related causing hematuria, with the remaining primarily urinary adverse events, mainly urinary tract infection and dysuria. 85.7% of events (18/21) were Clavien-Dindo grade I-II, with 3 events graded as grade III (bronchiectasis, coronary artery stenosis and hematuria); all of which resolved within 2 weeks of onset. There were 4 device-related events, and all resolved without sequelae within a month of onset.

ROBUST III

ROBUST III is the only RCT with a comparator and at 1-year reported adverse types and rates that were well matched between groups, however the ROBUST III

paper (Elliott et al., 2021a) reported very little detail on adverse events, with no total adverse event figures reported. The Optilume group had higher rates of post-procedure hematuria and dysuria compared to controls (11.4% Vs 2.1% for both event types). SAEs occurred in 16.7% of controls and 10.1% of the DCB group. One serious event of urinary tract infection was judged as possibly related to the device/procedure in each group.

Further to this, in the EACs discussion with clinical experts using Optilume, they noted that the device was tolerated very well with minimum side effects. The EAC queried the likelihood of adverse events happening later than 30 days post-procedure. 5 of the 6 experts noted that this was unlikely for Optilume.

The EAC believe that the lack of adverse events and serious adverse events related to the device and/or procedure reported in the clinical trials, databases, and in clinical experience by clinical experts, demonstrates that the device does not raise any safety concerns for the technology.

Table 20: Summary of reported adverse events

Study	ROBUST I	ROBUST II	ROBUST III
Total Adverse Events, n (SAEs)	1 Year (Virasoro et al., 2020) n=52 (SAE: 2 (3.8%)) 2 Year (Mann et al., 2021) n=71 (SAE: None at 2-year post-procedure) 4 year (Elliott et al., 2022a): Non-serious adverse event: 74/80 (92.5%) SAE: 6/80 (7.5%)	1 year (DeLong et al., 2022) n=21 (SAE: 0)	1 year (Elliott et al., 2021a) Control: n=5 Optilume: n=19 SAE (No. events/subject N) Control: 8/48 (16.7%) Optilume: 10/79 (12.6%)
Treatment-related Adverse event, n (%)	4 years: 14 Device related: 4/14 Procedure related: 10/14	No serious treatment-related complications at 90 days post-procedure.	No serious device-or procedure-related events at 90-days post procedure
Urinary adverse events	4-years, n/N (%): • UTI: 12/80 (15%) • Acute urinary retention: 6/80 (7.5%) • Dysuria: 5/80 (6.25%) • Irritative urinary symptom: 2/80 (2.5%) • Poor/weak urinary stream: 1/80 (1.25%)	At 1-year n/N (%): • UTI: 2/21 (9.5%) • Haematuria: 3/21 (14.2%) • Urinary retention: 1/21 | (4.7%) • Urinary frequency: 2/21 | (9.5%) • Bladder spasm: 1/21 (4.7%)	At 1-year - No. events/Total no. events (%) Control | Optilume • Dysuria: 0/5 (0%) | 5/19 (26%) • Bladder spasm: 2/5 (40%) | 2/19 (10.5%) • Haematuria: 0/5 (0%) | 3/19 (15.7%) • Urethral Stenosis: 1/5 (20%) | 1/19 (5.2%) • Urinary Incontinence: 0/5 (0%) | 2/19 (10.5%)

Study	ROBUST I	ROBUST II	ROBUST III
			• Urinary retention: 0/5 (0%) | 2/19 (10.5%) • Urine Flow Decreased: 1/5 (20%) | 1/19 (5.2%) • LUTS: 1/5 (20%) | 0/19 (0%) • Terminal Dribbling: 0/5 (0%) | 1/19 (5.2%) • Urethral Haemorrhage: 0/5 (0%) | 1/19 (5.2%) • Urethritis: 0/5 (0%) | 1/19 (5.2%)
Treatment related SAE	0/80 (0%)	0/21 (0%)	One serious event of UTI judged as possibly related to the device/procedure in each group.
Other, n	4 years n/N (%): • Abdominal pain: 3/80 • Allergic reaction: 6/80 • Constipation: 1/80 • Damage to the urethral system: 1/80 • Erectile dysfunction: 1/80 • Extravasation: 1/80 • Fever: 6/80 • Flu-like symptoms: 2/80 • Headache: 4/80 • Hypertension: 3/80 • Low back pain: 1/80 • Myocardial infarction, angina, ischemia: 1/80	1-year: • Abdominal pain: 1/21 • Flank pain: 1/21 • Oropharyngeal pain: 1/21 • Pelvic pain: 1/21 • SOB • Urethral false passage: 1/21 • Bronchiectasis: 1/21 • Epididymitis: 1/21 • Coronary artery stenosis: 1/21 • Hematuriac: 1/21	

Study	ROBUST I	ROBUST II	ROBUST III
	• Other: 17/80 • Renal colic: 1/80 • Urethrorrhagia or Haematuria with or without clot in urethra: 3/80 • Worsening of stricture or de novo stricture: 7/80		

Abbreviations: AE: adverse event; N/A: Not reported; SAE: serious adverse event; SD: standard deviation; SOB: Shortness of breath; UTI: Urinary Tract Infection

Table 21: Summary of six SAEs reported in ROBUST I to 4-years (Taken from company unpublished ROBUST I study report).

AE Name	Days to Onset	Relation to Device	Relation to Procedure	Outcome
Urinary Tract Infection	30	Not Related	Not Related	Resolved
Other: Fall	492	Not Related	Not Related	Resolved
Myocardial infarction, angina, ischemia	194	Not Related	Not Related	Resolved
Abdominal pain	318	Not Related	Not Related	Resolved
Abdominal pain	404	Not Related	Not Related	Resolved
Other: Prostatic Adenocarcinoma	598	Not Related	Not Related	Resolved

7 Evidence synthesis and meta-analysis

The company submission did not include meta-analysis, citing heterogeneity as the reason this was not appropriate. The EAC note that there is consistency across all three ROBUST studies in terms of the outcome reported and duration of follow-up, with all studies reporting 12-month outcomes. As only one of the studies (ROBUST III) is comparative however, meta-analysis of available data will not provide any further indications of the effectiveness of Optilume compared with other treatment alternatives. Because of this, the EAC consider that meta-analysis is not appropriate.

8 Interpretation of the clinical evidence

In assessing the clinical evidence and deciding upon the most important outcomes for patients after treatment of urethral strictures, the EAC queried with clinical experts which objective (anatomic success, freedom from repeat intervention, Qmax, and PVR), and subjective (IPSS/IPSS QoL/IIEF/USS-PROM) efficacy outcomes were most important in deciding upon a course of treatment for a bulbar urethral stricture. Of the 6 clinical experts, 4 stated that patient reported outcomes (IPSS-USS-PROM) and flow rate were the most important, 1 noted post-void residual (PVR), and another freedom from repeat intervention. One expert noted that there is no right or wrong answer, as if you have a patient with no symptoms, it is difficult to justify treatment on the basis of imaging or endoscopy alone [see correspondence log]. It is clear that the decision of whether to treat a patient is multifactorial, but primarily depends upon the subjective experience of the patient and whether their symptoms are bothersome.

Throughout all three ROBUST trials, the Optilume DCB demonstrated a 70-74% rate of anatomical success post-treatment. When compared to standard care (26.8%) in ROBUST III, it was significantly superior with demonstrable [redacted] This successful treatment with Optilume is also seen when assessing the rate of patients being stricture free following treatment, right through to

4-year follow-up, irrespective of the method used to define being stricture free. Interpreting evidence from both anatomical success and stricture free outcomes demonstrates the effectiveness of Optilume in prevention of stricture recurrence. However, as discussed, anatomical success does not always correlate with worsening LUTS. Anatomical success and stricture free outcomes may not be the most reliable method of assessing treatment success and deciding upon future treatment of a patient, as it is the often the symptoms experienced by the patient which are more of important measure. When considering all subjective symptoms in the ROBUST trials, treatment of bulbar urethral strictures with Optilume caused a rapid and sustained improvement in all outcomes, leading to an improvement in all measured symptoms (IPSS, Qmax, and PVR) and quality of life (IPSS QoL, USS-PROM, and IIEF).

As ROBUST III was the only RCT with a comparator to Optilume, it is the most important study in the evidence base, with the most significant impact for integration of Optilume into the NHS. When compared to standard care (DVIU/dilatation) in ROBUST III, all primary and secondary outcomes measured across both groups (anatomical success, stricture free outcome by freedom from repeat intervention, IPSS, IPSS QoL, IPSS responder, IIEF overall satisfaction, Qmax, and PVR) were superior in the Optilume group versus control, with the exception of the VAS pain score. Such a rapid and sustained improvement across all outcomes useful to assessing stricture recurrence and quality of life makes Optilume a suitable treatment option alternative to further endoscopic procedures for recurrent bulbar urethral strictures ≤ 3cm in length who have underdone at least one prior endoscopic procedure. Treatment with Optilume is likely to rapidly improve patients' quality of life through long-term alleviation of symptoms.

In assessing the safety of Optilume, pharmacokinetic, biochemical and serological tests were performed in ROBUST I and III. Pharmacokinetic studies found an elimination profile of paclitaxel as expected. Biochemical and haematological investigations in ROBUST III identified no significant impact upon the subject's health. Additionally, the device causes very few adverse events and is deemed safe by the EAC.

As all ROBUST studies were in the U.S and Canada with different ethnicities to that of the UK, the generalisability of the results to the UK population being treated in the NHS needs to be considered. There is also no published evidence of the use of Optilume in the UK, and no proposed clinical trials for the UK that the EAC are aware of. In the EACs discussion with clinical experts, they noted that randomised control trial data would be helpful in facilitating the adoption of Optilume in the UK, specifically with long-term data.

8.1 *Integration into the NHS*

There is currently no recognised pathway for anterior urethral stricture disease management in the NHS, patients treated for urethral strictures come from a variety of

treatment pathways and are often identified serendipitously during investigations for other conditions such as benign prostatic hyperplasia. Patients most commonly reach urethral stricture disease diagnosis through lower urinary tract symptom problems during investigations for such problems and currently, treatment options include urethral dilatation, direct visual internal urethrotomy (DVIU) and urethroplasty.

The Optilume DCB device has been available in the UK since June 2021, and is currently used in four NHS organisations in England [redacted]. It is also approved for use in a further [redacted] in the UK, suggesting that Optilume is considered to be a suitable treatment option for urethral strictures. Clinical experts consulted for this assessment report however reported that evidence is currently lacking, particularly long-term data. One expert stated that they were not willing to adopt Optilume without any longer term RCT data, and another added that they would prefer to see some longer-term data before using Optilume.

The company propose Optilume be used in a day-case procedure or in an outpatient setting however the clinical experts had some concerns about use in an outpatient setting. The main concern was the pain inflicted upon the patient during the procedure as experts felt it would be very uncomfortable for the patient to use local anaesthesia without sedation. Secondly, experts noted that outpatient treatment using Optilume is unlikely to be feasible within the NHS due to a lack of facilities to diagnose and image the stricture and balloon during inflation making accurate placement of the balloon difficult. If Optilume were to be used within the NHS, it would likely be a day-case procedure, requiring in-patient care. However, the company has noted that there is 1 trust that is using Optilume in an outpatient setting under local anaesthesia.

Although the company propose that Optilume could be used in both bulbar and penile strictures, the evidence for use in penile strictures is limited to only 8 patients in the ROBUST III trial. Clinical experts also stated that they would not consider Optilume as an option for penile strictures at this time due to the lack of evidence. Future research may look to assess the use of Optilume in penile/meatal strictures, but as it stands, the evidence limits Optilume to the treatment of bulbar urethral strictures. Therefore, if integrated into the NHS, Optilume would be an additional treatment option for bulbar urethral strictures alongside endoscopic treatments (DVIU and urethrotomy). The EAC believe that there may be a potential equalities issue with Optilume in regards to trans men. There were no trans men with urethral strictures included in any of the ROBUST trials. It is unclear whether the evidence for cis men can be generalised to trans men clinical experts indicated they would not use Optilume in for trans men due to a lack of evidence. As a result, this may represent a potential issue around access to treatment. Future studies should therefore include trans men.

Optilume is not currently indicated or proposed by the company as a potential first-line endoscopic treatment, but may be integrated into the pathway of care once a patient has had at least one failed endoscopic treatment. The EAC asked the clinical experts if their centre offered both Optilume and other endoscopic procedures, how would the

decision to choose between them be made. One expert noted that they would offer it to those with recurrent bulbar strictures ≤3cm in length with a failed other endoscopic treatment. A second would base the decision on a patient's stricture location and size, general health and the patient's wishes. A third noted that they would offer urethrotomy plus self-dilatation versus urethroplasty versus Optilume and try to explain the differences and the patient would choose. During discussion with clinical experts, the EAC queried whether experts would consider using Optilume more than once i.e. retreatment of a recurrent stricture following Optilume DCB. One expert noted that there is no data for repeating Optilume and so they wouldn't consider it outside the context of a clinical trial. Another expert stated that they would consider using it again and several experts agreed that they would see no issue with considering Optilume for re-treatment as there is no rigid pathway and so this decision would likely be patient driven.

It is therefore possible that Optilume could be used as a first line treatment option or could be used again following a failed Optilume treatment however the most likely scenario in an NHS setting is that Optilume would be offered following a failed endoscopic procedure with the intention of delaying or preventing the need for urethroplasty. When it comes to treatment options the clinical experts agreed that the primary consideration in choosing the retreatment method, patient choice would be the most important driver and that the decision of whether to use Optilume and at what point, will be a multidisciplinary decision primarily influenced by the wishes of the patient.

Due to the specialist nature of urethroplasty and limited number of surgeons trained in urethroplasty in the UK, waiting lists for this surgery can be extensive. The coronavirus pandemic has exacerbated this problem, causing up to a two-year waiting list according to one clinical expert. Optilume however can be performed by a general urologist and therefore if integrated into the NHS, could help to reduce waiting list times for patients requiring treatment. The EAC asked clinical experts to approximate the treatment time between a recurrence being identified and re-treatment with Optilume. One expert noted that if Optilume was available, patients could be offered a date within 4 weeks. A second expert noted that this timeframe would be 4-6 months. The durations were the same when considering re-treatment with endoscopic procedures [see correspondence log]. It is likely that incorporating the Optilume device into the NHS would reduce the demand for urethroplasty and pressures upon the few specialist urological centres able to perform urethroplasty, which would likely reduce the waiting times for urethroplasty surgery.

The company states that the technology is to be used by trained consultants in urology, urology trainees, and urology nurse specialists. Training is predominantly undertaken by urological surgeons in the form of an online education program. The company stated that this online training programme takes up to 30 minutes to complete, and where requested, peer to peer training can be provided free of

charge. This is usually a one-day training event and clinical experts noted that learning how to use the device would not be too different to existing treatment and therefore would not require a great degree of training. One expert stated that anyone who is competent in endourology procedures and in endoscopic stricture management would be able to use Optilume. Another expert noted that Optilume would be able to be used by core urology consultants as trainees, but doubted urology nurse specialists would be able to perform the procedure as they do not tend to perform procedures other than flexible cystoscopies and standard urethral dilatation.

8.2 *Ongoing studies*

The company note that the company did not identify any ongoing studies relevant for inclusion. [redacted]

The EAC searched the Clinical Trials.gov and International Clinical Trials Registry Platform (ICTRP) registries for relevant ongoing trials and identified four studies where Optilume was used or mentioned. In total, one study related to urethral stricture disease management using Optilume were considered potentially relevant to the decision problem. This study was ROBUST III (NCT03499964), which is an active study no longer recruiting. The last update posted online was 06/08/2021. One-year results were submitted by the company and form part of the evidence base of the report (Elliott et al., 2021), and post-treatment follow-up is planned for up to 5 years.

One study identified by the EAC was the ROBUST IV trial (NCT03851952). This was a single-arm, open-label, registry study sponsored by the company. It is noted on the Clinical trials.gov website that this study was withdrawn in 2019, and in discussion with the company, this was confirmed.

The EAC also identified an active study using Optilume DCB, but for the treatment of Lower Urinary Tract Symptoms (LUTS) secondary to Benign Prostate Hyperplasia (BPH), and is therefore outside the scope of this assessment (NCT03423979). Similarly, the EAC identified a prospective, multicentre, double-blind, randomised, clinical study in the recruitment phase which will use Optilume, but the trial is also to evaluate the safety and efficacy of Optilume in men with symptomatic BPH and is therefore outside the scope of this assessment (NCT04131907).

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company presented the same search details for identifying economic evidence as for clinical evidence. It is noted that the company stated that they filtered their results for clinical evidence using ‘‘Clinical Trial’ and ‘Randomised Controlled Trial’, however there is no mention of whether the same search results were filtered for economic evidence. The company listed 4 studies as identified during their search. All studies were appropriate for selection and are included in the evidence base.

To ensure that all relevant and recent literature had been identified, the EAC conducted their own combined systematic searches for both clinical and economic evidence. Details of the company and EAC searches are provided in Appendix E.

Published economic evidence review

The company and the EAC did not identify any economic studies specifically related to Optilume. The company submission included 4 publications (Pickard et al., 2020; Wright et al., 2006; Rourke et al., 2005; Harris et al., 2016) which are relevant to the comparators and so are discussed briefly as background and supporting information. No data extraction or critical appraisal of these studies has been conducted by the EAC as they do not include Optilume.

Results from the economic evidence

One randomised controlled trial comparing open urethroplasty with endoscopic urethrotomy for recurrent bulbar urethral stricture (Pickard et al., 2020) included a within trial health economic evaluation and a longer term (10 year) Markov model to analyse the cost-effectiveness of open urethroplasty against endoscopic urethrotomy in an NHS setting. Results of the modelling indicated that in the base case analysis, urethroplasty is unlikely to be considered cost effective over a 10-year time horizon, mainly due to its higher cost. The company economic model uses clinical outcome data and micro-costing outputs from this trial, both in the base-case and in some scenarios. This will be discussed further in the cost analysis section.

One study (Wright 2006) is a decision analysis to determine the cost effectiveness of different management strategies for short bulbar urethral strictures (1-2cm length) using a decision tree model. The treatment options in the decision tree included direct vision internal urethrotomy (DVIU) and urethroplasty, with the number of planned possible DVIUs before urethroplasty defined for each primary branch point. The study was not designed to collect clinical outcomes, rather these were identified from published literature. Results from the analysis indicate that the incremental cost of

performing a second DVIU before attempting urethroplasty was $141,962 for each additional successfully voiding patient. The most cost-effective strategy therefore, is to reserve urethroplasty for patients in whom a single endoscopic attempt fails. The costs were estimated from a US societal perspective (cost reported in dollars) therefore will have limited applicability to the NHS setting. Conversely, a cost analysis (Rourke 2006) comparing treatment with DVIU to primary urethroplasty reported that urethroplasty was more cost effective with a base case cost of $17,728 per patient for DVIU and $16,444 for urethroplasty. This was driven by a high recurrence rate with DVIU; DVIU became more cost effective when long-term recurrence rates were <60%.

One study (Harris 2016) is a non-comparative study assessing the total costs of urethroplasty procedures. Results indicated that the cost of a urethroplasty was significantly higher at high volume urethroplasty centers, with the use of grafts, with high number of patient comorbidities, and when a complication occurred.

9.2 *Company de novo cost analysis*

Economic model structure

The company created a new model for the submission (Figure **2**), using a Markov structure to compare Optilume to standard care for the treatment of recurrent anterior urethral strictures equal to, or less than 3cm. A comparison with Urethroplasty was included as an additional scenario. The model used an NHS and personal social services perspective, and applied a 3.5% discount, as described in the NICE reference model. The time horizon was 5 years, which the company stated was due to a lack of long-term data, and the initial years having most impact. A ten-year time horizon was included as an additional scenario and the EAC has investigated the impact of a longer time horizon (20 years).

The EAC believe the model reflects the clinical pathway in that patients who experience recurrence may be retreated with either Urethroplasty, or an endoscopic method, and subsequent recurrences are dealt with in the same way. There is an assumption in the model that patients receiving Optilume for their initial treatment are then re-treated with Optilume again, if they do not receive Urethroplasty. In practice it is likely that patients not receiving Urethroplasty would receive a mixture of sequential endoscopic treatments, including Optilume depending on patient and clinician choice, and availability of resources. The company have addressed this in an additional scenario where retreatment is by endoscopic methods, and the EAC have completed additional modelling to allow for a mix of Optilume and endoscopic methods for retreatment.

Figure 2: Model diagram, taken from company submission and accepted by EAC.

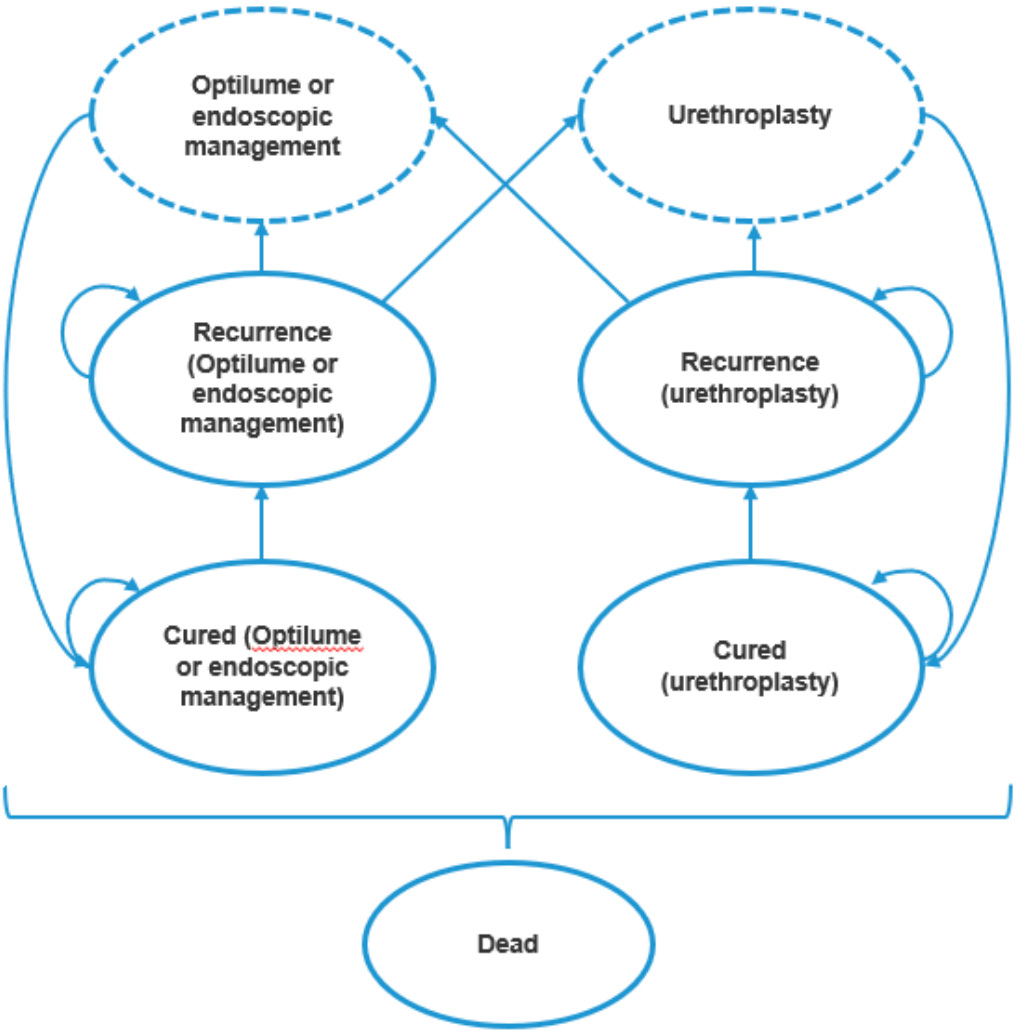


Table 22: Assumptions identified by company, with EAC comment and additional assumptions.

Assumption	Justification (summarised, see Company submission for full detail)	EAC comment
One monthly cycle	Sufficiently granular to capture recurrence rates of patients with urethral stricture.	Agree that this is suitable
Patients could remain in the recurrence health state for more than one cycle	Literature suggests that the time to treatment following recurrence is longer than one month. (Pickard et al., 2020)	Agree that this is suitable, and note that there is wide variation in waiting times. Investigated in sensitivity analysis. Some experts stated that there could be a very long waiting list for

Assumption	Justification (summarised, see Company submission for full detail)	EAC comment
		urethroplasty (considerably longer than 90 days). Longer urethroplasty treatment times mean that this treatment is less likely to occur in each cycle, leading to increased endoscopic procedures and subsequent repeat interventions.
10% of patients remained untreated following recurrence	Pickard et al., reported that 90% of patients would receive treatment when symptomatic (Pickard et al., 2020)	This is correctly referenced, however there is no explanation of the calculation in the source. A higher proportion of patients remaining untreated would reduce cost savings, however the model remains cost saving unless the proportion is close to 100%
No difference in efficacy was assumed between initial and repeat procedures (i.e. the recurrence rate was not dependent on the number of previous procedures)	Literature suggests that the efficacy of endoscopic procedures is likely to reduce as procedures are repeated, therefore this was considered to be a conservative assumption as more repeat procedures are required for the comparator arm. No evidence is available to suggest that efficacy of second line Optilume procedures would not also reduce(see submission for full justification).	(Heyns et al., 1998, Santucci and Eisenberg, 2010) This assumption is also made for economic model by Pickard et al (2020). It is accepted by the EAC as an assumption, and is likely to be conservative given the greater number of repeats for the comparator. There is little evidence available for the efficacy of Optilume repeat procedures.
Recurrence is applied at the same rate throughout the time horizon of the model	Simplifying assumption that the same probability of failure of treatment occurs throughout the time horizon of the model to avoid overcomplicating the model structure.	Evidence indicates that the likelihood of needing retreatment diminishes over time. As this is likely to be similar in both arms, although the absolute number of retreatments and costs may be reduced, the impact on the incremental costs is small.
Patients could only incur procedural adverse events within the cycle in which they receive the procedure	The majority of adverse events present less than one month after the procedure and the treatment costs incurred seem to be short-term. (Elliott et al., 2021a, Elliott et al., 2021b, Pickard et al., 2020, DeLong et al., 2022)	The EAC accept this as a reasonable assumption for adverse events directly related to the procedure. Some events such as UTI for patients who are self-catheterising may be expected to occur over a longer period. As patients spend longer in the recurrence state in the

Assumption	Justification (summarised, see Company submission for full detail)	EAC comment
		comparator arm, this is a conservative assumption.
The waiting time to treatment following recurrence was assumed to be equivalent between endoscopic management and Optilume	Assumption. It is noted that time to treatment could be less for Optilume as it is less resource intensive than urethrotomy. The treatment time for endoscopic management was based on the OPEN RCT and so could be overstated because this was treatment time to urethrotomy only rather than a mix of urethrotomy and dilatation. This was explored in sensitivity analysis and is not expected to substantially impact the results of the model (Pickard et al., 2020)	The EAC accept this assumption.
Additional assumptions identified by the EAC		
There are no complications that occur in the recurrence section	The costs accumulated while waiting for a repeat procedure include 4 follow up appointments a year and self-catheterisation for 16.8% of patients. There are no costs included for complications of self-catheterisation, or any other complications that may occur during this period. Although adverse events associated with catheterisation can be serious and costly, it is unlikely that this will have a large impact on the overall model, and any impact will be conservative as people spend more time in the recurrence state in the comparator arm.	
Patients who are initially treated with either Optilume or endoscopic methods are re-treated using the same method	This is unlikely to be correct, however there is not yet any evidence as to the likely mix of treatments, and it is likely to vary over time and across sites. The EAC have created an additional scenario with sensitivity analysis to explore the potential impact.	
In the recurrence cycle, patients have the same probability of retreatment method regardless of time in that cycle	Markov models do not have a memory of how long a patient has been in a disease state. The concept of a patient being allocated to urethroplasty and waiting 90 days does not directly translate to the model. Rather, the probability of receiving urethroplasty at 90 days is recalculated to give a monthly probability. This is applied to all patients in the recurrence state at each month. Therefore, if the waiting time is high for urethroplasty, the monthly probability is reduced, and more patients will receive endoscopic surgery. The EAC have accepted this, as it may reflect clinical realities where patients will receive endoscopic interventions due to long waiting times for urethroplasty.	
For the cured health state, the need for follow up appointments is assumed to be constant over time.	There is an assumption that there will be 2 follow up appointments a year for the cured health state, based on a reference stating that three visits were needed in the first year and thereafter one per year. For simplicity this was assumed to be 2 visits per year. The EAC could not locate the source data, but have accepted the value. Expert advice and the OPEN study suggest the initial follow up is similar or slightly	

Assumption	Justification (summarised, see Company submission for full detail)	EAC comment
	less, making this a conservative assumption (patients spend longer in the cured state in the Optilume arm). The base case is not very sensitive to changes in the cost of this health state.	
For the recurrent health state, follow up appointments are assumed to be double the cured requirement, and constant over time.	This is an assumption from the Company. The EAC have accepted this, as there would be likely to be an increased need for health care in a recurrent state. As above, the base case is not very sensitive to changes in the cost of the state. If the cost of this health state is overestimated, this would overestimate the cost saving due to Optilume.	

Economic model parameters

The model is based on the ROBUST III comparative RCT (Elliot 2021a), comparing Optilume with endoscopic management at one year, and presented in the clinical evidence section. Some additional data (both clinical and cost) has been taken from the OPEN study; a comparative RCT between Urethroplasty and Urethrotomy, with a two year follow up, and discussed in section 9.1 (Pickard 2021).

The clinical and resource use parameters are discussed in subsequent sections, with summary tables, however each parameter is detailed fully in Appendix E.

Clinical parameters and variables

The model is driven by the number of recurrences and retreatments that occur in each arm. This is determined by the following factors:

- Recurrence rate

And for re-treatments this is modified by:

- Likelihood of treatment following recurrence
- Type of treatment (urethroplasty has lower subsequent recurrence rate)
- Time to treatment – as this influences type of treatment obtained

Robust III is a prospective RCT, yielding appropriate, comparative data at 1 year follow up. The EAC agree that this is the most appropriate data source for the model, however there is some longer-term data available from the single arm trials which will be discussed for individual parameters.

Recurrence rates

For each of the studies there are several outcomes reported that can be used to indicate recurrence, and also a re-intervention rate. These have been discussed in detail in the clinical section, and Table 23 summarises the recurrence or re-intervention data available for modelling and where further details can be found within

the clinical section of this report. All study data has been converted appropriately to monthly probabilities for use within the model.

Table 23: Summary of outcomes used to indicate recurrence or repeat treatment

	EAC report	ROBUST I	ROBUST II	ROBUST III	OPEN RCT
Follow up		4 years	2 years	1 year	2 years
Interventions considered					
Optilume		✓	✓	✓	
Other endoscopic procedures				✓	✓
Urethroplasty					✓
Success/responder definitions reported (trial report, correspondence or publications)					
Functional: IPSS (≥50% improvement) responders		✓	✓	✓	
Functional: IPSS (≥30% improvement) responders		✓		✓	
Anatomical: 16Fr flexible cystoscope or a 14Fr catheter	5.1.1 table 11	✓(1 year)	✓(6 mth)	✓(6 mth)	
Qmax (reported but not used to define responders)	5.1.5 table 15	✓	✓	✓	✓
Composite outcome*	n/a				✓
Modelled probability	n/a				✓
Reinterventions carried out	5.1.2, table 12	✓	✓	✓	✓

*Any one of: a reintervention had occurred or was scheduled, the Qmax had deteriorated to the preintervention value or the voiding score had deteriorated to baseline value.

The Company base case used data from the ROBUST III study (Elliot 2021a) at one year following both Optilume and the comparator endoscopic methods. This is an appropriate choice as it is the only comparative data available.

The Company base case uses a responder definition of IPSS improvement greater than 30% at 1 year to model the recurrence, taken from the ROBUST III unpublished study report. The EAC agree that this is an appropriate measure for the base case, as a patient reported outcome, combining several different symptoms, although unpublished. Advice from clinical experts is that it is not a single outcome measure that is used consistently, therefore the approach taken by the company of providing several additional scenarios is necessary (summarised in Table 24).

Table 24: Clinical parameters: monthly probability of recurrence, Company model and additional EAC scenario

Company base case	Company Scenarios	EAC Scenario

	ROBUST III One Year (IPSS score)	ROBUST III 6 month (anatomic)	OPEN RCT	ROBUST III One year (Retreatments)
With endoscopic management as a comparator				
Optilume	2.6%	4.8%	0.5%##	1.4%
Endoscopic management	16.3%	19.7%	1.9%	11.1%
Urethroplasty	0.9%#	0.9%#	0.9%#	0.9%#
With Urethroplasty as a comparator				
Optilume	2.6%	4.8%	0.5%##	11.9%
Urethroplasty	0.9%#	0.9%#	0.9%#	0.9%#
# Taken from the OPEN RCT ## Relative risk ratio from ROBUST III IPSS score applied to OPEN RCT data for Urethrotomy				

The published data for ROBUST III (Elliot 2021a) also includes the rate of anatomical stricture at 6 months (an alternative scenario in the company model) and the proportion of patients retreated after one year (EAC alternative scenario).

The recurrence following Urethroplasty, for all scenarios, is taken from the OPEN RCT (Pickard 2021), and is 19/93 (20.4%) in patients who received Urethroplasty, with recurrence at any point up to 24 months after the procedure. Recurrence was measured based on a review at 24 months where at least one of the following conditions were met:

- a reintervention had occurred or was scheduled;
- the maximum flow rate had deteriorated to the preintervention value;
- the voiding score had deteriorated to baseline value.

The company presented an additional scenario where endoscopic recurrence rates were based on those reported by Pickard (2021), where 39/104 (37.5%) in men who received Urethrotomy experienced recurrence within 24 months. For this scenario, the recurrence for Optilume was calculated by applying the relative risk of recurrence (Optilume versus standard endoscopy interventions) from ROBUST III based on IPSS responder rate.

In addition to scenarios presenting different data sources for the comparator of endoscopic management, the company presented a scenario where Urethroplasty is the comparator.

Retreatment

A 90% probability of retreatment is applied to all those who experience recurrence. This is taken from the model presented by Pickard (2021) and while it is unclear how the authors derived this from the clinical data, the figure reflects the proportion of

patients randomised, but who did not receive treatment in either arm. This value is investigated in one-way sensitivity analysis.

Time to retreatment is taken as 90 days for Urethroplasty and 47.5 days for endoscopic management, again from the Pickard (2021) model. There is an assumption that the waiting time for endoscopic management, Urethrotomy and Optilume will be equivalent. Consultation with clinical experts indicated a wide range of possible waiting times, ranging from 4 weeks to 2 years. Most experts indicated that urethroplasty waiting times were likely to be longer than endoscopic or Optilume procedures.

For patients treated endoscopically, or with Optilume, the model applies a 70% probability that retreatment will be with Urethroplasty. For those treated with Urethroplasty there is an 88% probability of retreatment using an endoscopic method, or Optilume. This is taken from the Pickard (2021) model, reported as based on study data, although the precise data source is not clear from the report. Clinical experts found it difficult to estimate the likely retreatment methods, and the impact is investigated further in sensitivity analysis.

Monthly probability of retreatment

Once in the recurrence state, a probability of retreatment using a particular method is applied each month in the model. This is calculated by multiplying the probability of retreatment (90%) by the probability of retreatment by that method (70% urethroplasty if previous treatment was Optilume or endoscopic). The waiting time is 90 days for urethroplasty, and the calculated probability over 90 days is converted to a monthly probability. This means that a longer waiting time results in a lower monthly probability of that treatment method. The same approach is used for all retreatment calculations.

$$1 - \left(1 - (probability\ of\ treatment\ x\ probability\ of\ method)\right)^{(30/days\ waiting)}$$

Table 25: Monthly Probability of Retreatment

Initial treatment	Retreatment method	Retreatment received	% for each method	Wait (days)	Monthly probability of retreatment
Optilume / endoscopic methods	Optilume / endoscopic	90%	30%	47.5	18%
	Urethroplasty	90%	70%	90	28%
Urethroplasty	Optilume / endoscopic	90%	88%	47.5	63%
	Urethroplasty	90%	12%	90	4%

In each case, those not retreated remain in the recurrence state, and the next cycle the same probabilities of retreatment will be applied.

Adverse events

Adverse events for these procedures are generally not serious or long lasting. The model assumes that they will only occur in the month immediately after the procedure, and the EAC accept this as a reasonable assumption for events related to the procedure.

Table 26: Adverse events for each treatment type, applied only in the month following the procedure.

	Optilume	Endoscopic management /urethrotomy	Urethroplasty
Haematuria	0.0%[#]	0.0%[#]	2.0%[##]
Urinary tract infection	7.6%[#]	8.3%[#]	3.1%[##]
Wound infection	0.0%	1.0%[##]	2.0%[##]
Readmission to hospital	0.0%	0.0%	3.1%[##]
Urinary retention*	1.3%[#]	6.3%[#]	0.0%
* Requiring emergency intervention [#] From ROBUST III RCT (1 year) [##] From OPEN RCT (2 years)			

There is no clinical evidence that includes both Optilume, standard endoscopic management and urethroplasty, therefore inputs are based on a mixture of ROBUST III and OPEN studies. This leads to some uncertainty around how adverse events are reported, their severity, and if comparable events are being reported from each study. For urinary tract infection, Elliot (2021a) report 1/ 79 (1.3%) for Optilume and 1/48 (2.1%) for endoscopic management, however these are defined as serious adverse events and it is noted that UTI was one of the more common adverse events, and this is also reported in ROBUST I and II. The EAC have accepted the submitted values, and noted that the cost of adverse events forms a relatively small part of the total procedure costs, with the model being insensitive to changes.

Impact of clinical parameters

The state graphs (Figure 3 and Figure 4) show the number of the original cohort of 100 patients that are in each possible modelled health state over an extended time horizon of 20 years. Over time the number of people who have had only a single Optilume procedure (Cured Optilume 1st proc) gradually declines, and the number in a cured state following a retreatment of either Urethroplasty or further Optilume increases. In

both arms the Urethroplasty has a very low recurrence probability, and therefore the numbers in this state increase to a plateau. As patients age this will drop down as mortality from general causes increases. For other retreatments, a similar plateau is seen, as patients move into the cured state, but for endoscopic treatments it is much lower, as patients move more readily to recurrence (it is also less obvious to see, as both initial and retreatments are included in the same arm for endoscopic management).

Figure 3: Optilume: EAC and company base case extended to 20 years

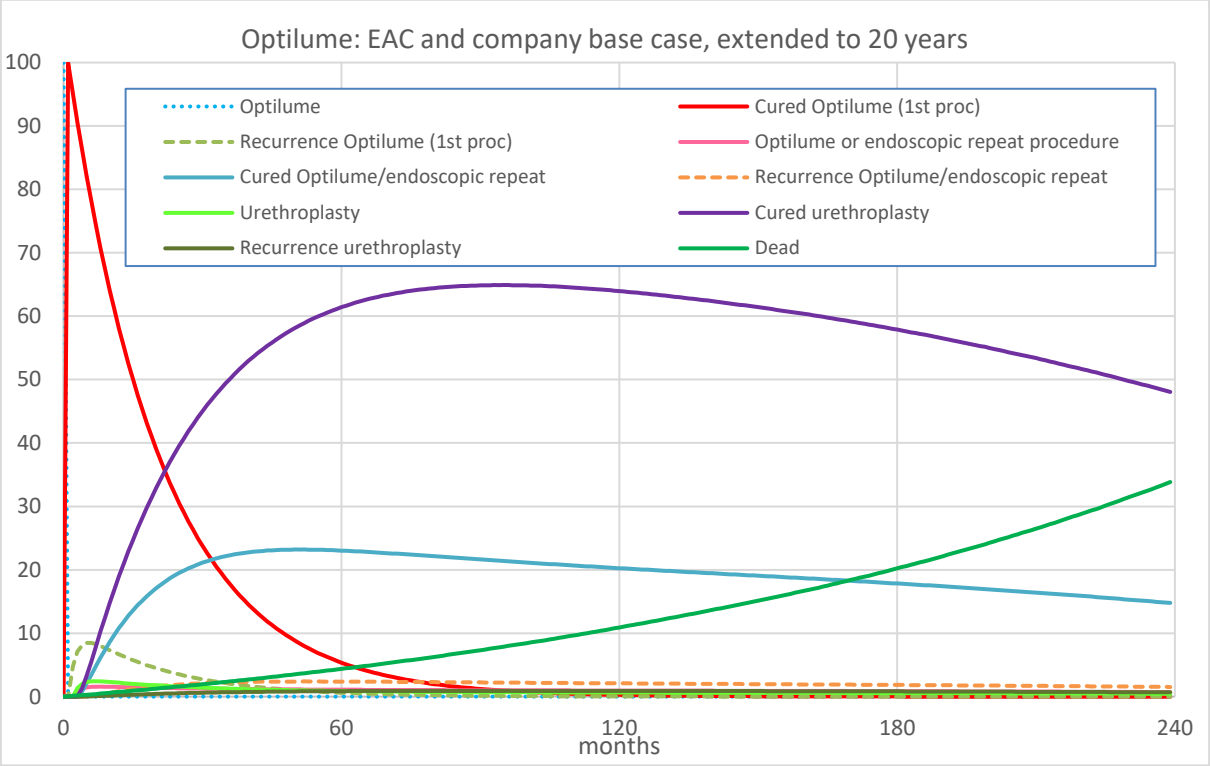
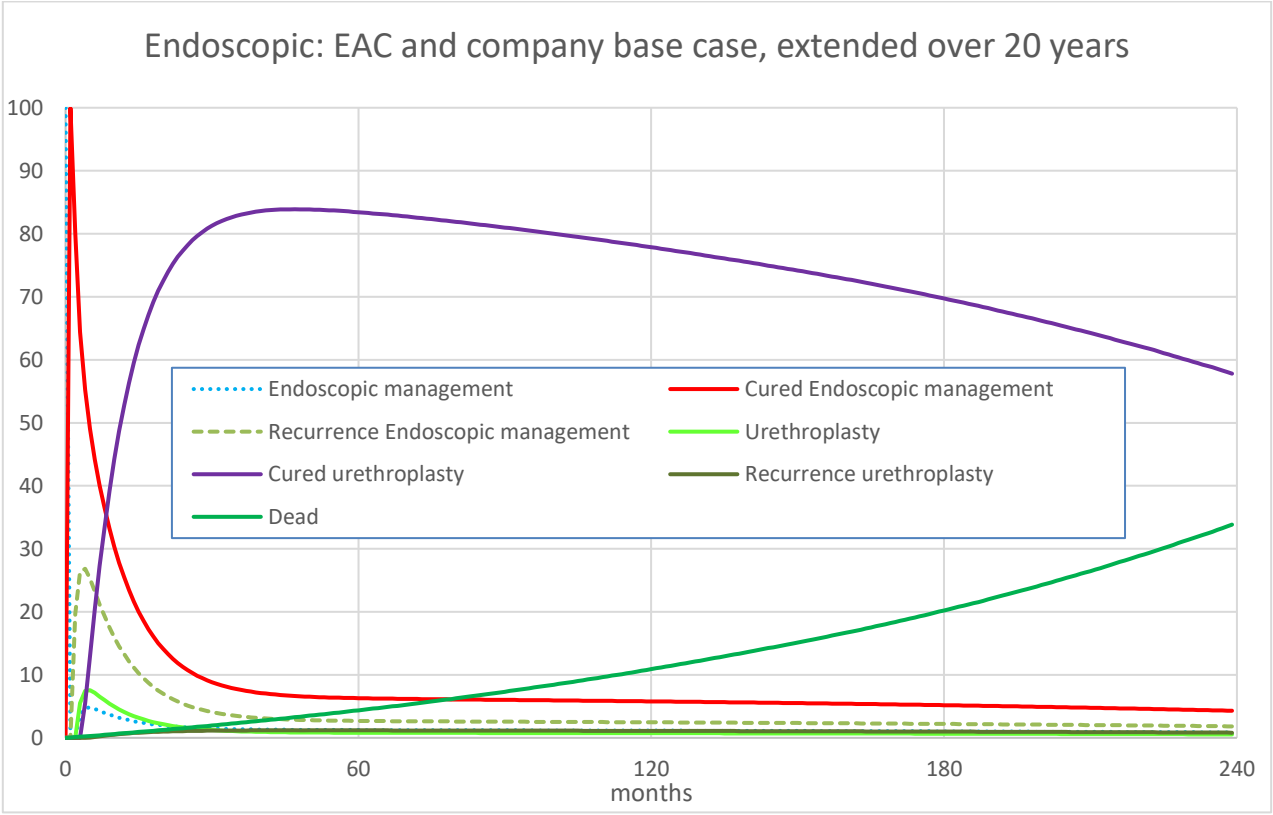


Figure 4 Endoscopic: EAC and company base case extended to 20 years



Resource identification, measurement and valuation

The costs can be grouped as follows:

- Cost of procedure (including variations for setting)
- Cost of device and training
- Cost of adverse events
- Cost of recurrence
- Cost of cured state

The key parameters are listed in Table 27 below, however the details of how they are calculated, and individual costs plus full references are contained in Appendix E.

Table 27: Resource parameters for company and EAC base case

Parameter	Company	EAC value	Comment
Procedure costs			
Endoscopic management procedures	£1,196	No change	Weighted average of all NHS Ref Costs 2019/20 LB55A, except outpatients.
Urethroplasty procedure	£4,761	No change	Total HRG costs for NHS Ref Costs 2019/20
Optilume procedure	£635	£1,067	NHS References Costs 2019/20 Company: Mean of LB55A Day Cases and Outpatients EAC: LB55A Day Cases only
Optilume device	£1,350	No change	List price, company submission

Total procedure cost: Optilume	£1,986	£2,418	EAC cost includes day case only, without use of outpatient procedures.
Other related costs			
Predilatation	£20.36	No change	This is applied to 5% of all patients treated with Optilume only.
Training for Optilume	£8.53	£2.62	Staff training and 3 supervision sessions. EAC changed calculation method and assumptions
Adverse events			
Haematuria	£33	No change	GP Appointment (PSSRU 2020)
Urinary tract infection	£43	No change	7 days antibiotics, urinalysis test plus GP appointment
Wound infection	£107	No change	Mean of oral or IV antibiotics plus GP appointment (hospital admission counted separately)
Readmission to hospital	£434	£508	Weighted average of non-elective short stay with and without intervention (LB57C and LB57D)
Urinary retention	£941	No change	Outpatient procedures, Accident and Emergency. LB55A Minor or intermediate, urethra procedure
Subsequent health state costs (per month)			
Cured state	£18	No change	2 x GP appointments per year
Recurrent state	£44.74	No change	4 x GP appointments per year, plus 16.8% using self-catheterisation

Cost of procedure (including variations for setting)

These are taken from NHS Reference costs and accepted by the EAC. However, the costs of the Optilume procedure are based on a mean between day case and outpatient procedures. Expert advice was that it is unlikely in the NHS that Optilume would be adopted as an outpatient procedure, as it requires sedation in addition to local anaesthesia, however the company have provided information that 1 centre is now offering the procedure in an outpatient setting. The EAC have used only the day case costs, changing the procedure cost from £635 to £1,067 to reflect current use, but this may change in the future.

The company have allowed for 5% of cases receiving predilatation, at a cost of 10 min consultant time plus a dilatation catheter. Expert advisors told the EAC that predilatation was not normally required, however the EAC have left this as it may be used on some occasions. There is minimal impact on the incremental cost saving at 5 years.

Cost of device and training

The device cost is £1,350, the list price supplied by the Company. Training is assumed to be very brief. The company submission is for 95% of staff to require 45 min training, with 5% requiring an in-depth delivery for 4 hours. In addition, 3 procedures are supervised for each staff members. There is an assumption that no new training would be required for 10 years. The EAC accepts most assumptions, but disagree with the calculation of the total price. Training was assumed to last only 3 years to allow for new staff entering the unit. The EAC total cost of training is £2.62 per procedure,

rather than £8.53 from the submitted model. This change has minimal impact on the incremental cost saving.

Cost of adverse events

All adverse events are assumed to be related to a procedure, and happen within the same month as the procedure. The EAC have not identified any information that contradicts this assumption. The company submission and model do not give full details of how the costs of adverse events were calculated, however these have been clarified with the company, and full details of the costs are included in Appendix E.

- Haematuria costs are for a GP appointment only.
- UTIs are treated with either 7 days antibiotics or a urinalysis test and GP appointment.
- Wound infection is a mean cost from antibiotics delivered by tablet or IV, plus a GP appointment (hospital admission is not included, as it is a separate category).
- Hospital readmission is a weighted average of non-elective short stay for urethral disorders with or without interventions, from NHS Reference Costs.
- Urinary retention requiring emergency intervention is based on accident and emergency NHS Reference costs.

The EAC agreed with the majority of these costs, however the costs we identified for hospital readmission were £508 rather than £434, with minimal change to the overall incremental cost. For acute urinary retention, the treatment would normally be emergency catheterisation followed by investigation of causes. The company selected an NHS Reference cost for outpatient's procedure, with an accident and emergency code for Minor or Intermediate, Urethra Procedures, 19 years and over (LB55A) of £941. There was only one recorded incidence of this in 2019/20, however the EAC have not identified an improved alternative. The model is not sensitive to changes in the costs of adverse events.

Table 28: Costs used for adverse events, and the impact on the cost per procedure type (EAC base case)

	Cost per adverse event	Adverse event costs per procedure carried out (see Table 26 for clinical probability)		
		Optilume	Endoscopic management /urethrotomy	Urethroplasty
Haematuria	£33	£0.00	£0.00	£0.67

Urinary tract infection	**£43**	£3.25	£3.57	£1.31
Wound infection	**£107**	£0.00	£1.03	£2.18
Readmission to hospital	**£508****	£0.00	£0.00	£15.54
Urinary retention*	**£941**	£11.91	£58.81	£0.00
* Requiring emergency intervention ** £508 in EAC base case, £434 in Company base case resulting in £13.30 for Urethroplasty				

Cost of recurrence

Costs are based on 4 follow-up outpatient appointments per year plus 16.8% of patients using intermittent self-catheterisation (with 1 clean catheter per week, and 5 uses per day). The EAC made a small change to the cost calculation that had minimal impact.

Cost of cured state

Costs are based on 2 follow-up outpatient appointments per year. The EAC did not make any changes to this.

Sensitivity analysis

The company submission included one way, two way and probabilistic sensitivity analysis, as well as several alternative scenarios. The EAC found that the sensitivity analysis was comprehensive and accurate. Where the EAC altered parameter values, the sensitivity analysis was also updated to reflect the changed parameters. The EAC two additional scenarios:

- Use of direct re-treatment rate rather than outcomes to indicate recurrence figures
- Possible use of any of Urethroplasty, endoscopic treatment or Optilume for additional re-treatments

In addition, the EAC investigated the effect of an extended time horizon of 20 years.

9.3 *Results from the economic modelling*

Base case results

The company base case found that there was a cost saving of £2,502 per patient using Optilume at 5 years. The EAC changed the setting to day-case only, and adjusted some costs for training and adverse events. Following this the cost saving was reduced to £1,877 per patient. This was associated with a reduction from 2.31 to 1.11 repeat procedures over the 5 years (a reduction of 1.20).

The change in results for the base case is almost entirely due to the change from 50% day-case and 50% outpatient in the submitted model, to 100%-day case in the EAC amendments. If an outpatient setting were widely used there would be an increase in the cost saving due to Optilume.

Table 29: Summary of base case results

	Company's results			EAC results		
	Technology	Comparator	**Cost saving per patient**	Technology	Comparator	**Cost saving per patient**
Initial procedure	£2,001	£1,259	**-£742**	£2,433	£1,259	**-£1,174**
Repeat procedures (Endoscopic)	£931	£1,286	**£355**	£1,132	£1,286	**£154**
Repeat procedures (Surgical)	£2,658	£5,514	**£2,856**	£2,659	£5,516	**£2,857**
Training costs	£9	£0	**-£9**	£3	£0	**-£3**
Cured health state	£925	£860	**-£65**	£925	£860	**-£65**
Recurrence health state	£97	£203	**£107**	£98	£205	**£107**
Total	£6,620	£9,122	**£2,502**	£7,249	£9,126	**£1,877**

Sensitivity analysis results

The most important parameter for the model is the initial recurrence probability, and the only one which in the one-way sensitivity analysis can make the base case model cost-incurring for Optilume at 5 years. The impact of this is also seen in the scenarios using different input data. The company submitted a two-way sensitivity analysis for Optilume and endoscopic recurrence probabilities, and this has been recreated in Figure 6 for the EAC base case. The upper bound for the cost of the Optilume procedure has been changed from £1,067 to £1,195 (the cost

of an endoscopic procedure). Figure 5: Torndao diagram updated to EAC base case at 5 years

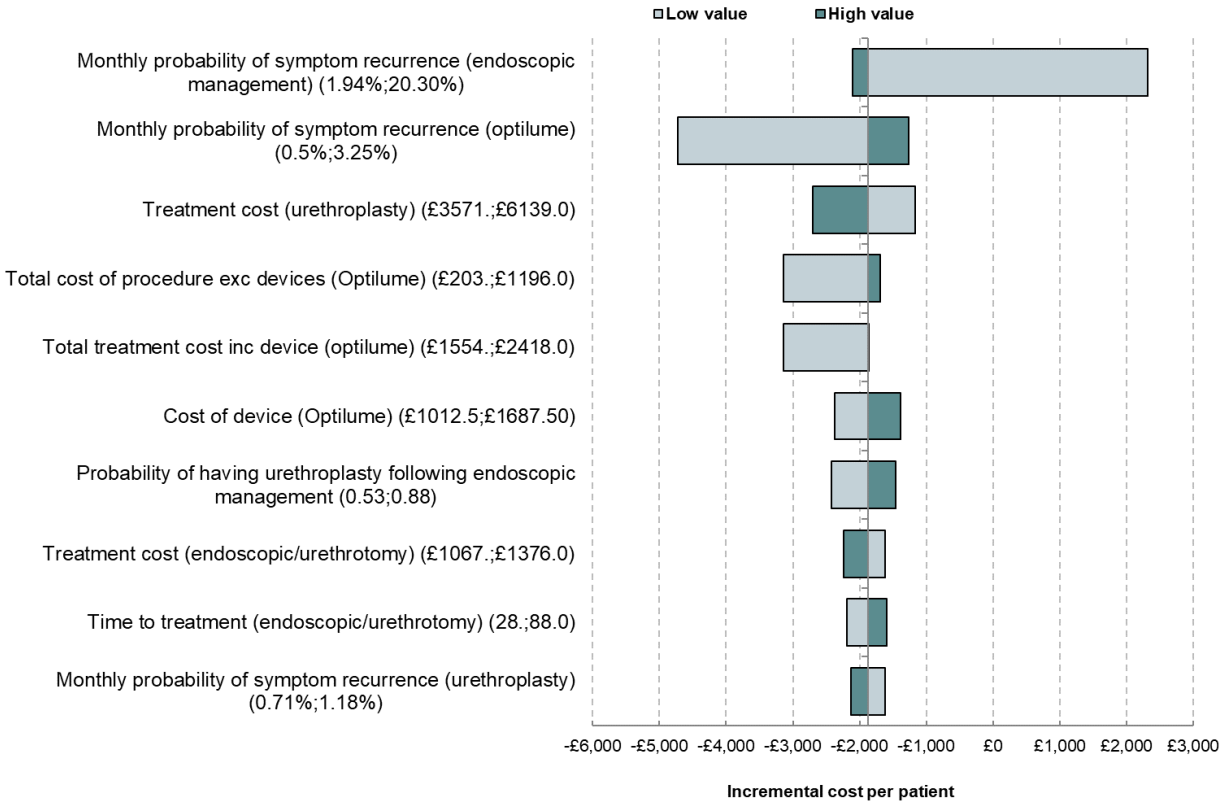


Table 30: Two-way sensitivity analysis of monthly probabilities of recurrence for both Optilume and standard endoscopic procedures.

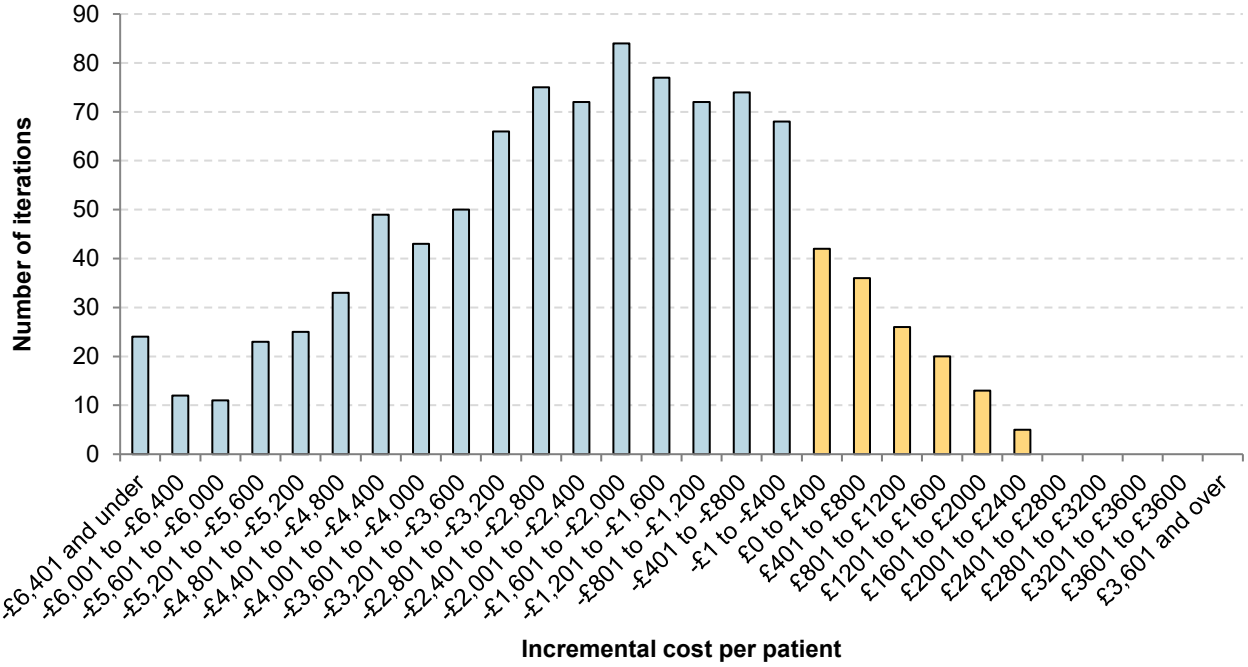
		Monthly probability of recurrence with Optilume										
		0.2%	0.6%	1.0%	1.4%	1.8%	2.2%	2.6%	3.0%	3.4%	3.8%	4.2%
Baseline monthly probability of recurrence with endoscopic	1.0%	£13	£767	£1,435	£2,029	£2,558	£3,030	£3,430	£3,831	£4,171	£4,477	£4,754
	3.0%	-£2,037	-£1,283	-£615	-£21	£508	£980	£1,380	£1,781	£2,121	£2,427	£2,704
	5.0%	-£3,230	-£2,476	-£1,807	-£1,213	-£684	-£212	£187	£588	£929	£1,235	£1,511
	7.0%	-£3,966	-£3,211	-£2,543	-£1,949	-£1,420	-£948	-£548	-£147	£193	£499	£776
	9.0%	-£4,447	-£3,693	-£3,024	-£2,430	-£1,901	-£1,429	-£1,030	-£629	-£289	£18	£294
	11.0%	-£4,779	-£4,025	-£3,356	-£2,762	-£2,234	-£1,762	-£1,362	-£961	-£621	-£315	-£38
	13.0%	-£5,020	-£4,266	-£3,597	-£3,003	-£2,474	-£2,002	-£1,603	-£1,202	-£862	-£555	-£279
	16.3%	-£5,295	-£4,540	-£3,872	-£3,278	-£2,749	-£2,277	-£1,877	-£1,476	-£1,136	-£830	-£553
	17.0%	-£5,344	-£4,590	-£3,921	-£3,327	-£2,798	-£2,326	-£1,927	-£1,526	-£1,186	-£879	-£603
	19.0%	-£5,458	-£4,704	-£4,035	-£3,441	-£2,912	-£2,440	-£2,041	-£1,640	-£1,300	-£993	-£717
	21.0%	-£5,551	-£4,797	-£4,129	-£3,535	-£3,006	-£2,534	-£2,134	-£1,733	-£1,393	-£1,087	-£810

Other parameters such as retreatment method or waiting time have some impact, but where the recurrence for Optilume is low, for a 5-year time horizon most patients will not undergo a second treatment. Therefore, these parameters have a reduced impact on the model.

Probabilistic sensitivity analysis (PSA) was repeated for the EAC base case. No parameters were changed other than the standard error for the probability of having treatment following recurrence of symptoms. This was corrected to 0.02, as quoted in Pickard (2020).

The PSA found that 86% of the 1,000 iterations were cost saving. The distribution is shown in Figure 6.

Figure 6: Distribution of PSA iteration results for the EAC base case (orange bars are cost incurring)



Additional results

Table 31: Additional results for company and EAC scenarios

		Company's results			EAC results		
		Technology	Comparator	**Saving**	Technology	Comparator	**Saving**
Base Case	Cost	£6,620	£9,122	**£2,502**	£7,249	£9,126	**£1,877**
	Re-treat	1.11	2.31	**1.20**	1.11	2.31	**1.20**
Alternative clinical inputs							
R III anatomical	Cost	£8,200	£9,319	**£1,119**	£8,920	£9,324	**£404**
	Re-treat	1.59	2.38	**0.79**	1.59	2.38	**0.79**
OPEN RCT	Cost	£3,938	£4,925	**£988**	£4,416	£4,927	**£511**
	Re-treat	0.29	0.91	**0.62**	0.29	0.91	**0.62**
R III Re-interventions	Cost				£5,879	£8,662	**£2,783**
	Re-treat				0.712	2.147	**1.435**
Extended time horizon, 20 years							
Base Case	Cost				£14,410	£16,562	**£2,152**
	Re-treat				3.41	5.44	**2.03**
R III anatomical	Cost				£16,972	£16,832	**-£140**
	Re-treat				4.30	5.55	**1.25**
R III Re-interventions	Cost				£11,808	£15,937	**£4,129**
	Re-treat				2.47	5.17	**2.70**
Retreatment options include both Optilume and standard endoscopic methods							
% of endoscopic retreatment using Optilume		**EAC base case, 5 years**			**EAC base case, 20 years**		
		Technology	Comparator	**Saving**	Technology	Comparator	**Saving**
0%	Cost	£7,813	£9,126	**£1,313**	£15,730	£16,565	**£834**
	Re-treat	1.475	2.312	**0.838**	4.74	5.44	**0.70**
40%	Cost	£7,550	£9,126	**£1,576**	£15,096	£16,565	**£1,468**
	Re-treat	1.304	2.312	**1.008**	4.10	5.44	**1.34**
60%	Cost	£7,439	£9,126	**£1,687**	£14,839	£16,565	**£1,726**
	Re-treat	1.232	2.312	**1.080**	3.84	5.44	**1.60**
80%	Cost	£7,339	£9,126	**£1,787**	£14,613	£16,565	**£1,952**
	Re-treat	1.168	2.312	**1.144**	3.61	5.44	**1.83**

For the base case, the extended time horizon increases the cost saving slightly. In the anatomical stricture (ROBUST III 6 months) scenario, where recurrence rates are slightly higher for Optilume, the extended time horizon results in the model becoming very slightly cost incurring. This illustrates the impact of different using different outcome measures and different reporting time points for the clinical inputs to the

model. Appendix F contains additional information showing changes in costs, and reinterventions over the exploratory 20-year time horizon for each of the scenarios.

9.4 *The EAC's interpretation of the economic evidence*

The EAC changed the setting for Optilume from a 50% mix of Outpatients and 50% day-case, to being entirely carried out as a day-case, following expert advice. Other EAC changes are listed in Table 32, but had minimal impact on incremental cost savings.

Table 32: EAC Changes to model and impact

Description of EAC change	Impact
Company base case	**£2,502**
Cost of readmission to hospital from £434.34 to £507.68	Minimal increase in cost saving (~£1)
Change of training costs calculations	Minimal increase in cost saving (~£5)
Change of assumption of 10 years to 3 years until retraining	Minimal decrease in cost saving (~£2)
Change in inflated cost of self-catheterisation from £48 to £50 per month.	Negligible change in cost saving (<£1)
Change proportion of outpatient procedures from 50% to 0%	Decrease in cost saving of £632
EAC base case	**£1,877**
Additional scenarios:	
Increase time horizon to 20 years	Increase to base case cost saving, impact varies for other scenarios
Use re-treatment values from ROBUST III	Increase in cost saving
Allow retreatment to be by Optilume, endoscopic methods or Urethroplasty for Optilume arm	Increase in proportion re-treated using standard endoscopic treatment results in moderate decrease in cost saving.

The key driver in the model is the probability of recurrence, and hence re-intervention. As modelled, Optilume reduces recurrence, and repeat interventions. Cost savings largely depend on the saving due to reduced repeat interventions being greater than the additional cost of an Optilume procedure (compared to standard endoscopic procedures).

While clinical evidence points to Optilume improving clinical outcomes, at least in the short term, there is some uncertainty around the extent and duration of the change, and how this translates to recurrence in the model. This is due to the following factors:

- There is only one comparative study available for Optilume
- This study is limited to one-year follow-up (although single arm studies are up to 4 years)
- there is not an agreed single outcome measure that defines recurrence
- standard endoscopic methods encompass several different procedures

Both the EAC and company base cases are cost saving at 5 years, and remain cost saving if the time horizon is extended. The company and the EAC have modelled a variety of scenarios using different clinical data for the probability of recurrence, and all scenarios remained cost saving at 5 years. Using deterministic one-way sensitivity analysis, the only variable that caused the model to be cost incurring was the recurrence probability for endoscopic treatment.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The clinical evidence for Optilume DCB device consists of three U.S studies; ROBUST I, II and III. All studies are relevant to the decision problem, but only ROBUST III meets all PICO elements of the scope. All three are multicentre and use Optilume as an intervention, however ROBUST I and II are both single arm studies with no comparator. Comparative evidence is limited to the ROBUST III trial, using standard care as direct vision internal urethrotomy/dilatation.

Several outcomes in the ROBUST trials were presented differently, with emphasis placed upon less clinically important outcomes. However, all clinically significant outcomes improved from baseline irrespective of the definition used. Optilume consistently achieved a rapid improvement in symptoms post-treatment including participants quality of life. ROBUST I was the only study with outcome data beyond 1 year, and [redacted], ultimately reducing the need for repeat interventions overall. Similarly, in ROBUST III, those treated with Optilume had superior outcomes to the control group post-treatment through to follow-up, whereas many of the outcomes in the control group deteriorated towards baseline values.

Adverse events were limited to urinary symptoms, and serious side effects were rare, suggesting Optilume is safe for use.

Consensus on the management of male urethral stricture disease has historically been hindered by a lack of definitive practice recommendations. In the UK there is no rigid clinical pathway for these patients as treatment is multifactorial and usually patient driven. In discussion with clinical experts, they were largely in agreement that Optilume has a place in therapy alongside existing endoscopic treatments for men with recurrent bulbar urethral strictures ≤3 cm in patients who have previously undergone ≥1 failed endoscopic procedure. Experts agreed that such a procedure should only take place in an inpatient setting under sedation to ensure the comfort of the patient and precision of the surgery.

Overall the EAC consider that the Optilume DCB device is an effective treatment for patients with bulbar urethral strictures and can be integrated into the NHS clinical practice.

10.2 *Conclusions from the economic evidence*

The submitted model reflected the published scope, and used the most appropriate source of available clinical evidence. The EAC made minor amendments to the model and changed the assumption for procedures settings, meaning that Optilume is modelled as entirely a day case procedure, with no outpatient procedures taking place. This changed assumption resulted in a small decrease in the incremental cost saving due to Optilume from £2,502 to £1,877 compared to standard endoscopic treatment at 5-year time horizon.

The strongest driver for the model is the probability of recurrence (or retreatment). This is based on comparative data from an RCT, but the additional scenarios created by the company and EAC demonstrate that plausible changes in recurrence can have a significant impact. This is illustrated in both the tornado diagram (Figure 5) and the two-way sensitivity analysis (Table 30). In both the EAC and Company models, Optilume remained cost saving at 5 and 10 years for all scenarios modelled.

Increasing the time horizon to 20 years has a small impact on the base case, increasing the cost saving from £1,877 to £2,152 in the EAC base case. On some of the alternative scenarios it can decrease the cost saving, causing a small cost to be incurred. This is an exploratory analysis, and does not form the EAC base case. The change in costs and retreatments are shown over time in Appendix F for the different scenarios.

When Urethroplasty is set as the comparator arm, Optilume provides a much smaller cost-saving, due to the low recurrence probability following both procedures. However, experts agreed that standard endoscopic procedures were the appropriate comparator for Optilume. Therefore, in the base case, standard endoscopic treatments or Optilume are used for the first procedure in the model. The model then routes subsequent re-treatments to a mix of the original intervention method or urethroplasty.

Modelling suggests the introduction of Optilume would provide a cost-saving alternative to further standard endoscopic procedures in men with recurrent bulbar urethral stricture who have previously undergone a failed endoscopic procedure. There is remains uncertainty around the most appropriate inputs for recurrence or retreatment, and therefore the extent of the cost saving due to Optilume.

11 Summary of the combined clinical and economic sections

The clinical evidence for the Optilume DCB device consists of three U.S studies; ROBUST I, II and III, comparative evidence is limited to the ROBUST III trial. Optilume consistently achieved a rapid improvement in symptoms post-treatment including participants quality of life. ROBUST I was the only study with outcome

data beyond 1 year, and [redacted], ultimately reducing the need for repeat interventions overall.

In the EAC base case, cost savings with Optilume were £1,877 at 5 years compared to standard endoscopic management. The strongest driver for the model is the probability of recurrence (or retreatment). In both the EAC and Company models, Optilume remained cost saving at 5 and 10 years for all scenarios modelled.

Optilume is currently in use in a small number of centres in the NHS, however clinical experts have expressed a need for further long-term data.

Overall, based on the current evidence, the EAC consider that the Optilume DCB device is a clinically effective treatment for patients with recurrent bulbar urethral strictures and is cost saving, but further investigation of long-term outcomes would strengthen the evidence base.

12 Implications for research

The EAC consider that additional research is needed to support the early promising results reported in the currently available literature and has identified some key considerations for decision makers when considering research approaches:

- A multicentre, randomised controlled trial in the UK would help better understand the true prevalence of UK patients eligible for Optilume treatment. Randomisation to a treatment or control group would build upon findings in the RCT ROBUST III, but consideration should be given to the comparator and where in the urethral stricture treatment Optilume would be positioned. The potential places for Optilume may include:
    - As a first-line treatment, with the comparator any first-line endoscopic procedure (DVIU/dilatation).
    - After 1 prior endoscopic procedure, with the comparator as any other endoscopic procedure used after 1 prior intervention (DVIU/dilatation)
    - After several prior failed treatments, with the comparator as urethroplasty.
- A study with a larger subgroup population with penile strictures would help elucidate any potential use of Optilume for treatment of this stricture type.
- The majority of patients receiving Optilume across the three ROBUST studies were pre-dilated prior to treatment, whereas the control groups were not predilated. As pre-dilatation prior to Optilume would be unlikely to be performed

in the NHS, generalisability must be considered. Therefore, any future research should avoid pre-dilatation to accurately assess the impact of Optilume alone.

- There is very limited evidence in the ROBUST trials for the repeated use of Optilume DCB after a previous Optilume DCB. Future research could help to address this by recruiting patients previously treated with Optilume.

- Future research could look to include longer strictures ≥3 cm in length, as these patients were excluded from all ROBUST trials and Optilume may be of some benefit for patients with these strictures.

Research needs to include trans men to better understand the treatment pathway for these patients and how Optilume may impact this. Trans men could be a subgroup in a randomised controlled trial.

The company submission included a number of claimed benefits (Table 33) of the Optilume device and some of these claimed benefits have been met or partially met by the current evidence. The EAC considers that the Optilume device shows promise, however there are still gaps in the evidence.

Table 33: Summary of company claimed benefits

Claimed benefit	Benefit to	Supporting evidence	Rationale	EAC comment
Rapid and sustained improvement in symptoms and urinary flow	Patient	ROBUST I ROBUST II ROBUST III	Published outcomes show immediate and sustained improvement in IPSS, USS-PROM, and Qmax	**Met** The EAC agree that the current evidence suggests that Optilume rapidly improved symptoms post-procedure (IPSS, USS-PROM and Qmax). Evidence also demonstrates sustained improvement through to 1 year in ROBUST II and III, and [redacted]
Effective minimally invasive treatment	Patient	ROBUST III	Optilume DCB showed superiority to standard of care endoscopic management	**Met** The EAC agree that the Optilume device is both effective, and minimally invasive. The procedure is not open surgery and is similar procedurally to existing endoscopic procedures (DVIU/dilatation).
Reduces the need for retreatments or invasive surgical procedures	Patient System Cost	ROBUST III	Optilume DCB had significantly lower rate of retreatment	**Partially Met** The EAC agree that the evidence suggests Optilume DCB device reduces the need for retreatments as the freedom from repeat intervention in Optilume-treated patients was much lower versus patients treated with standard care (83% Vs. 22%), however limited long-term follow-up data mean it is difficult to know whether this is a sustained outcome. The economic model is based on the reduced need for retreatment, taken from 1-year data (ROBUST III).
Reduces the need for self-catheterisation management	Patient Cost Sustainability	ROBUST III	Optilume DCB had significantly lower rate of retreatment	**Not met**

Claimed benefit	Benefit to	Supporting evidence	Rationale	EAC comment
				Self-catheterisation was not an outcome measured in the ROBUST trials therefore there is no evidence to support this claim. The economic model associates this with the recurrent state. Men in the Optilume arm spend less time in the recurrent state, and therefore have a decreased need for self-catheterisation. This is based on the number of men self-catheterising at the start of the OPEN study (and thus in the recurrent state).
Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty	Patient System Cost		Minimally invasive endoscopic treatment Vs open surgical procedure	**Not met** None of the ROBUST trials compared Optilume against open surgical procedure (urethroplasty), and therefore a comparison of side effects and post-operative complications cannot be made.
Rapid return to normal daily living and improved quality of life	Patient	ROBUST III	ROBUST I, ROBUST II, and ROBUST III studies	**Met** The EAC agree that post-procedure, all outcomes were improved to normal or near-normal. Quality of life assessed by IPSS QoL was improved significantly from baseline post-treatment, and had a sustained improvement through to [redacted] Conversely, standard care quality of life deteriorated through to 1-year follow-up. USS-PROM scores were not an outcome assessed in ROBUST III and so comparator data is unavailable. However USS-PROM scores were all significantly improved from baseline in ROBUST I and II when treated with Optilume.
Preservation of sexual function	Patient	ROBUST I ROBUST II ROBUST III	No treatment related sexual function AEs, no change in function	**Partially met**

Claimed benefit	Benefit to	Supporting evidence	Rationale	EAC comment
			per IIEF questionnaire	Erectile dysfunction was reported as an AE in the 4-year report for ROBUST I, however the AE was mild and not related to the device or procedure. The International Index of Erectile Dysfunction (IIEF) has 5 domains to assess sexual function. Two of these (erectile function and overall satisfaction) were reported in the ROBUST trials and therefore it is not known what the effect Optilume had upon the remaining domains; Orgasmic function, sexual desire and intercourse satisfaction. When considering the overall satisfaction domain of the IIEF, all studies found a slight improvement post-procedure through to one-year outcomes, but none demonstrated a significant improvement.
Reduced risk of hospital acquired infection	Patient System Cost		Wound infection rates in urethroplasty ~4%, no wound created for endoscopic treatment	**Not met** The risk of hospital acquired infection was not assessed and there were no studies comparing Optilume to Urethroplasty.
Reduced waiting times	Patient System Cost Sustainability		Limited surgeons trained in urethroplasty, while general urologist can perform Optilume procedure	**Partially met** Clinical experts confirmed that limited surgeons are trained in urethroplasty in the UK and the surgery is done in specialist centres, of which there are only few. Experts also confirmed that Optilume can be performed by general urologists. The evidence indicates that treatment with Optilume reduces the need for retreatments however a lack of long-term follow-up data mean it is difficult to know whether

Claimed benefit	Benefit to	Supporting evidence	Rationale	EAC comment
				this is a sustained outcome and therefore to what extent Optilume might reduce waiting list times for urethroplasty.
Reduced burden of repeat procedures	System Sustainability			**Partially Met** Limited evidence for sustained reduction in repeat procedures, as in previous discussion.
Reduced re-admission rates (elective or non-elective)	System Cost	ROBUST I ROBUST II ROBUST III	ROBUST III lower repeat treatment	**Partially Met** Evidence suggests that Optilume results in fewer repeat treatments compared with other minimally invasive procedures. There is no evidence comparing Optilume with urethroplasty however.
Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources	System Cost Sustainability	ROBUST I ROBUST II ROBUST III	Less repeat interventions	**Partially met** Limited evidence for sustained reduction in repeat procedures, as in previous discussion. Economic model cost saving is driven by this reduction. The EAC have not included any reduction of use associated with a possible move from day case to outpatient settings.
Reduced number of post-discharge follow up visits, providing physician resource saving	System Cost Sustainability			**Not met** The economic model has an assumption of fewer visits in the cured state than in the recurrence state. This results in fewer total follow-up visits for Optilume than the comparator. The EAC has accepted this as a reasonable assumption, but it is not based on direct evidence.
Minimal requirement for training of healthcare professionals	System Sustainability			**Met** The training required to use Optilume is minimal and considered by the clinical experts to be no more difficult

Claimed benefit	Benefit to	Supporting evidence	Rationale	EAC comment
				or time-consuming than training required for alternative endoscopic procedures.

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14 Appendices

Appendix A: Clinical and economic evidence identification

Company search strategy, screening criteria and process for clinical evidence

A literature search was performed in 1 database, Medline (PubMed), to include the period from database inception to 3rd December 2021. The searches mostly comprised of free text terms except for the population concept where MeSH terms were included. Two clinical trial databases were searched using a very broad search term. The searches were not restricted by language of publication but were restricted to identify randomised controlled trials only.

Date search conducted:	03Dec21
Date span of search:	01Jan1900 to 03Dec21
List the complete search strategies used, including all the search terms: text words (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	

Search terms were developed by concept utilising the PICO approach (Population, Intervention, Comparator, Outcome). The population under study included male urethral stricture, the intervention of interest was drug coated balloons, the comparator of interest was standard of care endoscopic treatments or urethroplasty, and the outcomes of interest were stricture recurrence.

The search was conducted the MEDLINE library via PubMed utilising the search terms and Boolean operators as listed in Table A-1. Search #31 and #33, returned large numbers of results and were further filtered for 'Clinical Trial' and 'Randomised Controlled Trial'.

Table A-1. MEDLINE Search terms and operators

Search	Search Terms	Search	Search Terms
1	Urethral Stricture [mh]	16	Urethral Dilatation [tiab]
2	Urethral Stenosis [mh]	17	S-curve dilator [tiab]
3	Urethral Stricture [tiab]	18	s-curve dilator [tiab][all]
4	Urethral Stenosis [tiab]	19	Bougie Dilatation [tiab]
5	#1 OR #2 OR #3 OR #4	20	Urethrotomy [tiab]

6	Drug Coated Balloon [tiab]	21	Optical Urethrotomy [tiab]
7	Drug Eluting Balloon [tiab]	22	DVIU [tiab]
8	Paclitaxel Coated Balloon [tiab]	23	Urethroplasty [tiab]
9	Optilume [tiab]	24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
10	In.Pact Admiral [tiab]	25	Stricture Recurrence [tiab]
11	Lutonix [tiab]	26	Redilatation [tiab]
12	Ranger Drug Coated Balloon [tiab]	27	Revision Urethroplasty [tiab]
13	Stellarex [tiab]	28	Repeat Urethrotomy [tiab]
14	Biolux [tiab]	29	#24 OR #25 OR #26 OR #27
15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	30	#5 AND #15
		31	#5 AND #24
		32	#5 AND #15 AND #29
		33	#5 AND #24 AND #29
		34	#5 AND #15 AND #24 AND #29

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional searches were conducted to identify ongoing studies that may report results in the near future. Two clinical trial registration databases were searched (US National Library of Medicine registry [clinicaltrials.gov/ct2/home] and EU Clinical Trials Register [https://www.clinicaltrialsregister.eu/ctr-search/search]) using the keyword 'Urethral Stricture'.

Inclusion and exclusion criteria:

Inclusions:

- Male urethral stricture
- Outcomes after endoscopic treatment, single arm
- Outcomes after open surgical treatment (urethroplasty), single arm

- Randomised comparative studies

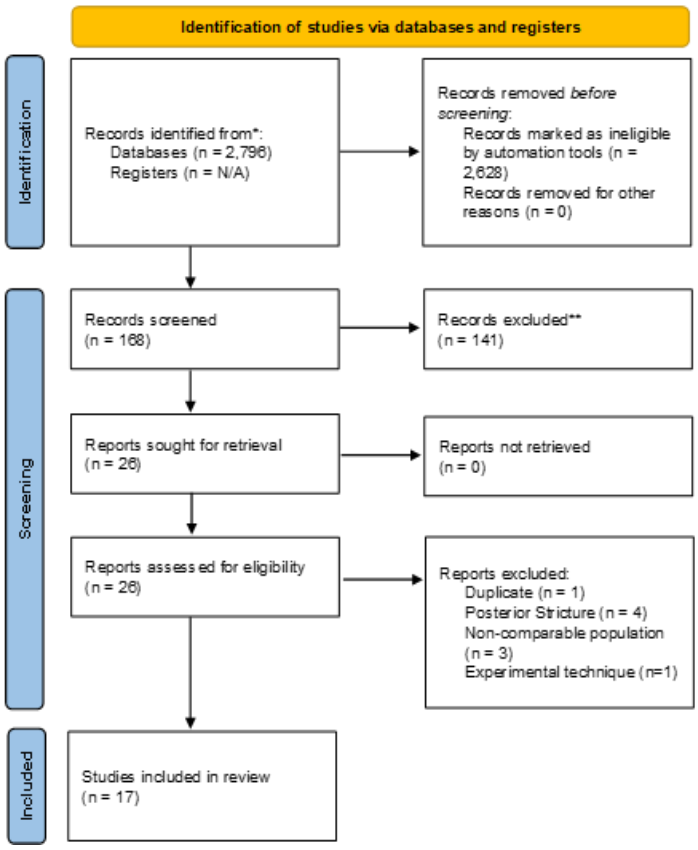
Exclusions:

- Preclinical/animal studies
- In-vitro studies
- Paediatric studies
- Case reports or early experimental techniques
- Editorials, commentary, technology assessments
- Posterior or membranous strictures
- Hypospadias repair, meatal/glans stricture repair
- Studies of adjunct therapies (e.g. steroids, mitomycin C)
- Diagnostic assessments
- Female strictures
- Cost effectiveness or other non-recurrence outcome measures
- Clean intermittent catheterisation or home dilatation
- Study protocol or design discussion
- Non-comparable population (e.g. length >5cm, urethral dislocation)

Data abstraction strategy:

Summary search results (title, brief description) for Search 30-34 were reviewed for relevant articles (P&I, P&C, P&I&O, P&C&O, P&I&C&O). Articles possibly meeting inclusion were identified and abstracts were reviewed for exclusion criteria. Articles continuing to meet criteria after abstract review were given full text review and final determination for inclusion was made.

Company study selection for clinical evidence



Company search strategy, screening criteria and process for economic evidence

The search process described in the company economic submission is exactly the same as for identifying the clinical evidence. However, the company list 4 studies as being identified.

Company search strategy for adverse events

The company searched two databases (FDA MAUDE and MHRA) using the product name between 1st January 1900 and 9th December 2021.

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched to include the period from 1st January 2000 to 24th November 2021, using a range of free text terms and, where appropriate, indexed terms, the searches were not restricted by language of publication. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the FDA MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
11/11/21	Cochrane Library CDSR CENTRAL	 2 8	
11/11/21	CRD (DARE, NHS EED)	0	
24/11/21	EMBASE	20	
11/11/21	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	9	
11/11/21	PubMed	4	
24/11/21	Scopus	9	
24/11/21	Web of Science	17	
18/11/21	company website: Optilume	1	
18/11/21	MAUDE adverse events	0	
18/11/21	MHRA – search MDA & FSN	0	
18/11/21	Clinicaltrials.gov	3	42 records after manual deduplication
18/11/21	ICTRP	4	

EAC Search strategies

COCHRANE

ID Search Hits

#1 ((Urethral NEAR/3 stricture*)):ti,ab,kw (Word variations have been searched) 493

#2 MeSH descriptor: [Urethral Stricture] this term only 136

#3 MeSH descriptor: [Prostatic Hyperplasia] this term only 1833

#4 ("benign prostatic hyperplasia"):ti,ab,kw (Word variations have been searched) 2785

#5 #1 or #2 or #3 or #4 3800

#6 (Optilume):ti,ab,kw (Word variations have been searched) 4

#7 ("balloon treatment"):ti,ab,kw (Word variations have been searched) 36

#8 (((drug or paclitaxel) NEAR/3 balloon)):ti,ab,kw (Word variations have been searched) 1053

#9 MeSH descriptor: [Paclitaxel] this term only 3675

#10 MeSH descriptor: [Dilatation] this term only 450

#11 #6 OR #7 OR #8 OR #9 OR #10 4935

#12 #5 AND #11 16

#13 #12 16

#14 #12 with Publication Year from 2000 to 2021, in Trials 8

#15 #12 with Cochrane Library publication date Between Jan 2000 and Nov 2021, in Cochrane Reviews 2

CRD

Zero results for: (Optilume) IN DARE, NHSEED

, Line , Search, Hits,

1, (Urethral stricture*) IN DARE, NHSEED, HTA, 35, Delete

2, MeSH DESCRIPTOR Urethral Stricture EXPLODE ALL TREES, 17, Delete

3, MeSH DESCRIPTOR Prostatic Hyperplasia EXPLODE ALL TREES, 207, Delete

4, (benign prostatic hyperplasia) IN DARE, NHSEED, HTA, 174, Delete

5, #1 OR #2 OR #3 OR #4, 264, Delete

6, (Optilume) IN DARE, NHSEED, HTA, 0, Delete

7, (balloon treatment) IN DARE, NHSEED, HTA, 0, Delete

8, (drug balloon) IN DARE, NHSEED, HTA, 0, Delete

9, (paclitaxel balloon) IN DARE, NHSEED, HTA, 0, Delete

10, MeSH DESCRIPTOR Albumin-Bound Paclitaxel EXPLODE ALL TREES, 1, Delete

11, MeSH DESCRIPTOR Paclitaxel EXPLODE ALL TREES, 240, Delete

12, MeSH DESCRIPTOR Dilatation EXPLODE ALL TREES, 42, Delete

13, #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12, 282, Delete

14, #5 AND #13, 0, Delete

Embase <1974 to 2021 November 23>

1 (Urethral adj3 stricture*).tw. 7347

2 urethra stenosis/ 5006

3 prostate hypertrophy/ 38508

4 "benign prostatic hyperplasia".tw. 19981

5 1 or 2 or 3 or 4 49772

6 Optilume.tw. 15

7 "balloon treatment".tw. 298

8 ((drug or paclitaxel) adj3 balloon).tw. 2731

9 paclitaxel/ and "balloon dilatation"/ 313

10 6 or 7 or 8 or 9 3122

11 5 and 10 25

12 limit 11 to (human and yr="2000 -Current") 20

INHTA

((OPTILUME) OR (BALLOON TREATMENT) OR (DRUG BALLOON) OR (PACLITAXEL BALLOON) OR (DILATATION) OR (DILATATION) OR (PACLITAXEL)) and ((URETHRAL STRICTURE) OR (PROSTATIC HYPERPLASIA))

NO RESULTS FOR YEARS 2000 TO 2021

OPTILUME 0 RESULTS

Ovid MEDLINE(R) ALL <1946 to November 10, 2021>

1	(Urethral adj3 stricture*).tw.	4555
2	Urethral Stricture/	5249
3	Prostatic Hyperplasia/	22811
4	"benign prostatic hyperplasia".tw.	14451
5	1 or 2 or 3 or 4	33926
6	Optilume.tw.	4
7	"balloon treatment".tw.	186
8	((drug or paclitaxel) adj3 balloon).tw.	1411
9	Paclitaxel/	28549
10	Dilatation/pc, th [Prevention & Control, Therapy]	6
11	6 or 7 or 8 or 9 or 10	29521
12	5 and 11	13
13	exp animals/ not humans.sh.	4913215
14	12 not 13	11
15	limit 14 to yr="2000 -Current"	9

PubMed

Optilume 4

Scopus

((TITLE-ABS-KEY ((urethral W/2 stricture*))) OR (TITLE-ABS-KEY (("benign prostatic hyperplasia"))) OR (TITLE-ABS-KEY ((prostatic AND hyperplasia)))) AND ((TITLE-ABS-KEY (Optilume)) OR (TITLE-ABS-KEY (("balloon treatment"))) OR (TITLE-ABS-KEY ((paclitaxel) AND (dilatation OR dilatation))) OR (TITLE-ABS-KEY (((drug OR paclitaxel) W/2 balloon)))) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021

) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) result = 9

Web of Science

12 #11 17
11 #5 and #10 17

10 #6 OR #7 OR #8 OR #9 3,091

9 TS=((Dilatation or dilatation) AND (Paclitaxel)) 192

8 TS=((((drug or paclitaxel) NEAR/3 balloon))) 2,875

7 TS=("balloon treatment") 207

6 TS=(Optilume) 11

5 #1 OR #2 OR #3 or #4 25,719

4 TS=("benign prostatic hyperplasia") 17,449

3 TS=(Prostatic Hyperplasia) 20,566

2 TS=((Urethral stricture)) 5,483

1 TS=(((Urethral NEAR/3 stricture*))) 4,821

MHRA

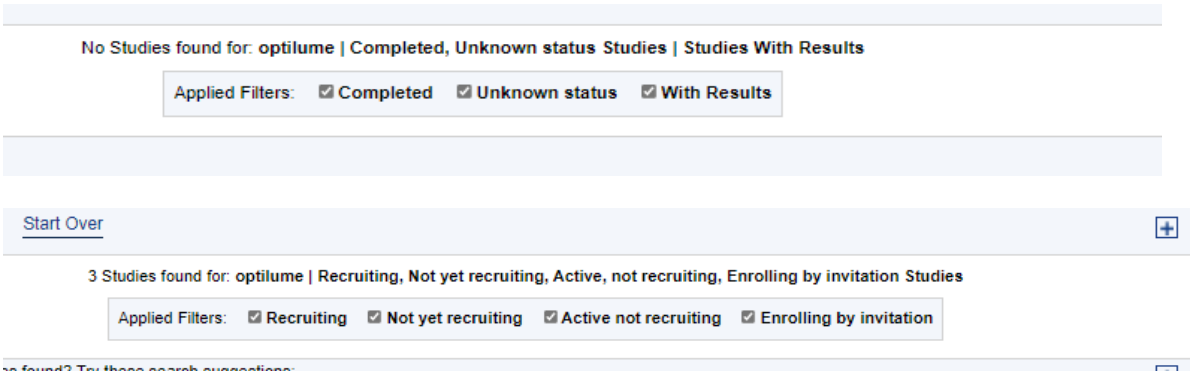
Optilume =0 hits

“Paclitaxel balloon” = 0 hits

FDA MAUDE

Optilume = 0

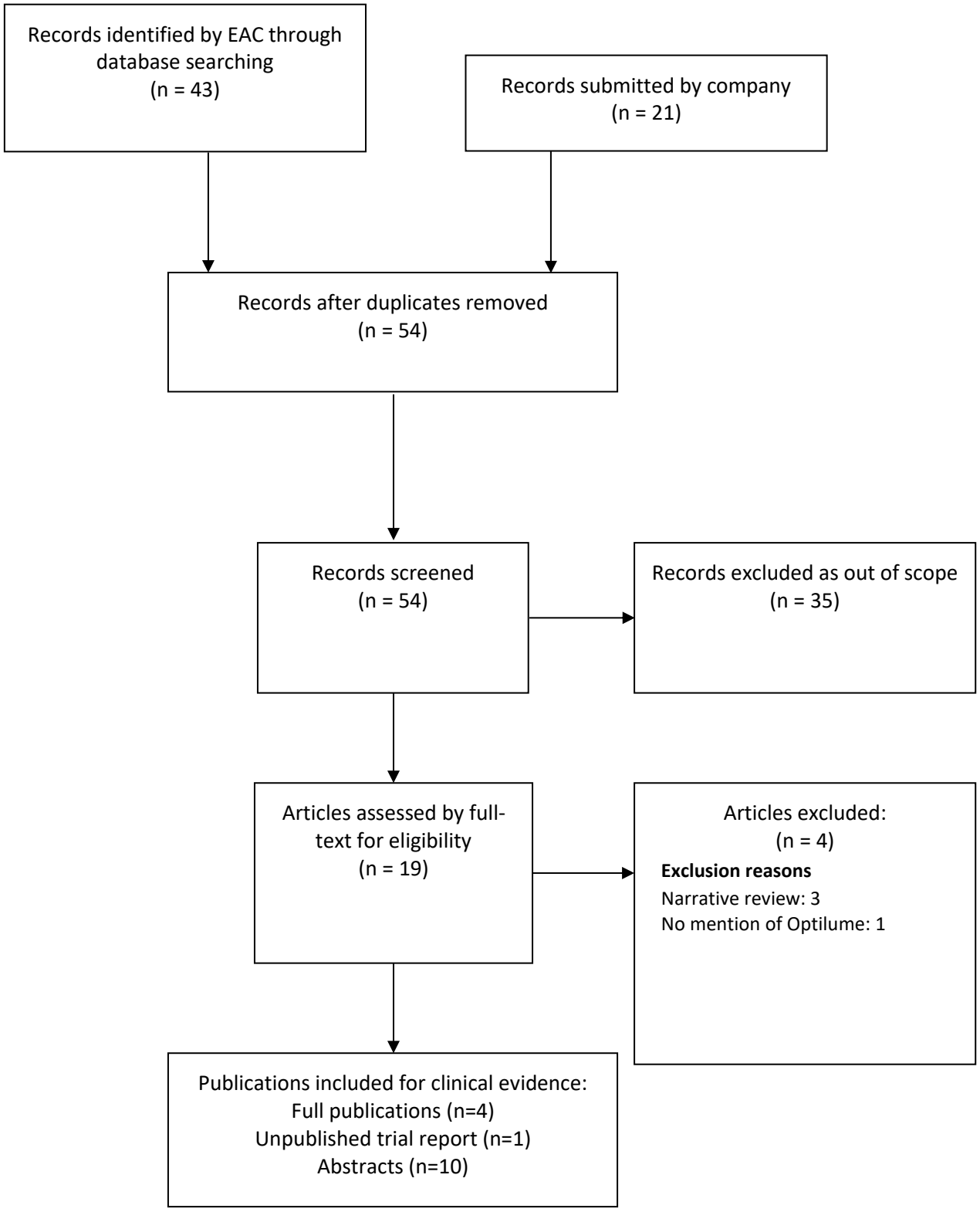
ClinicalTrials.gov



Ictrp

Optilume 4 results

EAC study selection



Appendix B: Data Extraction and guidelines

All conference abstracts included in the company submission and identified by the EAC can be found in the table below. Data was not extracted for any of the conference abstracts as each relate to the published papers in the evidence base.

Table 34: Conference abstracts

Study	Included in company submission	Identified by EAC	EAC comment
Chee et al., 2021 (3-year results from ROBUST I)		✓	Data not extracted as results reported in unpublished Elliott et al., 2022a report
Elliott et al., 2021b (Interim results from ROBUST III)		✓	Data not extracted as results reported in Elliott et al., 2021a
Elliott et al., 2021c (3-year results from ROBUST I)	✓		Data not extracted as results reported in unpublished Elliott et al., 2022a report
Elliott et al., 2020 (2-year results from ROBUST I)		✓	Data not extracted as results reported in Mann et al., 2021
Elliott et al., 2019 (1-year results from ROBUST I)		✓	Data not extracted as results reported in Virasoro et al., 2020
Elliott et al., 2022b (4-year results from ROBUST I)	✓		Data not extracted as results reported in unpublished Elliott et al., 2022a report
Justin et al., 2021 (1-year results for ROBUST III)		✓	Data not extracted as results reported in Elliott et al., 2021a
Pichardo et al., 2019 (1-year results from ROBUST I)		✓	Data not extracted as results reported in Virasoro et al., 2020

Virasoro et al., 2021 (Interim-results from ROBUST III)		✓	Data not extracted as results reported in Elliott et al., 2021a
Wang et al., 2019 (6-month sexual function outcomes for ROBUST I)		✓	Data not extracted as results reported in Virasoro et al., 2020

Table 35: Additional Relevant Guidelines and Recommendations

AUA (Wessells et al. 2017)	**Diagnosis/Initial Management** • Clinicians should include urethral stricture in the differential diagnosis of men who present with decreased urinary stream, incomplete emptying, dysuria, urinary tract infection (UTI), and after rising post void residual. (Moderate Recommendation; Evidence Strength Grade C) • After performing a history, physical examination, and urinalysis, clinicians may use a combination of patient reported measures, uroflowmetry, and ultrasound post void residual assessment in the initial evaluation of suspected urethral stricture. (Clinical Principle) • Clinicians should use urethro-cystoscopy, retrograde urethrography, voiding cystourethrography, or ultrasound urethrography to make a diagnosis of urethral stricture. (Moderate Recommendation; Evidence Strength Grade C) • Clinicians planning non-urgent intervention for a known stricture should determine the length and location of the urethral stricture. (Expert Opinion) • Surgeons may utilise urethral endoscopic management (e.g. urethral dilatation or direct visual internal urethrotomy [DVIU]) or immediate suprapubic cystostomy for urgent management of urethral stricture, such as discovery of symptomatic urinary retention or need for catheterisation prior to another surgical procedure. (Expert Opinion) **Dilatation/Internal Urethrotomy/Urethroplasty** • Surgeons may offer urethral dilatation, direct visual internal urethrotomy (DVIU), or urethroplasty for the initial treatment of a short (< 2 cm) bulbar urethral stricture. (Conditional Recommendation; Evidence Strength Grade C) • Surgeons may perform either dilatation or direct visual internal urethrotomy (DVIU) when performing endoscopic treatment of a urethral stricture. (Conditional Recommendation; Evidence Strength Grade C) • In patients who are not candidates for urethroplasty, clinicians may recommend self-catheterisation after direct visual internal urethrotomy (DVIU) to maintain urethral patency. (Conditional Recommendation; Evidence Strength Grade C) • Surgeons should offer urethroplasty, instead of repeated endoscopic management for recurrent anterior urethral strictures following failed dilatation or direct visual internal urethrotomy (DVIU). (Moderate Recommendation; Evidence Strength Grade C) • Surgeons who do not perform urethroplasty should offer patients referral to surgeons with expertise. (Expert Opinion) **Anterior Urethral Reconstruction** • Surgeons may initially treat meatal or fossa navicularis strictures with either dilatation or meatotomy. (Clinical Principle) • Surgeons should offer urethroplasty to patients with recurrent meatal or fossa navicularis strictures. (Moderate Recommendation; Evidence Strength Grade C) • Surgeons should offer urethroplasty to patients with penile urethral strictures, given the expected high recurrence rates with endoscopic treatments. (Moderate Recommendation; Evidence Strength Grade C)

	• Surgeons should offer urethroplasty as the initial treatment for patients with long (≥2cm) bulbar urethral strictures, given the low success rate of direct visual internal urethrotomy (DVIU) or dilatation. (Moderate Recommendation; Evidence Strength Grade C) **Special circumstances** • In men who require chronic self-catheterisation (e.g. neurogenic bladder), surgeons may offer urethroplasty as a treatment option for urethral stricture causing difficulty with intermittent self-catheterisation. (Expert Opinion) • Clinicians may perform biopsy for suspected lichen Sclerosus (LS), and must perform biopsy if urethral cancer is suspected. (Clinical Principle) **Post-operative follow-up** • Clinicians should monitor urethral stricture patients to identify symptomatic recurrence following dilatation, direct visual internal urethrotomy (DVIU) or urethroplasty. (Expert Opinion)
CUA (Rourke et al. 2020)	**Presentation and assessment** • Suggest using cystoscopy rather than urethrography for the initial diagnosis of suspected urethral stricture (Conditional recommendation, low certainty in evidence of effects). • Suggest performing retrograde urethrography to further stage urethral stricture or referring the patient to a physician with expertise in reconstructive urology, when a recurrent stricture is suspected (Conditional recommendation, low certainty in evidence of effects). • Suggest against using magnetic resonance imaging for routine initial diagnosis of suspected stricture (Conditional recommendation, low certainty in evidence of effects). • Suggest endoscopic management as the initial treatment of the symptomatic undifferentiated stricture (Conditional Recommendation, Low levels of certainty of evidence). • In the setting of men with recurrent urethral stricture failing prior endoscopic treatment, we suggest performing urethroplasty rather than repeat endoscopic management (DVIU or dilatation) (Conditional recommendation, very low certainty in evidence of effects).

Appendix C: Risk of Bias Assessment

ROBUST I

JBI Critical Appraisal Checklist for Case Series

Reviewer: Helen Morgan

Date: 25/08/21

Citation: Mann et al., 2021

	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	Yes – clear description
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes – single bulbar urethral stricture <12 Fr, and ≤2.0 cm long on urethrogram.
3. Were valid methods used for identification of the condition for all participants included in the case series?	Yes – see above
4. Did the case series have consecutive inclusion of participants?	Unclear – no details provided
5. Did the case series have complete inclusion of participants?	No – 46/53
6. Was there clear reporting of the demographics of the participants in the study?	Yes – table provided
7. Was there clear reporting of clinical information of the participants?	Yes - table provided
8. Were the outcomes or follow up results of cases clearly reported?	Yes – narrative description and table

9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes – four Latin American centres, 83% Hispanic or Latino
10. Was statistical analysis appropriate?	Yes

Overall appraisal: Small case series, note no information on consecutive recruitment so possibility of sampling bias

ROBUST II

JBI Critical Appraisal Checklist for Case Series

Reviewer: Michael Beddard

Date: 12/01/22

Citation: DeLong et al., 2022

	Yes/No/Unclear/Not applicable
11. Were there clear criteria for inclusion in the case series?	Yes, clear description • Adult men with a single anterior urethral stricture ≤3 cm in length with lumen diameter <12 F • ≥2 prior endoscopic treatments of the stricture • Bothersome LUTS • IPSS ≥13 • Qmax <15 mL/sec
12. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes, see above. Also, anatomic success was assessed by the ability to pass a 16F flexible cystoscope through the treatment site. Pain assessed using the

	visual analog scale. QOL assessed by IPSS QOL at baseline and 1 year. Voiding function measured by Qmax and PVR.
13. Were valid methods used for identification of the condition for all participants included in the case series?	Yes – Baseline retrograde urethrogram
14. Did the case series have consecutive inclusion of participants?	Unclear – no details provided
15. Did the case series have complete inclusion of participants?	No – 9/16. Also, only 8/9 reported PROM with no explanation.
16. Was there clear reporting of the demographics of the participants in the study?	No. Age is only demographic given.
17. Was there clear reporting of clinical information of the participants?	Yes. Baseline characteristics and procedure type table provided.
18. Were the outcomes or follow up results of cases clearly reported?	Yes. Results summary table of baseline, 30d, 90d, 6m and 12m data provided.
19. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No. 5 investigational sites not specified
20. Was statistical analysis appropriate?	Yes

Overall appraisal:

Small case series of just 16 patients with only 9 available for 1 year follow up. Possible sampling bias due to no information on consecutive recruitment. Demographics of participants limited to just age and baseline characteristics, and no information on investigational sites beyond country of investigational sites.

Risk of Bias Assessment: Elliott et al., 2021a

Study details

Reference	Elliott, 2021a. 'One-Year Results for the ROBUST III Randomised Controlled Trial Evaluating the Optilume((R)) Drug-Coated Balloon for Anterior Urethral Strictures', *J Urol*: 101097JU0000000000002346.

Study design

X Individually-randomised parallel-group trial

☐ Cluster-randomised parallel-group trial

☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Optilume	Comparator:	Endoscopic method considered routine care

Specify which outcome is being assessed for risk of bias	Anatomical success at 6 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	74.6% in experimental and 26.8% in the control group. Estimated difference of 44.4% using multiple imputation p <0.0001

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐	non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x	Journal article(s) with results of the trial
☐	Trial protocol
☐	Statistical analysis plan (SAP)
x	Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐	Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomisation process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	No information given just states "Eligible participants were randomised prior to the index procedure…."	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI was given in the paper	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	2:1 allocation of treatment vas controls was planned but ended up with 48 standard care and 79 Optilume so difference to 2:1 which was planned. No significant difference in baseline characteristics.	Y
Risk-of-bias judgement		High
Optional: What is the predicted direction of bias arising from the randomisation process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Participants were blinded till 6 months. Prior to 6 months unblinding could occur only if medically necessary Single blind trial stated	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Some patients in the control group crossed over to Optilume. It was not clear when they were told they could cross over	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns

Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	From the Optilume group 6 missed visit at 6 months	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The missing data was imputed but no sensitivity analysis was carried out	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		N
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator /

		Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	"the proportion of participants in whom we could atraumatically pass a 16Fr flexible cystoscope or a 14Fr catheter through the treated area at 6 months"	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Single blind trial	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Not stated in paper Clinical trilas.gov states two primary outcome measures 1. Efficacy: Stricture Free Rate [Time Frame: 6 months] Stricture Free Rate 2. Safety: Rate of Major Device or Procedure Related complications [Time Frame: 3 months] Rate of Major Device or Procedure Related complications	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No information on clinical trials on method of measuring strictures	NI

5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		High risk of bias
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix D: Economic stress testing

Table 36: Stress testing – Does the model function as it should

Stress testing				
Scenario	**Cost of Intervention**	**Cost of Comparator**	**Cost difference**	**Notes**
Base Case (Optilume Vs Endoscopic, using ROBUST III 1 year)	£6,620	£9,122	-£2,502	Base case per patient, for endoscopic management
Start age 21	£6,706	£9,228	-£2,522	Only a 5-year time horizon, so very little difference – slight change in mortality
Start age 85	£5,605	£7,838	-£2,233	As above, slight decrease in cost difference, as higher mortality, less people to benefit.
Time horizon =1	£2,944	£4,336	-£1,391	Less time to accumulate benefit
Time horizon = 10	£9,648	£12,316	-£2,668	More time to accumulate benefit, but not much more being accumulated – there is a plateau of people who are in “cured”, but the cost difference then starts to increase again slightly over time
Optilume device = £10,000	£19,294	£9,122	£10,173	Becomes cost incurring
Optilume device = £0	£4,642	£9,122	-£4,480	Some increase in cost saving, but there is also difference in procedure cost and adverse events.
Endoscopic management procedure = 0	£6,620	£6,705	-£85	Still cost saving even if procedure free – adverse events, numbers of urethroplasty?
Urethroplasty - 0	£3,972	£3,628	£343	More repeats means more urethroplasty in comparator – but in this case that has zero cost.
Both urethroplasty and endoscopic = 0	£3,972	£1,211	£2,760	What is the 1,211 from – adverse events and from cured health state costs and recurrence health state costs – follow up appointments and self-catheterisation.
Endoscopic recurrence = Optilume recurrence	£6,620	£5,524	£1,096	Cost incurring – Optilume procedure costs more.
Optilume recurrence = 0	£2,993	£9,122	-£6,129	
Endoscope recurrence = 0	£6,620	£2,242	£4,378	Cost incurring – Optilume procedure costs more.

Appendix E: Additional Economics Tables

Clinical inputs

Parameter	Company submission	Source	EAC value	Comment
Average patient starting age	59.42	ROBUST III (Elliott et al., 2021a)	No change	Used to apply the mortality rate throughout the model
Mortality rate	Age dependant	Office for National Statistics	No change	Background mortality rate applied to all health states throughout model
Monthly probability of recurrence: Base Case				
Endoscopic management	16.3%	ROBUST III (trial report) from 88.1 % at 1 year	No change	Recurrence is calculated as people who report less than a 30% improvement in IPSS score at 12 months. A constant monthly probability is calculated, with an assumption that this is appropriate and can be carried forward.
Optilume	2.6%	ROBUST III (trial report) from 26.9 % at 1 year	No change	
Urethroplasty	0.9%	OPEN RCT (Pickard, 2020) from 20.4% at 2 years	No change	Composite measure from review at 24 months where at least one of the following were met: reintervention occurred or scheduled; maximum flow rate deteriorated to preintervention value; voiding score deteriorated to baseline value.
Retreatment following recurrence of symptoms				
Probability of having treatment following recurrence of symptoms	90%	OPEN RCT (Pickard, 2020) Table 33, model inputs	No change	This is taken from the model transition probability reported by Pickard (table 33), and stated that it is derived from the trial data, but method unclear, and does not agree with trial results (table17). It may be the proportion of patients randomised, but who did not receive treatment in either arm. Alternatively, Pickard (2020) report that at the end of the study, they recorded recurrence of stricture without a planned or completed further intervention. The 90% may come from inclusion of planned procedures
Probability of retreatment being with Urethroplasty (remainder treated with endoscopic management / Optilume)				
Following endoscopic management/ Optilume	70%	OPEN RCT (Pickard, 2020) Table 33, model inputs	No change	This is not reported in the clinical data for OPEN RCT, but text states "The parameters used in the model were based on observations from the trial, in which about 70% of patients would receive urethroplasty and 30% of patients would receive urethrotomy if the last treatment was urethrotomy, and about 12% of patients would receive urethroplasty and 88% of patients
Following Urethroplasty	12%	OPEN RCT (Pickard, 2020) Table 33, model inputs	No change	

				would receive urethrotomy if the last treatment was urethroplasty." (p68)
Time to treatment				
Endoscopic management/urethrotomy	47.5 days	OPEN RCT (Pickard, 2020)	No change	Median time between randomisations and interventions was 47.5 days for patients for urethrotomy
Optilume	47.5 days	Assumption	No change	It was assumed the waiting time for Optilume was equivalent to endoscopic therapy.
Urethroplasty	90 days	OPEN RCT (Pickard, 2020)	No change	Median time between randomisations and interventions was 90 days for patients for urethroplasty
Adverse events following Optilume procedure				
Haematuria	0.0%	ROBUST III study (Grade 2 events and above i.e. requiring intervention)	No change	ROBUST III: 11.4% had hematuria, however these were classed as mild, resolving within 30 days in 10 out of 11 men. - the paper does not state if any intervention was required.
UTI	7.6%	ROBUST III study	No change	Elliot (2021a) reported 1 serious UTI in each arm, however text reports that UTI was one of the most frequent adverse events. Numbers not reported for all UTIs.
Wound infection	0.0%	Not expected for dilatation	No change	Assumption, accepted by EAC
Readmission	0.0%	Not expected for dilatation	No change	Assumption, accepted by EAC
Urinary retention (emergency intervention)	1.3%	ROBUST III study	No change	Reported 1 acute urinary retention requiring emergency catheterisation within 6 months
Adverse events following Endoscopic management procedure				
Haematuria	0.0%		No change	As for Optilume. 2.1% were reported as hematuria, but classified as mild.
UTI	8.3%	ROBUST III study	No change	Elliot (2021a) reported 1 serious UTI in each arm. As for Optilume previously.
Wound infection	1.0%	OPEN RCT (Table 20).	No change	Taken from model (Pickard, 2020) paramters
Readmission	0.0%	Assumption	No change	Assumed to avoid potential double counting with urinary retention.
Urinary retention (emergency intervention)	6.3%	ROBUST III study	No change	Reported 3 acute urinary retention requiring emergency catheterisation within 6 month
Adverse events following Urethroplasty				
Haematuria	2.0%	OPEN RCT (Table 20)	No change	The 2% reported in Pickard (2020) are SAEs. Values used are those from the OPEN model parameters
UTI	3.1%		No change	
Wound infection	2.0%		No change	
Readmission	3.1%		No change	
Urinary retention (emergency intervention)	0.0%	Assumption	No change	Assumed none, as inclusion could double count with readmission to hospital

Alternative inputs for scenarios, using Endoscopic management as a comparator, Urethroplasty recurrence unchanged at 0.9%				
6 month data from ROBUST III				
Endoscopic management	19.7%	ROBUST III (Elliot 2021a) from 73.2 % at 6 months	No change	This is based on outcome of anatomical stricture free, based on being able to atraumatically being able to pass a 14F catheter at 6 months.
Optilume	4.8%	ROBUST III (Elliot 2021a) from 25.4 % at 6 months	No change	
OPEN RCT data				
Endoscopic management	1.9%	OPEN RCT, 37.5% at 24 months	No change	Composite measure of recurrence taken during clinical review at 24 months
Optilume	0.5%	Assumption	No change	Calculation using the relative risk ratio from ROBUST III 1 year data (based on functional success, IPSS score) and applying to recurrence following endoscopic management.
Alternative inputs for scenarios, using Urethroplasty a comparator				
Endoscopic management	1.9%	OPEN RCT	No change	See information from previous sections of the table.
Urethroplasty	0.9%	OPEN RCT	No change	
Optilume, OPEN RCT	0.5%	OPEN RCT	No change	
Optilume 6 mth ROBUST III	2.6%	ROBUST III	No change	
Optilume 12 mth ROBUST III	4.8%	ROBUST III	No change	

Resource and cost inputs

Parameter	Company value	Source	EAC value	Comment
Treatment cost				
Endoscopic management	£1,196	NHS Ref. costs 2019/20	No change	Weighted average of all: LB55A Minor or Intermediate, Urethra Procedures, 19 years and over, except outpatients.
Urethroplasty	£4,761		No change	Total HRG costs for LB29A Major Open Urethra Procedures, 19 years and over, elective
Optilume procedure (excl. device)	£635		£1,067	LB55A Minor or Intermediate, Urethra Procedures, 19 years and over, Day Cases only
Cost of device: Optilume	£1,350	List price	No change	Company submission, accepted by EAC
Total procedure cost: Optilume	**£1,986**		**£2,418**	**EAC cost includes day case only, without use of outpatient procedures.**
Predilatations				
Cost of consultant	£114	PSSRU 2020	No change	Hospital based doctors. Cost per working hour Consultant: Surgical.

Time for predilatation	10 min		No change	Estimation, accepted by EAC
Cost of predilatation: Optilume	£20.36		No change	This is applied to 5% of all patients treated with Optilume only.
Adverse events, applied once only in the month of the procedure. Not applied subsequently unless there is a repeat procedure.				
Haematuria				
GP appointment	£33	PSSRU 2020	No change	10.3b General practitioner unit costs. £33 for GP appointment (incl direct staff costs, without qualification costs)
Total	**£33**		No change	
UTI				
Antibiotic course (7 days)	£5.27		No change	Mean of Trimethoprim, 200mg 2 x 7 days at £1.04 per 14 tablets Nitrofurantoin 100mg 2 x 7 days at £9.50 for 14 tablets
Urinalysis Test	£4.51	NICE preoperative tests NG45 Appendix M	No change	Cost of urinalysis £4.08. Inflated from 2012 to 2020 using PSSRU inflation indices
GP appointment	£33		No change	PSSRU 2020 (incl direct staff costs, without qualification costs)
Total	**£43**		No change	
Wound Infection				
Antibiotic Treatment (mean of tablet and IV costs for different severities)	£74.09	NHS Northern Care Alliance NHS Group Skin and soft tissue infections antibiotic guidelines	No change	Mean of tablet and IV costs for different severities. 5.3 Empiric treatment of SSTI Average of Class I and Class II treatment: Flucloxacillin 500mg tables £2.30 for 28 tablets, 8 tablets for 5 days; 1g powder for solution for injection vials £34.50 for 10. 1g every 6 hours for 10.5 days (average of 7-14).
GP appointment	£33		No change	PSSRU 2020 (incl direct staff costs, without qualification costs)
Hospital admission	£0		No change	Not included to avoid double counting
Total	**£107**		No change	
Readmission to hospital				
Hospital readmission	£434	NHS Ref. costs 2019/20	£507.68	Weighted average of non-elective short stay with and without intervention (LB57C and LB57D) EAC used same reference, but with different cost result
Urinary retention (requiring emergency intervention)				
Emergency intervention cost	£941	NHS Ref. costs 2019/20	No change	OPROC Accident and emergency. LB55A Minor or intermediate, urethra procedures, 19 years and over. Service code 180
Health States				
Cured health state costs				
Follow up appointments	£110	NHS Ref. costs 2019/20	No change	Outpatient attendance. Service cost 101 Urology. Total unit cost
Annual appointments	2	NHS England Integrated impact assessment report for clinical	No change	Assume 2 per year, based on recommendation to follow up every 3 months for 1 year. Thereafter patients would likely be followed up once per year. EAC have not identified the information from the given reference.

		commissioning policies, p15		
Monthly cost	£18		No change	
Recurrent health state costs				
Follow up appointments	£110	NHS Ref. costs 2019/20	No change	Outpatient attendance. Service cost 101 Urology. Total unit cost
Annual appointments	4	Assumption	No change	Assumption based on cured health state costs
Self-catheterisation cost	£48	Bermingham, 2013	£50	Cost of £502, inflated using PSSRU 2020. Based on 1 x clean catheter per week, lubrication on each use (mean 1825 uses, or 5 per day)
Proportion using self-catheterisation	16.8%	Pickard, 2020	No change	
Monthly cost	**£44.74**		**£45.08**	
Training costs				
Training costs for Optilume				
Staff costs (per hour)	£114	PSSRU,2020	No change	Hospital based doctors. Cost per working hour Consultant: Surgical.
Basic training	£85.50		No change	Per staff member, based on 45 minutes per consultant
In depth training	£456		No change	Per staff member, based on 4 hours per consultant
Average training cost	Not reported		£104.03	Assuming 95% of staff receive basic training only
Training cost per patient	**£3.64**		**£1.63**	Both assume 35 procedures completed per staff member per year. The company assume retraining after 10 years, the EAC have reduced to 3 years to allow for staff turnover. Calculation method was changed by EAC to divide cost per staff member by 35 procedures, and by 3 years.
Number of procedures supervised	3		No change	Assumption that each staff member has 3 procedures supervised as part of training
Time for supervision	0.5 hours		No change	Assumption
Cost per staff member	Not reported		£171	
Supervision cost per patient	**£4.89**		**£1.63**	EAC calculation is cost per staff member divided by 35 procedures a year divided by 3
Total training cost per patient	**£8.53**		**£2.62**	This will make almost no difference to the result (£8 more cost saving)

Appendix F: Additional Economics Results

Cumulative retreatment procedures and costs over time

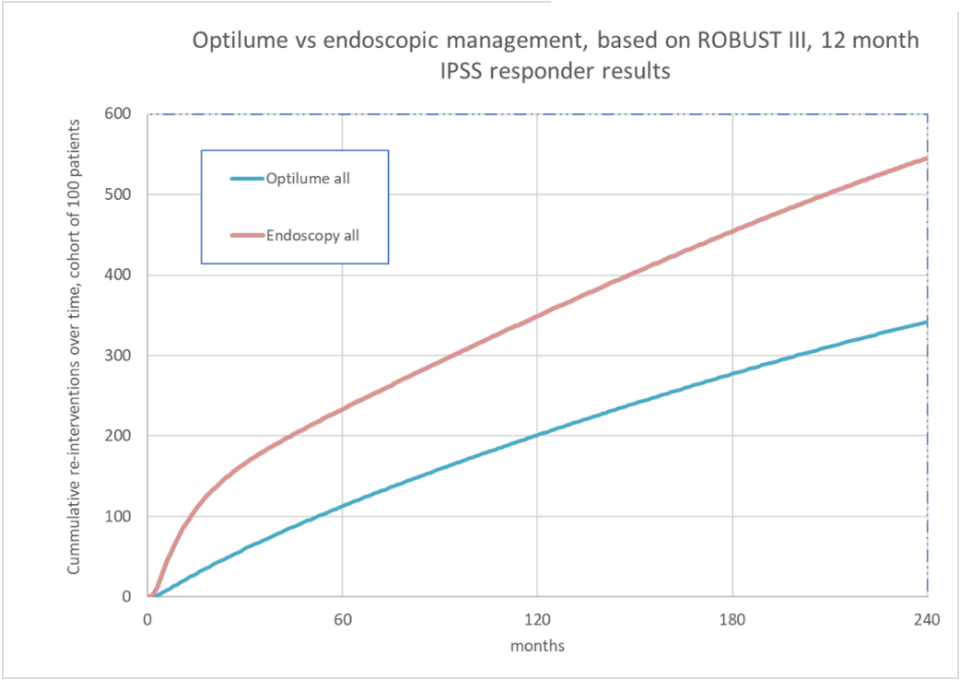
All diagrams illustrate the cumulative impact for the cohort of 100 patients, over a 20-year period.

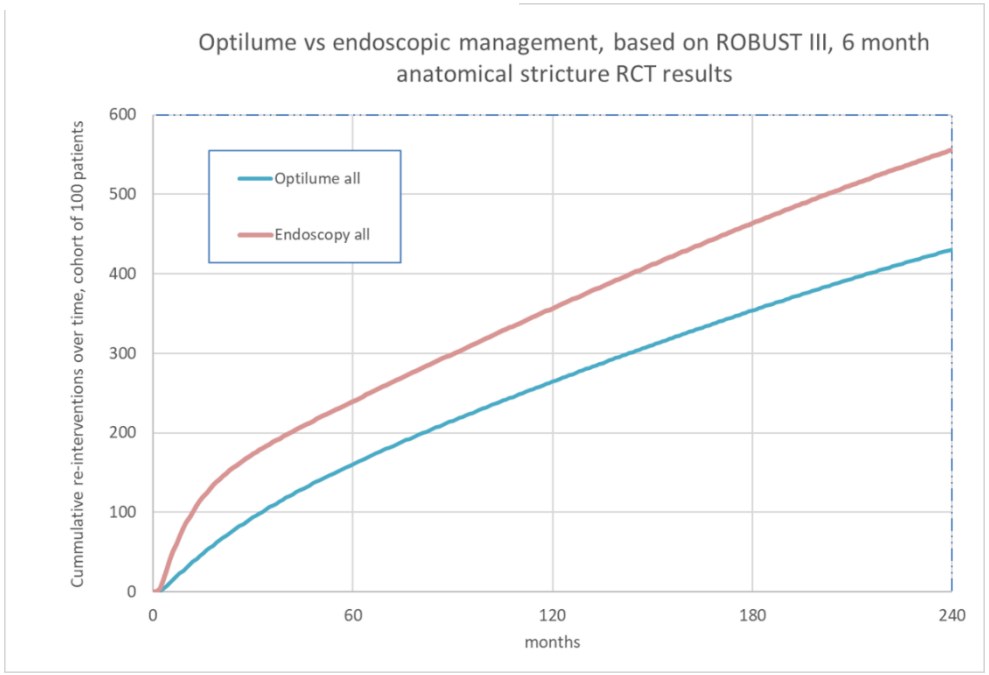
The following diagrams show the impact of choosing different clinical inputs for recurrence rates, as used in the company and EAC Scenarios. It can be seen that for each scenario there are more retreatments in the endoscopic management arm, than in the Optilume arm at all time points, although the total number of procedures and the magnitude of the difference between arms varies.

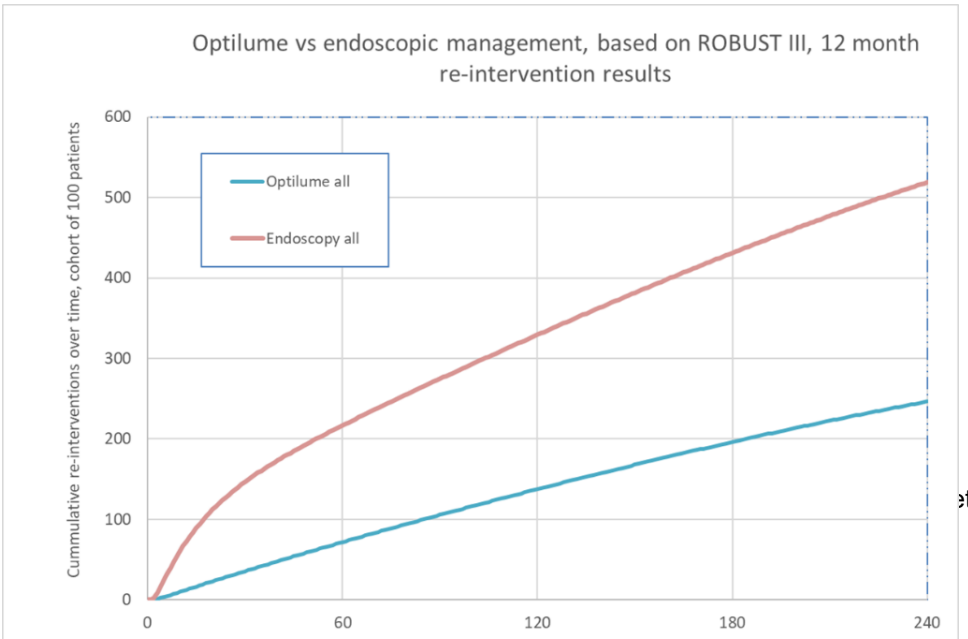
When this is split into a repeat endoscopic / Optilume treatment, or urethroscopy, all arms start with a greater number of the endoscopic / Optilume retreatments, but at some point, the cumulative number of urethroplasty procedures becomes greater. The point at which this happens, and the overall number of procedures is different for each scenario.

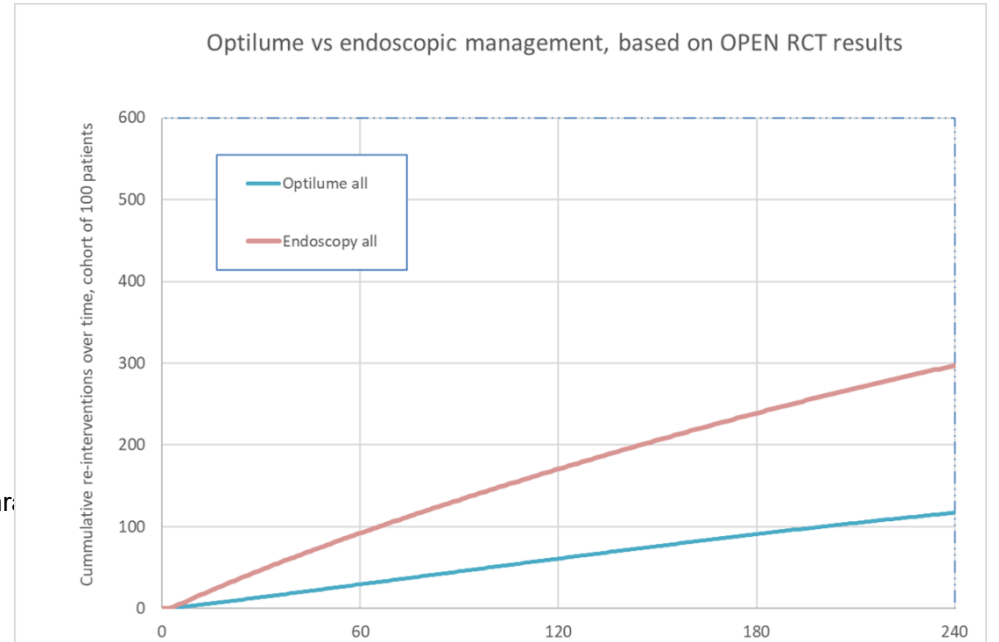
For all scenarios, considering the costing, due to the higher initial costs of the Optilume procedure, Optilume arm total costs are higher in the first few months, and at some point Optilume becomes cost saving, as the greater number of repeat procedures in the endoscopic arm makes an impact. The trajectory of the costs over the 20-year period is very different for each scenario, and points to this extended time horizon being useful as an exploratory analysis, but needing longer comparative follow up to be used as a base case.

Total cumulative retreatment procedures, modelled over 20 years

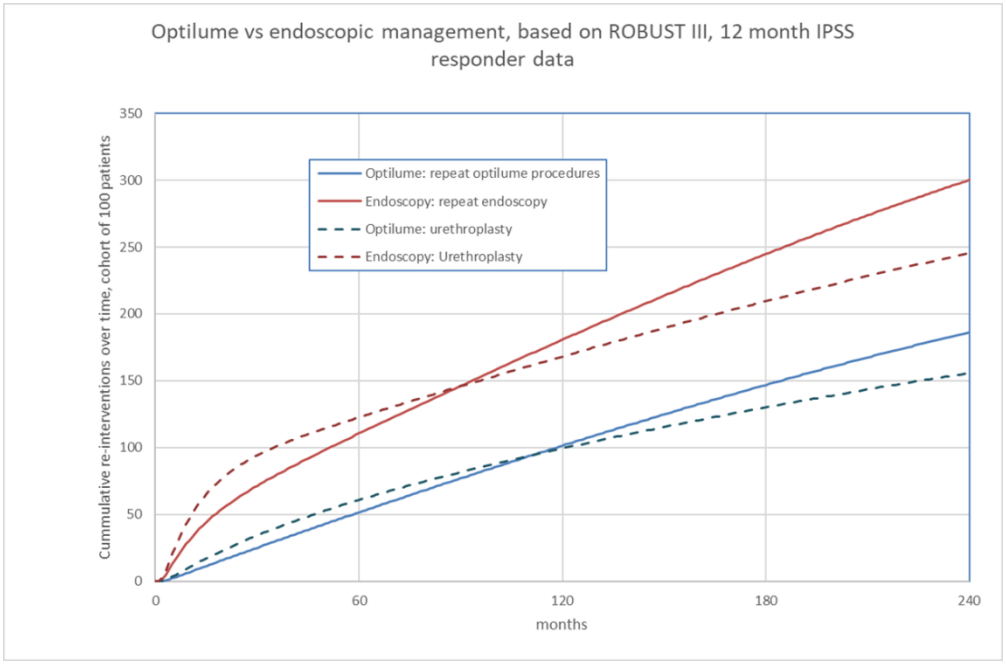


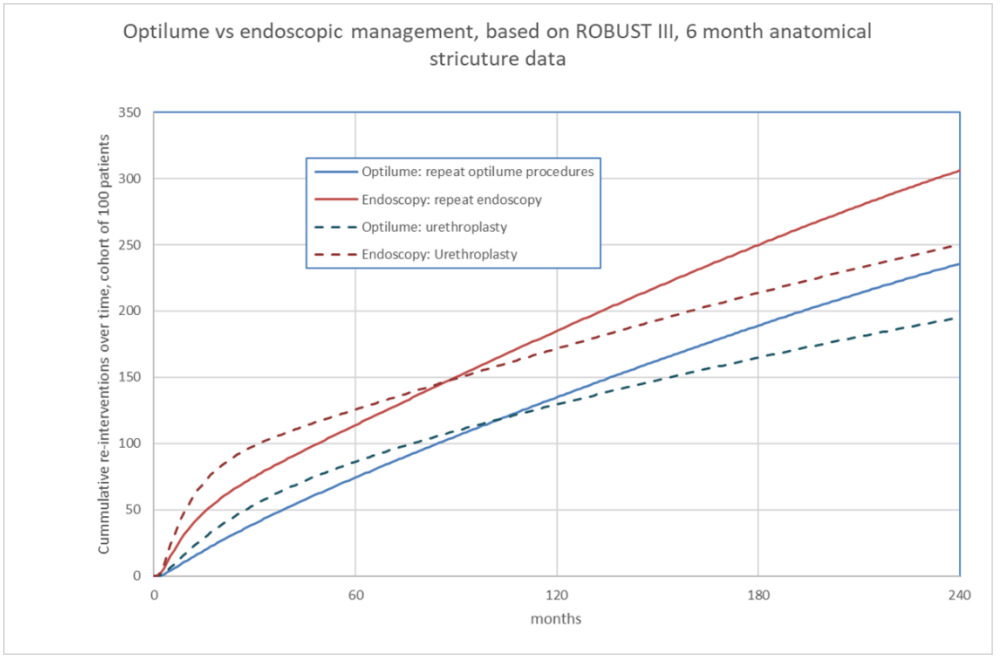


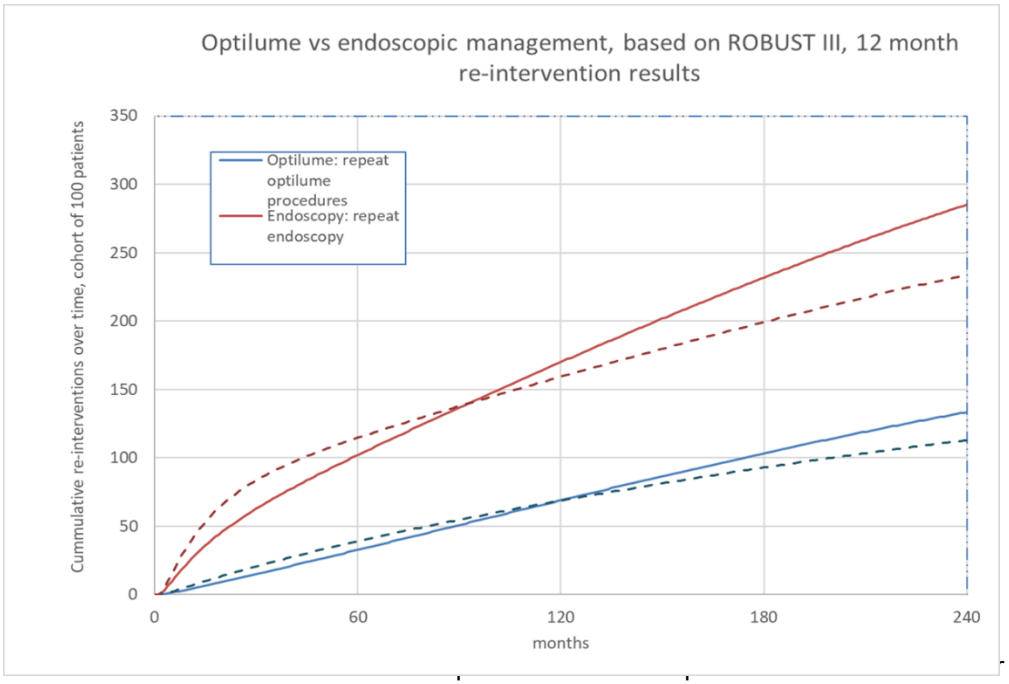


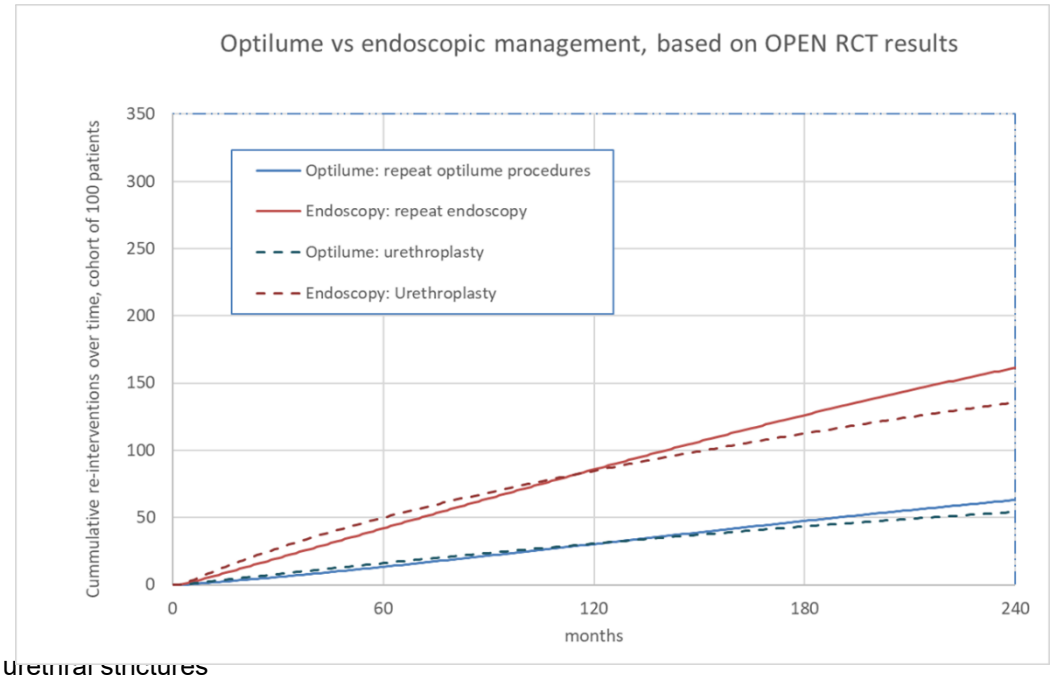


Total cumulative endoscopic / Optilume and urethroplasty retreatment procedures, modelled over 20



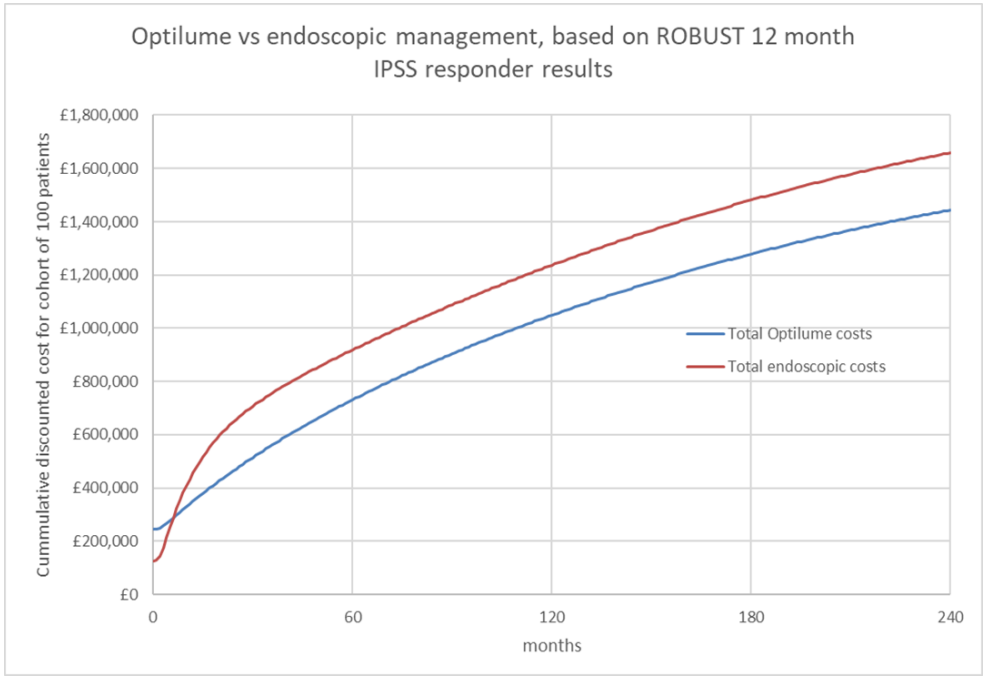


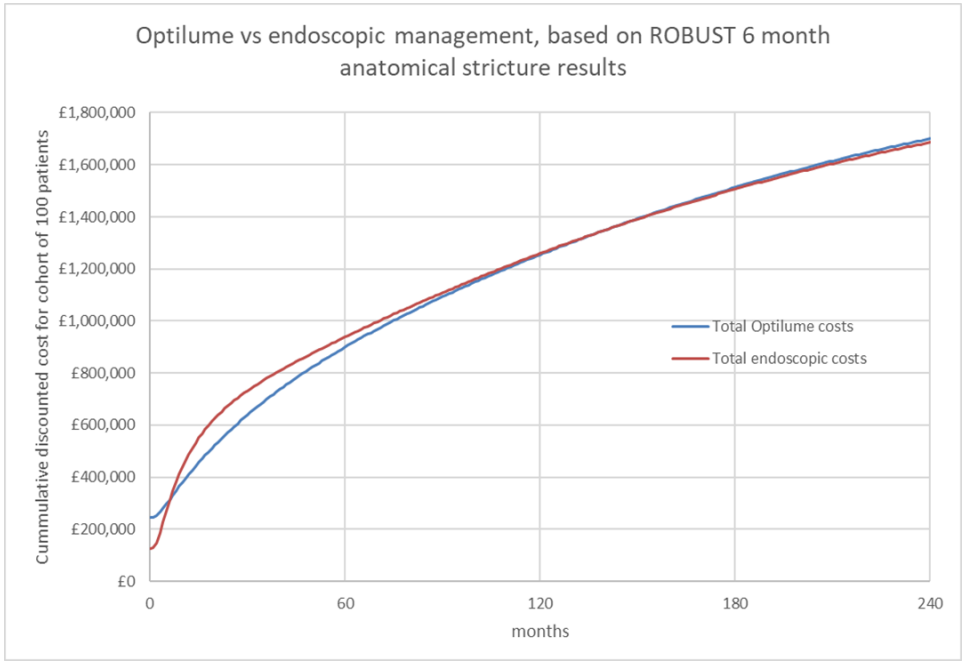


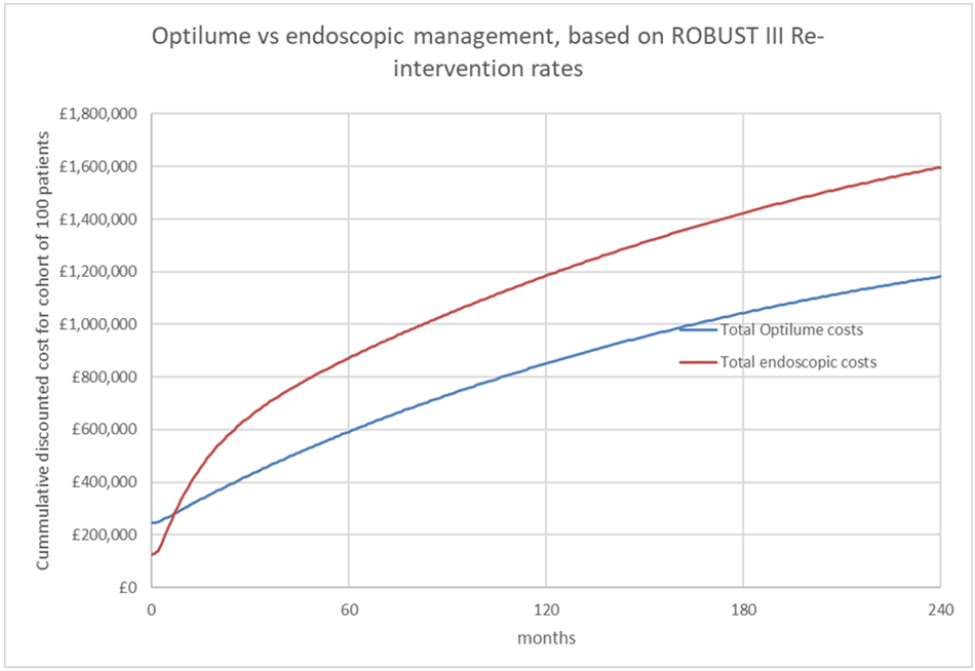


urethral strictures

Total cumulative cost, modelled over 20 years







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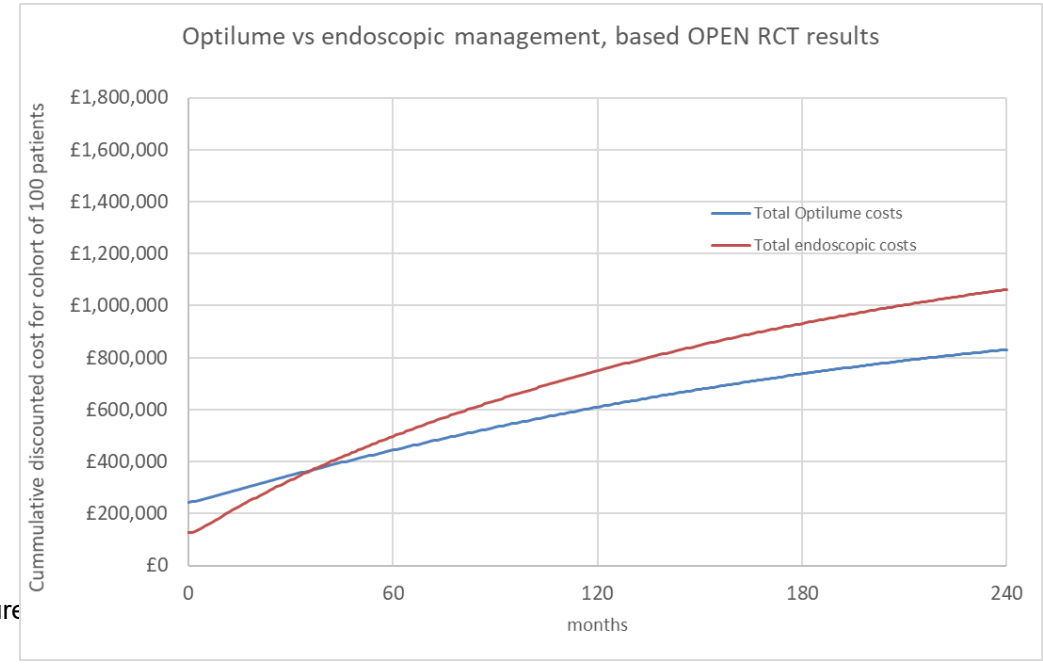


Appendix G: Additional economic information

Appendix created for MTAC, following lead team meeting

During the lead team meeting on 7th March 2022, clinical experts presented information on their recent experience of having introduced Optilume in an outpatient setting. They reported that this had been successfully used with a small number of patients and that this was likely to be used more widely in the future, although not for all patients.

Following this meeting the EAC revised their base case, which had assumed that 100% of patients would be treated as day cases, based on the expert opinion at the time of writing. The updated results and sensitivity analysis were presented in the committee slides at MTACT (18th March 2022. This appendix contains the information presented to the committee with some additional explanation, and additional results from the report that have been updated. Tables and results reported in the appendices have not been changed to reflect the updated EAC base case.

Changes in model

The following changes were made from the model described in the main Assessment Report text.

Assumptions

There are no changes in the listed assumptions. It should be noted that clinical outcomes and adverse events are assumed to be the same for patients treated in outpatient or day case settings.

Resource inputs

The following table shows only the resource input that have been updated following the lead team meeting (March 2022). All other inputs remain the same.

Expert advice was updated following the introduction of Optilume in an outpatient setting in one location within the NHS. The EAC accepted that it was likely that this setting would be more widely adopted in the future and updated their base case to match the company submission. This assumes that 50% of the procedures would be in an outpatient setting, and the remainder as day case setting.

Resource	Company	Previous EAC case	Updated EAC case	Source
Optilume procedure	£635	£1,067	£635	NHS References Costs 2019/20 Company: Mean of LB55A Day Cases and Outpatients EAC: LB55A Day Cases only
Optilume device	£1,350	No change	No change	List price, company submission
Total procedure cost: Optilume	**£1,986**	**£2,418**	**£1,986**	Updated EAC Optilume procedure is unchanged from Company base case

Results: Updated EAC base case, using 50% outpatients

The company base case found that there was a cost saving of £2,502 per patient using Optilume at 5 years. Although the initial EAC base case reduced this to £1,877 per patient by changing the setting to day-case only, the updated EAC base case is £2,510 cost saving, and very similar to that submitted by the company.

	Company base case			Updated EAC base case		
Cost breakdown (per patient)	**Optilume**	**Endoscopic management**	**Cost saving**	**Optilume**	**Endoscopic management**	Cost saving
Initial procedure cost	£2,001	£1,259	**-£742**	£2,001	£1,259	**-£742**
Repeat procedure costs (Endoscopic)	£931	£1,286	**£355**	£931	£1,286	**£355**
Repeat procedure costs (Surgical)	£2,658	£5,514	**£2,856**	£2,659	£5,516	**£2,857**
Training costs	£9	£0	**-£9**	£3	£0	**-£3**
Cost of cured health state	£925	£860	**-£65**	£925	£860	**-£65**
Cost of recurrence health state	£97	£203	**£107**	£98	£205	**£107**
Total	£6,620	£9,122	**£2,502**	**£6,616**	**£9,126**	**£2,510**

Additional results: Updated EAC base case, using 50% outpatients

Table 31 from the EAC assessment report has been reformulated using the updated EAC base case with 50% of treatments in an outpatient setting, and 50% in a day case setting. Additional changes are the inclusion of OPEN RCT scenario with a 20 year time horizon and clarification of the scenario title where patients in the Optilume arm who would (in the base model) be retreated with Optilume, can be retreated using either standard endoscopic methods or Optilume.

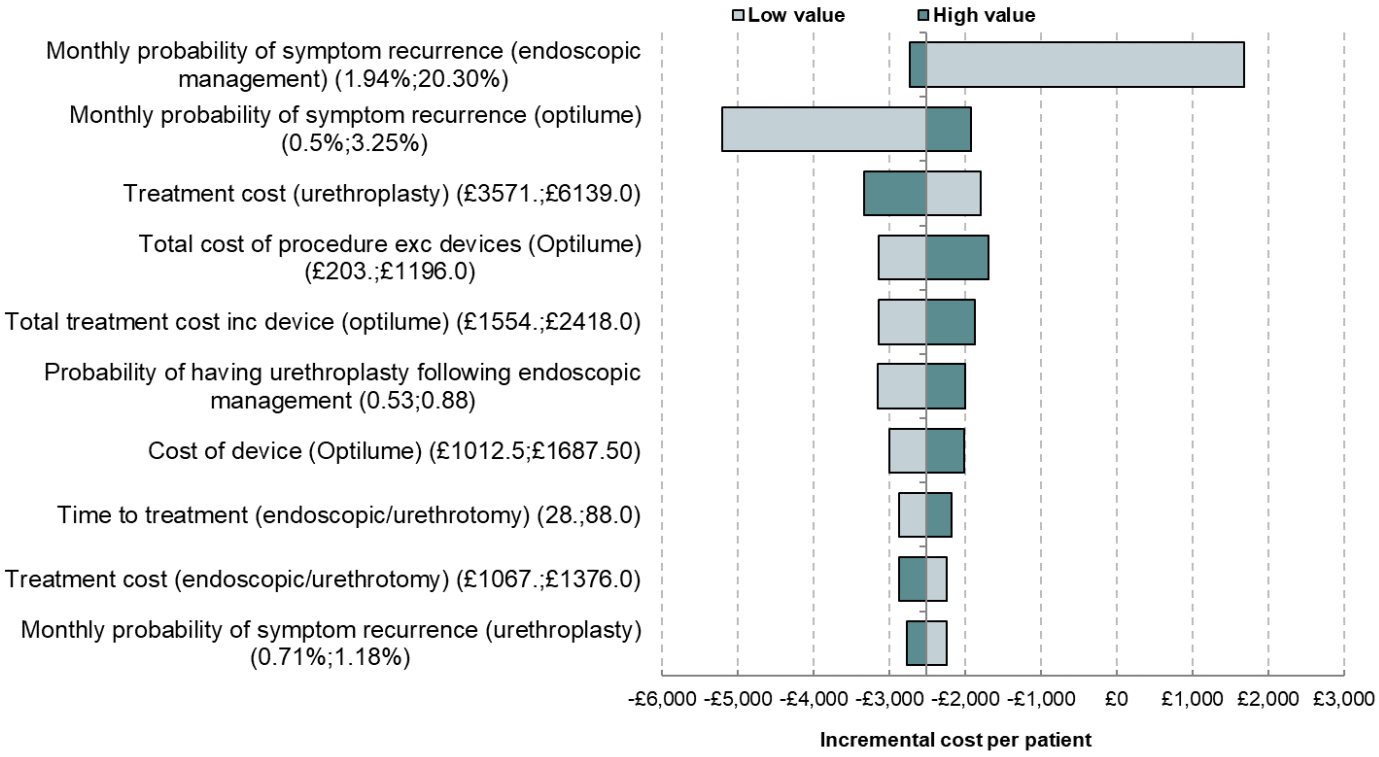
		Company's results			EAC results (with 50% outpatients)		
		Technology	Comparator	**Saving**	Technology	Comparator	**Saving**
Base Case	Cost	£6,620	£9,122	**£2,502**	£6,616	£9,126	**£2,510**
	Re-treat	1.11	2.31	**1.20**	1.11	2.31	**1.20**
Alternative clinical inputs							
R III anatomical	Cost	£8,200	£9,319	**£1,119**	£8,197	£9,324	**£1,127**
	Re-treat	1.59	2.38	**0.79**	1.59	2.38	**0.79**
OPEN RCT	Cost	£3,938	£4,925	**£988**	£3,932	£4,927	**£995**
	Re-treat	0.29	0.91	**0.62**	0.29	0.91	**0.62**
R III Re-interventions	Cost				£5,322	£8,662	**£3,340**
	Re-treat				0.712	2.147	**1.435**
Extended time horizon, 20 years							
Base Case	Cost				£13,390	£16,565	**£3,175**
	Re-treat				3.41	5.44	**2.03**
R III anatomical	Cost				£15,782	£16,832	**£1,051**
	Re-treat				4.30	5.55	**1.25**
OPEN RCT	Cost				£7,674	£10,602	**£2,927**
	Re-treat				1.17	2.96	**1.80**
R III Re-interventions	Cost				£10,962	£15,937	**£4,975**
	Re-treat				2.47	5.17	**2.70**
Retreatment options include both Optilume and standard endoscopic methods for Optilume arm							

% of retreatment, other than Urethroplasty, that use Optilume (others retreated endoscopically)		EAC base case, 5 years			EAC base case, 20 years		
		Technology	Comparator	**Saving**	Technology	Comparator	**Saving**
0%	Cost	£7,382	£9,126	**£1,744**	£15,299	£16,565	**£1,266**
	Re-treat	1.475	2.312	**0.838**	4.74	5.44	**0.70**
40%	Cost	£7,024	£9,126	**£2,102**	£14,382	£16,565	**£2,183**
	Re-treat	1.304	2.312	**1.008**	4.10	5.44	**1.34**
60%	Cost	£6,874	£9,126	**£2,252**	£14,009	£16,565	**£2,555**
	Re-treat	1.232	2.312	**1.080**	3.84	5.44	**1.60**
80%	Cost	£6,738	£9,126	**£2,388**	£13,681	£16,565	**£2,883**
	Re-treat	1.168	2.312	**1.144**	3.61	5.44	**1.83**

Sensitivity analysis: Updated EAC base case, using 50% outpatients

One-way sensitivity analysis

Deterministic sensitivity analysis, re-run without any changes in high and low parameter values from the EAC base case as submitted in the assessment report. The probability of symptom recurrence remains the most influential driver of the model, with the model still becoming cost incurring when there is a low monthly probability of symptom recurrence with endoscopic management.



Additional deterministic sensitivity analysis

Sensitivity table, considering variable proportions of Optilume procedures carried out in Outpatient clinics using local anaesthesia, or as day case procedures using general anaesthesia. This maintains all other variables and assumptions that are set out for the EAC base case

Proportion of procedures carried out as Outpatient clinics	Cost saving due to Optilume	
0%	**£1,877**	**Previous EAC base case**
25%	£2,194	
50%	**£2,510**	**Updated EAC base case**
75%	£2,826	
100%	£3,142	

Two way sensitivity analysis for recurrence

The EAC agree with the methods used for two way sensitivity analysis for recurrence as presented in p48 of the company submission, and updated with the original EAC base case in page 105 (table 30) of the EAC assessment report. The company presented a relatively small range of recurrence probabilities for Optilume (0.2 – 4.2%), whereas the scenario analyses, with alternative data sources, considered values of 2.6% and 4.8%. For completeness the EAC have extended the monthly probability of recurrence for Optilume to include an equivalent range as the comparator, and presented this with the updated EAC base case of 50% outpatient and 50% day case setting for Optilume.

		Monthly probability of recurrence with Optilume (Updated EAC Base case with 50% outpatients)										
		1.0%	2.6%	3.0%	5.0%	7.0%	9.0%	11.0%	13.0%	16.0%	17.0%	19.0%
Baseline **m**onthly probability of recurrence with endoscopic	1.0%	£908	£2,797	£3,177	£4,501	£5,320	£5,858	£6,230	£6,501	£6,705	£6,865	£6,994
	3.0%	-£1,142	£747	£1,127	£2,451	£3,270	£3,808	£4,180	£4,451	£4,655	£4,815	£4,943
	5.0%	-£2,334	-£445	-£66	£1,258	£2,078	£2,616	£2,988	£3,258	£3,463	£3,623	£3,751
	7.0%	-£3,070	-£1,181	-£801	£523	£1,342	£1,880	£2,252	£2,523	£2,727	£2,887	£3,015
	9.0%	-£3,551	-£1,662	-£1,283	£41	£861	£1,399	£1,771	£2,041	£2,246	£2,406	£2,534
	11.0%	-£3,883	-£1,995	-£1,615	-£291	£528	£1,066	£1,439	£1,709	£1,913	£2,073	£2,202
	13.0%	-£4,124	-£2,235	-£1,856	-£532	£288	£825	£1,198	£1,468	£1,673	£1,832	£1,961
	16.3%	-£4,399	**-£2,510**	-£2,130	-£806	£13	£551	£923	£1,194	£1,398	£1,558	£1,686
	17.0%	-£4,448	-£2,559	-£2,180	-£856	-£36	£502	£874	£1,144	£1,349	£1,509	£1,637
	19.0%	-£4,562	-£2,673	-£2,294	-£970	-£150	£388	£760	£1,030	£1,235	£1,395	£1,523
	21.0%	-£4,656	-£2,767	-£2,387	-£1,063	-£244	£294	£666	£937	£1,141	£1,301	£1,429

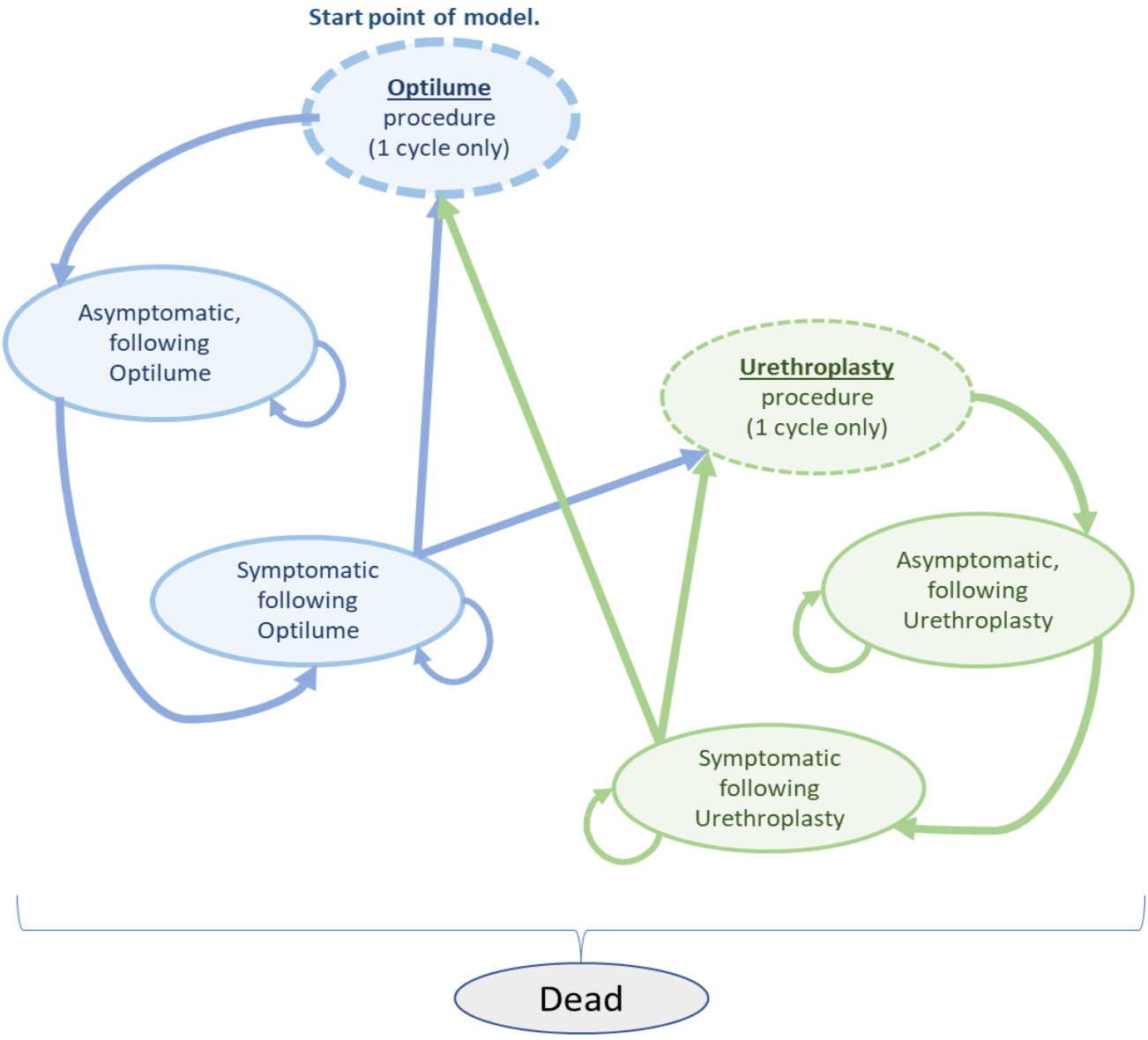
Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was repeated for the updated EAC base case with 50% of patients being treated in outpatients. No parameters were changed other than the standard error for the probability of having treatment following recurrence of symptoms, which was corrected to 0.02, as quoted in Pickard (2020) in the EAC assessment report results. The PSA found that 94% of the 1,000 iterations were cost saving.

Additional requests following the lead team meeting

Alternative model diagram

Note the model structure is unaltered, however the EAC has attempted to simplify the diagram. This shows the Optilume arm only. The comparator arm would be structured similarly, however all mentions of "Optilume" would be replaced with "Endoscopic procedure".



Key to diagram	
Alternative EAC model diagram states	Equivalent company diagram states
Optilume procedure (1 cycle only)	Optilume or endoscopic management

Asymptomatic	Cured
Symptomatic	Recurrence
Urethroplasty procedure (1 cycle only)	Urethroplasty

Cycle transitions	Description
	Movement between cycles following Optilume procedure
	Movement between cycles following Urethroplasty procedure

Catheterisation post procedure

Catheterisation is not explicitly included after either the Optilume, Urethroplasty or endoscopic management procedures. However all of these procedures are based on standard NHS Reference cost for LB55A Minor or Intermediate, Urethra Procedures, 19 years and over, but in different settings. This means that the cost of catheterisation would be included if it were part of normal care, but any differences due to changes in the procedure (that were not associated in the change of setting) would not be captured.

Model input	Cost	LB55A, categories of cost used
Optilume, Company submission and updated EAC base case	£635	Mean of outpatient procedure (£203) and day case procedure (£1067)
Optilume original EAC base case	£1,067	Day case procedure only
Endoscopic management	£1,196	Weighted average of all inpatient procedures and day cases (including elective and non-elective)
Urethroplasty	£1,622	Weighted average of all inpatient procedures excluding day cases (including elective and non-elective)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Optilume for recurrent bulbar strictures

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It 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 and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

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

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Claimed benefits and decision problem from the scope

1 The technology

Optilume is a urethral drug-coated balloon indicated for managing urethral stricture disease in adult males. It is designed to be used as a dilation balloon for an anterior urethral stricture less than or equal to 3 cm in length.

The technology combines balloon dilation, to widen the narrowed area, with locally delivered paclitaxel (3.5 µg/mm2) to the tissue of the strictured area of the urethra. Paclitaxel is an antifibrotic and antiproliferative drug which acts to prevent new tissue growth and reduce scar formation.

Optilume is available in 6 sizes (3 different diameters for both the 3 cm or 5cm length versions). It is passed over a guidewire under direct vision with or without fluoroscopy and placed in position along the length of the stricture. The distal end of the catheter has a semi-compliant inflatable balloon which is inflated using normal saline/water with a pressure inflation device provided by the company for a minimum of 5 minutes to mechanically dilate the urethral stricture and facilitate drug uptake. Once adequate inflation time and urethral dilatation have been achieved, the balloon can be deflated, removed, and safely disposed of. A catheter may be placed at the discretion of the clinician and can be administered post-operatively.

Optilume DCB received a CE mark in September 2020 as a class III medical device.

2 Proposed use of the technology

2.1 Disease or condition

The incidence of urethral strictures is relatively common, but differs based on worldwide populations, geography and income. Prevalence increases with age, rising from around 20 per 100,000 in their 50s, to over 100 per 100,000 for men over 65. Urethral stricture disease accounted for 17,000 hospital admissions in 2016-2017 in the UK, with management of strictures equating to an NHS cost of £18 million in the 12-month period (Bugeja et al., 2021).

Stricture recurrence rates for endoscopic procedures vary considerably between 8 to 77% for direct vision internal urethrotomy (DVIU) and 36 to 92% after dilatation. However, they lead to progressively worse outcomes over time, with an almost 100% failure rate after 3 treatments (Al Taweel and Seyam 2015; Heyns et al., 1998).

2.2 Patient group

Optilume is used to treat urinary symptoms associated with recurrent bulbar urethral strictures in adult men 18 years of age and over. Men are more likely to have a urethral stricture or injury because of a longer urethra. They are rare in women and children. Urethral stricture can happen at any point from the bladder to the tip of the penis. This narrowing can lead to reduced flow or blockage of urine, and other complications such as penile swelling and pain, and pain in the pelvic or lower abdominal area.

Urethral stricture disease has several different aetiologies including iatrogenic (caused by medical treatment), idiopathic (cause unknown), inflammatory or traumatic causes. Iatrogenic causes are the most common (45%). These can be the result of urethral manipulations related to indwelling catheters, transurethral manipulation, surgery for hypospadias (congenital condition), prostatectomy and brachytherapy (internal radiation therapy). The least prevalent cause in the UK is infection (20%), including untreated gonorrhoea and chlamydia, Balanitis Xerotica Obliterans (BXO) and Lichen Sclerosus (Lumen et al. 2009).

2.3 Current management

When considering management options for people with a urethral stricture, many factors need to be considered including:

- Stricture length, aetiology, location, number of strictures
- Timing of previous interventions
- Symptom severity and the presence of complications

- Patient factors including co-morbidities, contraindications and patient preference
- Age and general well-being of the patient
- Impact of management on quality of life
- The expertise available to the patient

Current treatment options for urethral stricture include urethral dilatation, direct visual internal urethrotomy (DVIU) and urethroplasty:

- Urethral dilatation – an endoscopic procedure carried out by a urologist and performed under local or general anaesthesia with or without sedation and cystoscopy. Dilatation involves the sequential dilatation of a stricture with a balloon, filiform and followers, urethral sounds, or self-dilatation with catheters. A standard non-drug coated balloon dilatation may also be available. A stricture that narrows again following dilatation often requires repeated dilatation and/or direct visual internal urethrotomy.

- Direct Visual Internal Urethrotomy (DVIU) – an endoscopic procedure carried out by a urologist and performed under general anaesthesia using a cold or hot-knife transurethral incision to release the stricture tissue. Like urethral dilatation, urethrotomy may be offered as a first line therapy. However, patients with longer strictures (>2 cm), multiple, penile or distal strictures typically do not respond well to repeat incisions and are usually offered urethroplasty as it is more effective for treating such stricture types.

- Urethroplasty – a highly-invasive open surgical procedure done under general anaesthesia by specialist urologists in a limited number of tertiary UK centres. Urethroplasty is the ‘gold standard’ curative treatment option for patients with urethral strictures, with a higher success rate in resolving urethral strictures with no further treatment needed, compared with the existing standard endoscopic treatments aforementioned. However, urethroplasty takes an average of two to three hours operative time, followed by a 1-2-night hospital stay, post-operative catheterisation for 2-3

weeks during a 2-6-week recovery period at home (Shen et al., 2021). A cheek or lower lip buccal mucosal graft may also be required for augmentation and as noted by one clinical expert, if grafting were needed, it would be done as part of the initial urethroplasty.

The number of urethral dilatation and/or urethrotomy treatments performed in a patient with a urethral stricture before urethroplasty varies and is dependent upon the local facilities available and the patient's preference. Treatment options are considered as part of a multi-disciplinary team, and people with urethral strictures will undergo further investigation with a urethrogram or flexible cystoscopy to confirm the stricture before a decision is made about having surgery (NHS England, 2016). Uroflowmetry will be also performed as this objectively demonstrates the severity of restriction to urinary flow (Bugeja et al, 2021).

There is no NICE guideline on the management of urethral strictures, but there is a clinical guideline on the management of lower urinary tract symptoms in men. The European Association of Urology guideline (Lumen et al., 2021), the American Urological Association guideline (Wessells et al., 2017) and the Canadian Urological Association guideline (Rourke et al., 2020) provide recommendations on managing urethral strictures.

2.4 Proposed management with new technology

Optilume is proposed as a second line treatment for bulbar urethral strictures in men who have undergone a prior endoscopic procedure which have failed. Optilume is intended to be an additional intervention offered alongside the current treatment options to prevent or delay the need for the more invasive urethroplasty surgery.

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem from the scope are described in Appendix C.

The company has proposed some variations to the decision problem in the scope, the main changes being to the population (table 1).

Table 1. Decision problem

Decision problem	Variation proposed by company	EAC view of the variation
Population: men 18 years of age and over with recurrent bulbar urethral strictures equal to or less than 3 cm in length.	Men 18 years of age and over with bothersome urinary symptoms associated with recurrent urethral stricture disease for a single, tandem or diffuse anterior urethral stricture equal to or less than 3 cm in length	Rationale for addition of 'bothersome urinary symptoms' is valid as per Optilume company indications for use (pg.4). The terms 'tandem' and 'diffuse' are terminology not used in clinical practice but would still be treated using Optilume according to clinical experts. As discussed throughout the report, there is insufficient evidence for the use of Optilume in anterior urethral strictures as the evidence base is limited to 'bulbar urethral strictures. The EAC has amended the population to 'Men 18 years of age and over with bothersome urinary symptoms associated with recurrent bulbar urethral stricture of equal to or less than 3 cm in length.'
Outcomes: the outcome measures to consider include: • Stricture free rate • Rate of reintervention procedures • Time to treatment failure (time until additional stricture treatment is required)	The outcome measures to consider include: • Stricture free rate • Rate of reintervention procedures • Time to treatment failure (time to additional stricture, including self-catheterisation)	Change to scope outcomes to include self-catheterisation when considering time to treatment failure. As self-catheterisation was not considered a relevant outcome by the clinical experts, the EAC do not agree with the addition of self-

• Qmax (Peak flow rate) as measured by uroflowmetry • International Prostate Symptom Score • Post-void residual (PVR) urine volume • Device-related adverse events	• Qmax (Peak Flow Rate) as measured by uroflowmetry • International Prostate Symptom Score • Post-voice residual (PVR) urine volume • Device-related adverse events	catheterisation to the scope.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 17 published studies, 1 journal article in press and a published conference abstract from its literature search. The company also provided the EAC with an additional unpublished trial report and an additional abstract due for publication in March 2022. The EAC included 4 publications, 1 unpublished trial report and 10 abstracts as evidence. All publications and abstracts related to 3 studies (ROBUST I, ROBUST II and ROBUST III). The rationale for the selection of these studies is in section 4.1 and 4.2 of the EAC assessment report. Of the included ROBUST studies, ROBUST III was a randomised control trial comparing Optilume with standard care, and ROBUST I and ROBUST II were single arm, non-comparative open label studies.

Table 2 Included and excluded studies

Studies included by both EAC and company	
Publication and study design	5 publications comprising 3 studies were included by both • 1 RCT (ROBUST III: Elliot et al. 2021a) • 1 single arm, non-comparative open label study (ROBUST I: Elliot et al., unpublished; Mann et al., 2021; Virasoro et al., 2020) • 1 single arm, non-comparative open label study (ROBUST II: DeLong et al., 2022)
Studies in submission excluded by EAC	
Publication and study design	14 studies were excluded by the EAC because they did not include the use of Optilume

	• 2 prospective randomized multi center trials (Pickard et al., 2020; Jordan et al., 2013) • 6 prospective randomized single center trials (Azab et al., 2020; Elkady et al., 2019; Aldaqadossi et al., 2014; Cecen et al., 2014; Steenkamp et al., 1997; Heyns et al., 1998) • 1 prospective non-comparative multi center study (Erickson et al., 2014) • 3 prospective non-comparative single center studies (Isen et al., 2015; Hoy et al., 2013; Guo et al., 2010) • 2 retrospective non-comparative single center studies (Santucci et al., 2010; Pansadoro et al., 1996)
Abbreviations: EAC external assessment center; RCT randomized controlled trial	

The EAC assessed the quality of all 3 ROBUST studies, and they were all industry sponsored by the company (Urotronic Inc.). ROBUST I was a small non-comparative study of 53 participants and ROBUST II was a small case series of 16 participants. The EAC identified issues around the recruitment of participants for both studies, including potential selection bias. In addition, for ROBUST I there were some inconsistencies in defining the primary outcome in the reporting of follow-up. The EAC concluded that these issues reduced the reliability of the findings of ROBUST I and ROBUST II. ROBUST III was a randomised controlled trial and the EAC identified issues regarding the randomisation process including that there is no information on the concealment of allocation and an imbalance in the treatment allocation between the 2 groups. The EAC deemed that this trial is at high risk of bias because domain 1 (randomisation) was at high risk of bias.

In assessing the safety of Optilume DCB, pharmacokinetic, biochemical, and serological tests were performed in ROBUST I and ROBUST III. Pharmacokinetic results showed that paclitaxel was eliminated from the body as expected. Also, biochemical, and haematological investigations in ROBUST III identified no significant health impact. The most commonly reported adverse events in the literature were urinary tract infection (UTI) and acute urinary retention. The clinical experts that used Optilume noted that the device was tolerated very well with minimum side effects. Serious side effects were rare and Optilume was deemed safe by the EAC.

The details of the ROBUST trials are reported in table 3 and the results are summarised in table 4. As ROBUST III was the only RCT with a comparator to Optilume, it was considered the most important study in the evidence base, with the most significant impact for integration of Optilume into the NHS.

In summary, in all 3 ROBUST trials Optilume DCB demonstrated a 70-74% rate of anatomical success post-treatment. In ROBUST III, it was significantly superior compared to standard care (26.8%). Similar results were found for stricture free outcomes. Interpreting evidence from both anatomical success and stricture free outcomes demonstrates the effectiveness of Optilume in prevention of stricture recurrence. Anatomical success and stricture free outcomes may not be the most reliable method of assessing treatment success and deciding upon future treatment of a patient, as it is the often the symptoms experienced by the patient which are a more important measure.

When considering the secondary outcomes in all 3 ROBUST trials, Optilume demonstrated a rapid and sustained improvement in all outcomes, leading to an improvement in all measured symptoms (IPSS, Qmax and PVR) and quality of life (IPSSQoL, USS-PROM and IIEF). In ROBUST III, Optilume also had superior outcomes compared to the control group post-treatment through to follow-up (IPSS, IPSS QoL, IPSS responder, IIEF overall satisfaction, Qmax, and PVR), except for the VAS pain score.

The EAC noted that such a rapid and sustained improvement across all outcomes useful to assessing stricture recurrence and quality of life makes Optilume a suitable treatment option alternative to further endoscopic procedures for recurrent bulbar urethral strictures equal to or less than 3cm in length who have undergone at least 1 prior endoscopic procedure. Treatment with Optilume is likely to rapidly improve patients' quality of life through long-term alleviation of symptoms. Overall, the EAC concluded that the Optilume DCB device is an effective treatment for patients with bulbar urethral strictures and can be integrated into the NHS clinical practice.

Table 3: general details of the peer-reviewed studies included in the assessment report

Study	Design	Location	Participants/ Population	Intervention & comparator	EAC comments
ROBUST I					
Virasoro et al., (2020), 1-year outcomes Mann et al., (2021), 2-year outcomes Elliot et al., (unpublished), 4-year outcomes	Prospective multi center non-comparative study	Panama (2) and Dominican Republic (2)	53 adult men with a single bulbar urethral stricture 12Fr and equal to or less than 2.0 cm long on urethrogram with 1 to 4 prior endoscopic treatments	**Intervention**: Optilume DCB **Comparator:** none – single arm	Participants were ineligible if their stricture was less than 2.0 cm versus equal to or less than 3.0 cm scope. Participants were pre-treated with a combination of uncoated balloon and/or DVIU. This is not standard of care. A total of 58 DCB procedures were performed for 53 participants: including 5 re-treatments. All outcomes were measured but there was an incomplete inclusion of patients. There was no information on consecutive recruitment, so possibility of sampling bias. Freedom from repeat intervention was not reported in one-year outcomes. PROMS were not measured at 1-year and anatomic success not measured at 2-years. There was a change in primary outcome from one-year anatomic success without retreatment, regardless of symptoms or flow rate, to 50% improvement in IPSS compared to baseline in the absence of retreatment. This was because cystoscopy was not conducted at follow-up after 1 year and therefore the emphasized endpoint was improvement in subjective symptoms. There was no statistical analysis of the data, only descriptive statistics were done.
ROBUST II					
Deong et al., (2022)	Prospective multi center non-comparative study	United states	16 adult men with a single anterior urethral stricture equal to or less than 3 cm in length with lumen diameter <12 F and 2 or more prior endoscopic treatments	**Intervention**: Optilume DCB **Comparator:** none – single arm	Small case series of just 16 patients with only 9 available for 1 year follow up. Possible sampling bias due to no information on consecutive recruitment. Demographics of participants limited to just age and baseline characteristics, and no information on investigational sites beyond country of investigational sites. Partially meets scope criteria as includes Optilume but no comparator. However, participants were only eligible if they had 2 or

					more prior endoscopic procedures which does not fit with where the Optilume device would be considered by clinicians (≥1 prior endoscopic treatment).
ROBUST III					
Elliot et al., (2021)	Multi center RCT	United States (21) and Canada (1)	127 adult men with anterior strictures ≤12F and equal to or less than 3cm in length and 2 or more prior endoscopic treatments 15 additional participants were non-randomised to a PK arm	**Intervention**: Optilume DCB (n=79) **Comparator**: standard endoscopic care (DVIU/dilatation) (n=48)	Participants were unblinded after 6 months which could bias some secondary outcomes, for instance in the crossover at 6 months. Pre-dilatation in the intervention arm was likely to favour successful efficacy endpoint. Primary outcome was missing for 7 control and 12 intervention participants. Outcomes were not statistically measured; descriptive statistics were used. USS-PROM was not a reported outcome. VAS pain score was not an outcome for ROBUST III.

Table 4: summary results for all outcomes

	ROBUST III control		ROBUST III intervention		ROBUST II (1 year)		ROBUST I (1-year)		
	Baseline	1-year	Baseline	1-year	Baseline	1-year	Baseline	1-year	4-years
Anatomical success, n/N (%)	NA	11/41 (26.8%)Δ	NA	50/67 (74.6%)**Δ	NA	11/15 (73.3%)Δ	NA	32/46 (70%)	[redacted]
IPSS responder rate	[redacted]	[redacted]	[redacted]	[redacted]	NA	8/13 (61.5%)	NA	37/48 (77%)	[redacted]
Stricture free outcome (measured by ULT)	NR	NR	NR	NR	NR	NR	NA	77%	[redacted]
Stricture free outcome (measured by IPSS ≤11)	NR	NR	NR	NR	NR	NR	NA	79%	[redacted]
Stricture free outcome (measured by freedom from repeat intervention)	NA	22%	NA	83%	NA	11/15 (73.3%)	NA	40/48) 83%	[redacted]
IPSS Score, mean ± SD (n)	22.8±7.0 (47)	19.9±7.5 (42)	22.0±6.8 (79)	9.0±7.1 (67)	18.4±4.9 (16)	6.0±6.1 (9)	25.2±4.46 (53)	4.9±5.63 (42)	[redacted]
IPSS QOL, mean ± SD (n)	4.7±1.2 (47)	4.0±1.3 (42)	4.5±1.3 (79)	1.9±1.5 (67)	4.4±1.3 (16)	1.4±1.5 (9)	4.9±0.86 (53)	0.8±1.06 (42)	[redacted]
USS-PROM, mean ± SD (n)	NR	NR	NR	NR	10.8±3.4 (16)	4.3±4.0 (8)	15.9±4.69 (53)	1.4±1.78 (40)	[redacted]
IIEF - Erectile function, mean ± SD (n)	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
IIEF - Overall satisfaction, mean ± SD (n)	6.0±3.2 (46)	5.8±2.7 (13)	5.8±2.9 (72)	6.9±3.0 (59)	6.7±2.9 (16)	7.3±2.8 (9)	6.5±2.62 (53)	8.1±2.5 (40)	[redacted]
Qmax, mean ± SD (n)	7.4±3.5 (47)	7.6±4.0 (41)	7.6±3.4 (78)	15.5±9.0 (65)	6.9±3.7 (16)	20.8±9.1 (9)	5.0±2.56 (46)	19.5±9.96 (42)	[redacted]
PVR, mean ± SD (n)	181.5±201.7 (42)	109.8±116.9 (77)	109.8±116.9 (77)	94.6±121.8 (66)	187.1±227.1 (16)	66.4±57.5 (9)	141.4±105.05 (43)	26.79±33.10 (42)	[redacted]
VAS pain score, mean ± SD (n)	1.9±2.3 (47)	0.2±0.6 (47)†	1.6±2.2 (78)	0.6±1.0 (78)†	1.7±2.3 (16)	0.3±0.6 (9)†	2.9±2.87 (53)	0.9±1.87 (51)†	[redacted]

* Compared to the baseline value, p<0.0001
** Compared to control group, p<0.0001
⌂ 30 days IPSS responder rate
Δ 6 months
†30 days post-procedure VAS pain score
ULT: Ability to pass a 14Fr flexible rubber catheter through the treated area in the urethra

4.2 Summary of economic evidence

The company and the EAC did not identify any economic studies specifically related to Optilume. The company submission included 4 publications (Pickard et al., 2020; Wright et al., 2006; Rourke et al., 2005; Harris et al., 2016) which were relevant to the comparators. Pickard et al., (2020) was a RCT comparing urethroplasty with endoscopic urethrotomy for recurrent bulbar strictures and included a within trial health economic evaluation. The company's economic model used clinical outcome data and micro-costing outputs from this trial, both in the base-case and in some scenarios. For full details on the published economic evidence, please see section 9.1 of the assessment report.

De novo analysis

The company submitted a new model (see Figure 2, section 9.2 of the assessment report) because none of the economic studies included Optilume. It is a Markov model comparing Optilume with endoscopic management for the treatment of recurrent anterior urethral strictures, equal to, or less than 3cm. People start with either Optilume or endoscopic management, following a recurrence. They then all move initially to the cured state, from which some will have a recurrence and would be retreated with either the original treatment or urethroplasty. The model used an NHS and personal social services perspective, and applied a 3.5% discount, as described in the NICE reference model. The base-case time horizon was 5 years. The company stated that this was because of a lack of long-term data, and the initial years having most impact. They included a 10-year time horizon as an additional scenario and the EAC investigated the impact of a 20-year time horizon.

Model assumptions

The company made several model assumptions and the EAC has provided comments on their suitability and has identified additional assumptions (see section 9.2, table 22 of the assessment report).

The EAC considered that the model reflects the clinical pathway. Patients who experience a recurrent stricture may be treated with either endoscopic methods or urethroplasty, and subsequent recurrences are dealt with in the same way. The company base case assumed that if patients received Optilume for their initial treatment and had a recurrent stricture, they would be re-treated with Optilume again, if they do not receive urethroplasty. In practice, it is likely that patients who do not receive urethroplasty would receive a mixture of sequential endoscopic treatments, including Optilume depending on patient and clinician choice and availability of resources. The company addressed this by developing an initial scenario whereby patients would receive other endoscopic methods post-Optilume. However, the EAC completed additional modelling to allow for a mix of Optilume and endoscopic methods for retreatment.

Model parameters

The model is based on the ROBUST III RCT (Elliot et al. 2021), comparing Optilume with endoscopic management at 1 year, which is presented in the clinical evidence section. The EAC agreed that this is the most appropriate data source for the model, however as there is longer-term data available from single arm trials, these were discussed for individual parameters (see section 9.2 of the assessment report). Some additional clinical and cost data has been taken from the OPEN trial, an RCT comparing urethrotomy with urethroplasty, with a 2-year follow-up (Pickard et al. 2020).

The model is driven by the number of recurrences (recurrence rate) and retreatments (likelihood of retreatment, type of treatment and time to treatment) that occur in each arm. The recurrence rates using different outcomes are presented in table 5. Once in a recurrent state, the monthly probability of retreatment was calculated (Table 6). For more details, please see section 9.2 in the assessment report.

Table 5. Clinical parameters: monthly probability of recurrence, company model and additional EAC scenario

	Company base case	Company Scenarios		EAC Scenario
	ROBUST III One Year (IPSS score)	**ROBUST III 6 month (anatomic)**	**OPEN RCT**	**ROBUST III One year (Retreatments)**
With endoscopic management as a comparator				
Optilume	2.6%	4.8%	0.5%##	1.4%
Endoscopic management	16.3%	19.7%	1.9%	11.1%
Urethroplasty	0.9%#	0.9%#	0.9%#	0.9%#
With Urethroplasty as a comparator				
Optilume	2.6%	4.8%	0.5%##	11.9%
Urethroplasty	0.9%#	0.9%#	0.9%#	0.9%#

Taken from the OPEN RCT (Pickard et al. 2020)

Relative risk ratio from ROBUST III IPSS score applied to OPEN RCT data for Urethrotomy

Table 6. Monthly Probability of Retreatment

Initial treatment	Retreatment method	Retreatment received	% for each method	Wait (days)	Monthly probability of retreatment
Optilume / endoscopic methods	Optilume / endoscopic	90%	30%	47.5	18%
	Urethroplasty	90%	70%	90	28%
Urethroplasty	Optilume / endoscopic	90%	88%	47.5	63%
	Urethroplasty	90%	12%	90	4%

Costs and resource use

The costs were grouped as follows: cost of procedure, cost of device and training, cost of adverse events, cost of recurrence and cost of cured state (Table 7). The company base case procedure costs were based on a mean between day case and outpatient procedures. The EAC only used day costs, based on expert feedback. Full details can be found in section 9.2 of the assessment report.

Table 7. Resource parameters for company and EAC base case

Parameter	Company	EAC value	Comment
Procedure costs			
Endoscopic management procedures	£1,196	No change	Weighted average of all NHS Ref Costs 2019/20 LB55A, except outpatients.
Urethroplasty procedure	£4,761	No change	Total HRG costs for NHS Ref Costs 2019/20
Optilume procedure	£635	£1,067	NHS References Costs 2019/20 Company: Mean of LB55A Day Cases and Outpatients EAC: LB55A Day Cases only
Optilume device	£1,350	No change	List price, company submission
Total procedure cost: Optilume	£1,986	£2,418	EAC cost includes day case only, without use of outpatient procedures.
Other related costs			
Predilatation	£20.36	No change	This is applied to 5% of all patients treated with Optilume only.
Training for Optilume	£8.53	£2.62	Staff training and 3 supervision sessions. EAC changed calculation method and assumptions
Adverse events			
Haematuria	£33	No change	GP Appointment (PSSRU 2020)
Urinary tract infection	£43	No change	7 days antibiotics, urinalysis test plus GP appointment
Wound infection	£107	No change	Mean of oral or IV antibiotics plus GP appointment (hospital admission counted separately)
Readmission to hospital	£434	£508	Weighted average of non-elective short stay with and without intervention (LB57C and LB57D)
Urinary retention	£941	No change	Outpatient procedures, Accident and Emergency. LB55A Minor or intermediate, urethra procedure
Subsequent health state costs (per month)			
Cured state	£18	No change	2 x GP appointments per year
Recurrent state	£44.74	No change	4 x GP appointments per year, plus 16.8% using self-catheterisation

Results

The company base case found that there was a cost saving of £2,502 per person using Optilume over a 5-year time horizon. For the EAC's revised base case the cost saving was reduced to £1,877 per person. This was associated with a reduction from 2.31 to 1.11 repeat procedures over the 5 years (a reduction of 1.20). The change in results for the base case is almost entirely

due to the change from 50% day-case and 50% outpatient in the company model, to 100%-day case in the EAC amendments. If an outpatient setting were widely used there is likely to be an increase in the cost saving due to Optilume.

Table 8. Summary results for company and EAC economic analyses

Cost category	Company's base-case				EAC's base-case		
	Device	**Comparator**	**Cost saving per person***		**Device**	**Comparator**	**Cost saving per person***
Initial procedure	£2,001	£1,259	**-£742**		£2,433	£1,259	**-£1,174**
Repeat procedures (Endoscopic)	£931	£1,286	**£355**		£1,132	£1,286	**£154**
Repeat procedures (Surgical)	£2,658	£5,514	**£2,856**		£2,659	£5,516	**£2,857**
Training costs	£9	£0	**-£9**		£3	£0	**-£3**
Cured health state	£925	£860	**-£65**		£925	£860	**-£65**
Recurrence health state	£97	£203	**£107**		£98	£205	**£107**
Total	£6,620	£9,122	**£2,502**		£7,249	£9,126	**£1,877**
** A minus sign indicates device is more expensive than the comparator in this cost category*							

Sensitivity analysis

The company submission included one-way, two-way, and probabilistic sensitivity analysis, and several alternative scenarios. The EAC found that the sensitivity analysis was comprehensive and accurate. Where the EAC altered parameter values, the sensitivity analysis was also updated to reflect the changed parameters. The EAC conducted 2 additional scenarios:

- Use of direct re-treatment rate rather than outcomes to indicate recurrence figures
- Possible use of any treatment method (urethroplasty, endoscopic treatment or Optilume) for additional re-treatments

In addition, the EAC investigated the effect of an extended time horizon of 20 years.

The key driver for the model is the probability of recurrence, and hence re-intervention. As modelled, Optilume reduces recurrence, and repeat interventions. Cost savings largely depended on the saving due to reduced repeat interventions being greater than the additional cost of an Optilume procedure (compared to standard endoscopic procedures). Using deterministic one-way sensitivity analysis, this was the only variable that could make the base case model cost-incurring for Optilume at 5-years. The impact of this was also seen in the scenarios using different input data. The probabilistic sensitivity analysis (PSA) for the EAC base case found that 86% of the 1,000 iterations were cost saving, when only the standard error or the probability of having treatment following recurrence of symptoms (full details on the sensitivity analysis can be found in section 9.3 of the assessment report).

The EAC noted that while the clinical evidence points to Optilume improving clinical outcomes, at least in the short term, there is some uncertainty around the extend and duration of the change and how this translates to recurrence in the model. This is because of the following factors:

- There is only 1 comparative study available for Optilume (ROBUST III)

- The study is limited to 1-year follow-up, although 1 single arm study had follow-up to 4-years
- There is not an agreed single outcome measure that defines recurrence
- Standard endoscopic methods encompass several different procedures

The company and the EAC modelled a variety of scenarios that used different clinical data for the probability of recurrence, and all scenarios remained cost saving at 5-years. Increasing the time horizon to 20 years had a small impact on the base case, increasing the cost saving from £1,877 to £2,152 in the EAC base case (full details of the scenario analysis can be found in table 31, section 9.3 of the assessment report).

In conclusion, both the EAC and company base cases were cost-saving at 5-years and remained cost-saving if the time horizon was extended. The additional scenarios modelled by the company and EAC also remained cost saving. The EAC stated that modelling suggested that the introduction of Optilume would provide a cost-saving alternative to further standard endoscopic procedures in men with recurrent bulbar urethral stricture who have previously undergone a failed endoscopic procedure. There remains uncertainty around the most appropriate inputs for recurrence or retreatment, and therefore the extent of the cost saving due to Optilume.

5 Ongoing research

The company did not identify any ongoing studies relevant for inclusion. The EAC identified 1 study that was considered potentially relevant to the decision problem. This is the ROBUST III study (NCT03499964), which is an active study no longer recruiting. One-year results were submitted by the company and form part of the evidence base of the assessment report (Elliott et al., 2021), and post-treatment follow-up is planned for up to 5 years.

The EAC also identified the ROBUST IV trial (NCT03851952). This was a single-arm, open-label, registry study sponsored by the company. It is noted

on the Clinical trials.gov website that this study was withdrawn in 2019, and in discussion with the company, this was confirmed.

[redacted]

6 Issues for consideration by the Committee

Clinical evidence

- The clinical evidence for Optilume comes from 2 non-comparative (ROBUST I and II) and 1 comparative study (ROBUST III). Only the latter met all PICO elements of the scope and none of the studies were done in the UK. The committee may wish to consider the strength and generalisability of the evidence.

- The 1-year evidence demonstrated that Optilume improved clinical and patient related outcomes and is an effective treatment for patients with recurrent bulbar urethral strictures. ROBUST I, a single arm trial in 53 men showed demonstrable long-term efficacy through to a 4-year follow-up. There is lack of long-term comparative data, however the ROBUST III trial is ongoing and will continue to collect 5-year follow up data. The committee may wish to consider the lack of long-term comparative data.

- There is not an agreed single outcome measure that defines recurrence. There are objective efficacy outcomes such as anatomic success, freedom from repeat intervention, Qmax, and PVR and subjective efficacy outcomes that include IPSS, IPSS QoL, IIEF, and USS-PROM. Of the 6 clinical experts, 4 stated that patient reported outcomes (IPSS-USS-PROM) and flow rate were the most important, 1 noted post-void residual (PVR), and another freedom from repeat intervention. One expert noted that there is no right or wrong answer, as if you have a patient with no symptoms, it is difficult to justify treatment based on imaging or endoscopy alone. The decision of

whether to treat a patient is multifactorial, but primarily depends upon the subjective experience of the patient and whether their symptoms are bothersome. The committee may wish to consider the most appropriate outcome measure.

- Most study participants receiving Optilume were pre-dilated prior to treatment across all 3 ROBUST studies. The clinical experts noted pre-dilatation is normally not needed and unlikely to be performed in the NHS. Optilume is intended as second line treatment post 1 failed endoscopic treatment. Participants in ROBUST I had between 1 to 4 prior endoscopic treatments and participants in ROBUST II and III had 2 or more endoscopic treatments prior to Optilume. The committee may wish to consider the generalisability of the evidence to the UK population.

- The number of urethral dilatation and/or urethrotomy treatments performed in a patient with a urethral stricture before urethroplasty varies and is dependent upon the local facilities available and the patient's preference. Because of the specialist nature of urethroplasty and limited number of surgeons trained in urethroplasty in the UK, waiting lists for this surgery can be extensive. The coronavirus pandemic has exacerbated this problem, causing up to a two-year waiting list according to 1 clinical expert. Optilume, however can be performed by a general urologist and therefore if integrated into the NHS, could help to reduce waiting list times for patients requiring treatment. The committee may wish to consider the system benefits of Optilume.

Cost evidence

- The company submitted a new model and their base case found that there was a cost-saving of £2,502 per person using Optilume over a 5-year time horizon. The EAC accepted the model structure and most of the assumptions and parameters. For the EAC's revised base case the cost saving was reduced to £1,877 per person. Optilume remained

cost-saving for a range of scenario and sensitivity analyses. The results were robust for all other parameters tested. Probabilistic sensitivity analysis found that 86% of the 1,000 iterations were cost saving.

- The clinical experts advised that Optilume would be done as a day case rather than as an outpatient procedure. The change in cost-saving in the EAC base case is almost entirely because of the change from 50% day-case and 50% outpatient in the company model, to 100%-day case in the EAC amendments. If an outpatient setting were widely used there is likely to be an increase in the cost saving due to Optilume.

- The key driver for the model is the probability of recurrence, and thus re-treatment. Cost savings largely depended on the saving due to reduced repeat interventions being greater than the additional cost of an Optilume procedure (compared to standard endoscopic procedures). However, although Optilume improves clinical outcomes, there is some uncertainty around the clinical evidence:

    - There is only 1 comparative study available for Optilume (ROBUST III), with 1-year follow up, although 1 single arm study had follow-up to 4-years
    - There is no agreed single outcome measure that defines recurrence
    - Standard endoscopic methods encompass several different procedures.

  Longer term data and experience in the NHS is lacking to present a robust longer-term case for Optilume.

- The company base case time horizon was 5 years, which they stated was because of lack of long-term data, and the initial years having most impact. Increasing the time horizon to 20 years had a small impact on the base case, increasing the cost saving from £1,877 to £2,152 in the EAC base case. The EAC noted that this is an

exploratory analysis and because of the lack of longer-term comparative data the results are uncertain.

7 Authors

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Lizzy Latimer, Health Technology Assessment Adviser

NICE Medical Technologies Evaluation Programme

February 2022

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

A Details of assessment report:

- Beddard M., Morgan H., Morris R et al. MTG565 Optilume for recurrent bulbar urethral strictures: external assessment centre report. February 2022.

B Submissions from the following sponsors:

- Laborie Medical Technologies

C Related NICE guidance

- Lower urinary tract symptoms in men: management (2015) NICE guideline CG97.

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Prof Chris Chapple

Consultant Urologist – Sheffield Teaching Hospitals NHS Foundation Trust

Mr. Trevor Dorkin

Consultant Urologist – The Newcastle upon Tyne Hospitals NHS Foundation Trust

Mr. Amr Emara

Consultant Urologist – Hampshire Hospitals NHS Foundation Trust

Miss Katie Moore

Consultant Urologist – Manchester University NHS Foundation Trust

Miss Louise Olsen

Consultant Urologist – Salford Royal NHS Foundation Trust

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Consultant Urologist – St George's University Hospitals NHS Foundation Trust

Mr. Ian Eardley

Consultant Urologist – St James's University Hospital, Leeds

Appendix C: claimed benefits and decision problem from scope

The benefits to patients claimed by the company are:

- Rapid and sustained improvement in symptoms and urinary flow
- Effective minimally invasive treatment
- Reduces the need for retreatments or invasive surgical procedures
- Reduces the need for self-catheterisation management
- Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty
- Rapid return to normal daily living and improved quality of life

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

- Reduced burden of repeat procedures
- Reduced re-admission rates (elective or non-elective)
- Improved bed capacity
- Improved theatre capacity
- Reduced burden on community care by reducing post-operative complications such as infection, incontinence, discomfort, sexual dysfunction
- Capacity improvements and cost/resource savings
- Easy and rapidly deployable. No capital investment on behalf of the Trust is required.

Population	Men 18 years of age and over with recurrent bulbar urethral strictures equal to or less than 3 cm in length
Intervention	Optilume
Comparator(s)	•Urethral dilation o S-Curve Dilators o Rigid rod (metal or plastic) dilation •Urethrotomy (Steel blade mounted on a urethroscope)

	•Urethroplasty	
Outcomes	The outcome measures to consider include: •Stricture free rate •Rate of reintervention procedures •Time to treatment failure (time until additional stricture treatment is required) •Qmax (Peak Flow Rate) as measured by uroflowmetry •International Prostate Symptom Score •Post-void residual (PVR) urine volume •Device-related adverse events	
Cost analysis	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.	
Subgroups to be considered	•None identified	
Special considerations, including those related to equality	Optilume is intended for men with recurrent bulbar urethral strictures. These can be caused by injury to the penis, surgery or infection. Some people may not identify as men but have a penis. Urethral strictures become more common in people over 55. Sex, gender reassignment and age are protected characteristics under the Equality Act (2010).	
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	None	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Optilume for recurrent bulbar urethral strictures

1 Technology

1.1 Description of the technology

Optilume (Laborie Medical Technologies) is a drug-coated balloon indicated for treating bulbar urethral strictures (narrowing of the urethra) in adult males. It is designed to be used as a dilation balloon for a single, tandem or diffuse anterior urethral stricture less than or equal to 3 cm in length.

The technology combines balloon dilation, to widen the narrowed area, with locally delivered paclitaxel (3.5 μg/mm^2) to the tissue of the strictured area of the urethra. Paclitaxel inhibits cell proliferation preventing thickening and enlargement of tissue.

Optilume is available in 6 sizes (3 different diameters for both the 3 cm or 5 cm length versions). It is inserted using endoscopic vision with or without fluoroscopy and then inflated under pressure. It stays inflated along the length of the stricture for up to 10 minutes. The balloon's inflation pressure can be measured with an inflation device, and can be visualised, using radiography and contrast media, or with direct visualisation using cystoscopy.

The technology is used by trained consultants in urology, urology trainees and urology nurse specialists. It can be done using local anaesthesia as a day case or in an outpatient setting.

1.2 Relevant diseases and conditions

Optilume is used to treat urinary symptoms associated with recurrent bulbar urethral strictures in men aged over 18. Men are more likely to have a urethral stricture or injury because of a longer urethra. They are rare in women and children. Urethral stricture can happen at any point from the bladder to the tip of the penis. This narrowing can lead to reduced flow or blockage of urine, and other complications such as penile swelling and pain, and pain in the pelvic or lower abdominal area. Although in most cases, no cause can be found, some common causes are (The British Association of Urological Surgeons [BAUS]):

- trauma to the urethra
- infection such as a sexually transmitted disease
- damage from surgical tools
- conditions that cause swelling
- congenital.

It is estimated that the prevalence of urethral strictures is approximately 20 per 100,000 men in their 50s, rising to 100 per 100,000 men aged over 65. According to Bugeja et al, 2021, urethral stricture disease accounted for 17,000 hospital admission in 2016-2017 in the UK. Regardless of the treatment, urethral strictures tend to reform, usually within one year, requiring repeat procedures.

1.3 Current management

Current treatment options for urethral stricture depend on the site and length of stricture, age and general well-being of the person undergoing treatment and include:

- Urethral dilation (widening) of the stricture using metal or plastic dilators or non-drug coated dilation balloons. This is done endoscopically under local or general anaesthesia.

- Urethrotomy. This is done endoscopically under general anaesthesia and involves making an incision to the strictured area of the urethra to widen the urethral lumen. About 50% of people have a successful widening of their urethral stricture after this procedure.

- Urethroplasty. This is open surgery done under general anaesthesia and depending on the length and location of the stricture, different options are available: removal of the stricture and reconnection of healthy urethra, or augmentation of the urethra, with or without removal of the strictures segment. It has a higher success rate in resolving urethral strictures with no further treatment needed compared with existing standard endoscopic treatments.

Certain factors need to be taken into account when deciding how to manage a stricture including (Bugeja et al, 2021):

- the length, location aetiology and number of strictures
- type, number, and timing of previous interventions
- symptoms severity and the presence of complications
- patient factors including co-morbidities and patient preference
- the expertise available.

Treatment options are considered as part of a multi-disciplinary team, and people with urethral strictures will undergo further investigation with a urethrogram or flexible cystoscopy to confirm the stricture before a decision is made about having surgery (NHS England, 2016). Uroflowmetry will be also performed as this objectively demonstrates the severity of restriction to urinary flow (Bugeja et al, 2021).

Both urethrotomy and urethral dilation should be considered as first-line treatments for strictures shorter than 3 cm in length unless men are contraindicated or would prefer to undergo urethroplasty. Self-dilation is advised after urethrotomy or dilation when the stricture is long and complex,

when major surgery is not possible or as a temporising measure until urethroplasty can be performed (Bugeja et al, 2021). Urethroplasty should be considered for people with short bulbar urethral strictures following at least one urethrotomy, unless after counselling about treatment options the individual would prefer to undergo primary urethroplasty and is aware of the risks and benefits of surgery (NHS England, 2016).

1.4 Regulatory status

Optilume received a CE mark in September 2020 as a class III medical device.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Rapid and sustained improvement in symptoms and urinary flow
- Effective minimally invasive treatment
- Reduces the need for retreatments or invasive surgical procedures
- Reduces the need for self-catheterisation management
- Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty
- Rapid return to normal daily living and improved quality of life

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

- Reduced burden of repeat procedures
- Reduced re-admission rates (elective or non-elective)
- Improved bed capacity
- Improved theatre capacity
- Reduced burden on community care by reducing post-operative complications such as infection, incontinence, discomfort, sexual dysfunction
- Capacity improvements and cost/resource savings
- Easy and rapidly deployable. No capital investment on behalf of the Trust is required.

2 Decision problem

Population	Men 18 years of age and over with recurrent bulbar urethral strictures equal to or less than 3 cm in length	
Intervention	Optilume	

Comparator(s)	• Urethral dilation
	  ○ S-Curve Dilators
	  ○ Rigid rod (metal or plastic) dilation
	• Urethrotomy (Steel blade mounted on a urethroscope)
	• Urethroplasty	

Outcomes	The outcome measures to consider include: • Stricture free rate • Rate of reintervention procedures • Time to treatment failure (time until additional stricture treatment is required) • Qmax (Peak Flow Rate) as measured by uroflowmetry • International Prostate Symptom Score • Post-void residual (PVR) urine volume • Device-related adverse events	
Cost analysis	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.	
Subgroups to be considered	• None identified	
Special considerations, including those related to equality	Optilume is intended for men with recurrent bulbar urethral strictures. These can be caused by injury to the penis, surgery or infection. Some people may not identify as men but have a penis. Urethral strictures become more common in people over 55. Sex, gender reassignment and age are protected characteristics under the Equality Act (2010).	
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	None

3 Related NICE guidance

Published

- Lower urinary tract symptoms in men: management (2015) NICE guideline CG97.

4 External organisations

4.1 Professional

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

- British Association of Urological Nurses
- British Association of Urological Surgeons
- British Urological Foundation
- British Uro-Oncology Group
- North of England Urological Society
- Urology Foundation

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 Foundation
- Bladder and Bowel UK
- Everyman
- Kidney Care UK
- Men's Health Forum (MHF)
- Prostate Cancer Network (PCaSO)
- Prostate Cancer UK
- Prostate Help Association (PHA)
- Prostate Scotland

- Tackle Prostate Cancer

Adoption report: GID-MT565 Optilume for recurrent bulbar urethral strictures

Summary

Adoption levers identified by contributors

- Provides an alternative treatment option.
- May reduce the frequency of stricture recurrence and need for further treatment.
- Perceived to be more cost effective compared to urethroplasty.
- May be preferred by patients over urethroplasty because it does not require hospital stay, reduced recovery time and potentially avoids general anaesthesia.
- Can be done as a day case and potentially outpatient setting.
- Procedure can be carried out in secondary care as opposed to tertiary care.
- Minimal training required.

Adoption barriers identified by contributors

- Initial cost may be higher compared to urethral dilation or urethrotomy.
- Perceived lack of long-term evidence.

1 Introduction

The adoption team has collated information from 7 healthcare professionals working within 6 NHS organisations, one with experience of using Optilume. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

Optilume has been available in the UK since June 2021 and is currently used in one NHS organisations in England and one in Wales. The user from England contributed to this adoption report.

2 Contributors

Details of contributing individuals are listed in the below table.

Site	Job title	Experience
1	Consultant Urologist	Yes. Started use in June 2021. 10 procedures undertaken. Aiming to trial on a further 5 patients.
2	Consultant Urological Surgeon	No. Business case awaiting approval. Estimates using it on 50-60 patients per year.
2	Consultant Urological Surgeon	No. Business case awaiting approval. Estimates using it on 40-50 patients per year.
3	Consultant Urologist	No. Business case awaiting approval. Not aware of numbers of suitable patients.
4	Consultant Urologist	No. Business case awaiting approval. Estimates using it on 40 patients per year.
5	Consultant Urologist	No. Business case approved recently. Estimates using it on some of the 200 patients that require an intervention per year.
6	Consultant Urologist	No. Business case awaiting approval. Estimates using it on 30-40 patients per year

3 Current practice in clinical area

Current practice varies widely between clinicians. A urethrogram or urethroscopy is usually carried out to show the location, calibre, and length of the stricture. This together with other factors such as the age of person with the stricture, cause of stricture and comorbidities helps focus on treatment options available. The health professional and patient together then decide on which treatment to undertake. Treatments can include:

- Urethral dilation (widening): may be offered first line and carried out by a urologist in secondary care. It usually involves a general or local anaesthesia with or without sedation and cystoscopy. All contributors use either s- shaped coaxial dilators or clutton bougies (sounds) for the procedure. A standard non-drug coated balloon dilation may also be available.

- Urethrotomy: may be offered first line and carried out by a urologist in secondary care. The type of anaesthesia used varies either general or reginal anaesthesia with rigid cystoscopy.

- Urethroplasty: usually offered for recurrent bulbar strictures and carried out by a urological surgeon with a specialist interest in urethral reconstruction in a tertiary care setting. It involves general anaesthesia, up to 3-hour operating time, a 1 to 2 night hospital stay and 2 to 6 weeks recovery at home. A cheek or lower lip buccal mucosal graft may be required for augmentation.

The number of urethral dilation or urethrotomy treatments carried out before an alternative is considered varies between clinicians and patients.

Patients may also be asked to self dilate to reduce the rate of urethral strictures recurrence. For some patients it may be their only long term option for managing their condition because they may be unsuitable for hospital treatments or reconstruction due to comorbidity. Patients are trained to self-dilate using a single use catheter at a variable frequency from daily to once every few weeks depending on the case and nature of their stricture, but most are done once a week. Contributors report compliance is generally poor because some patients find the procedure difficult to perform and uncomfortable.

4 Use of Optilume in practice

Contributors believe a urethrogram and urethroscopy will help determine the size of balloon length required for the Optilume procedure. The procedure currently takes the user 20 to 25 minutes. The user has completed all 10 procedures as day cases in a theatre where the patient lies in a lithotomy position with either general anaesthesia or local anaesthesia with sedation, using a rigid ureteroscope and fluoroscopy. This arrangement is not possible in an outpatient setting at the user's trust. The user reports very few of their patients would tolerate local anaesthesia without sedation during balloon inflation and allow for accurate placement of the balloon, which is critical for high quality results. Therefore, they aim to continue with general anaesthesia or local anaesthesia with sedation to ensure patient comfort and accuracy of the procedure.

Patients do not require catheterisation post procedure in the user's experience. To ensure the drug remains effective in the urethral tissue the bladder can be emptied prior to balloon dilatation to avoid the need to void in the first hour post procedure. Passing urine may be uncomfortable and bloodstained initially, but usually settles after 1 to 2 days. Patients are asked to avoid sexual activity for 2 weeks and subsequently use a barrier contraceptive for 3 months, if partners are of childbearing age, to avoid possible drug transmission.

Contributors report that they would provide long term follow up in line with their current practice for other treatments. Some follow patients for up to 5 years either in person or by telephone, and others offer patient initiated follow up (PIFU).

Follow up appointments may include:

- Uroflowmetry and post-void residual urine volume to check how fast and completely the bladder empties. This initial measurement may be used to compare with future measurements to assess stricture recurrence.
- Urinalysis to screen for an infection.
- Urethral stricture surgery patients reported outcome measure (USS PROM).

5 Reported benefits

The potential benefits of adopting Optilume, as reported to the adoption team by the healthcare professionals using the technology are:

- Provides an alternative treatment option.
- May reduce the frequency of stricture recurrence and need for further treatment.
- Perceived to be more cost effective compared to urethroplasty.
- May be preferred by patients over urethroplasty because it does not require hospital stay, reduced recovery time and potentially avoids general anaesthesia.
- Can be done as a day case and potentially outpatient setting.
- Procedure can be carried out in secondary care as opposed to tertiary care.

- Minimal training required.

6 Insights from the NHS

Care pathway

Non-users report that they would initially use Optilume in a secondary care theatre with general anaesthesia. Once they have gained experience, they plan to use it with sedation or local anaesthesia as a day case, outpatient setting or in a radiology suite if possible. The user has concerns about tolerability, accuracy, and reproducibility of results with local anaesthesia alone.

One contributor suggested that once they have experience, they may fill the balloon with saline rather than contrast media avoiding the need for radiography for simple procedures. This would benefit patients because it would reduce radiation exposure for health care professionals and patients, and it gives more options for treatment rooms.

All contributors are planning to introduce Optilume differently into their pathway. Some aim to offer it first line whereas others plan to use it for recurrent bulbar strictures as an alternative option to repeat dilatation or urethroplasty.

Patient selection

Patient selection for Optilume varies between contributors. Some of the criteria include:

- Urethral bulbar strictures less than or equal to 3cm in length. The user explained it is because the maximum balloon length is 5cm. It is preferred to have the balloon 1cm either side of the stricture to ensure best results, limiting this procedure to the treatment to 3 cm strictures.
- have had 3 or less previous treatments.
- where urethroplasty is not suitable.

- where self-dilation is not reducing stricture recurrence or is not an option for the patient

Clinician confidence

All contributors said the lack of long-term evidence presents uncertainties about stricture recurrence and complication rates. Because of this they are unable to compare Optilume with other treatments.

Contributors are interested in the treatment outcomes offered after Optilume. They are interested in whether the drug would have a positive or negative impact on carrying out subsequent treatments and their stricture recurrence rate. Similarly, contributors would also like to see data when Optilume is offered first rather than second line.

One contributor reported some urologists and patients may be reluctant to use new technologies without long term evidence available. When stents were first introduced for urethral the contributor reports long term data showed multiple complications in some patients.

Commissioning

All the contributors have submitted or will be submitting a business case to their trust for adopting Optilume. Once information is gathered for a business case approval is sought from management and committees. This process varies between trusts. Some contributors have identified this can be time consuming and a barrier. One contributor reported that if a new technology could release theatre capacity this would help long waiting lists. Similarly, technology that needs a local rather than general anaesthesia is favoured because it is usually more cost effective.

Resource impact

Initial cost of Optilume may be higher compared to urethral dilation or urethrotomy but all contributors said if it prevents the frequency and number of further treatments, especially urethroplasty, it may be cost saving. If it reduces the need for patients to self-dilate, especially those not suitable for other treatments, it may be cost saving. This is by reducing the cost of specialist nurse review and equipment such as single

use catheters required to self-dilate. Contributors stated that reducing the disposal of this equipment would also have a positive environmental impact and may also have a positive impact on patient quality of life.

Training

The company offer free training which includes:

- Online education program reviewing existing treatment options and Optilume. The topics include clinical data review of existing treatment options, Optilume mode of action, indication and patient selection, and a clinical review of the Optilume study series data with a short multiple choice question assessment for knowledge check.

- Peer to peer training at an experienced Optilume user centre (if requested). Usually a one-day training event where the urologist shadows an experienced Optilume user performing the procedure, is introduced to the clinical resources required, and discusses the clinical data and real-world experience.

All contributors agree trained consultants in urology can use Optilume with minimal training as they are experienced in endoscopic techniques for dilation of urethral strictures.

Patient experience

The user reports no drug or balloon dilatation specific side effects, such as a headache or urethral injury, after using Optilume on 10 patients since June 2021 and none of the patients have been required to self-dilate yet.

Two contributors said research shows there is possibly increased short term discomfort for the patient post procedure, but this may not deter most patients because the reported benefits outweigh the side effects. The user reports post procedure discomfort and symptoms with Optilume is like that with standard dilatation procedures.

Contributors report patients may prefer Optilume over other treatments as it may reduce stricture recurrence and need for further treatment, including self-dilation.

Compared to urethroplasty it does not require hospital stay and has reduced recovery time.

Contributor's report some of their patients are reluctant to have urethroplasty because it is an open surgical procedure requiring general anaesthesia, the wound takes weeks to heal and requires 2 nights stay in hospital. Patients are often catheterised for 2 weeks post procedure and are recommended to take at least 2 weeks off work to recover at home. Contributors added the increased risk of oral numbness (if a buccal mucosal graft is taken for augmentation) and erectile problems can add to the patient's reluctance.

Another contributor added Optilume would benefit patients who are not suitable for urethroplasty. This is because they may have comorbidities where this is contraindicated, or their stricture may not be suitable for reconstruction.

Patient safety

Most contributors agree the risks and complications would be like other balloon dilation done with cystoscopy such as infection and bleeding. One contributor added the Optilume procedure could potentially damage the urethral lining and cause a further stricture if too much pressure was caused by the balloon, but they are not aware of any data to support this risk.

Contributors were not concerned with using paclitaxel for recurrent bulbar urethral strictures.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT565 Optilume for anterior urethral strictures

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Laborie Medical Technologies
Submission date	10th December 2021
Regulatory documents attached	CE Certification (Full Quality Assurance System, EC Design Examination, Annex), Declaration of Conformity, Instructions For Use, Sample Product Labels, Authorised Representative Certificate of CE Registration) 1434-MDD-033_2021-EC Design-sgn.pdf 1434-MDD-033_2021 Annex-sgn.pdf 1434-MDD-034_2021-Quality Assurance-s EMEA Optilume IFU.pdf RA1003 rD Declaration of Confor CE labels Combined.pdf MDSS Certificate of CE Registration.pdf
Contains confidential information	Yes

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Men, 18 years of age and over, with recurrent bulbar urethral strictures equal to or less than 3 cm in length	Men ≥18 years of age with bothersome urinary symptoms associated with recurrent urethral stricture disease for a single, tandem or diffuse anterior urethral stricture of ≤3 cm in length	Aligns to Optilume® indications for use as stated in the IFU documentation (page 4)
Intervention	Optilume®	Enter text.	Enter text.
Comparator(s)	Urethral dilation (S-curve dilators, Rigid rod dilators (metal or plastic)) dilation, Urethrotomy (Steel blade mounted on a urethroscope), Urethroplasty	Enter text.	Enter text.
Outcomes	Stricture free rate, Rate of reintervention procedures, Time to treatment failure (time until additional stricture treatment is required), Qmax (Peak Flow Rate) as measured by uroflowmetry, International Prostate Symptom Score, Post-void residual (PVR) urine volume, Device-related adverse events	Stricture free rate, Rate of reintervention procedures, Time to treatment failure (time until additional stricture treatment is required, including self-catheterisation), Qmax (Peak Flow Rate) as measured by uroflowmetry, International Prostate Symptom Score, Post-void residual (PVR) urine volume, Device-related adverse events	A patient who must self-catheterise to manage symptoms should be considered as to requiring additional treatment to manage their disease. ROBUST studies included self-catheterisation as an additional treatment
Cost analysis	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	Enter text.	Enter text.

	between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.		
Subgroups to be considered	None identified	Enter text.	Enter text.
Special considerations, including issues related to equality	Optilume® is intended for men with recurrent bulbar urethral strictures. These can be caused by injury to the penis, surgery or infection. Some people may not identify as men but have a penis. Urethral strictures become more common in people over 55. Sex, gender reassignment and age are protected characteristics under the Equality Act (2010).	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Optilume® Urethral Drug Coated Balloon
Approved name	Optilume®
UKCA/ CE mark class and date of authorisation	CE 1434 Class III (Rule 13) Date of authorisation: 14/01/2021

Version(s)	**Launched**	**Features**
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Rapid and sustained improvement in symptoms and urinary flow	ROBUST I[1] ROBUTS II[2] ROBUST III[3]	Published outcomes show immediate and sustained improvement in IPSS, USS-PROM, and Qmax
Effective minimally invasive treatment	ROBUST III[3]	Optilume DCB showed superiority to standard of care endoscopic management
Reduces the need for retreatments or invasive surgical procedures	ROBUST III[3]	Optilume DCB had significantly lower rate of retreatment
Reduces the need for self-catheterisation management	ROBUST III[3]	Optilume DCB had significantly lower rate of retreatment
Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty		Minimally invasive endoscopic treatment vs open surgical procedure
Rapid return to normal daily living and improved quality of life	ROBUST III[3]	ROBUST I, ROBUTS II, and ROBUST III studies
Preservation of sexual function	ROBUST I[1] ROBUST II[2] ROBUST III[3]	No treatment related sexual function AEs, no change in function per IIEF questionnaire
Reduced risk of hospital acquired infection		Wound infection rates in urethroplasty ~4%, no wound created for endoscopic treatment
Reduced waiting times		Limited surgeons trained in urethroplasty, while general urologist can perform Optilume procedure

System benefits		
Reduced burden of repeat procedures	ROBUST I[1] ROBUST II[2] ROBUST III[3]	
Reduced re-admission rates (elective or non-elective)	ROBUST I[1] ROBUST II[2] ROBUST III[3]	ROBUST III lower repeat treatment
Reduced risk of hospital acquired infection		Wound infection rates in urethroplasty ~4%, no wound created for endoscopic treatment
Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources	ROBUST I[1] ROBUST II[2] ROBUST III[3]	Less repeat interventions
Reduced number of post-discharge follow up visits, providing physician resource saving		
Reduced number of post-operative complications		Minimally invasive endoscopic treatment vs open surgical procedure
Reduction in waiting list by offering a minimally invasive alternative to patients who have suffered recurrence awaiting open surgical consultation		Limited surgeons trained in urethroplasty, while general urologist can perform Optilume procedure
Minimal requirement for training of healthcare professionals		
Cost benefits		
Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources	Enter text.	Enter text.
Reduces the need for self-catheterisation management	ROBUST III[3]	Enter text.
Reduces the need for retreatments or invasive surgical procedures	ROBUST I[1] ROBUST II[2] ROBUST III[3]	
Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty		
Reduced risk of hospital acquired infection		
Reduced waiting times		

Reduced re-admission rates (elective or non-elective)		
Reduced number of post-discharge follow up visits, providing physician resource saving		
Reduction in waiting list by offering a minimally invasive alternative to patients who have suffered recurrence awaiting open surgical consultation		
Sustainability benefits		
Reduced burden of repeat procedures		Enter text.
Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources	Enter text.	Enter text.
Reduces the need for self-catheterisation management		
Minimal requirement for training of healthcare professionals		
Reduced number of post-discharge follow up visits, providing physician resource saving		
Reduced waiting times		

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The Optilume® Urethral Drug Coated Balloon (DCB) is an innovative technology for the treatment of anterior urethral stricture in adult males ≥18 years old. It is novel compared to existing endoscopic standard of care as the technology incorporates urethral balloon dilation to dilate the urethral stricture, with an anti-proliferative drug (Paclitaxel) that is pre-coated onto the balloon, which is delivered to the inner urethral wall during the procedure to prevent the fibrotic tissue response associated with urethral stricture recurrence. Paclitaxel is circumferentially delivered along the length of the urethral stricture to inhibit new scar tissue growth that is commonly associated with urethral stricture recurrence.

The procedure itself follows the established practices for urethral dilation, with the ability to be performed under direct visualization, compatible with existing hospital resources, and can be performed in an outpatient setting under local anaesthesia or conscious sedation removing the requirement for inpatient stay, general anaesthesia and theatre time.

The Optilume DCB procedure can also be performed with rigid cystoscopy or with flexible cystoscopy in a clinic setting or day-case environment. Fluoroscopy is not a must at the time of the procedure as long as the stricture length and location has been adequately assessed and confirmed preoperatively through appropriate diagnostic investigation. The Optilume DCB is passed over a guidewire under direct vision, placed in position along the length of the US, inflated using normal saline/sterile water with a pressure inflation device (provided with the Optilume DCB) mechanically dilating the urethral stricture. The Optilume DCB remains in-situ across urethral stricture for a minimum of 5 minutes under pressure to facilitate drug uptake to the target tissue. Once adequate inflation time and urethral dilation have been achieved, the Optilume DCB is then deflated, removed, and safely disposed of via standard biowaste disposal protocols. A catheter may be placed at the discretion of the clinician and can be administered post-operatively as is seen in existing standard of care treatments.

Post-operative side effects are similar to current endoscopic standard of care – urethral dilation and direct vision internal urethrotomy (DVIU) – with the risk of urethral stricture recurrence reduced by using Optilume DCB as clinical evidence has shown the treatment to further reduce the need for further reintervention[1,2,3].

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

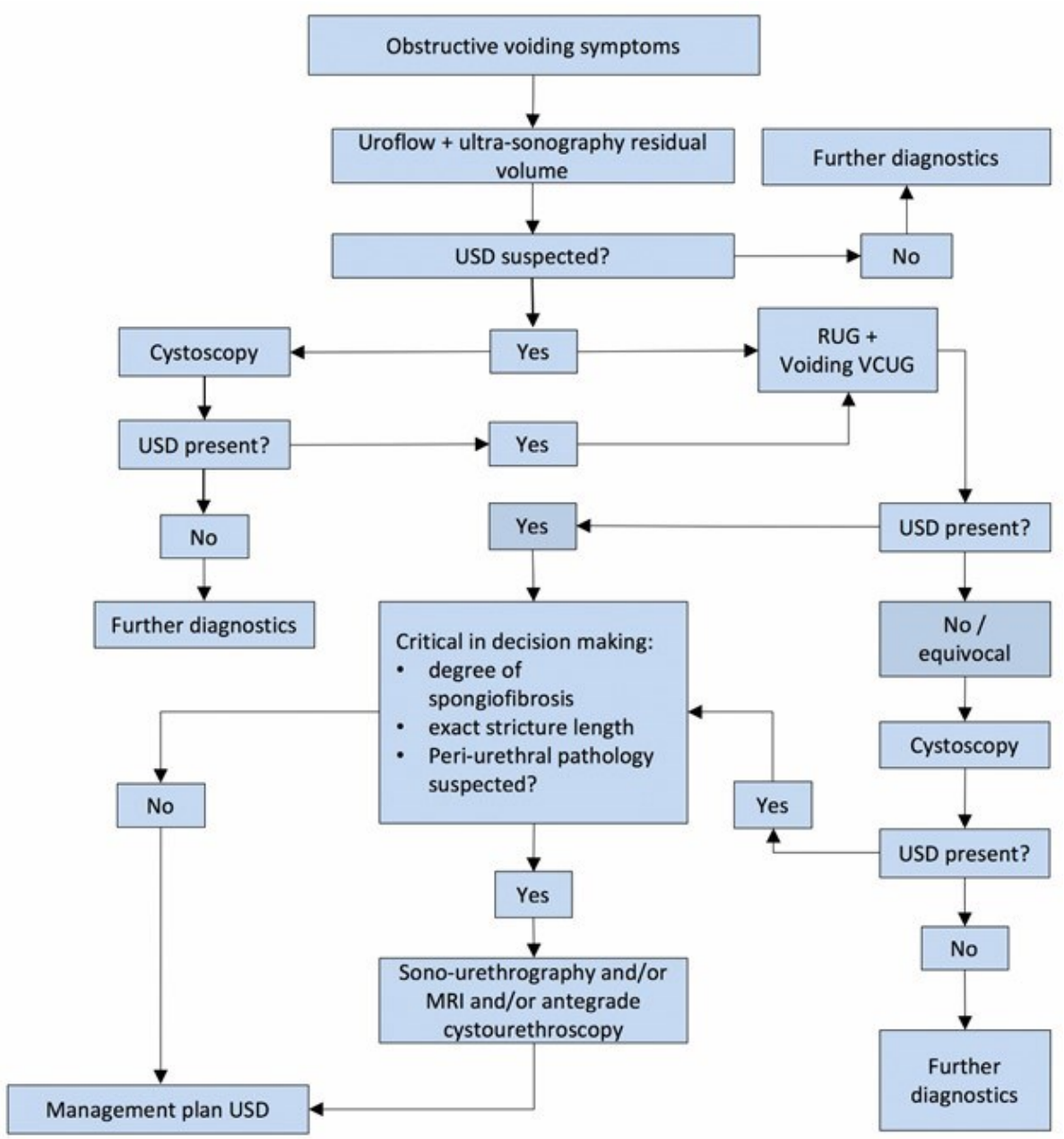
Adoption of the Optilume DCB could result in fewer requirements of repeat procedures in a population of adult males >18 years of age suffering from anterior urethral stricture. As a result of no, or less frequent, requirement of retreatment, this could lead to:

- Fewer consumables being used than is needed in standard care (DVIU or urethroplasty, or both)
- Fewer follow up clinic visit requirements
- Reduced requirement for catheterisation to manage recurrent symptoms associated with existing endoscopic standard of care

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

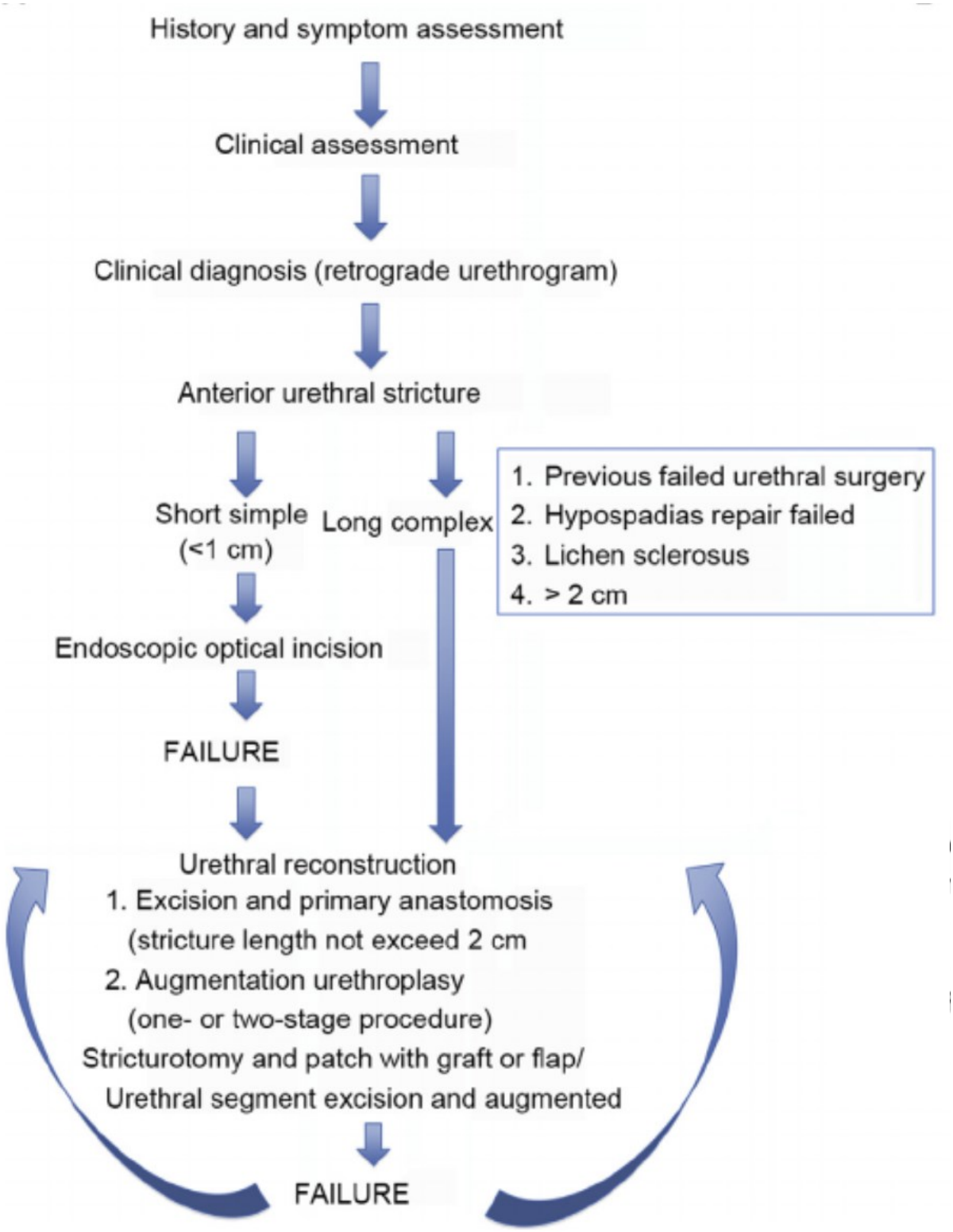
Diagnostic flowchart of patients with suspected urethral stricture disease



MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cysto-urethrogram

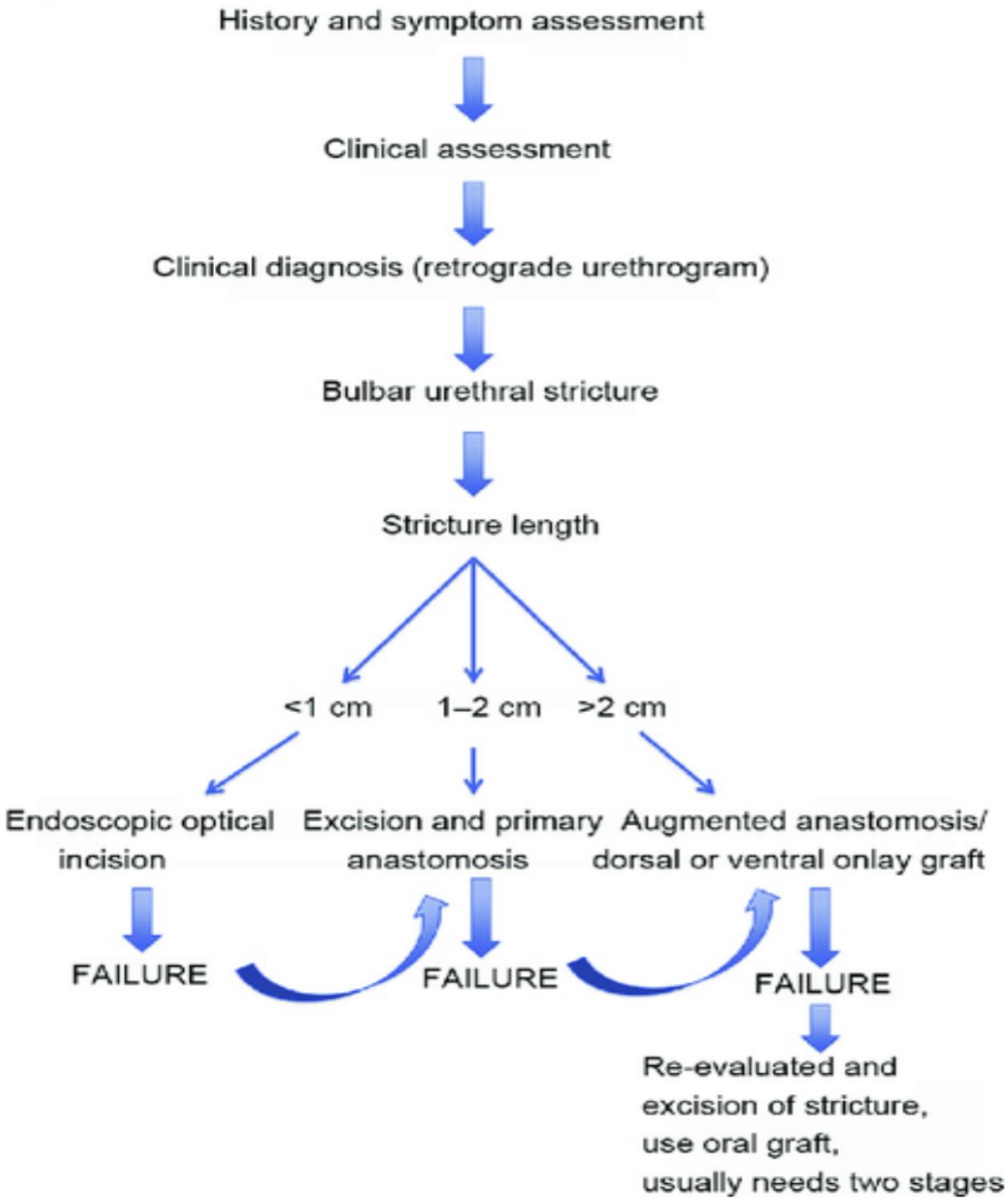
EAU Guidelines for Urethral Stricture[4]

Algorithm of anterior urethral stricture treatment



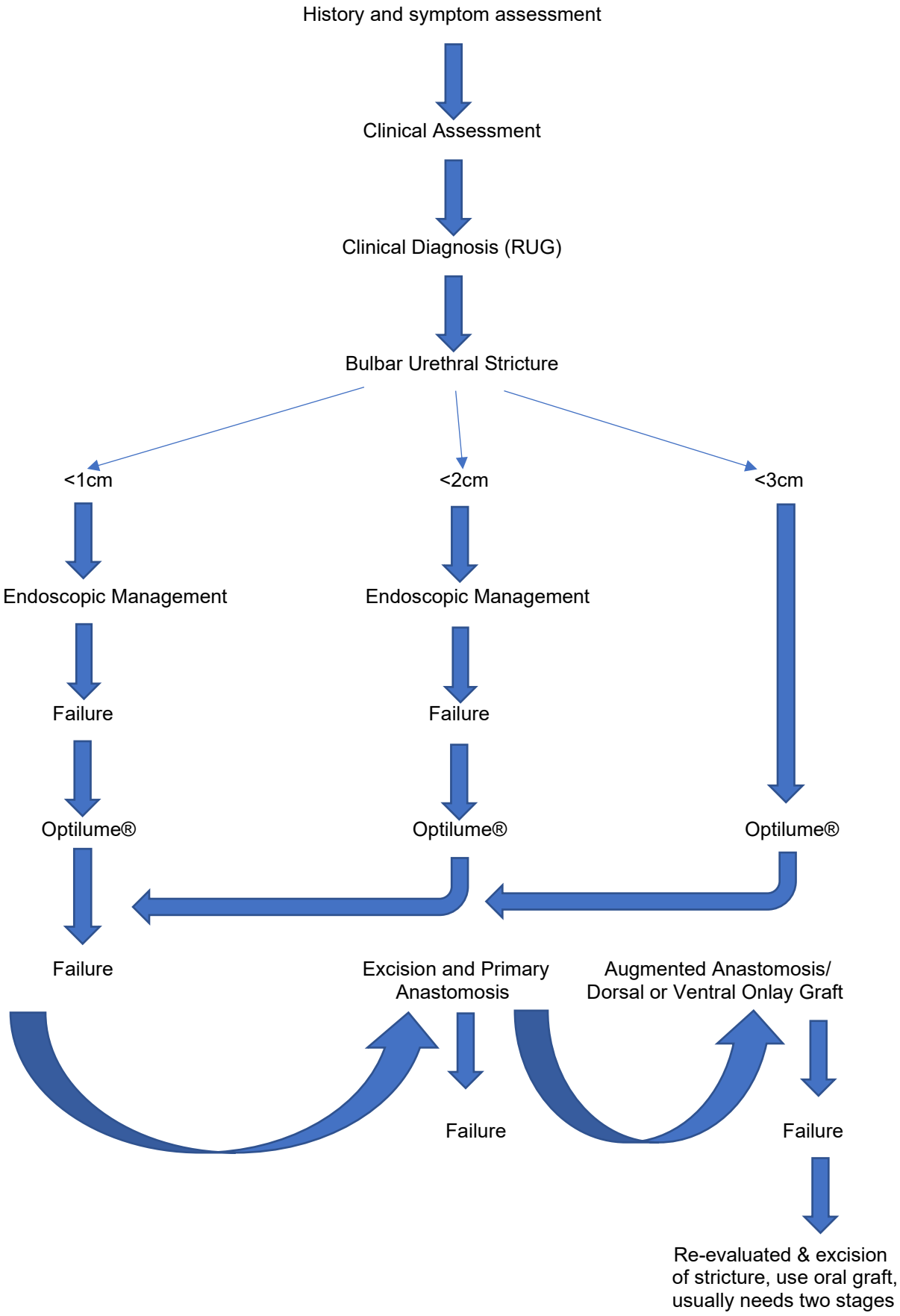
Simsek et al[5]

Algorithm of bulbar urethral stricture treatment



Simsek et al[5]

Proposed algorithm of bulbar urethral stricture treatment inc. Optilume®



First line treatment for anterior urethral stricture, following appropriate clinical assessment and diagnostics, is typically endoscopic management via dilation (non-drug coated balloon or rigid rod) or, more commonly, direct vision internal urethrotomy (DVIU). Clinical evidence, and recommended guidelines[4], state there is no statistically significant difference between the success of urethral dilation and DVIU, at 24 months follow up.[6]

Both treatments are associated with a high failure rate, requiring repeated treatment. Multiple treatments of the same stricture can lead to progressively worse outcomes over time.[7] After a third endoscopic treatment, the failure rate approaches 75% by 6 months and 100% by two-years post-treatment. Subsequent recurrences can lead to a chronic stricture state requiring self-catheterisation and/or repeat treatments.

Men undergoing urethroplasty in the UK have had a median of three and five previous endoscopic urethral stricture treatments[8] for, thus resource utilisation and costs associated with carrying out these multiple procedures prior to urethroplasty are a prolonged and significant issue. Urethroplasty is a highly invasive procedure, taking an average of two to three hours operative time[9] and an associated length of stay of two days on average.[10] Patients are required to be catheterised for two to three weeks post-surgery.[11] Urethroplasty is a specialist procedure, only offered in centres that have urologists with specialist training.

Three-year data from the ROBUST I clinical trial highlighted 77% (33/43) of men who had failed multiple (>1) prior endoscopic treatments were free from repeat intervention (including self-catheterisation) at 3 years following their procedure[1]. This clinical data has shown a 176% increase in urinary flow rate and a 65% decrease in symptoms such as frequency of urination, incomplete bladder emptying, weak stream, straining, and waking at night to urinate from baseline.[1]

One-year data from the ROBUST III Randomised Control Trial (RCT) versus standard of care (dilation/DVIU) highlighted 83% of men who had failed multiple (>2) prior endoscopic treatments were free from repeat intervention 1 year following their procedure[3]. This clinical data has shown a 104% increase in urinary flow rate and a 59% decrease in symptoms such as frequency of urination, incomplete bladder emptying, weak stream, straining, and waking at night to urinate from baseline.[3]

As part of an alternative pathway including the technology, it is proposed to treat patients presenting with anterior urethral strictures <3cm with the Optilume DCB as a standalone treatment or as an adjunctive therapy to existing endoscopic management of urethral stricture.

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Non-drug coated balloon dilation is accepted as existing practice as part of urological services offered by the NHS. The company (Laborie) also offer a training program to meet the needs of healthcare professionals if required. This generally follows this pattern:

- Online learning modules for understanding of existing treatment options and the published clinical data for these options, Optilume mechanism of action, indications and patient selection and the published clinical data available
- Should healthcare professionals request, the company offer peer to peer education whereby the healthcare professional can attend an experienced hospital familiar with the technology and procedure to witness best practice and discuss at a clinical level. This is generally a one-day education day where the attendee will witness procedures, be presented with the published clinical data, discuss patient selection, and understand further the resources required to perform the procedure in a clinical working environment

All training and education is provided by Laborie free of charge.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		2,796
Number of studies identified as being relevant to the decision problem.		17
Of the relevant studies identified:	Number of published studies (included in table 1).	15
	Number of abstracts (included in table 2).	1
	Number of ongoing studies (included in table 3).	1

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Optilume Urethral DCB						
Journal Article	Elliott SP, 2021, J Urology[3]	Prospective, randomized, multi-center (ROBUST III)	Recurrent anterior urethral stricture, average ~1.6cm in length, 3.2 prior dilations	Optilume DCB	Dilation/DVIU	Recurrence Retreatment Symptom scores Peak flow rate
Journal Article	Mann RA, 2021, Can Urol Assoc J[12]	Prospective, single arm, multi-center (ROBUST I 2 year)	Recurrent anterior urethral stricture, average 0.9cm length, 1.7 prior dilations	Optilume DCB	N/A	Recurrence Retreatment Symptom scores Peak flow rate
Journal Article	Virasoro R, 2020, Can Urol Assoc J[13]	Prospective, single arm, multi-center (ROBUST I 1 year)	Recurrent anterior urethral stricture, average 0.9cm length, 1.7 prior dilations	Optilume DCB	N/A	Recurrence Retreatment Symptom scores Peak flow rate
Endoscopic Management						
NIHR Report	Pickard R, 2020, Health Technology Assessment[14]	Prospective, randomized, multi-center (OPEN RCT)	Recurrent anterior urethral stricture, average ~2cm in length, 1.8 prior dilations	Urethroplasty (n=109 randomized, n=69 treated)	DVIU (n=112 randomized, n=90 treated)	Symptom Scores Peak flow rate Recurrence Retreatment
Journal Article	Steenkamp JW, J Urol, 1997[6]	Prospective, randomized, single center	Mixed recurrent and primary (30% recurrent), 2.3cm stricture length	DVIU (n=104)	Dilation (n=106)	Recurrence
Journal Article	Heyns CF, J Urol, 1998[7]	Prospective, randomized, single center	Recurrent anterior urethral strictures, 2.3cm stricture length	DVIU (n=104)	Dilation (n=106)	Recurrence

Journal Article	Azab SS, Scand J Urol, 2020 [15]	Prospective, randomized, single-center	Primary anterior urethral strictures, average 1cm length	Amplatz renal dilator (n=44)	DVIU (n=44)	Symptom scores Peak flow rate Recurrence
Journal Article	Cecen K, Urol Int, 2014[16]	Prospective, randomized, single-center	Primary anterior urethral strictures, average 1.3cm length	Laser urethrotomy (n=70)	DVIU (n=66)	Recurrence Peak Flow Rate
Journal Article	Guo FF, World J Urol[17]	Prospective, single arm, single center	Primary anterior urethral strictures, 2.6cm length	Laser urethrotomy (n=238)	N/A	Recurrence Symptom scores Peak flow rate
Journal article	Jordan GH, J Urol, 2013[18]	Prospective, randomized, multi-center	Recurrent anterior urethral strictures, 2.7cm length, average 2 prior dilatoins	MemokathTW44 (n=63)	DVIU (n=29)	Recurrence Symptom scores Peak flow rate
Journal Article	Isen K, Int Urol Nephrol, 2015[19]	Prospective, single arm, single center	Primary urethral strictures, average 0.7cm length	DVIU (n=21)	N/A	Peak flow rate Retreatment
Journal Article	Pansadoro V, J Urol, 1996[20]	Retrospective, single arm, single center	Primary anterior urethral stricture, average length 1.6cm	DVIU (n=224)	N/A	Recurrence
Journal Article	Santucci R, J Urol, 2010[21]	Retrospective, single arm, single center	Recurrent anterior urethral stricture, average length of 1.5cm	DVIU (n=76)	N/A	Recurrence
Urethroplasty						
Journal Article	Hoy NY, Urology, 2013[22]	Prospective, single arm, single center	Recurrent anterior urethral stricture, average length 4.9cm	Dorsal onlay buccal mucosal graft urethroplasty (n=163)	N/A	Recurrence
Journal Article	Aldaqadossi H, Int J Urol, 2014[23]	Prospective, randomized, single center	Mostly recurrent anterior stricture, average ~4.5cm length, average 1.7 prior dilations	Dorsal onlay bucceal mucosal graft urethroplasty (n=25)	Dorsal inlay buccal mucosal graft urethroplasty (n=22)	Recurrence

Journal Article	Elkady E, Urology, 2019[24]	Prospective, randomized, single center	Recurrent anterior urethral strictures, average length 3.2cm	Standard urethroplasty (n=25)	Muscle/nerve sparing urethroplasty (n=25)	Recurrence
Journal Article	Erickson, BA, Urology, 2014[25]	Prospective, single-arm, multi-center	Anterior urethral strictures	Urethroplasty	N/A	Recurrence

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Published Abstract	Elliott SP, 2021, AUA[1]	Prospective, single arm, multi-center (ROBUST I 3 year)	Recurrent anterior urethral stricture	Optilume DCB	N/A	Recurrence Retreatment Symptom scores Peak flow rate

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Journal Article (in press)	DeLong J, SIU Journal, 2022[2]	Prospective, single arm, multi-center	Recurrent anterior urethral strictures, average 2.1cm length, 4.1 prior dilations	Optilume DCB	N/A	Recurrence Repeat Intervention Symptom scores Peak flow rate

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
ROBUST I	Study Population A total of 53 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture	Text

	length was 0.9cm, while average number of prior dilations was 1.7. The first 25 subjects were treated with a 24F drug coated balloon, and the last 28 subjects were treated with a 30F drug coated balloon. Efficacy Outcomes Subjects were assessed for anatomic success at 6 months and 12 months via the ability to pass a 16F flexible cystoscope. Success was achieved in 75% (36/48) of subjects at 6 months and 77% (36/47) at 12 months. Symptom scores (IPSS, USS-PROM) showed immediate improvement that was sustained through 3-year follow-up. A total of 67% of subjects exhibited functional success at 3 years, defined as at least a 50% improvement from baseline in IPSS score without repeat intervention. Freedom from repeat intervention was 83% at 1 year, 81% at 2 years, and 77% through 3 years. Only 2 of 24 (8.3%) subjects treated with a 30F DCB received repeat treatment at 2 years. Safety Outcomes Adverse events reported through 2 years included urinary tract infection (17%), fever (8%), dysuria (7%), and acute urinary retention (6%).	
ROBUST II	Study Population A total of 16 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture length was 2.1cm and the average number of prior dilations was 4.1. Subjects were treated with a mix of 30F and 24F balloons based on urethrogram measurements, with the majority (88%) utilizing 30F. Efficacy Outcomes Anatomic success was measured at 6 months post-procedure, with 11 of 15 subjects (73%) exhibiting success. Symptom scores (IPSS and USS-PROM) showed immediate improvement from baseline that was sustained through 1 year. Qmax also showed immediate improvement sustained through 1 year. Safety Outcomes	Text

	Post-procedure adverse events possibly related to the Optilume DCB included 2 subjects with hematuria (12.5%), 1 bladder spasm (6.3%), and 1 acute urinary retention (6.3%)	
ROBUST III	Study Population A total of 127 subjects with recurrent anterior urethral strictures were randomized 2:1 to receive the Optilume DCB (n=79) or dilation/DVIU (n=48). Average stricture length was 1.7cm, and subjects had an average of 3.6 prior dilations. The majority of subjects (~90%) received a 30F DCB. Control group strictures were treated with standard dilation (~75%) or DVIU (~25%). Efficacy Outcomes Anatomic success was measured at 6 months post-procedure, with 75% of DCB subjects exhibiting success compared to 27% in the Control arm. This treatment effect was consistent among subgroups, including stricture length (≥2cm vs <2cm) and prior dilations. Outcomes were not statistically different between dilation and DVIU in the Control group, with DVIU having an anatomic success rate of 17%). IPSS and Qmax improved in both arms immediately post-procedure. These improvements were sustained through 1 year in the Optilume DCB group, while they returned to approximately baseline levels in the Control group by 1 year. Kaplan Meier estimates of freedom from repeat intervention at one year (395 days) were 83% in the Optilume arm and 21.7% in the Control arm. Safety Outcomes Adverse event rates were generally similar between arms, with a non-statistically significant trend toward higher rates of mild hematuria and dysuria in the Optilume group (11.2% vs 2.1% for both). These events did not require treatment. The rate of urinary tract infection was 8.9% in the Optilume arm and 12.5% in the Control arm.	Text
The OPEN RCT	Study Population The OPEN RCT enrolled subjects with recurrent bulbar urethral strictures. Subjects were randomized to receive urethroplasty or urethrotomy. Baseline characteristics included an average stricture length of 2.0cm in the urethroplasty group and 1.7cm in the urethrotomy group. Patients had undergone an average of 1.9	Text

	or 1.8 prior urethrotomies at the time of the index procedure for urethroplasty and urethrotomy groups, respectively. A total of 71 of 108 (66%) of subjects randomized to urethroplasty underwent the surgery, while 90 of 112 (83%) of those randomized to urethrotomy underwent the procedure. Only 47.2% of subjects randomized to urethroplasty completed 24-month questionnaires, while 50.9% randomized to urethrotomy completed 24-month questionnaires. Efficacy Endpoint: The primary efficacy endpoint was the Area Under the Curve (AUC) over 24 months for symptom scores according to the USS-PROM questionnaire (0 to 24, higher being more symptomatic). The AUC for urethroplasty was 7.4 ± 3.8 at 24 months, while the AUC for urethrotomy was 7.8 ± 4.2. The outcome was not significantly different between arms. Freedom from repeat intervention was seen in 78 of 93 (84%) men in the urethroplasty arm and 75 of 104 (72%) in the urethrotomy arm. Initiation of intermittent self-dilation was not considered a repeat intervention. Recurrence, identified as repeat intervention or significant evidence of stricture recurrence (symptoms or flow), occurred in 19 of 93 urethroplasty patients (20.4%) and 39 of 104 (37.5%) in the urethrotomy arm. Freedom from recurrence was therefore 79.6% and 62.5% respectively. Safety Endpoints Reported complications over the course of the study are summarized by adding those reported in the perioperative period to those during follow-up. Complications included mouth pain (13.9%), urinary tract infection (8.0%), erectile dysfunction (5.0%), wound pain (5.0%), wound infection (4.0%), bladder spasm (2.0%), and urethrocutaneous fistula (1.0%) in the urethroplasty arm. Urethrotomy complications included urinary tract infection (5.8%), mouth pain (5.7%), erectile dysfunction (1.9%), and wound infection (1.9%).	
Steenkamp, J Urol, 1997	Study Population Subjects presenting with anterior urethral strictures were randomized to receive dilation with bougies/sounds (n=106) or	

	DVIU (n=104). Approximately 30% of subjects in each arm had received a prior dilation of the study stricture. Average stricture length was 2.4cm in the dilation arm and 2.2cm in the urethrotomy arm. Strictures were in the bulbar urethra in 53% of dilation subjects and 67% of urethrotomy subjects. Subjects were followed every 3 months for one year, and annually thereafter. Assessments for stricture recurrence included urethrogram and/or passage of a 16F catheter. Efficacy outcomes Freedom from stricture recurrence was noted in approximately 50% of subjects at 12 months, and was maintained above 40% through 4 years. Rate of recurrence was maximal at 6 months post-treatment and was not different between arms. Strictures >4cm in length had the worst outcomes. Safety Outcomes Adverse events were not reported	
Heyns, J Urol, 1998	Study Population Population is the same as reported by Steenkamp (J Urol, 1997). Further analysis was conducted evaluating performance after repeat dilation/urethrotomy. Follow-up included on 163 of original 210 subjects. Efficacy Outcomes Freedom from stricture recurrence was evaluated through 48 months follow-up and was not different between dilation and urethrotomy. Repeat urethrotomy/dilation performed progressively worse, with higher recurrence rates and faster time to recurrence for each subsequent endoscopic treatment. Subjects undergoing a third dilation/urethrotomy for recurrent stricture had a 20% success rate at both 6 and 12 months, compared to an approximately 55% success rate for a second dilation/urethrotomy, and approximately 70% for a single dilation/urethrotomy at 12 months. Long-term success for 2 or 3 dilations was 0%. Safety Outcomes Adverse events were not reported	Text

Jordan, J Urol, 2013	Study Population The study evaluated the Memokath 044TW urethral stent against standard of care endoscopic dilation/urethrotomy in the treatment of recurrent bulbar strictures, randomized in a 2:1 fashion. A total of 63 subjects were randomized to receive Memokath, 29 randomized to Control. Average stricture length was 2.7cm for Memokath and 2.7cm for Control. Subjects in both arms had an average of 2 prior interventions for the study stricture. Efficacy Outcomes Stricture recurrence was measured by the ability to pass a calibrated 16F cystoscope through the treated area during follow up. Freedom from recurrence was noted in approximately 80% of subjects in the Memokath arm and 40% of subjects in the Control arm at 6 months. This figure decreased to 45% and 20% in Memokath and Control, respectively, at 12 months. In the entire study period (15 months), 3 of 27 (11.1%) of subjects were free from recurrence in the Control arm. IPSS and Qmax showed immediate improvement in both arms post procedure. Safety Outcomes Bacteriuria/UTI was noted in 49% of subjects in the Memokath group and 7% in the Control group. The Memokath group also experienced high rates of incontinence (19%) and hematuria (16%).	
Hoy NY, Urology, 2013	Study Population A total of 163 underwent open reconstruction of bulbar urethral strictures utilizing a buccal mucosal graft in a dorsal onlay fashion. Follow-up data was collected prospectively at 3 weeks (Foley removal), 6 months (cystoscopy), and 12 months if findings of concern at 6 months. Mean stricture length was 4.9cm and 93% had at least one prior dilation. Efficacy Outcomes Freedom from stricture recurrence was identified in 157 of 163 patients (97%) at 6 months. Safety Outcomes	

	Post-void dribbling was noted in 68 of 163 subjects (41.7%), UTI noted in 6 (3.7%), ED in 5 (3.1%), and testicular pain in 17 (10.4%).	
Cecen K, Urol Int, 2014	Study Population A total of 136 male patients with urethral stricture were randomized between PlasmaKinetic urethrotomy (n=70) vs cold-knife urethrotomy (DVIU, n=66). The majority of strictures (57%) were in the bulbar urethra and none had received prior dilations/urethrotomy. Average stricture length was 1.3cm. Follow up was conducted at 3 months, 9 months, and 18 months. Efficacy Outcomes Stricture recurrence was monitored by uroflowmetry, with subjects exhibiting Qmax <12mL/sec having urethrogram/cystoscopy to verify stricture recurrence. In the PlasmaKinetic group, 14% of subjects exhibited a recurrence at 9 months while 37% had recurrence at 18 months. The DVIU group had 30% and 33% recurrence rates at 9 and 18 months, respectively. Measured Qmax at 3 months was 16.1 mL/sec in PlasmaKinetic group vs 15.2 mL/sec in the DVIU group. Safety Outcomes Adverse events were not reported.	
Azab SS, Scan J Urol, 2020	Study Population A total of 88 subjects with verified strictures were randomized to Amplatz dilators (n=44) or DVIU (n=44). Strictures were primarily located in the bulbar urethra (45% and 41% for Amplatz and DVIU. Average stricture length in each group was 1cm, and all were primary (i.e. no prior interventions). Follow-up continued through 12 months. Efficacy Outcomes Symptom scores measured via IPSS improved from 21 at baseline to 16 and 18 at 12 months for Amplatz and DVIU, respectively. Qmax improved from 8mL/sec at baseline to 18 and 22 mL/sec for Amplatz and DVIU, respectively, at 12 months. No recurrence was noted in either arm through 12 months, however this was not clearly defined. Safety Outcomes	

	The Amplatz group showed a 16% rate of mild hematuria, while the DVIU group had 11% of patients develop intra-operative bleeding and 7% showing urethral extravasation.	
Elkady E,	Study Population A total of 60 patients were randomized to standard urethroplasty (n=30) or muscle/nerve sparing technique urethroplasty (n=30). Mean stricture length was 3.3cm and 3.5cm for these groups, respectively. Efficacy Outcomes Success reported as freedom from repeat intervention, which was achieved in 88% of the standard urethroplasty group and 92% of the muscle-sparing group. Safety Outcomes Subjects in the standard urethroplasty group experienced complications including ejaculatory dysfunction (40%), post-void dribbling (36%), wound infection (4%), and urethral extravasation (4%). Subjects in the muscle sparing group experienced ejaculatory dysfunction (8%), post-void dribbling (4%), and wound infection (4%).	
Isen K, Int Urol Nephrol, 2015	Study Population A total of 21 subjects with short (<1cm) primary urethral strictures were treated with DVIU utilizing endoscopic scissors. Mean stricture length was 0.7cm, with no prior dilations. Efficacy Outcomes Stricture recurrence as measured by urethrogram was 0% at 3 months. Mean follow-up was 8 months, with 3 of 21 (14%) requiring repeat DVIU in that time period. Qmax increased from 8mL/sec at baseline to 19.4mL/sec at 3 months. Safety Outcomes Urinary tract infection was reported in 2 of 21 subjects (9.5%).	
Guo FF, World J Urol, 2010	Study Population A total of 238 subjects were treated with thulium laser urethrotomy. Stricture length was 2.6cm on average, with no detail given on prior interventions. Efficacy Outcomes	

	Stricture recurrence occurred in 43 of 238 subjects (18%) through 6 month follow-up. IPSS improved from 28 to 5.3 at 6 months, while Qmax improved from 3.2mL/sec to 19.2mL/sec. Safety Outcomes Seven patients (3%) experienced incontinence (type not specified).	
Aldaqadossi H, Int J Urol, 2014	Study Population Subjects were prospectively randomized to receive dorsal onlay buccal graft urethroplasty (n=25) vs dorsal inlay (n=22). Mean stricture length was 4.9cm for the onlay group and 4.4cm for the inlay group. Strictures were primarily penile (56% onlay, 55% inlay). Strictures were recurrent in 34 of 47 (72%), with an average of 1.7 prior interventions per patient/ Efficacy Outcomes Freedom from stricture recurrence was experienced in 88% in the dorsal onlay group vs 86.4% in the dorsal inlay group through 12 months. IPSS and Qmax improved postoperatively, with no timeframe given for measurements. Safety Outcomes One patient in the dorsal onlay group (4%) required blood transfusion during the surgery. Wound infections were noted in 12% and 13.6% of patients in the onlay and inlay group, respectively. Other complications included chordee (8%), extravasation (4%), and post-void dribble (16%).	
Pansadoro V, J Urol, 1996	Study Population A total of 450 subjects with anterior urethral stricture were evaluated, with 224 subjects treated with DVIU included in this series. Subjects were excluded if they had less than 5 years of follow-up. Mean stricture length was 1.6cm, with only 12% being recurrent. Efficacy Outcomes Overall success was achieved in 62% at 1 year, 46% at 2 years. Urethrotomy failed in all subjects with recurrent strictures. Stricture length >1cm was a significant predictor for recurrence,	

	with only 18% of subjects with a bulbar stricture >1cm in length having a successful outcome. Safety Outcomes Urethral bleeding occurred in 24 of 224 (10.7%), extravasation in 6 (2.7%), and chordee in 2 (0.9%).	
Erickson BA, Urology, 2014	Study Population Subjects were prospectively enrolled in a multi-institutional study with defined cystoscopic follow-up at 3 months and 12 months. No information was given on stricture characteristics, but the techniques used were excision and primary anastomosis (63.8%) and substitution (36.2%). The majority of urethroplasties being EPA indicate the stricture length was relatively short. Compliance with follow-up cystoscopy was 79.8% at 3 months and 54.4% at 12 months, indicating poor follow-up compliance. Efficacy Outcomes Stricture anatomic success was defined as the ability to pass a 16F flexible cystoscope. Success was 97.2% for EPA and 85.5% for substitution urethroplasty at 3 months. Those outcomes at 12 months were 85.5% and 77.5%, respectively. Safety Outcomes No safety outcomes were reported here.	
Santucci R, J Urol, 2010	Patient Population A retrospective chart review was conducted to review outcomes after multiple repeat DVIU procedures in non-complex anterior strictures. Average stricture length was 1.5cm in the 50 subjects in whom this data was available. Efficacy Outcomes Freedom from stricture recurrence (repeat intervention) was approximately 35% at 1 year and 30% at 2 years for those receiving only 1 DVIU. Freedom from recurrence after the third DVIU was approximately 20% at 1 year and 0% at 2 years. Safety Outcomes None listed	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

ROBUST I	
How are the findings relevant to the decision problem?	A total of 53 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture length was 0.9cm, while average number of prior dilations was 1.7. Subjects were assessed for anatomic success at 6 months and 12 months via the ability to pass a 16F flexible cystoscope. Success was achieved in 75% (36/48) of subjects at 6 months and 77% (36/47) at 12 months. Symptom scores (IPSS, USS-PROM) showed immediate improvement that was sustained through 3-year follow-up. A total of 67% of subjects exhibited functional success at 3 years, defined as at least a 50% improvement from baseline in IPSS score without repeat intervention. Freedom from repeat intervention was 83% at 1 year, 81% at 2 years, and 77% through 3 years. Only 2 of 24 (8.3%) subjects treated with a 30F DCB received repeat treatment at 2 years. In comparison, multiple endoscopic treatments of the same stricture are proven to lead to progressively worse outcomes. After a third endoscopic treatment, the failure rate is as high as 75% by 6 months and 100% by two-years post-treatment[7].
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The study is small in terms of patient numbers and was done in the Dominican Republic and Panama. Pre-dilation was a requirement as part of the design protocol in the study. Non-comparative study.

How was the study funded?	Urotronic, Inc. (the Manufacturer)

ROBUST II	
How are the findings relevant to the decision problem?	A total of 16 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB without prior-pre-dilation in 56% of the study population (N=9/16). Average stricture length was 2.1cm and the average number of prior dilations was 4.1. Anatomic success was measured at 6 months post-procedure, with 11 of 15 subjects (73%) exhibiting success. Symptom scores (IPSS and USS-PROM) showed immediate improvement from baseline that was sustained through 1 year. Qmax also showed immediate improvement sustained through 1 year.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The study is small in terms of patient numbers in a limited number of US centres. Non-comparative study and lacked a control arm.
How was the study funded?	Urotronic, Inc. (the Manufacturer)
ROBUST III	
How are the findings relevant to the decision problem?	A total of 127 subjects with recurrent anterior urethral strictures were randomized 2:1 to receive the Optilume DCB (n=79) or dilation/DVIU (n=48). Average stricture length was 1.7cm, and subjects had an average of 3.6 prior dilations. The majority of subjects (~90%) received a 30F DCB. Control

	group strictures were treated with standard dilation (~75%) or DVIU (~25%). Anatomic success was measured at 6 months post-procedure, with 75% of DCB subjects exhibiting success compared to 27% in the Control arm. This treatment effect was consistent among subgroups, including stricture length (≥2cm vs <2cm) and prior dilations. Outcomes were not statistically different between dilation and DVIU in the Control group, with DVIU having an anatomic success rate of 17%). IPSS and Qmax improved in both arms immediately post-procedure. These improvements were sustained through 1 year in the Optilume DCB group, while they returned to approximately baseline levels in the Control group by 1 year. Kaplan Meier estimates of freedom from repeat intervention at one year (395 days) were 83% in the Optilume arm and 21.7% in the Control arm.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population Effective minimally invasive treatment
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Pre-dilation was a requirement as part of the design protocol in the study.
How was the study funded?	Urotronic, Inc. (the Manufacturer)
The OPEN RCT	
How are the findings relevant to the decision problem?	The OPEN RCT represents a large-scale, multi-center randomized trial comparing endoscopic management with urethroplasty for recurrent bulbar strictures. The study encountered numerous issues during execution of the study, including slow enrolment leading to early termination/sample size adjustment. Randomization was completed well before treatment (approximately 3 months on

	average), leading to a large proportion of subjects opting to not receive their randomized therapy. Only 67% of subjects randomized to receive urethroplasty received the treatment. The authors attempt to account for this issue by only reporting results for those that received each therapy (As-Treated), however the large degree to which this population differs from the Intent-to-Treat (ITT) analysis set largely negates the benefit of randomization and introduces a high degree of bias. Lastly, follow-up was conducted remotely via mailing of questionnaires to the subjects. Subject response to questionnaires was below 50% at the 2-year timepoint. Despite the challenges identified with study design and execution, the data offer one of the only multi-institution comparative analyses of endoscopic and surgical management of urethral strictures. It appears as though symptom improvement was similar between the two therapies throughout the 24-month follow-up, with both showing immediate improvement that was generally sustained through 24 months. The low rate of questionnaire response may introduce bias, although the direction of bias is unclear (i.e., no response because feeling good or no response because unhappy with outcomes and sought treatment elsewhere). Freedom from repeat intervention was assessed via patient response to a questionnaire, so the low rate of response leads to uncertainty in the outcome. However, freedom from repeat intervention rates in the urethroplasty group were comparable to those reported in the ROBUST I trial at 2 years in a similar patient population.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Could include only 159/220 (72%) participants in the primary analysis: 69 (63%) allocated to urethroplasty and 90 (81%) to urethrotomy. The

	study timeframe ceases at 24-months whereas previous published data indicate further subject deterioration out to 48-months in the group of patients receiving endoscopic treatment, suggesting longer term evidence would be more applicable to determine true freedom from recurrence and reintervention. Whilst the study is a comparative study, the study sites included are all reconstructive urology sites with experienced urethral reconstructive experts familiar in treating urethral stricture disease thus, findings likely represent a better than real world experience outside of the reconstructive urology field
How was the study funded?	National Institute of Health Research (NIHR)
Steenkamp, J Urol, 1997	
How are the findings relevant to the decision problem?	This study represents one of the largest randomized comparisons between different endoscopic therapies, i.e. dilation with sounds/bougies or direct vision internal urethrotomy. The follow-up protocol was also one of the most extensive reported, with urethral calibration (i.e. determination of urethra diameter) conducted at each visit to screen for recurrence. Key findings from this study that have been confirmed in subsequent analyses include the fact that recurrence outcomes after dilation and DVIU are statistically similar. Additionally, long-term outcomes after dilation/DVIU are sub-optimal, with success below 50% at 4 years. Other key learnings include a hazard analysis for recurrence, which shows the highest risk for recurrence is centred around 6 months post-procedure.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population

Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Dated, single centre study
How was the study funded?	Unknown
Heyns, J Urol, 1998	
How are the findings relevant to the decision problem?	This publication is a follow-on to the Steenkamp publication listed above. Subjects in the initial cohort that had recurrence and required subsequent repeat dilation were continued to be followed. Key learnings from this publication are the fact that subsequent dilation or internal urethrotomies lead to increasingly poor outcomes, with repeat dilation/DVIU exhibiting recurrence 100% of the time by 2 years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Dated, Single centre study
How was the study funded?	Unknown
Jordan, J Urol, 2013	
How are the findings relevant to the decision problem?	The Momokath 044TW is a self-expanding urethral stent intended to be placed in the intermediate term (e.g. <12m) and eventually removed. This study was well designed and executed, with follow-up including both anatomic assessments and symptom/flow rate assessments. A 6 month endpoint for recurrence, assessed by passage of a

	16F flexible scope, was chosen largely on the outcomes reported by Steenkamp indicating stricture recurrence was likely to occur by 6-9 months. Anatomic success and repeat intervention outcomes for the Control arm in this study were generally similar to those reported in ROBUST III and the Heyns publication for repeat dilation. This study confirms that repeat DVIU has low long-term success, with only 11% of subjects in the Control arm being free from recurrence at 15 months..
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Rapid return to normal daily living and improved quality of life Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Relatively short follow-up duration, small population,
How was the study funded?	Unknown
Hoy NY, Urology, 2013	
How are the findings relevant to the decision problem?	This is one of the largest cohort studies published utilizing currently accepted urethroplasty techniques for dorsal onlay buccal mucosal graft. Pre-specified follow-up was well documented and compliance was high. Success rates at 6 months were very high, potentially owing to the high volume nature of the center leading to significant experience and skill for the single surgeon performing the surgeries. Hospital stay (48hrs) and catheter dwell time (3 weeks) for urethroplasty are much longer than for endoscopic procedures, it is uncertain the degree to which mild adverse events were documented through the full follow-up period
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Rapid return to normal daily living and improved quality of life

	Reduces the need for retreatments or invasive surgical procedures Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Lack of surgeon heterogeneity, a reliance on the patients to report obstructive symptoms after the second follow-up period at 12 months after surgery, which might have led to an underestimation of stricture recurrence, and the smaller number of patients with long-term follow-up data. Dependence on both subjective reporting of symptoms and a normal cystoscopic appearance at 6 months to determine the need for 12-month cystoscopy might have led to an underestimation of cystoscopic recurrence but not symptomatic recurrence. Single arm, Single centre
How was the study funded?	Unknown
Cecen K, Urol Int, 2014	
How are the findings relevant to the decision problem?	This large, randomized study evaluated a 'hot knife' or laser urethrotomy device against the standard 'cold knife' urethrotome for DVIU. The strictures under study were primary, meaning they had not received prior treatment. Both arms showed freedom from recurrence around 65% at 18 months even for treatment-naïve strictures, which is a much easier population than those enrolled in the ROBUST series.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Single centre
How was the study funded?	Unknown
Azab SS, Scan J Urol, 2020	
How are the findings relevant to the decision problem?	This moderately sized randomized study compared dilation with DVIU and showed only modest improvement in symptom scores (IPSS) with more apparent improvement in peak flow rate. These short, treatment naïve strictures did not recur over the course of follow-up, however it is not clear how diligent the follow-up program and compliance was. Of note, this study was one of the only to report peri-procedural adverse events, noting mild hematuria in up to 16% of subjects and a relatively high rate of extravasation after DVIU which required extended Foley catheter time.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Single centre, all primary treatments of small stricture length >3cm
How was the study funded?	Unknown
Elkady E,	

How are the findings relevant to the decision problem?	This small randomized study evaluated a new technique to attempt to reduce the rate of post-void dribbling and ejaculatory dysfunction. Follow-up was short (1 year) and success was approximately 90%, with minimal surveillance criteria for recurrence.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Single centre, long average stricture length
How was the study funded?	Unknown
Isen K, Int Urol Nephrol, 2015	
How are the findings relevant to the decision problem?	This small case series on DVIU utilizing endoscopic scissors on short, treatment naïve strictures. Follow-up was short (mean 8 months), however freedom from recurrence was 86%. The rate of UTI noted in this study after DVIU was comparable to ROBUST III.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources

	Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Single centre, single arm, small study of short stricture length, all primary stricture treatments
How was the study funded?	Unknown
Guo FF, World J Urol, 2010	
How are the findings relevant to the decision problem?	This large cohort study from China reported the use of a 'hot knife' urethrotomy device in treatment naïve strictures. Follow-up was generally short, with 82% free from recurrence at 6 months.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Single centre, single arm, small study, all primary stricture treatments
How was the study funded?	Unknown
Aldaqadossi H, Int J Urol, 2014	
How are the findings relevant to the decision problem?	Freedom from stricture recurrence was experienced in 88% in the dorsal onlay group vs 86.4% in the dorsal inlay group through 12 months. IPSS and Qmax improved postoperatively, with no timeframe given for measurements.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	No timeframe given for IPSS and Qmax measurements, single centre
How was the study funded?	Unknown
Pansadoro V, J Urol, 1996	
How are the findings relevant to the decision problem?	This is one of the earliest large reports of DVIU outcomes with long-term follow-up. Most strictures were treatment naïve, with freedom from recurrence only 62% at 1 year. Recurrent strictures had a 0% success rate. Complications reported included urethral bleeding/hematuria at a similar rate to that reported for Optilume in ROBUST III
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population

Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Dated, Single centre, single arm
How was the study funded?	Unknown
Erickson BA, Urology, 2014	
How are the findings relevant to the decision problem?	This multi-institutional report on anatomic outcomes after urethroplasty offers one of the only multi-institution reports of urethroplasty outcomes. Success at 1 year ranged from 77.5% to 85.5% depending on surgery type. These lower rates of success than those reported previously may indicate that outcomes may vary by surgeon and by experience/skill level.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Study design was meant only to analyze the utility of the short-term cystoscopic protocol, compliance rates for follow-up were poor, perhaps biasing our anatomic success rates. Dated, Single centre study
How was the study funded?	Unknown
Santucci R, J Urol, 2010	
How are the findings relevant to the decision problem?	This article reinforces the idea that repeat treatments, including repeat DVIU, lead to progressively worse outcomes. After the second treatment, subsequent treatments would be expected to fail 100% of the time.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	It was a retrospective review and there was no standard objective measure for recurrence. Not all urethrotomies were performed by the same surgeon. Single arm, single centre study
How was the study funded?	Unknown

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

No adverse events/incidents have been reported in any regulatory database

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Event rates and types for the Optilume DCB are generally similar to other endoscopic therapies. There was a trend toward higher rates of mild hematuria (blood in urine) and dysuria (pain/discomfort during urinary) in the immediate post-operative setting, however the differences did not reach statistical significance and these events did not require any treatment.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

N/A

Report all relevant results, including diagrams if appropriate.

N/A

Explain the main findings and conclusions drawn from the evidence synthesis.

N/A

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

A quantitative review is not appropriate for this literature summary, as the outcome measures reported and follow-up protocols for each of the referenced studies were very heterogeneous. This would lead to over-simplification of outcome definitions/measures and high uncertainty in outcome results for a quantitative assessment. The clinical program sponsored by Urotronic, the manufacturer of the Optilume DCB, includes three separate studies. ROBUST I was a first-in-man study conducted in Panama and the Dominican Republic that enrolled 53 subjects. Follow-up has been completed through 3 years and will continue through 5 years. ROBUST II is an early feasibility study conducted in the United States and enrolled 16 subjects. Follow-up is complete through 2 years and is planned through 5 years. ROBUST III is a large, randomized study evaluating the Optilume DCB against standard-of-care endoscopic management, which included both dilation and DVIU. A total of 127 subjects were enrolled at 22 sites, with 79 randomized to receive the Optilume DCB and 48 randomized to receive Standard Of Care (SOC). Follow-up is complete through 1 year and will continue through 5 years for those treated with the Optilume DCB. The sizing approach for the Optilume DCB was under investigation in ROBUST I, with approximately half the subjects treated with a 24F diameter DCB and half with a 30F DCB. Outcomes from ROBUST I lead to a recommendation of using the 30F balloon when the healthy urethra is >23F to allow for adequate expansion of the urethra and more complete drug delivery in the ROBUST II and ROBUST III studies. Reported literature for the Optilume DCB includes journal articles for 1 and 2 year results from the ROBUST I study and 1 year results for the ROBUST III study. 1 year results for the ROBUST II study have been accepted for publication in *Soc Int Urol J* and are expected to be published in the January 2022 edition. 3 year results for the ROBUST I study have been presented at several congresses during 2021.

The patient populations enrolled in the ROBUST studies are comprised of recurrent anterior urethral strictures, with ROBUST I enrolling a relatively less complex patient population (0.9cm length, 1.7 prior dilations) and ROBUST II and III enrolling a more difficult population (1.7-2.1cm length, ~3.5 average prior dilations, ROBUST III included ~10% penile strictures and ~10 with prior pelvic radiation). Anatomic outcomes at 6 months were similar across all three studies, with approximately 75% exhibiting freedom from recurrence as measured by the ability to pass a 16F cystoscope. ROBUST I additionally measured anatomic success at 1 year, again with approximately 75% experiencing freedom from recurrence. Anatomic success at 6 months in the Control arm of the ROBUST III study was 27%, representing a significantly lower success rate than the Optilume DCB. Freedom from repeat intervention was also similar between studies and ranged from 75-85% at one year, with ROBUST I reporting 81% and 77% freedom from repeat intervention at 2 and 3 years, respectively. Freedom from repeat intervention in ROBUST I was 91.7% in those subjects treated with a 30F DCB. Freedom from repeat intervention in the Control arm of ROBUST III was estimated at 21.7% at 12 months via Kaplan-Meier, representing a significantly lower success rate than Optilume when compared via the log-rank test.

IPSS and Qmax were reported to improve significantly post-treatment with the Optilume DCB in all studies. Improvement in IPSS from 20-25 at baseline to 5-8 at follow-up was seen in each study, with IPSS remaining below 10 through 3 years in ROBUST I. Qmax improved from 5-8mL/sec at baseline to >15mL/sec at all follow-up timepoints in each study, including 15.5mL/sec at 3 years in the ROBUST I study. IPSS and Qmax initially improved in the Control arm of the ROBUST III study, but returned to baseline levels by 1 year.

The reported evidence largely supports the ease and availability of endoscopic treatments for anterior urethral stricture, and the similarity in outcomes regardless of endoscopic method utilized (dilation vs DVIU). Long-term outcomes reflect poor durability even for those subjects with short, treatment naïve strictures (Steenkamp 1997, Pansadoro 1996), with 2-5 year success ranging from 40-60%. Multiple publications have identified that repeated dilation/DVIU of the same stricture will lead to progressively worsening outcomes, with higher rates and earlier recurrence with each additional procedure (Heyns 1998, Santucci 2010). Reported rates of freedom from recurrence for the third dilation approached 20-30% at 6 months and 0% at 24 months.

Urethroplasty has been identified consistently as the ‘gold standard’ for anatomic resolution of anterior urethral stricture. Publications reviewed in this literature search were limited to those evaluating strictures of a similar complexity (i.e. <5cm, non-revision, no obliterative or hypospadias repair). Freedom from stricture recurrence was reported in 77-96% at varying follow-up timepoints, which is largely similar to a recently published systematic review (Barratt R, Eur Urol, 2021) that summarized available literature and concluded one could generally expect freedom from recurrence >80% for urethroplasty over medium term follow-up (1-5 years). Complications were infrequently and inconsistently reported, with the most common being post-void dribbling (16-40%), ejaculatory dysfunction (highly varied), wound infection (4-15%), and UTI (~4%). Duration of hospitalization and Foley duration were infrequently reported but were typically 2-5 days for hospitalization and at least 3 weeks for Foley catheter placement. Most publications were from single, high-volume centers, with outcomes reported for the two multi-center studies being less than those reported for single-center series. This may point to outcomes being less consistent in more ‘community’ based practice, where they are not conducting such significant volumes of surgeries.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The primary clinical evidence for the Optilume DCB is the ROBUST III study, which is a large, multi-center, randomized trial comparing the Optilume to standard-of-care endoscopic management. The Optilume DCB showed significant benefit over SOC in anatomic success at 6 months (75% vs 27%, p<0.001), freedom from repeat intervention at 12 months (83% vs 22%, p<0.001), symptom scores (IPSS 9 vs 20) at 12 months, and Qmax (15.5 vs 7.6mL/sec) at 12 months. Adverse event rates were generally similar between arms, with a trend toward higher rates of mild hematuria and dysuria post procedure that resolved within 30 days without treatment.

Outcomes from ROBUST III were consistent with earlier studies such as ROBUST I and ROBUST II. ROBUST I has long-term follow-up through 3 years, with freedom from repeat intervention maintained in 77% of subjects.

The study population evaluated in ROBUST III was more difficult than those reported elsewhere, with the eligibility criteria focusing on subjects with multiple recurrences that have historically not performed well with endoscopic management. Outcomes in the Control group of ROBUST III were similar to those reported by Heyns and Santucci for multiple prior dilations, with success approaching 20% at 1 year. Even in this difficult population, the Optilume DCB showed a success rate comparable to that of urethroplasty.

The patient population evaluated in ROBUST I was generally more similar to those reported by Pickard et al. in the OPEN trial. The rate of freedom from repeat intervention at 2 years for urethroplasty in the OPEN trial was 84%, which compares favorably with the 81% rate observed for the Optilume DCB at 2 years (91% for 30F DCB).

Risks with the Optilume DCB are comparable with other endoscopic treatments for urethral stricture, while recovery, catheter dwell time, and complications are lower for these less invasive technologies when compared to open reconstruction via urethroplasty. Endoscopic treatment avoids potential complications such as wound infection, urethro-cutaneous fistula, and sexual dysfunction associated with urethroplasty. The rate of complications reported in the literature for urethroplasty is inconsistent and likely under-reported when compared to a large, actively managed clinical trial such as the ROBUST III study.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The published and unpublished evidence from the ROBUST clinical program support claimed benefits of lower rates of repeat stricture treatments (repeat dilation, urethroplasty, self-catheterization) for the Optilume DCB compared to standard endoscopic management (17% vs 78%). The ROBUST program also showed immediate and sustained improvement in IPSS, USS-PROM, and Qmax immediately after the procedure through up to 3 years follow-up. Rapid return to daily living can be claimed based on comparison to urethroplasty, which requires extended hospital stay (>2d) and Foley catheter usage (~3 weeks). Reduced complication rates compared to urethroplasty are generally based on the Optilume DCB being a minimally invasive procedure, compared to the open surgical procedure of urethroplasty.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The poor performance of repeat urethrotomy and dilation has been published across many geographies, such as South Africa (Steenkamp), Italy (Pansadoro), the United Kingdon (Pickard), and the United States (ROBUST III). As discussed, the patients in the ROBUST III study likely represent a more difficult patient population than those receiving routine care in the UK NHS. The longer term outcomes of the ROBUST I study are likely most comparable with those reported in the OPEN RCT in the UK.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The evidence base for the Optilume DCB has been generated in patients with anterior urethral strictures <3cm in length. Patients with posterior strictures (e.g. membranous, bladder neck) have not been studied, although the treatment effect and benefits are not expected to be different from anterior strictures.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The ROBUST clinical program represents a large, multi-national series of studies that have shown a significant benefit over standard endoscopic management when patients are treated with the Optilume DCB. This benefit was shown directly in the ROBUST III randomized study, which also compares favorably to published literature for both endoscopic and surgical management. ROBUST III represents level 1 clinical evidence.

Limitations of the ROBUST clinical program include lack of a UK population in the clinical studies, although the poor performance of repeat urethrotomy has been published across the globe. The Control arm of the ROBUST III study included both urethrotomy and dilation at the physicians discretion. Urethrotomy is standard of care for endoscopic treatment in the UK, however multiple studies (including ROBUST III) have shown comparable outcomes for subjects treated with dilation and urethrotomy.

9 References

Please include all references below using NICE's standard referencing style.

Elliott SP, Virasoro R, Estrella R, et al. (2021) MP56-06 The Optilume Drug Coated Balloon for Recurrent Anterior Urethral Strictures: 3-Year Results from the ROBUST I Study. *J Urol* 206 (Suppl. 3S):e971 (Abstract).

[2] DeLong JM, Ehlert MJ, Erickson BA, et al. (2022) One-year outcomes of the ROBUST II study evaluating the use of a drug-coated balloon for treatment of urethral stricture. *Soc Int Urol J* (in press)

[3] Elliott SP, Coutinho K, Roberston KJ, et al. (2021) One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume Dug-Coated Balloon for Anterior Urethral Strictures. *J Urol* doi: 10.1097/JU.0000000000002346.

[4] EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.

[5] Simsek A, Aldamanhori R, Chapple CR, MacNeil S. (2019) Overcoming scarring in the urethra: Challenges for tissue engineering. *Asian J Urol*. 5(2):69-77.

[6] Steenkamp JW, Heyns CF, De Kock MLS. (1997) Internal Urethrotomy Versus Dilation as Treatment for Male Urethral Strictures: A Prospective, Randomized Comparison. *J Urol* 157:98-101.

[7] Heyns CF, Steenkamp JW, De Kock ML, Whitaker P. (1998) Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? *J Urol* 160(2):356-8.

[8] Andrich DE, O'Malley K, Greenwell TJ, Mundy AR. (2003) Does urethrotomy jeopardize the outcome of urethroplasty? *BJU Int* 91 (Suppl. s2):21

[9] Stephenson, R., Carnell, S., Johnson, N. et al. (2015) Open urethroplasty versus endoscopic urethrotomy - clarifying the management of men with recurrent urethral stricture (the OPEN trial): study protocol for a randomised controlled trial. *Trials* 16: 600

[10] Shen, J., Vale, L., Goulao, B. et al. (2021) Endoscopic urethrotomy versus open urethroplasty for men with bulbar urethral stricture: the OPEN randomised trial cost-effectiveness analysis. *BMC Urol* 21, 76.

[1] Beiske MJ, Holm HV, Nilsen OJ. (2021) A comparison of urethral catheterization duration - three weeks versus two weeks after bulbar urethroplasty, *Scan J Urol*, 55(4):313-6.

[12] Mann RA, Virasoro R, DeLong JM, et al. (2021) A drug-coated balloon treatment for urethral stricture disease: Two-year results from the ROBUST I study. *Can Urol Assoc J* 15(2):20-5.

[3] Virasoro R, DeLong JM, Mann RA, et al. (2020) A drug-coated balloon treatment for urethral stricture disease: Interim results from the ROBUST I study. *Can Urol Assoc J* 14(6):187-91.

[4] Pickard R, Goulao B, Carnell S, et al. (2020) Open urethroplasty versus endoscopic urethrotomy for recurrent urethral stricture in men: the OPEN RCT. *Health Tech Assess.* 24(61):

[5] Azab SS. (2020) Comparative study between Amplatz renal dilator vs visual internal urethrotomy (cold knife) for the treatment of male urethral stricture. *Can J Urol* DOI: 10.1080/21681805.2020.1798504

[6] Cecen K, Karadag MA, Demir A, Kocaaslan R. (2014) PlasmaKinetic™ versus cold knife internal urethrotomy in terms of recurrence rates: a prospective randomized study. *Urol Int* 93:460-3.

[7] Guo FF, Lu H, Wang GJ, et al. (2010) Transurethral 2μm laser in the treatment of urethral stricture. *World J Urol* 28:173-5.

[8] Jordan GH, Wessells H, Secrest C, et al. (2013) Effect of a temporary thermo-expandable stent on urethral patency after dilation or internal urethrotomy for recurrent bulbar urethral stricture: Results from a 1-year randomized trial. *J Urol* 190:130-6

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[22] Hoy NY, Kinnaird A, Rourke KF. (2013) Expanded use of dorsal onlay augmented anastomotic urethroplasty with buccal mucosa for long segment bulbar urethral strictures: Analysis of outcomes and complications. *Urology* 81:1357-61.

[23] Aldaqadossi H, Gamal SE, El-Nadey M, et al. (2014) Dosral onlay (Barbagli technique) versus dorsal inlay (Asopa technique) buccal mucosal graft urethroplasty for anerior urethral stricture: A prospective randomized study. *Int J Urol* 21:185-8.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	03Dec21
Date span of search:	01Jan1900 to 03Dec21

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Search terms were developed by concept utilizing the PICO approach (Population, Intervention, Comparator, Outcome). The population under study included male urethral stricture, the intervention of interest was drug coated balloons, the comparator of interest was standard of care endoscopic treatments or urethroplasty, and the outcomes of interest were stricture recurrence.

The search was conducted the MEDLINE library via PubMed utilizing the search terms and Boolean operators as listed in Table A-1. Search #31 and #33, returned large numbers of results and were further filtered for 'Clinical Trial' and 'Randomized Controlled Trial'.

Table A-1. MEDLINE Search terms and operators

Search	Search Terms	Search	Search Terms
1	Urethral Stricture [mh]	16	Urethral Dilation [tiab]
2	Urethral Stenosis [mh]	17	S-curve dilator [tiab]
3	Urethral Stricture [tiab]	18	s-curve dilator [tiab][all]
4	Urethral Stenosis [tiab]	19	Bougie Dilation [tiab]
5	#1 OR #2 OR #3 OR #4	20	Urethrotomy [tiab]
6	Drug Coated Balloon [tiab]	21	Optical Urethrotomy [tiab]
7	Drug Eluting Balloon [tiab]	22	DVIU [tiab]
8	Paclitaxel Coated Balloon [tiab]	23	Urethroplasty [tiab]
9	Optilume [tiab]	24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
10	In.Pact Admiral [tiab]	25	Stricture Recurrence [tiab]
11	Lutonix [tiab]	26	Redilation [tiab]
12	Ranger Drug Coated Balloon [tiab]	27	Revision Urethroplasty [tiab]
13	Stellarex [tiab]	28	Repeat Urethrotomy [tiab]
14	Biolux [tiab]	29	#24 OR #25 OR #26 OR #27
15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	30	#5 AND #15
		31	#5 AND #24
		32	#5 AND #15 AND #29

	33	#5 AND #24 AND #29
	34	#5 AND #15 AND #24 AND #29

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional searches were conducted to identify ongoing studies that may report results in the near future. Two clinical trial registration databases were searched (US National Library of Medicine registry [clinicaltrials.gov/ct2/home] and EU Clinical Trials Register [https://www.clinicaltrialsregister.eu/ctr-search/search]) using the keyword 'Urethral Stricture'.

Inclusion and exclusion criteria:

Inclusions:

- Male urethral stricture
- Outcomes after endoscopic treatment, single arm
- Outcomes after open surgical treatment (urethroplasty), single arm
- Randomized comparative studies

Exclusions:

- Preclinical/animal studies
- In-vitro studies
- Pediatric studies
- Case reports or early experimental techniques
- Editorials, commentary, technology assessments
- Posterior or membranous strictures
- Hypospadia repair, meatal/glans stricture repair
- Studies of adjunct therapies (e.g. steroids, mitomycin C)
- Diagnostic assessments
- Female strictures
- Cost effectiveness or other non-recurrence outcome measures
- Clean intermittent catheterization or home dilation
- Study protocol or design discussion
- Non-comparable population (e.g. length >5cm, urethral dislocation)

Data abstraction strategy:

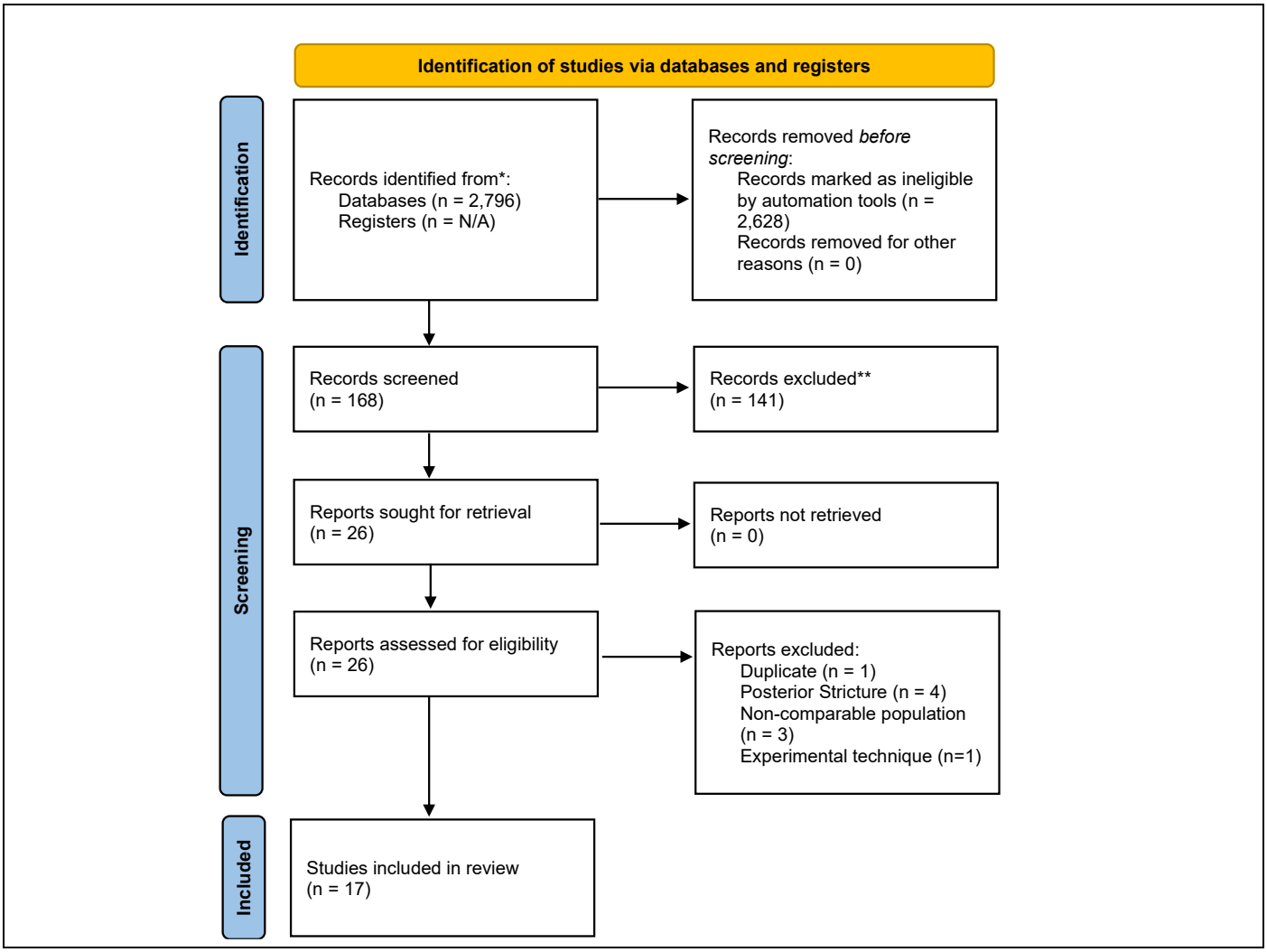
Summary search results (title, brief description) for Search 30-34 were reviewed for relevant articles (P&I, P&C, P&I&O, P&C&O, P&I&C&O). Articles possibly meeting inclusion were identified and abstracts were reviewed for exclusion criteria. Articles continuing to meet criteria after abstract review were given full text review and final determination for inclusion was made.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Guolao B, Eur Urol, 2020	OPEN randomized clinical trial	Duplicate	This was an abbreviated publication of results for the OPEN RCT. The Pickard reference included in the summary represented a more comprehensive reporting of study results.
Atak M, Kaohsiung Med, 2011	Randomized laser vs. cold-knife DVIU	Posterior urethral stricture	The Optilume DCB has not been evaluated in posterior strictures
Mehrsai A, Urology, 2007	Urethroplasty	Posterior urethral strictures	Text
Cai W, Clinics (Sao Paulo), 2016	Laser vs cold knife DVIU	Posterior urethral stricture	Text
Jablonowski Z, Photomed Laser Surg, 2010	Laser vs cold knife DVIU	Posterior urethral stricture	Text
Vasudeva P, Int J Urol, 2015	Dorsal vs ventral buccal graft urethroplasty	Non-comparable population (>5cm)	The Optilume DCB is limited to short urethral strictures that can be treated with a single DCB (<4cm max length)
Dubey D, J Urol, 2007	Dorsal vs penile skin graft urethroplasty	Non-comparable population (>5cm)	Text
Soliman MG, Scand J Urol, 2014	Dorsal vs penile skin graft	Non-comparable population (>5cm)	
Pansadoro V, J Urol, 1999	Buccal mucosal graft urethroplasty	Experimental technique	This was an initial reporting of outcomes from early experience with the buccal grafting technique.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	09Dec2021
Date span of search:	01/01/1900 to 09Dec2021
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The MAUDE database and MHRA national database were searched with the word 'Optilume', no results were found	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		Date:	10-Dec-2021
Print:	Ian Schorn	Role / organisation:	Vice President Clinical Affairs, Urotronic
Contact email:	[redacted]		

[1] Elliott SP, Virasoro R, Estrella R, et al. (2021) MP56-06 The Optilume Drug Coated Balloon for Recurrent Anterior Urethral Strictures: 3-Year Results from the ROBUST I Study. *J Urol* 206 (Suppl. 3S):e971 (Abstract).
[2] DeLong JM, Ehlert MJ, Erickson BA, et al. (2022) One-year outcomes of the ROBUST II study evaluating the use of a drug-coated balloon for treatment of urethral stricture. *Soc Int Urol J* (in press)
[3] Elliott SP, Coutinho K, Roberston KJ, et al. (2021) One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume Dug-Coated Balloon for Anterior Urethral Strictures. *J Urol* doi: 10.1097/JU.0000000000002346.
[4] EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.
[5] Simsek A, Aldamanhori R, Chapple CR, MacNeil S. (2019) Overcoming scarring in the urethra: Challenges for tissue engineering. *Asian J Urol*. 5(2):69-77.
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[15] Azab SS. (2020) Comparative study between Amplatz renal dilator vs visual internal urethrotomy (cold knife) for the treatment of male urethral stricture. *Can J Urol* DOI: 10.1080/21681805.2020.1798504
[16] Cecen K, Karadag MA, Demir A, Kocaaslan R. (2014) PlasmaKinetic™ versus cold knife internal urethrotomy in terms of recurrence rates: a prospective randomized study. *Urol Int* 93:460-3.
[17] Guo FF, Lu H, Wang GJ, et al. (2010) Transurethral 2μm laser in the treatment of urethral stricture. *World J Urol* 28:173-5.
[18] Jordan GH, Wessells H, Secrest C, et al. (2013) Effect of a temporary thermo-expandable stent on urethral patency after dilation or internal urethrotomy for recurrent bulbar urethral stricture: Results from a 1-year randomized trial. *J Urol* 190:130-6
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT565 Optilume for anterior urethral strictures

Company evidence submission

Part 2: Economic evidence

Company name	Laborie Medical Technologies
Submission date	12Jan22
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		2796
Number of studies identified as being relevant to the decision problem.		4
Of the relevant studies identified:	Number of published studies.	4
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
NIHR Report	Pickard R et al, 2020, Health Technology Assessment	Recurrent anterior urethral stricture <2cm in length, 1.8 prior dilations	Intervention: Urethroplasty (n=109 randomized, n=69 treated) Comparator: DVIU (n=112 randomized, n=90 treated)	Cost of urethroplasty (including initial surgery with catheter removal and hospital stay) – Value, Mean (SE) –By treatment received: £5808 (£219) Cost of urethrotomy (including initial surgery with catheter removal and hospital stay) – Value, Mean (SE) –By treatment received: £1367 (£90)	Data were available from 44 participants in the urethroplasty group and from 63 participants in the urethrotomy group at 12 or 24 months. At these time points, participants in the urethroplasty arm had 2.64 times greater odds of experiencing an improvement of ≥ 10ml/second in their maximum flow rate The mean AUC of multiple (at least three) voiding score measurements on a scale from 0 (no symptoms) to 24 (worst symptoms) over the 24 months after randomisation was 7.4 (SD 3.8) in the urethroplasty group and 7.8 (SD 4.2) in the urethrotomy group.	Urethroplasty was unlikely to be considered cost-effective over 24 months. The similar magnitude of symptom improvement seen for the two procedures over 24 months of follow-up shows that both provide effective symptom control. The lower likelihood of further intervention favours urethroplasty but this does require a longer period of indwelling catheterisation, and had a higher cost over the 24 months of follow-up thus was unlikely to be considered cost-effective. The trial showed no difference in the outcome of most importance to men with recurrent stricture, voiding symptom control, but did show a lower rate of recurrence and a higher rate of improvement in

					Stricture recurrence was observed in 19 (20%) participants in the urethroplasty group and 39 (38%) participants in the urethrotomy group. In total, 44 participants had at least one reintervention and there were 52 reinterventions overall. 15 (16%) men in the urethroplasty group required a reintervention at a median of 474 (IQR 399–577) days after initial surgery, compared with 29 (28%) men at a median of 308 (IQR 211–448) days for men allocated to the urethrotomy group. The mean cost to the NHS and participants over 24 months post randomisation for the urethroplasty group was £4869 (95% CI £4123 to £5614)	measured urinary flow rate in the urethroplasty group: outcomes that appear to be of lesser importance to patients but which are more valued by clinicians and providers of health care.

					compared with £2721 (95% CI £1444 to £3999) for the urethrotomy group.	
Journal Article	Wright J et al, J Urol 2006	Hypothetical cohort of patients with short, bulbar urethral strictures, 1 to 2cm in length	Treatment (Urethroplasty and DVIU)	The total costs per patient were: $8,575 with DVIU once before urethroplasty (not including urethroplasty cost); $9,285 with DVIU twice before urethroplasty (not including urethroplasty cost); $10,222 with primary urethroplasty; and $10,466 with DVIU three times before urethroplasty (not including urethroplasty cost);	The rate of success was: 0.95 (range: 0.76 to 0.98) for urethroplasty, 0.50 (range: 0.39 to 0.73) for first DVIU, 0.20 (range: 0.00 to 0.77) for second DVIU, and 0.05 for third DVIU. The overall success rate was: 0.975 with DVIU once before urethroplasty; 0.980 with DVIU twice before urethroplasty; 0.950 with urethroplasty; and 0.981 with DVIU three times before urethroplasty.	A univariate sensitivity analysis was performed to assess the robustness of the cost-effectiveness ratios to variations in success rate and operative costs. The sensitivity analysis revealed that the cost-effectiveness of urethroplasty depended on the success rate of DVIU. For example, primary urethroplasty was the most cost-effective strategy when the success rate of DVIU was less than 35%. Changes in the costs or in the success rates of other strategies did not substantially alter the conclusions of the analysis. Most cost-effective strategy for the management of short, bulbar urethral strictures is to reserve urethroplasty for patients

					The average CER was: $8,795 with DVIU once before UPL; $9,474 with DVIU twice before UPL; $10,760 with UPL; and $10,669 with DVIU three times before UPL. The ICER was $141,962 with DVIU twice before urethroplasty, and $1,181,168 with DVIU three times before urethroplasty. Urethroplasty was dominated by DVIU twice before urethroplasty, which was both more effective and less expensive.	in whom a single endoscopic attempt fails. Since it is unlikely that society would be willing to pay more than $140,000 for a successfully voiding patient, the strategy of DVIU once before urethroplasty was the most cost-effective.
Journal Article	Rourke KF, *Urology*, 2005	Primary Bulbar Strictures ≤2cm	Comparing treatment with DVIU to primary urethroplasty	Costs of DVIU and urethroplasty were based on 3rd party payer costs and utilizing OR time costs, anesthesia costs, hospital stay	Recurrence rate for DVIU was assumed 73% and recurrence for EPA was 4%. Complications associated with DVIU included UTI and	Sensitivity analysis found that primary urethroplasty was cost effective for scenarios where DVIU success rate was <40%, while DVIU became

				costs from the authors' institution. Costs are given in USD (2002) The average cost of an uncomplicated DVIU was $5,421 (outpatient/daycase) The average cost of an uncomplicated excision and primary anastomosis urethroplasty was $16,093 (3d hospital stay)	hematuria, while EPA included lithotomy complications and wound complications. Recurrence for DVIU was assumed to be managed with urethroplasty. Based on the high recurrence rate of DVIU, the total cost associated with uncomplicated primary DVIU was $17,748. This compared with a total associated cost of $16,444. Including a complication of hematuria and UTI drove DVIU costs to $27,162.61, while including a lithotomy complication and wound complication drove EPA costs to $24,774.64.	favorable with success ≥40%. The authors conclude that primary urethroplasty is more cost effective than primary DVIU, almost wholly driven by recurrence rates after DVIU. The cost of complications post urethroplasty were minimized in this analysis, with the focus being only on those major complications (DVT, wound infection) that are relatively infrequent, while complications post-DVIU were assigned a high cost for easily managed conditions (e.g. $7,650 for hematuria, more than the cost of the DVIU itself and $2,491 for a UTI, typically managed with oral antibiotics). The rate of UTI and hematuria post-urethroplasty is not expected to be lower than DVIU.
Journal Article	Harris CR, *Urology*, 2016	Men undergoing urethroplasty surgery	Patients undergoing urethroplasty based on ICD-9 diagnosis and procedural codes	The total cost of urethroplasty procedures were estimated based on NIS total charges	Urethroplasty cost was significantly higher at high volume urethroplasty centers, with the use	The cost of urethroplasty varies widely based on patient comorbidities and complexity/complications.

				multiplied by the HCUP cost-to-charge ratio from CMS. The median calculated charges for urethroplasty was $19,866 (IQR $14,346 - $29,382), while associated costs was $7,321 (IQR $5,677 - $10,000).	of grafts, with high number of patient comorbidities, and when a complication occurred.	

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Pickard R et al, 2020, Health Technology Assessment	
What are main differences in resource use and clinical outcomes between the technologies?	Upfront resource usage was highest with urethroplasty due to the inpatient nature of the procedure, while clinical outcomes were similar with regards to symptomology but favored urethroplasty for rate of recurrence and reintervention
How are the findings relevant to the decision problem?	This study provides micro-costing for urethroplasty and urethrotomy in the UK and provides a framework for a comparative cost effectiveness analysis for these two treatments.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, this study does not include Optilume and therefore does not act as a primary support for Optilume's cost effectiveness against the stated comparators
Will any information from this study be used in the economic model?	Yes, the micro-costing outputs for urethrotomy and urethroplasty, as well as clinical outcomes, are utilized as part of the sensitivity analyses presented in the economic model.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness was assessed by cost per quality-adjusted life-year (QALY) gained over 24 months. The mean cost to the NHS and participants over 24 months post randomisation for the urethroplasty group was £4869 (95% CI £4123 to £5614) compared with £2721 (95% CI £1444 to £3999) for the urethrotomy group. Men in the urethroplasty group accrued a mean QALY of 1.74 (95% CI 1.61 to 1.86) compared with 1.75 (95% CI 1.65 to 1.85) in the urethrotomy group. On average, urethroplasty was more costly, whereas QALYs were similar compared with urethrotomy. In the base-case analysis, urethroplasty never had a probability of being considered cost-effective, over the range of cost per QALY threshold values considered, over 25%.
What are the limitations of this evidence?	Only able to include 69 (63%) of the 109 men allocated to urethroplasty and 90 (80%) of the 113 men allocated to urethrotomy in the primary complete-case intention-to-treat analysis. The nature of the interventions did not allow blinding of participants, clinicians or local research teams to allocation, although central trial staff were blinded to allocated group when possible. There was an e imbalance in the proportion of randomised participants who received no intervention during the

	follow-up period (13.9% of the urethroplasty group and 7.1% of the urethrotomy group).
How was the study funded?	National Institute for Health Research Funding Programme

Wright J et al, J Urol 2006	
What are main differences in resource use and clinical outcomes between the technologies?	No direct clinical outcomes were reported in this report, rather existing clinical evidence was used to estimate recurrence rates for urethrotomy and urethroplasty. The study found that the most cost-effective treatment algorithm was treatment with DVIU once followed by urethroplasty in the case of recurrence.
How are the findings relevant to the decision problem?	This study provides a reference to costs associated with stricture recurrence and treatment strategies, as well as a reference for how the rate of stricture recurrence impacts overall costs.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	The analysis of the costs was conducted from a societal perspective. It included the direct medical costs associated with hospitalisations, procedures, professional fees and preoperative evaluation (visit, complex uroflowmetry, retrograde urethrography and basic laboratory values). The unit costs were not presented separately from the resource quantities. The costs were estimated on the basis of Medicare reimbursement rates (converted into actual costs using the authors' institution cost-to-charge ratio) and current procedural terminology. The sources of resource use were not explicitly reported. Discounting was presumably not relevant as the costs were incurred during less than 2 years. The price year was not explicitly reported but the direct costs were evaluated at 2004 prices. The indirect costs (i.e. productivity losses due to the disease) were considered in the analysis, which was appropriate given the societal perspective. The costs were derived from lost wages obtained from the Bureau of Labor and Statistics in 2003. Days of

	missed work appear to have been based on the authors' opinion. The unit costs and the quantities of resources used were presented separately. As in the analysis of the direct costs, no discounting was carried out. The costs were treated deterministically.
What are the limitations of this evidence?	It was not stated whether the primary studies were identified through a systematic review of the literature, and the authors did not report the methods and conduct of such a review. The impact of the interventions on quality of life was not investigated, even though it might have been relevant for patients with urethral strictures. Extensive information on the sources and details of the indirect costs were provided, but few details of the direct costs were presented. The unit costs and the resource quantities were not presented separately for the direct costs.
How was the study funded?	Unknown

Rourke KF, *Urology*, 2005	
What are main differences in resource use and clinical outcomes between the technologies?	No direct clinical outcomes were reported in this report, rather existing clinical evidence was used to estimate recurrence rates for urethrotomy and urethroplasty. The study found that excision and primary anastomosis urethroplasty was cost effective compared to urethrotomy when the assumed recurrence rates for urethrotomy exceeded 60%
How are the findings relevant to the decision problem?	This study provides a reference to costs associated with stricture recurrence and treatment strategies, as well as a reference for how the rate of stricture recurrence impacts overall costs.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	Clinical cost estimates were obtained from the author's institution and included surgeon fees, hospital/operative costs, and follow-up procedures. The procedural cost of an uncomplicated DVIU was $5,421, while the procedural cost of a urethroplasty was $16,093. Complications were included in the

	model, with costs derived in the same manner. The base case was obtained by folding back a decision tree for each treatment with and without the listed complications, with the probability of recurrence and complications defined by literature references, to derive the least costly strategy. The base case resulted in a cost of $17,728 per patient for DVIU and $16,444 for urethroplasty. DVIU became more cost effective when long term recurrence rates were <60%.
What are the limitations of this evidence?	The authors assumed a success rate of 96% for urethroplasty, which is on the high end of outcomes reported in the literature. A success rate of 27% for DVIU is well referenced for recurrent strictures, however the analysis assumes the treatments are primary (i.e. not recurrent), where the expected long term success of DVIU has been reported to be 40-50%. The cost analyses included costs for complications, however the rate of complications was identified as being more frequent in DVIU, which is counterintuitive to a less invasive procedure. In addition, costing for complications, including hematuria for DVIU, were quoted as much more expensive to treat than is commonly understood for minor complications (e.g $7,650 for hematuria, which is more than the DVIU procedure itself). This calls into question the costing methodology used in the analysis.
How was the study funded?	Unknown

Harris CR, *Urology*, 2016	
What are main differences in resource use and clinical outcomes between the technologies?	No direct clinical outcomes were reported in this report. Costs were estimated for urethroplasty only and were assessed for regional and other variability.
How are the findings relevant to the decision problem?	This study provides a reference to costs associated with the urethroplasty procedure and how it may vary based on indication, patient comorbidities, and place of service/geography.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No
Will any information from this study be used in the economic model?	No

What cost analysis was done in the study? Please explain the results.	A retrospective analysis was conducted using a centralized database of healthcare utilization and costing from between 2001 and 2010. The database captured hospital charges, which were converted to costs using an established cost-to-charge ratio. Variables associated with increase cost were determined via log linear regression. The median calculated cost was $7,321 (IQR 5,677 - $10,000). Patients with multiple comorbidities were associated with higher costs, as were graft urethroplasties (representing more difficult procedures). Age, race, hospital region, bed size, teaching status, payer type, and center volume were not associated with extremes of cost.
What are the limitations of this evidence?	The data utilized was based on procedural coding and does not include any information on stricture characteristics that may influence the difficulty of the procedure and thus procedure time and cost. Data was also limited to the initial inpatient hospital stay, so peri-operative complications (e.g. after discharge) and recurrence rates could not be accounted for.
How was the study funded?	Unknown

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Optilume was designed for the treatment of recurrent anterior urethral strictures equal to, or less than, 3 cm in length in men aged 18 years or older. The efficacy of Optilume has been assessed in a Phase III randomized, single blind study (ROBUST III) comparing Optilume to standard endoscopic management in which the inclusion criteria aligned with this description (Elliott et al., 2021a).

Therefore, a patient population of men aged 18 years or older with recurrent anterior urethral strictures equal to, or less than, 3 cm in length was used within the model. In alignment with the final scope produced by NICE, no sub-populations were included within the economic model.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Optilume was included in the analysis as per the recommended use within men aged 18 years or older with recurrent anterior urethral strictures equal to, or less than 3 cm in length.

In the base case analysis, endoscopic management, which includes urethral dilation (use of a urethral dilation balloon without paclitaxel or urethral sounds) and urethrotomy ("DVIU", use of a steel blade mounted on a urethroscope) was included as the comparator. This comparator was used within the base case analysis because urethrotomy and dilation were both outlined in the final NICE scope and this is considered to be standard care.

Urethroplasty is recommended by urologic society guidelines as the preferred treatment option for men with recurrent urethral stricture, however it can only be performed in specialist centres and many opt for endoscopic management as an alternative, less invasive treatment or require repeated dilation of a recurrent stricture while awaiting surgical reconstruction.

The key clinical data used to inform the comparison between Optilume and endoscopic management is the ROBUST III trial (Elliott et al., 2021a). In this study, Optilume was directly compared against standard endoscopic management in a randomized, controlled trial. The breakdown of treatments included within the endoscopic management arm of the trial comprised 29% urethrotomy, 54% balloon dilation, 17% rigid rod dilation (see Table 4, Clinical submission). As stated in Section 3 of the clinical submission, men undergoing urethroplasty have had a median of 3 to 5 previous endoscopic

treatments and it is a specialist procedure, only offered in centres that have urologists with specialist training (Andrich et al., 2003).

A secondary analysis has been conducted comparing Optilume with urethroplasty, as this comparator was also included within the NICE scope. However, it is noted that there is no direct evidence comparing Optilume with urethroplasty. The OPEN study (Pickard et al., 2020) assessed urethrotomy vs urethroplasty and concluded urethroplasty was unlikely to be cost-effective given its higher overall cost and therefore it was judged that, provided Optilume could demonstrate cost savings compared with endoscopic management, then it would likely also be cost saving compared with urethroplasty.

Optilume is not intended to be a direct replacement for urethroplasty, but rather a treatment option that provides a more definitive endoscopic treatment for recurrent strictures for those who are unwilling or not suitable for urethroplasty and to help alleviate the access to care issues (e.g. limited centres, long wait time) associated with urethroplasty.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

A pragmatic review of the literature was conducted to inform model development. Two studies were identified that were relevant to the decision problem. The first was a United States based analysis using a decision tree structure to assess the most cost-effective treatment for 1 to 2 cm bulbar urethral strictures (Wright et al., 2006). In this analysis different treatment strategies were compared – urethroplasty as a first line treatment, one endoscopic treatment followed by urethroplasty upon failure, two endoscopic treatments followed by urethroplasty upon failure, and three endoscopic treatments followed by urethroplasty upon failure. The second study, by Pickard et al, was based on the OPEN RCT which ran an economic analysis alongside the 2-year UK-based RCT comparing urethroplasty with urethrotomy for men with recurrent urethral stricture (2020). In order to extrapolate the results of the trial the authors also developed a *de novo* model with a Markov structure. The structure was based around the two available treatments with health states including 'symptomatic urethroplasty', 'cured urethroplasty', 'cured urethrotomy', 'symptomatic urethrotomy' and 'dead'. The second study was deemed more useful to inform our model development due to it being in the appropriate population (recurrent urethral stricture). A decision tree structure was considered, however, there was a concern that it would be difficult to capture the recurrent nature of the condition and therefore all subsequent treatments and the timing of these treatments, particularly over a longer time horizon. A patient level simulation model was also considered so as to model the different sequences of treatments dependent on previous treatment received as well as the heterogeneity in the population in terms of number of previous treatments received and the impact this might have on the efficacy of the treatments. However, it was judged that there was not sufficient data on which to model this that would give any advantage over a simpler structure such as a Markov structure and therefore introducing this level of complexity was not justified. A cohort Markov model was therefore deemed more appropriate

The model was developed in Microsoft Excel to estimate the cost-effectiveness of Optilume when compared with endoscopic management. The overall structure of the Markov model is shown in Appendix B. This analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) and in alignment with the NICE reference case (National Institute for Health and Care Excellence, 2012).

A 5-year time horizon was adopted in the base case analysis with longer and shorter time horizons explored in sensitivity analysis. This time horizon was chosen because it was judged that this would capture the benefits and costs associated with introducing Optilume whilst maintaining an acceptable level of uncertainty in the model given the availability of longer term data. A cycle length of one-month was used because this was expected to be sufficiently granular to capture patients having recurrent strictures and subsequent procedures, as well as any resource use incurred whilst waiting for treatment.

The cost outcomes within the model are largely driven by the recurrence rate of urethral strictures. Upon entry to the model, a hypothetical cohort of males with a recurrent anterior urethral stricture equal to, or less than 3 cm, in length underwent treatment with Optilume or endoscopic management (which is defined as per the ROBUST III trial) in the base case analysis (Elliott et al., 2021a). Patients remain in this tunnel health state for one monthly-cycle before transitioning to the treatment-dependent cured health state. Monthly probabilities of recurrence for Optilume and standard endoscopic management were calculated from 1-year outcomes reported for the randomized ROBUST III trial (Elliott et al, 2021) for the base case analysis. Annual probabilities were converted to monthly probabilities using standard formulae (Gidwani and Russell, 2020, Briggs, Sculpher et al, 2006)).

Patients remain within the cured health state until they experience a recurrence. Patients then transition into a recurrence health state that is dependent on the last treatment received. The number of cycles in which patients remain in this state is dependent on the median time to treatment following recurrence.

A small proportion of patients are assumed to receive no treatment following stricture recurrence and, hence, may remain in this health state for the remainder of the model time horizon or until death. The remainder of patients have a repeat procedure following recurrence. Within the Optilume or endoscopic treatment arms, patients can receive either a repeat endoscopic procedure or they could have a urethroplasty procedure. In the Optilume treatment arm the repeat endoscopic procedure is assumed to be another Optilume. However, a scenario analysis was also run, whereby patients could receive a repeat standard endoscopic procedure following Optilume. This required the addition of tunnel states for the Optilume treatment calculations. It was deemed important to have health states separated by treatment because the Pickard study noted that the choice of the next treatment given the previous treatment the patient had was an important model parameter, and that based on the RCT a large proportion of patients are likely to switch to a treatment different from their previous one every time they have a reintervention (Pickard et al., 2020).

Patients were assumed to transition to the cured health state following retreatment (because any treatment failure was assumed to be captured by recurrence rates) – patients remained in this health state until experiencing a further recurrence. It is also possible for patients to die within any health state. However, it was assumed that the presence of an anterior urethral stricture would not lead to an increased risk of death. Therefore, population mortality rates for England and Wales have been used within the model.

The model captures the upfront costs associated with each procedure (including adverse events) and training costs associated with Optilume. The model also captures the cost of follow-up appointments attended by patients within the cured health states and the costs incurred from follow-up appointments and intermittent self catherisation whilst patients wait for treatment following recurrence.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
One monthly cycle	Sufficiently granular to capture recurrence rates of patients with urethral stricture.	N/A
Patients could remain in the recurrence health state for more than one cycle	Literature suggests that the time to treatment following recurrence is longer than one-month.	(Pickard et al., 2020)
10% of patients remained untreated following recurrence	Pickard *et al*., reported that 90% of patients would receive treatment when symptomatic	(Pickard et al., 2020)
No difference in efficacy was assumed between initial and repeat procedures (i.e. the recurrence rate was not dependent on the number of previous procedures)	Evidence suggests that efficacy of endoscopic management may diminish the more attempts are made at treatment, however the exact relationship and expected decrease of efficacy with each additional treatment is not entirely clear. No data are available on the efficacy of a repeat Optilume procedure. This was a simplifying assumption to avoid an overcomplicated model structure. Literature that is available suggests that the efficacy of standard care endoscopic procedures is likely to reduce as procedures are repeated, therefore this was considered to be a conservative assumption. Given that more repeat procedures are required for the comparator arm, if efficacy was reduced for these repeat procedures, then this would likely improve the cost savings seen with Optilume. However, it is acknowledged that no evidence is available to suggest that efficacy of second line Optilume procedures would not also reduce. Additionally, the population upon which the model parameters are based is heterogenous and patients included in the key clinical studies may have had different numbers of previous endoscopic treatments at the time of entry into the study.	(Heyns et al., 1998, Santucci and Eisenberg, 2010)

Recurrence is applied at the same rate throughout the time horizon of the model	Simplifying assumption that the same probability of failure of treatment occurs throughout the time horizon of the model to avoid overcomplicating the model structure.	
Patients could only incur procedural adverse events within the cycle in which they receive the procedure	The majority of adverse events present less than one month after the procedure and the treatment costs incurred seem to be short-term.	(Elliott et al., 2021a, Elliott et al., 2021b, Pickard et al., 2020, DeLong et al., 2022)
The waiting time to treatment following recurrence was assumed to be equivalent between endoscopic management and Optilume	Assumption. It is noted that time to treatment could be less for Optilume as it is less resource intensive than urethrotomy. The treatment time for endoscopic management was based on the OPEN RCT and so could be overstated because this was treatment time to urethrotomy only rather than a mix of urethrotomy and dilation. This was explored in sensitivity analysis and are not expected to substantially impact the results of the model.	(Pickard et al., 2020)

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Average patient starting age	(Elliott et al., 2021a)ROBUST III (Elliott et al., 2021a)	59.42	Lower and upper values: 44.56 to 74.27	Informed the patient starting age in the model and impacted the mortality rate applied throughout (which was age-dependent).
Recurrence rates				
Monthly probability of recurrence: endoscopic management	(Elliott et al., 2021a)ROBUST III (Elliott et al., 2021a)	16.3% Recurrence rate based on probability of not being IPSS responder (≥30% improvement at 12 months w/o repeat	Lower and upper values: 1.94% to 20.3%	Used to inform the monthly risk of recurrence following treatment with endoscopic management.

		intervention) of 88.1% with endoscopic management, converted to a monthly probability.	Distribution Beta (Alpha 7.64, Beta 39.36)	
Monthly probability of recurrence: Optilume	(Elliott et al., 2021a)ROBUST III 1 year report (Elliott et al., 2021a)	2.6% Recurrence rate based on probability of not being IPSS responder ≥30% improvement at 12 months of 26.9% with endoscopic management, converted to a monthly probability.	Lower and upper values: 0.5% to 3.25% Distribution Beta (Alpha 2.01, Beta 75.99)	Used to inform the monthly probability of recurrence associated with Optilume
Monthly probability of recurrence: urethroplasty	OPEN trial (Pickard et al., 2020)	0.9% Recurrence rate of 20.4% over 24 months converted to a monthly probability. Recurrence defined as repeat treatment or deterioration of symptoms or peak flow rate to baseline levels.	Lower and upper values: 0.71% to 1.18% Distribution Beta (Alpha 0.88, Beta 92.12)	Used to inform the monthly risk of recurrence following treatment with urethroplasty
Treatment received following recurrence				
Probability of treatment following stricture recurrence	OPEN trial (Pickard et al., 2020)	90% Reported that 90% of patients would receive treatment when symptomatic	Lower and upper values: 67.5% to 100% Distribution Beta (Standard error 0.2, Alpha 1.13, Beta 0.13)	90% of patients would receive treatment and transition to one of the cured health states following recurrence. However, 10% of those experiencing recurrence each cycle would remain within the recurrence health state for the rest of the time horizon or until death
Proportion of patients treated with urethroplasty following recurrence after initial	OPEN trial (Pickard et al., 2020)	70% Reported that 70% of patients would receive urethroplasty if	Lower and upper values: 52.5% to 87.5%	Used to inform the treatment received if a patient experienced recurrence following treatment with either endoscopic management or Optilume. 70% of patients would receive treatment with urethroplasty whilst the

treatment with endoscopic management or Optilume		the last treatment received was urethrotomy	Distribution Beta (Alpha 22.27, Beta 9.54)	remaining 30% would receive re-treatment with either Optilume following recurrence (depending on the treatment arm)
Proportion of patients re-treated with endoscopic management or Optilume following recurrence		30% As per the row above, the remainder of patients would receive re-treatment with endoscopic management or Optilume following recurrence (depending on the treatment arm)	N/A (varied within row above)	
Proportion of patients re-treated with urethroplasty following recurrence	OPEN trial (Pickard et al., 2020)	12% Reported that 12% of patients would receive re-treatment with urethroplasty following recurrence if the last treatment received was urethroplasty	Lower and upper values: 9% to 15% Distribution Beta (Alpha 0.76, Beta 5.57)	Used to inform the treatment received if a patient experienced recurrence following a urethroplasty procedure. 12% of patients would receive re-treatment with urethroplasty, whilst the remaining 88% would receive treatment with either Optilume or endoscopic management (depending on the treatment arm)
Proportion of patients treated with endoscopic management or Optilume following recurrence after treatment with urethroplasty		88% As per the row above, the remainder of patients would receive treatment with endoscopic management or Optilume following recurrence (depending on the treatment arm)	N/A (varied within row above)	
Time to treatment following recurrence				
Median time to treatment following recurrence: endoscopic management and Optilume	OPEN trial (Pickard et al., 2020)	47.5 days Reported that the median time between randomisations and interventions was 47.5 days for patients for urethrotomy	Lower and upper values: 28 to 88 Distribution Normal	Used to inform the length of time patients remain in the recurrence health state before they receive subsequent treatment

		It was assumed the waiting time for Optilume was equivalent to endoscopic therapy.	(Standard deviation 0.8)	
Median time to treatment following recurrence: urethroplasty	OPEN trial (Pickard et al., 2020)	90 days Reported that the median time between randomisations and interventions was 90 days for patients for urethroplasty	Lower and upper values: 53 to 157 Distribution Normal (Standard deviation 0.8)	

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

The monthly probabilities of recurrence calculated from the ROBUST III trial were used to extrapolate the outcomes beyond the study period. It was assumed that the same monthly probabilities would apply for the time period beyond the trial.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	5 years base case, alternative scenarios explored in sensitivity analysis	As described in Model structure section	

Discount rate	3.5%	In alignment with NICE guidelines	(National Institute for Health and Care Excellence, 2012)
Perspective (NHS/PSS)	NHS and Personal Social Services	In alignment with NICE guidelines	(National Institute for Health and Care Excellence, 2012)
Health states	Procedure: Optilume, endoscopic management or urethroplasty Recurrence: Optilume, endoscopic management or urethroplasty Cured: Optilume, endoscopic management or urethroplasty	As described in Model structure section	
Sources of unit costs	National Schedule of Reference Costs NICE BNF Personal Social Services Research Unit	In alignment with NICE guidelines	(National Institute for Health and Care Excellence, 2012, National Institute for Health and Care Excellence, 2021a, Curtis and Burns, 2020)

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Clinical outcomes were based on sources stated in Table 3, i.e. the probability of, and treatment received, following recurrence. The values used are replicated here with further detail provided.

Risk of recurrence

Standard endoscopic management

The model contains three sources which can be used to determine the monthly probability of recurrence associated with endoscopic management; the ROBUST III study utilising an objective outcome at 6 months (anatomic success), the ROBUST III study utilizing a subjective outcome at 12 months (symptom recurrence without reintervention), and the OPEN RCT utilising a subjective outcome at 24 months (symptom recurrence without reintervention) (Elliott et al., 2021a, Pickard et al., 2020). Outcomes from the ROBUST III trial were utilized in the base case analysis, as these represent a direct comparison to Optilume in a randomized fashion.

The ROBUST III study presents direct comparative evidence comparing Optilume with standard care i.e. endoscopic management via urethrotomy or dilation (Elliott et al., 2021a). The ROBUST III study was conducted in a US setting, however, it is expected that the patients functional outcomes would be generalisable to a UK setting based on Pickard et al who state that outcomes from the OPEN trial are similar to those in other European countries and the US suggesting that the standards of care and surgical performance are similar across these settings (Pickard et al., 2020). In addition, urological society guidelines for management of anterior urethral stricture are largely similar between the two geographies. Two definitions of recurrence were available in the ROBUST III study (Elliott et al., 2021a). First, freedom from anatomic stricture recurrence at 6 months (≥14F urethral diameter measured by cystoscopy or calibration), and second, responder rates at 12 months based on IPSS improvement of ≥30% without repeat intervention. The latter was used in the base case analysis because of the longer time frame and it was judged to be more in line with definitions used in other studies such as the OPEN RCT (Pickard et al., 2020) used in the sensitivity analyses.

The baseline monthly probability of recurrence with standard endoscopic management appears quite different when comparing the OPEN RCT and ROBUST III studies (Elliott et al., 2021a, Pickard et al., 2020). It is expected that this may be because of differing inclusion criteria between the two studies. The ROBUST III study inclusion criteria stipulates patients must have had at least 2 prior procedures to be entered into the trial with patients having an average of 3 to 4 previous dilations in ROBUST III compared with 2 previous interventions in the OPEN RCT. The patient population in ROBUST III may therefore represent a group of patients who are less responsive to standard endoscopic management/have recurrent anterior urethral strictures that are more difficult to treat as discussed in the clinical submission (Section 8).

A scenario analysis is presented whereby the monthly probability of recurrence with standard endoscopic management was taken from the OPEN RCT (Pickard et al., 2020). This study is relevant as it is a recent UK RCT and therefore could represent a baseline probability of recurrence with standard endoscopic management that is in line with the general recurrent stricture population in the UK NHS. However, it is noted that this baseline monthly probability of recurrence in the OPEN RCT could be lower than that seen in daily practice due to possible selection bias in the trial, possible bias due to the proportion of subjects actually receiving their randomized treatment, and low rate of response for long-term outcome measures. As noted by Osman, recruitment for the OPEN study was

problematic with a high number of patients declining due to a preference for urethroplasty, likely because they have had a prior failed intervention, and it is not clear whether those declining to take part had more difficult strictures (Osman and Chapple, 2020). Only 65% (71/109) of those randomized to urethroplasty actually received surgery, while 82% (93/113) randomized to urethrotomy received this treatment. There was a significant proportion of subjects randomized to receive urethrotomy that actually received urethroplasty (9.7%, 11/113). It is unclear how this would impact reported outcomes. The rate of recurrence at 24 months was partly determined by patient response to a mailed survey, to which only 50% of subjects responded. Given the availability of direct comparative outcomes between Optilume and endoscopic management in ROBUST III and the above referenced uncertainties in the translation of OPEN RCT outcomes, outcomes from the OPEN RCT was considered as a secondary analysis.

It is noted that the OPEN study reports only on urethrotomy and not on endoscopic management including dilation, however, it has also been reported that recurrence rates are expected to be similar between different endoscopic management options (Steenkamp et al., 1997). Different baseline rates were explored in sensitivity analysis.

Optilume

The monthly probability of recurrence with Optilume was also estimated based on the ROBUST III study in the base case analysis (Elliott et al., 2021a). Different definitions of recurrence were available from the ROBUST III study. At 6 months freedom from anatomic stricture recurrence (≥14F urethral diameter measured by cystoscopy or calibration) was presented and at 12 months recurrence was defined as IPSS responder (≥30% improvement without repeat intervention). In the base case the monthly probability of recurrence with Optilume was estimated using the 12 month data because it is over a longer time frame and the definition is more in line with the definition of recurrence used for the OPEN RCT (Reintervention or deterioration of flow or symptoms to baseline levels) (Pickard et al., 2020).

In order to estimate the monthly probability of recurrence with Optilume in the scenario analysis using OPEN RCT data, two approaches were taken. The relative difference between Optilume and endoscopic management from the ROBUST III study was used and applied to the baseline monthly probability of recurrence with standard endoscopic management (Elliott et al., 2021a)(Elliott et al., 2021a). Although the patient population in ROBUST III is expected to be more difficult due to its higher rate of prior interventions and inclusion of penile strictures, it is expected that Optilume will have a similar treatment effect based on the ROBUST I study which showed freedom from both anatomic and symptomatic recurrence in 77% of patients at 12 months, and freedom from repeat intervention of 81% at 2 years and 77% at 3 years in a population more in line with the OPEN trial (stricture length ≤2cm, average 1.7 prior interventions) (Mann et al., 2021). The second approach used this ROBUST I study data directly.

Urethroplasty

The risk of stricture recurrence with urethroplasty was estimated based on the OPEN RCT using the probability of recurrence at 24 months (converted to a monthly probability) (Pickard et al., 2020). This study was chosen because it is a recent UK based study.

Treatment received following recurrence

The inputs used to inform the distribution of treatments received following recurrence were based on the OPEN RCT (Table 6 and Table 33 in Pickard et al., 2020). Therefore, 10% of patients experiencing recurrence each cycle would remain within the recurrence health state for the rest of the time horizon or until death.

Of the 90% of patients receiving treatment following recurrence, it was assumed that 70% of patients that initially received endoscopic management or Optilume would subsequently receive urethroplasty (OPEN RCT) (Pickard et al., 2020). Subsequently, the remaining 30% of patients would receive repeat treatment with endoscopic management or Optilume (depending on the treatment arm) in the base case analysis. A scenario analysis has also been presented whereby patients in the Optilume arm receive standard endoscopic management following recurrence rather than a repeat Optilume.

Following a urethroplasty procedure, it was assumed that 12% of patients would be retreated with the same treatment (OPEN RCT) and the remaining 88% of patients would receive treatment with either endoscopic management or Optilume (depending on the treatment arm) in the base case analysis.

Time to treatment following recurrence

In alignment with the literature, it was assumed that patients would not receive treatment immediately upon experiencing a recurrence. The time to recurrence associated with endoscopic management and urethroplasty was informed from the OPEN RCT and the waiting time associated with Optilume was assumed to be equivalent to endoscopic management. The median time between randomisations and interventions was reported to be 47.5 and 90 days for endoscopic management and urethroplasty respectively.

The inputs used to determine the treatments received following recurrence and time to treatment recurrence were combined to estimate the monthly transition probabilities which were used in the base case analysis are presented below:

- Recurrence following endoscopic management/Optilume > repeat endoscopic management or Optilume: 18%
- Recurrence following endoscopic management/Optilume > Urethroplasty: 28%
- Recurrence following urethroplasty > endoscopic management or Optilume procedure: 63%
- Recurrence following urethroplasty > repeat urethroplasty procedure: 4%.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Technology costs

The list price for Optilume is £1,350. This was used in the model for the cost of Optilume, and paired with the procedural costs listed below for the comparators. For urethroplasty and endoscopic management, the technology costs are assumed to be captured within the overall procedure costs.

Procedure costs

Endoscopic management

The cost of endoscopic management was taken from the National schedule of NHS costs (National Health Service, 2021). A weighted average by full consultant episode of elective, non-elective, non-elective short stay, regular day or night admissions and day cases were taken using code LB55A for Minor or Intermediate Urethra Procedures 19 years and over. This was based on an NHS England integrated impact assessment report for clinical commissioning policies which reported that urethrotomy was paid for under this HRG code (NHS England, 2016). This came to a total of £1,196. Alternative costs were included in the model based on the NICE MedTech Innovation Briefing (MIB) (updated to the most recent reference costs), and the OPEN RCT where micro costing of urethrotomy was performed (Pickard et al., 2020). The NICE MIB cost was based on the same HRG code as used in this analysis, however, the reported cost was lower due to only day case procedures being included within the cost. It was judged that, based on the OPEN RCT data which reported average LoS of 0.52 days, it could be reasonably assumed that some procedures would result in an inpatient stay. The OPEN RCT which micro costed the procedure for urethrotomy resulted in higher costs of £1,376 (after inflation from 2017 prices to 2020 prices), however, it is noted that this is just for urethrotomy and does not include dilations.

Optilume

For the Optilume procedure cost an average of day case and outpatient procedures were assumed based on the same HRG code used for endoscopic management (LB55A) (National Health Service, 2021). There is anecdotal evidence from trusts currently using the Optilume that it can be done using flexible cystoscopy, and the 'Getting it right first time' (GIRFT) report identifies cystoscopy as one of the procedures that can be moved from day surgery to the outpatient setting (GIRFT, 2020). Similarly, the Urolift, which is a minimally invasive technology for the treatment of benign prostatic hyperplasia (BPH), is a minimally invasive procedure using a similar local anaesthesia protocol as Optilume and is identified in this report as a procedure that can be moved from day surgery to the outpatient setting and piloting of this appears to be successful (National Institute for Health and Care Excellence, 2019).

The cost of the Optilume device (£1,350) was also incurred per procedure.

It was also assumed that a small proportion of patients (5%) could require predilation and therefore the staff time associated with this and the cost of a dilator was included in the total procedure cost. Although all patients received predilation within the ROBUST III study, only half of the patients received pre-dilation within the ROBUST II study and this did not impact on anatomic recurrence rates (DeLong et al, 2021; pre-print included in Clinical submission). Pre-dilation was included as a requirement in the ROBUST III study for consistency and to ensure the stricture was amenable to balloon dilation prior to treatment with the Optilume DCB, as a small proportion of strictures may not

be dilatable with a balloon (e.g. obliterative stricture requiring sounds or shallow DVIU to allow DCB passage and positioning). A cost of £20 was incurred by patients requiring predilation. This consisted of an additional 10 minutes of staff time which was costed using Personal Social Services and Research Unit costs (PSSRU) 2020 based on a surgical consultant (Curtis and Burns, 2020). The cost of a dilator was costed using the NHS electronic drug tariff (National Health Service, 2021) November 2021 by taking an average of all dilation catheters listed under Section (A)(iii).

Therefore, the overall cost of the Optilume procedure was estimated at £1,986 (£1,350 for the device, £635 for the procedure, and additional cost of £1 for pre-dilation).

Urethroplasty

The cost of a urethroplasty procedure was costed using the National schedule of NHS costs in the base case using HRG code LB29A for urethra major open procedure 19 years and over from Total HRGs. The choice of HRG was informed by an NHS England integrated impact assessment report for clinical commissioning policies (NHS England, 2016). This resulted in a cost of £4,761. It is noted that this is assumed to capture all resource use associated with the procedure, however, since patients require catheterisation following the procedure it is unclear whether the cost of catheter removal would be included within this HRG since it may happen weeks after the procedure. The OPEN RCT estimated the cost of catheter removal to be 10 minutes of nurse time in a standard treatment room, however they reported that 3 patients (out of 108) were recorded as having an overnight stay for catheter removal. Therefore if these costs are not covered within the original HRG the cost of urethroplasty in the model may be understated which would bias the results of the model against Optilume. The total cost of urethroplasty reported in the OPEN RCT was considerably higher at £6,139 (after inflation) and this was included as an option in the model and explored in sensitivity analysis.

If the list price is not used in the model, provide the price used and a justification for the difference.

The list price has been used in the model.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

M736 Urethroplasty

Combination M768+Y152 Endoscopic renewal of urethral stent

M763 Optical urethrotomy

M764 Endoscopic dilation of urethra

M766 Endoscopic insertion of urethral stent

M767 Endoscopic removal of urethral stent

M768 Other specified therapeutic endoscopic operations on urethra

M769 Unspecified therapeutic endoscopic operations on urethra

M791 Bouginage of urethra

M792 Dilation of urethra NEC

M793 Calibration of urethra

M794 Internal urethrotomy NEC

M798 Other specified other operations on urethra

M814 Dilation of meatus of urethra

M818 Other specified operations on urethral orifice

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

Cured health state resource use

It was assumed that patients within the cured health stated would attend two follow-up health care visits per year, with each visit costing £110 (NHS reference costs, outpatient urology (2021)) . This was informed from an Integrated Impact Assessment Report for Clinical Commissioning Policies for the policy titled “Urethroplasty for benign urethral strictures in adult men”(NHS England, 2016). The report advised that patients are expected to be followed up every three months for one year and, thereafter, patients would be followed up once per year. An assumption of two visits per year was made to prevent the need for multiple tunnel states to differentiate such resource use between the first and subsequent years following a cure. The annual cost, which was estimated to be £220 (£110*2),

was converted to a monthly cost of £18 per patient. A similar cost was reported in the OPEN RCT which recorded resource use following the procedure for 24 months and reported a cost of follow up for urethrotomy of £398 over 24 months which equates to a cost of around £16 per month (Pickard et al., 2020).

Recurrence health state resource use

It was assumed that patients would attend an average of 4 follow-up appointments per year whilst waiting for treatment following a recurrence. As with the cured health state, a cost of £110 was used to estimate an annual cost (£440), which was then converted to a monthly cost (£37) (NHS reference costs, outpatient urology (2021). It was assumed that any costs associated with diagnosis of recurrent stricture would be captured within these outpatient visits.

Data from Pickard et al., (2020) was used to inform the assumption that 16.8% of patients would require self-catheterisation whilst in the recurrence health state, at a unit cost of £48 per month. An annual unit cost associated with the use of a clean non-coated catheter (£502) was identified from a cost-effectiveness analysis of intermittent self-catheterisation with hydrophilic, gel reservoirs and non-coated catheters (Bermingham et al., 2013). This cost was inflated to the 2019/20 cost year and converted to a monthly cost of £48 per patient, which was then multiplied by 16.8% to determine the average monthly cost per patient which was used in the model (£8).

The monthly costs per patient associated with follow-up visits and intermittent self-catheterisation and urinary retention were summed to calculate a cycle cost of £45 per patient. It is noted that in practice costs of having untreated urethral stricture could result in further complications and health care resource use such as repeated urinary tract infection and therefore this cost could be understated in the model. This is explored in sensitivity analysis and is considered to be conservative.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The Optilume technology represents a direct replacement of procedures within the current treatment pathway. Therefore, the only additional resources that would be needed to implement Optilume within the NHS are associated with the staff training required before it can be used by health care professionals. Since dilation is already used within the NHS, these costs are expected to be minimal and all training is provided free of charge. However, costs associated with staff time for training are included within the model.

It has been assumed only hospital based surgical doctors would require training, as no other professionals would use Optilume within clinical practice. Therefore, an hourly cost of £144 was used to estimate the cost of training (PSSRU 2020, cost per working hour, surgical consultant (Curtis and Burns, 2020)). Two types of training are provided, the first is basic training lasting around 45 minutes and it was judged that this would be sufficient for the majority. A more in depth training session can also be provided which lasts 4 hours. It was assumed in the model that 5% of staff would require more in depth training, with the remaining receiving basic training.

It was estimated that each surgical consultant would undertake an average of 35 procedures with Optilume each year and that retraining would be required after 10 years. The average cost of training sessions per patient was estimated to be £3.64 per patient, assuming 3 staff members would be required to perform procedures for a cohort of 100 patients.

Furthermore, it was assumed that health care professionals could require supervision for the first three procedures based on feedback from experts during the development of the NICE MIB (National Institute for Health and Care Excellence, 2021b). It was assumed this supervision would last around 0.5 hours which is expected to be at the higher end of how long the procedure may last. Therefore, a cost of £4.89 associated with this supervision was also applied per procedure based on 3 surgeons being trained.

Subsequently, a total one-off cost of £8.53 was applied to all patients receiving a procedure with Optilume for the first time (upon entry to the model). This cost was not applied to future Optilume procedures following recurrence.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources would be needed to manage the change in patient outcomes after implementing as Optilume as the technology represents a direct replacement to other procedures within current treatment pathway. It is expected that resources would be saved by preventing future recurrences, and preventing the need for expensive procedures such as urethroplasty.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

No additional resources would be needed to manage the change in system outcomes after implementing as Optilume as the technology represents a direct replacement to other procedures within current treatment pathway and represents a potential resource saving through reducing the number of follow up visits required as a result of preventing future recurrences and preventing the need for expensive procedures such as urethroplasty.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Optilume costs	Endoscopic management costs	Urethroplasty costs	Difference in resource use costs (Optilume vs endoscopic management)	Difference in resource use costs (Optilume vs Urethroplasty)
Cost per procedure (inc device)	£1,986	£1,196	£4,761	£790	-£2,775
Cost of training (per procedure)	£8.53	£0	£0	£8.53	£8.53
Cost of adverse events (per procedure)	£15	£63	£17	-£48	-£2
Total costs	£2,010	£1,259	£4,779	£751	-£2,769

AdverseFurther, Optilume may enable movement from day case procedures to outpatient procedures which would further relieve pressure on waiting lists and free up resources for other procedures that are required to be carried out as a day case.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost of the device per treatment over lifetime of device	£1,350	Laborie
Consumables per year (if applicable) and over lifetime of device	£1	See Section on Technology costs
Procedure cost	£635	See Section on Technology costs
Training cost over lifetime of device	£8.53	See Section on Technology costs
Total cost per treatment over lifetime of device	**£1,995**	Calculation

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per treatment (including procedure cost, consumables)	£1,196	National schedule of NHS costs (National Health Service, 2021). Weighted average of elective procedure, non-elective procedure, non-elective short stay, regular day or night admission and day case. HRG LB55A Minor or intermediate urethra procedures 19 years and over.

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Base case results over a 5-year time horizon.

	Mean discounted cost per patient using Optilume (£)	**Mean discounted cost per patient using Endoscopic management (£)**	**Difference in mean discounted cost per patient (£): Optilume vs Endoscopic management**
Initial procedure cost (including device and adverse events)	£2,001	£1,259	£742
Repeat procedure costs (endoscopic)	£931	£1,286	-£355
Repeat procedure costs (urethroplasty)	£2,658	£5,514	-£2,856
Training costs	£9	£0	£9
Cost accrued in cured health state	£925	£860	£65
Costs accrued in recurrence health state	£97	£203	-£107
Total	**£6,620**	**£9,122**	**-£2,502**
* Negative values indicate a cost saving.			

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

The following scenario analyses were conducted to assess areas of the model where assumptions around the applicability of data were used. These scenarios are presented within this section.

The monthly probability of endoscopic management was informed from ROBUST III in the base case analysis (Elliott et al., 2021a). However, the monthly probability within ROBUST III was higher than what was reported within the OPEN RCT (16.3% vs 1.9% respectively). It is expected that this may be because of differing inclusion criteria and recurrence definitions between the two studies. The ROBUST III study inclusion criteria stipulates patients must have had at least 2 prior procedures in patients with a stricture length <3cm to be entered into the trial with patients having an average of 3 to 4 previous dilations in ROBUST III compared with 2 previous interventions in the OPEN RCT. In

addition, the ROBUST III trial included all anterior urethral strictures, including those in the penile urethra, while the OPEN RCT only included those primarily in the bulbar urethra. The definitions of stricture recurrence were generally similar between studies, with recurrence based on a combination of symptom recurrence and repeat intervention. ROBUST III utilized a pre-specified threshold for symptom recurrence based on responses to the IPSS questionnaire, while the OPEN RCT utilized a more open-ended definition of symptom recurrence as 'returning to baseline symptom levels'.

In order to address the discrepancy in recurrence rates between the two studies, the following scenarios were run:

1. A scenario was run using the OPEN RCT to inform the monthly probabilities of recurrence associated with endoscopic management and Optilume (1.9% and 0.5% respectively). The probability of recurrence associated with Optilume was estimated using the relative risk (0.31) of annual recurrence between Optilume and endoscopic management within ROBUST III using the IPSS responder ≥30% improvement definition. This was considered the strongest comparator using the OPEN RCT outcomes, as it incorporates the relative performance seen between endoscopic management and Optilume in a randomized comparison while still normalizing to the lower recurrence rates seen in OPEN.
2. A scenario was run using the OPEN RCT data to inform monthly probability of recurrence with endoscopic management (1.9%), with monthly probability for Optilume based on ROBUST I data (0.9%) (Table 4, clinical submission, freedom from repeat intervention at 2 years). The 2-year time point was chosen so as to be more in line with the results reported from the OPEN RCT which was also over 2 years. However, it is noted that 3-year data is also available which would result in a monthly probability of 0.7%. This scenario was run because, although not UK based, the inclusion criteria from ROBUST I is anticipated to be more generalisable to the OPEN RCT because it was less strict on the number of previous procedures and included only bulbar strictures. The OPEN RCT inclusion criteria stipulated that patients must have had at least one prior procedure to be entered into the trial, whilst the ROBUST I study stipulates that patients must have undergone one to four prior procedures (with the 82% having had one or two). However, the ROBUST III study inclusion criteria stipulates patients must have had at least 2 prior procedures to be entered into the trial, with patients having an average of 3 to 4 previous dilations. Though the populations were deemed more similar between the OPEN RCT and ROBUST I, ROBUST I was an early feasibility study conducted with the Optilume and further informed procedural best practices currently utilized, including appropriate size selection of the Optilume balloon diameter and length. Outcomes for the subgroup of patients treated per the current recommended sizing approach for Optilume (e.g. 30F balloon in bulbar urethra) had much better outcomes than the overall cohort.

The following scenario analysis was run to assess the uncertainty associated with the costs of each procedure:

3. In the base case analysis NHS Reference costs were used to determine the cost of endoscopic management and urethroplasty procedures. A scenario was run using a micro costing analysis based upon the OPEN RCT.

The remaining scenarios were combine some of the above scenarios and also explore an alternative comparator.

4. A scenario was run whereby the monthly recurrence probabilities associated with endoscopic management and Optilume informed from the OPEN RCT data (scenario 1) were combined with the micro costing approach for procedures associated with the OPEN RCT (scenario 3).
5. A scenario analysis was run comparing Optilume with urethroplasty because this comparator was included within the NICE scope.
6. A scenario analysis was run comparing Optilume with urethroplasty (scenario 5) and using the micro costing approach for procedures associated with the OPEN RCT (scenario 3)

All scenario analysis results are presented over a 5 year time horizon as per the base case.

Describe the differences between the base case and each scenario analysis.

The following scenarios were used in the model:

1. Alternative monthly probabilities of recurrence associated with endoscopic management and Optilume were used in this scenario. The inputs were based on the OPEN RCT rather than ROBUST III, which was used in the base case. The monthly probability of recurrence for endoscopic management was based on results from the OPEN RCT (37.5% recurrence at 24 months). A relative risk of 0.31 was used to estimate the monthly probability of Optilume compared to endoscopic management. The relative risk was estimated based upon annual recurrence rates between the two treatment arms within ROBUST III (26.9% vs 88.1%), and applied to the endoscopic management recurrence rate (37.5% x 0.305 = 11.5%) and then converted to a monthly probability.
2. The OPEN RCT and ROBUST I studies were used to inform the monthly probability of recurrence associated with endoscopic management and Optilume respectively within this scenario. An annual probability associated with endoscopic management of 37.5%, informed from the OPEN RCT, was converted to a monthly probability of 1.9%. An annual probability associated with Optilume of 19%, informed from ROBUST I, was converted to a monthly probability of 0.9% (See Table 4/5, Clinical submission, “Freedom from reintervention was 81% at two years”).
3. Within the base case analysis NHS reference costs were used to inform the cost of endoscopic and urethroplasty procedures. However, a scenario analysis was run using micro costs from the OPEN RCT because it was anticipated that the NHS reference costs may underestimate the true procedural costs. It is uncertain whether costs such as catheter removal (including nurse time and overnight stays) are accounted for within the NHS reference costs, which would bias the results of the model against Optilume (further information is provided in Section 3, Technology costs).
4. This scenario was a combination of scenarios 1 and 3, whereby the monthly recurrence probabilities associated with endoscopic management and Optilume were informed from the OPEN RCT data (scenario 1) and combined with the micro costs associated with the OPEN RCT (scenario 3).
5. A scenario analysis was run comparing Optilume with urethroplasty because this comparator was included within the NICE scope. Within this scenario, all inputs informing the probability of recurrence associated with urethroplasty were informed from the OPEN RCT and the procedural cost associated with urethroplasty was informed from NHS reference costs. The monthly probability of recurrence associated with Optilume in this scenario was equivalent to the base case (2.6%, ROBUST III).

6. This scenario was a combination of scenarios 5 and 3, whereby urethroplasty was compared to Optilume data (scenario 5) and the procedural costs were informed from the micro costing associated with the OPEN RCT (scenario 3). The monthly probability of recurrence associated with Optilume in this scenario was equivalent to the base case (2.6%, ROBUST III), although it is noted that this is based on a patient population that is likely harder to heal than those in the OPEN RCT and this therefore may overestimate the probability of recurrence with Optilume.

The different values used for each scenario are presented in the table below.

Input parameter	Base case value and source	Scenario value and source
1. Alternative monthly recurrence probabilities (OPEN RCT)	*Monthly recurrence probabilities* Endoscopic management: 16.3% (ROBUST III) Optilume: 2.6% (ROBUST III)	*Monthly recurrence probabilities* Endoscopic management: 1.9% (OPEN RCT) Optilume: 0.5% (RR of 0.31 between endoscopic management and Optilume within ROBUST III)
2. Alternative monthly recurrence probabilities (OPEN RCT + ROBUST I)	*Monthly recurrence probabilities* Endoscopic management: 16.3% (ROBUST III) Optilume: 2.6% (ROBUST III)	*Monthly recurrence probabilities* Endoscopic management: 1.9% (OPEN RCT) Optilume: 0.9% (ROBUST I)
3. Alternative procedural costs (OPEN RCT micro costing)	*Cost per procedure* Endoscopic management: £1,196 (NHS Reference Costs) Urethroplasty: £4,761 (NHS Reference Costs)	*Cost per procedure* Endoscopic management: £1,376 (OPEN RCT) Urethroplasty: £6,139 (OPEN RCT)
4. Combination of scenarios 1 and 3	As per rows above	As per rows above
5. Optilume vs urethroplasty	No inputs associated with Optilume change from base case in this scenario	*Monthly recurrence probability:* Urethroplasty: 0.9% (OPEN RCT) *Time to treatment following recurrence:* Urethroplasty: 90 days (OPEN RCT) *Procedure costs:* Urethroplasty: £4,761 (NHS Reference Costs)
6. Combination of scenarios 3 and 5	As per rows above	As per rows above

Describe how the scenario analyses were included in the cost analysis.

1. This scenario was run by manually changing the drop-down menu ”Data source for endoscopic management/Optilume” on the ‘Clinical’ tab.
2. This scenario was run by manually typing the updated monthly recurrence input associated with Optilume into cell E14 of the ‘Clinical’ tab.
3. This scenario was run by manually changing the drop-down menus in cells F16 and F32 on the ‘Costs’ tab.
4. As per scenarios 1 and 3.
5. This scenario was run by manually changing the drop-down menu in cell E15 of the ‘Set-up’ tab.
6. As per scenarios 3 and 5.

Describe the evidence that justifies including any scenario analyses.

The ROBUST III study was identified as the most applicable source for clinical outcomes, given the direct, randomized comparison between Optilume and endoscopic management (Elliott et al., 2021a). However, the OPEN RCT was conducted in the UK and represents a useful reference point for outcomes in a patient population likely to be treated in the NHS Trust and was included as a scenario analysis, even though it did not directly evaluate the Optilume DCB (Pickard et al., 2020). As described previously, the baseline monthly probability of recurrence with standard endoscopic management varies when comparing the OPEN RCT and ROBUST III studies(Pickard et al., 2020, Elliott et al., 2021a). It is expected that this may be because of the ROBUST III study enrolling a slightly more difficult patient population, which included patients with a higher number of prior dilations on average (3.6 vs 1.9) and also included the full range of anterior strictures (~10% in penile urethra for ROBUST III) rather than just the bulbar region. As discussed, a large number of potential patients declined participation in the OPEN RCT due to expressing a preference for urethroplasty, which may have lead to the exclusion of patients with more difficult strictures. Given the lack of direct inclusion of Optilume in the OPEN RCT, two separate scenarios were included in the analysis when choosing the recurrence rate for Optilume; one where the relative treatment effect from ROBUST III was applied to outcomes for endoscopic management from OPEN, and one where outcomes were utilized from a study with a more similar patient population (ROBUST I). Both of these approaches rely on assumption and extrapolation for comparative performance of the Optilume DCB vs endoscopic management, which is why they were not utilized as the base case, but still represent relevant analyses.

As aforementioned, alternative sources were available to estimate the procedural costs of endoscopic management and urethroplasty. Therefore, a scenario analysis was run using micro costs from the OPEN RCT. It was judged that, based on the OPEN RCT data which reported average LoS of 0.52 days, it could be reasonably assumed that some endoscopic procedures would result in an inpatient stay. The OPEN RCT which micro costed the procedure for urethrotomy resulted in higher costs of £1,376 (after inflation from 2017 prices to 2020 prices), however, it is noted that this is just for urethrotomy and does not include dilations. Furthermore, it is uncertain whether costs such as catheter removal (including nurse time and overnight stays) are accounted for within the NHS reference costs for urethroplasty, which would bias the results of the model against Optilume. The total cost of urethroplasty reported in the OPEN RCT was considerably higher at £6,139 (after inflation) and this was included as an option in the model and explored in sensitivity analysis. Further information is provided in Section 3, Technology costs).

Table 10 Scenario analyses results

The results of all scenario analyses are presented below over a time horizon of 5 years.

	Mean discounted cost per patient using Optilume (£)	Mean discounted cost per patient using endoscopic management (£)	Difference in cost per patient (£)* (Optilume vs endoscopic management)
Base case	**£6,620**	**£9,122**	**-£2,502**
Scenario 1 - Alternative monthly recurrence probabilities (OPEN RCT)	£3,938	£4,925	-£988
Scenario 2 - Alternative monthly recurrence probabilities (OPEN RCT + ROBUST I)	£4,541	£4,925	-£384
Scenario 3 - Alternative procedural costs (OPEN RCT micro costing)	£7,386	£11,076	-£3,690
Scenario 4 - Combination of scenarios 1 and 3	£4,138	£5,801	-£1,663
Scenario 5 - Optilume vs urethroplasty	£6,620	£6,863	-£243
Scenario 6 - Combination of scenarios 3 and 5	£7,386	£8,476	-£1,089
* Negative values indicate a cost saving.			

Sensitivity analysis

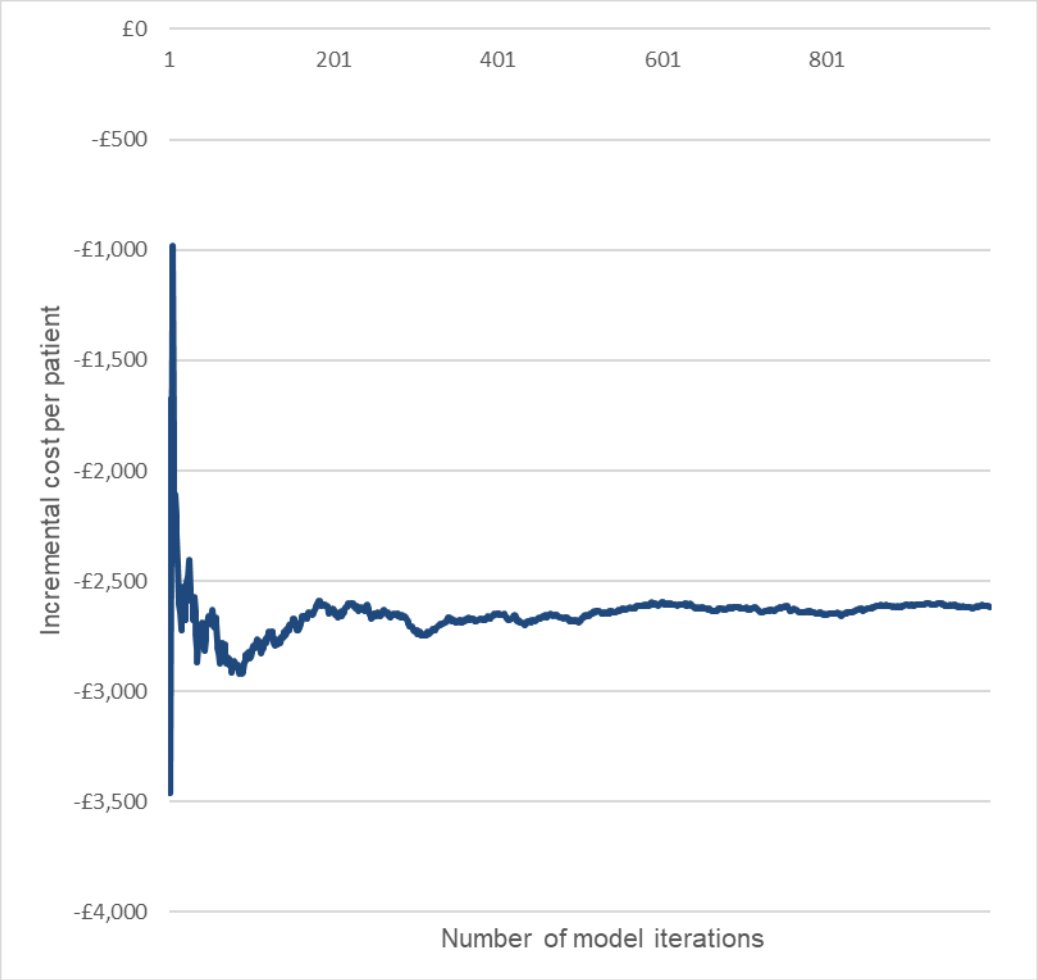
Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Three methods for sensitivity analysis were undertaken – One-way deterministic sensitivity analysis (presented using a tornado diagram), two-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

One-way deterministic sensitivity analysis was conducted to explore the impact on the results of varying individual model parameters and identify key drivers of the analysis. A tornado diagram is used to present one-way analysis for all model inputs. Ranges reported have, where possible, been taken from the literature. Where these data were unavailable, clinical opinion or assumptions have been used.

Three different two-way deterministic sensitivity analyses were conducted. The first around the baseline monthly probability of recurrence with endoscopic management and the monthly probability of recurrence with Optilume which are key drivers of the analysis. The second around the cost of the Optilume procedure (excluding device) and the cost of endoscopic management procedures because there is some uncertainty around the setting in which Optilume procedures may be performed which will impact on the costs. The third around the probability of urethroplasty following endoscopic management /Optilume and further urethroplasty following urethroplasty which is uncertain in the model due to a paucity of data.

Probabilistic sensitivity analysis (PSA) was also conducted in order to explore second order uncertainty in the results of the analysis. This was run using 1,000 iterations in the model because that was the number of iterations needed to produce stability in the results of the model as shown in the graph below.



Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Ranges used for deterministic and probability sensitivity analysis are summarised below.

Parameter	Base case value	Range and source used for DSA	Range and source used for PSA
Average patient starting age	59.42	Lower and upper bound 44.56 to 74.27 (Range taken from ROBUST III trial)	Not varied in PSA
Discount rate: costs	3.5%	Lower and upper bound 2% to 4% (Assumption of a plausible range)	
Monthly probability of recurrence: endoscopic management	16.3%	Lower and upper bound 1.94% to 20.3% (Lower from OPEN RCT, upper is 25% variation from mean) Wider variation explored in two-way SA, varied between 1% and 21%	Distribution Beta (Alpha 7.64, Beta 39.36) ROBUST III
Monthly probability of recurrence: Optilume	2.6%	Lower and upper bound 0.5% to 3.25% (Lower based on OPEN RCT and combined with RR estimated from ROBUST III, upper is 25% variation from mean) Wider variation explored in two-way SA, varied between 0.2% and 4.2%.	Distribution Beta (Alpha 2.01, Beta 75.99) OPEN RCT (Pickard, 2020, ROBUST III
Monthly probability of recurrence: urethroplasty	0.95%	Lower and upper bound 0.71% to 1.18% (Based on 25% variation from the mean) Wider variation explored in two-way SA, varied between 0.6% and 1.6%	Distribution Beta (Alpha 0.88, Beta 92.12) OPEN RCT (Pickard, 2020)
Probability of treatment following stricture recurrence	90%	Lower and upper bound 67.5% to 100% (Based on 25% variation from the mean)	Distribution Beta (Standard error 0.2, Alpha 1.13, Beta 0.13) OPEN RCT (Pickard, 2020)
Proportion of patients treated with urethroplasty following recurrence after	70%	Lower and upper bound 52.5% to 87.5%	Distribution Beta

treatment with endoscopic management or Optilume		(Based on 25% variation from the mean)	(Standard error 0.08, Alpha 22.27, Beta 9.54) OPEN RCT (Pickard, 2020)
Proportion of patients re-treated with urethroplasty following recurrence after urethroplasty	12%	Lower and upper bound 9% to 15% (Based on 25% variation from the mean)	Distribution Beta (Standard error 0.12, Alpha 0.76, Beta 5.57) OPEN RCT (Pickard, 2020)
Median time to treatment following recurrence: endoscopic management and Optilume	47.5 days	Lower and upper bound 28 to 88 days (Range stated in OPEN RCT)	Distribution Logormal (Standard deviation 0.8, standard error on log scale 0.08) Estimated using log of IQR divided by 1.35 due to mean not being reported (Pickard, 2020)
Median time to treatment following recurrence: urethroplasty	90 days	Lower and upper bound 53 to 157 (Range stated in OPEN RCT)	Distribution Lognormal Standard deviation 0.8, standard error on log scale 0.09) Estimated using log of IQR divided by 1.35 due to mean not being reported(Pickard, 2020)
Treatment cost: endoscopic management	£1,196	Lower and upper bound £1,067 to £1,376 (Lower based on NICE MIB and updated to most recent NHS reference costs, upper from OPEN RCT) Wider variation explored in two-way SA, varied between £900 and £1,900.	Distribution Gamma (Alpha 100, Beta 12) Standard error of 10% assumed
Treatment cost: urethroplasty	£4,761	Lower and upper bound £3,571 to £6,139 (Lower is 25% variation from mean, higher from OPEN RCT)	Distribution Gamma (Alpha 25, Beta 190) Standard error of 20% assumed
Treatment cost (including device): Optilume	£1,986	Lower and upper bound £1,554 to £2,418 (Lower based on assumption of an outpatient procedure,	Distribution Gamma (Alpha 100, Beta 20) Standard error of 10% assumed

		upper from assumption of a day case procedure)	
Treatment cost (excluding device): Optilume	£635	Lower and upper bound £203 to £1,067 (Lower based on assumption of an outpatient procedure, upper from assumption of a day case procedure) Wider variation explored in two-way SA, varied between £200 and £1,200.	Not varied within PSA, all varied as part of total treatment cost above.
Cost of device: Optilume	£1,350	Lower and upper bound £1,012.50 to £1,687.50 (Based on 25% variation from the mean)	
Cost of predilation: Optilume	£20.36	Lower and upper bound £15.27 to £25.45 (Based on 25% variation from the mean)	
Cost of adverse events: Optilume	£15.16	Lower and upper bound £11.61 to £19.35 (Based on assumption of 25% more or fewer adverse events)	Distribution Gamma (Alpha 25, Beta 1) Standard error of 20% assumed
Cost of adverse events: endoscopic management	£63.40	Lower and upper bound £47.92 to £79.88 (Based on assumption of 25% more or fewer adverse events)	Distribution Gamma (Alpha 25, Beta 3) Standard error of 20% assumed
Cost of adverse event: urethroplasty	£17.46	Lower and upper bound £13.19 to £24.13 (Based on assumption of 25% more or fewer adverse events)	Distribution Gamma (Alpha 25, Beta 3) Standard error of 20% assumed
Training cost (per patient): Optilume	£8.53	Lower and upper bound £6.40 to £10.66 (Based on 25% variation from the mean)	Distribution Gamma (Alpha 25, Beta 0) Standard error of 20% assumed
Cured health state cost (monthly)	£18.33	Lower and upper bound £9 to £37	Distribution Gamma (Alpha 25, Beta 1)

		(Based on assumption of changing the number of follow up appointments to 1 for lower and 4 for upper)	Standard error of 20% assumed
Total recurrence health state cost (monthly)	£44.74	Lower and upper bound £34 to £56 (Based on 25% variation from the mean)	Distribution Gamma (Alpha 25, Beta 2) Standard error of 20% assumed

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All parameters as listed in table 3 were included within the sensitivity analysis.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

A tornado plot presenting the one-way deterministic analysis is shown in Figure 1. Two-sensitivity analysis are presented in Figures 2, 3 and 4. PSA results are presented in Figure 5.

Figure 1: Tornado plot presenting one-way sensitivity analysis

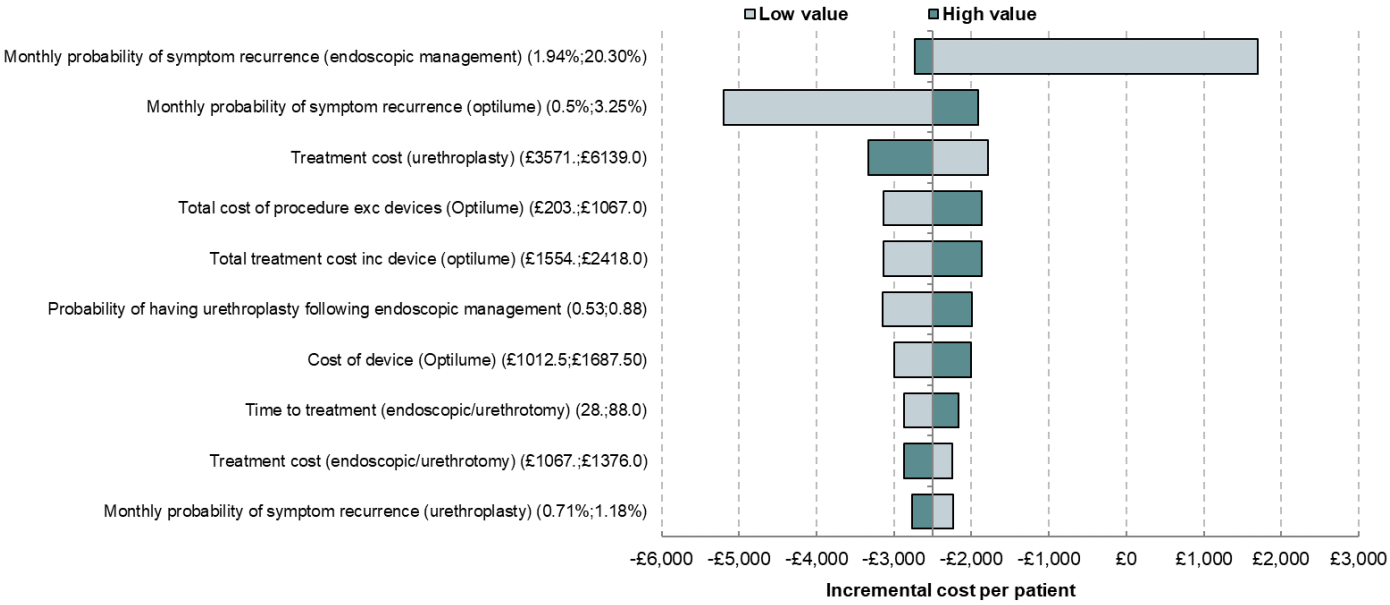


Figure 2: Two way sensitivity analysis of monthly probability of recurrence with Optilume and monthly probability of recurrence with endoscopic management

		Monthly probability of recurrence with Optilume										
		0.2%	0.6%	1.0%	1.4%	1.8%	2.2%	2.6%	3.0%	3.4%	3.8%	4.2%
Baseline monthly probability of recurrence with endoscopic management	1.0%	-£434	£281	£914	£1,477	£1,978	£2,424	£2,802	£3,182	£3,503	£3,793	£4,054
	3.0%	-£2,482	-£1,768	-£1,134	-£572	-£71	£375	£753	£1,133	£1,454	£1,744	£2,005
	5.0%	-£3,674	-£2,959	-£2,326	-£1,764	-£1,263	-£816	-£438	-£59	£263	£552	£813
	7.0%	-£4,409	-£3,695	-£3,061	-£2,499	-£1,998	-£1,552	-£1,174	-£794	-£473	-£183	£78
	9.0%	-£4,891	-£4,176	-£3,542	-£2,980	-£2,479	-£2,033	-£1,655	-£1,275	-£954	-£664	-£403
	11.0%	-£5,223	-£4,508	-£3,875	-£3,312	-£2,811	-£2,365	-£1,987	-£1,607	-£1,286	-£996	-£735
	13.0%	-£5,463	-£4,749	-£4,115	-£3,553	-£3,052	-£2,606	-£2,228	-£1,848	-£1,527	-£1,237	-£976
	16.3%	-£5,738	-£5,023	-£4,390	-£3,827	-£3,326	-£2,880	**-£2,502**	-£2,122	-£1,801	-£1,511	-£1,250
	17.0%	-£5,787	-£5,072	-£4,439	-£3,876	-£3,376	-£2,929	-£2,551	-£2,172	-£1,850	-£1,561	-£1,299
	19.0%	-£5,901	-£5,186	-£4,553	-£3,990	-£3,490	-£3,043	-£2,665	-£2,286	-£1,964	-£1,675	-£1,413
	21.0%	-£5,994	-£5,280	-£4,646	-£4,084	-£3,583	-£3,137	-£2,759	-£2,379	-£2,058	-£1,768	-£1,507

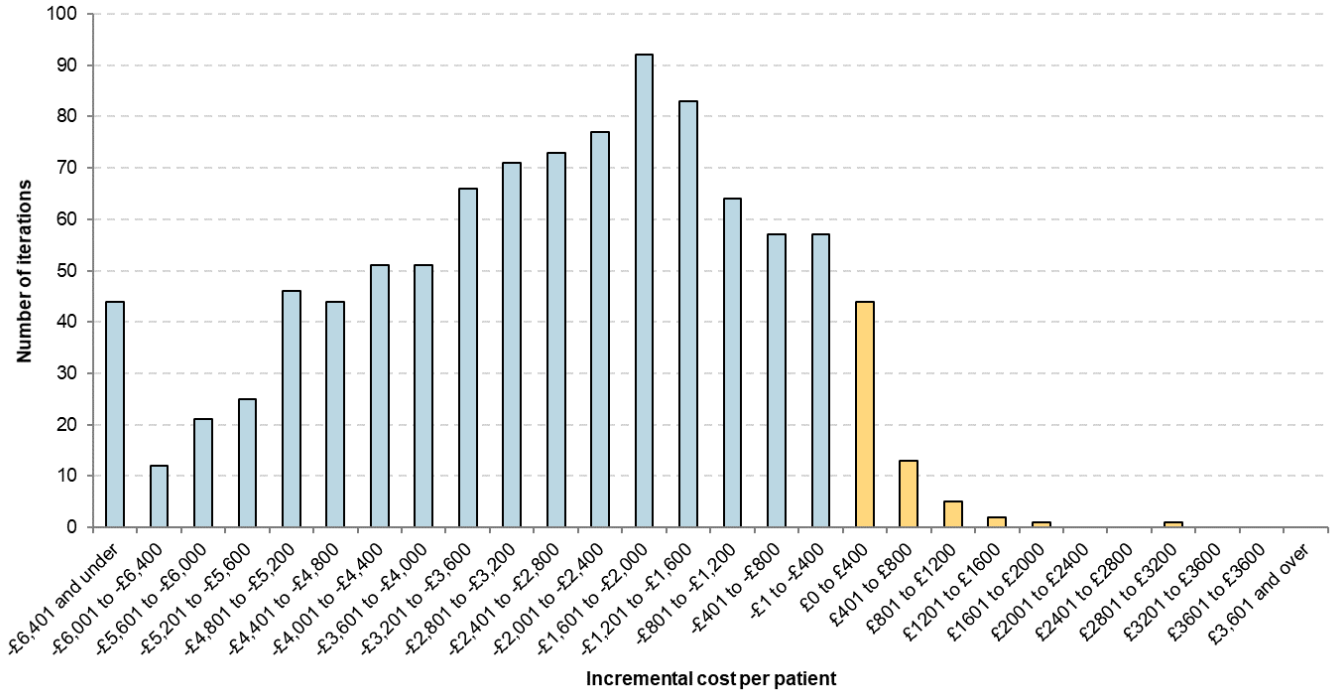
Figure 3: Two way sensitivity analysis of Optilume procedure cost and endoscopic management procedure cost

		Optilume procedure costs (excluding device)										
		£200.00	£300.00	£400.00	£500.00	£634.98	£700.00	£800.00	£900.00	£1,000.00	£1,100.00	£1,200.00
Procedure cost endoscopic management/urethrotomy	£900.00	-£2,541	-£2,395	-£2,248	-£2,102	-£1,904	-£1,809	-£1,662	-£1,516	-£1,369	-£1,223	-£1,076
	£1,000.00	-£2,743	-£2,597	-£2,450	-£2,304	-£2,106	-£2,011	-£1,864	-£1,718	-£1,571	-£1,425	-£1,278
	£1,100.00	-£2,946	-£2,799	-£2,653	-£2,506	-£2,308	-£2,213	-£2,066	-£1,920	-£1,773	-£1,627	-£1,480
	£1,195.78	-£3,139	-£2,993	-£2,846	-£2,700	**-£2,502**	-£2,407	-£2,260	-£2,114	-£1,967	-£1,820	-£1,674
	£1,300.00	-£3,350	-£3,203	-£3,057	-£2,910	-£2,712	-£2,617	-£2,471	-£2,324	-£2,178	-£2,031	-£1,885
	£1,400.00	-£3,552	-£3,405	-£3,259	-£3,112	-£2,915	-£2,819	-£2,673	-£2,526	-£2,380	-£2,233	-£2,087
	£1,500.00	-£3,754	-£3,608	-£3,461	-£3,315	-£3,117	-£3,021	-£2,875	-£2,728	-£2,582	-£2,435	-£2,289
	£1,600.00	-£3,956	-£3,810	-£3,663	-£3,517	-£3,319	-£3,224	-£3,077	-£2,931	-£2,784	-£2,638	-£2,491
	£1,700.00	-£4,158	-£4,012	-£3,865	-£3,719	-£3,521	-£3,426	-£3,279	-£3,133	-£2,986	-£2,840	-£2,693
	£1,800.00	-£4,360	-£4,214	-£4,067	-£3,921	-£3,723	-£3,628	-£3,481	-£3,335	-£3,188	-£3,042	-£2,895
	£1,900.00	-£4,563	-£4,416	-£4,270	-£4,123	-£3,925	-£3,830	-£3,683	-£3,537	-£3,390	-£3,244	-£3,097

Figure 4: Two way sensitivity analysis of probability of urethroplasty following endoscopic management/urethrotomy/Optilume and further urethroplasty following urethroplasty

		Proportion having urethroplasty following endoscopic management/urethrotomy/Optilume										
		0.0%	10.0%	20.0%	30.0%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%	100.0%
Proportion having further urethroplasty following urethroplasty	5.0%	-£4,538	-£4,389	-£4,191	-£3,928	-£3,605	-£3,241	-£2,866	-£2,511	-£2,201	-£1,951	-£1,766
	10.0%	-£4,538	-£4,389	-£4,191	-£3,928	-£3,603	-£3,237	-£2,861	-£2,505	-£2,193	-£1,942	-£1,757
	12.0%	-£4,538	-£4,389	-£4,191	-£3,928	-£3,603	-£3,236	-£2,859	**-£2,502**	-£2,190	-£1,938	-£1,753
	20.0%	-£4,538	-£4,391	-£4,193	-£3,928	-£3,600	-£3,231	-£2,850	-£2,490	-£2,175	-£1,921	-£1,735
	25.0%	-£4,538	-£4,391	-£4,194	-£3,928	-£3,599	-£3,227	-£2,844	-£2,482	-£2,165	-£1,910	-£1,722
	30.0%	-£4,538	-£4,393	-£4,195	-£3,929	-£3,598	-£3,224	-£2,838	-£2,473	-£2,155	-£1,897	-£1,709
	35.0%	-£4,538	-£4,394	-£4,197	-£3,930	-£3,598	-£3,221	-£2,832	-£2,464	-£2,143	-£1,884	-£1,694
	40.0%	-£4,538	-£4,395	-£4,199	-£3,932	-£3,597	-£3,217	-£2,825	-£2,454	-£2,131	-£1,870	-£1,678
	45.0%	-£4,538	-£4,397	-£4,202	-£3,933	-£3,597	-£3,214	-£2,819	-£2,444	-£2,118	-£1,854	-£1,661
	50.0%	-£4,538	-£4,399	-£4,205	-£3,936	-£3,597	-£3,211	-£2,812	-£2,434	-£2,104	-£1,838	-£1,643
	55.0%	-£4,538	-£4,402	-£4,208	-£3,938	-£3,598	-£3,208	-£2,805	-£2,423	-£2,089	-£1,821	-£1,624

Figure 5: PSA results showing cost difference on histogram



What were the main findings of each of the sensitivity analyses?

Scenario analysis

All scenario analyses demonstrate cost savings with the use of Optilume compared with endoscopic management or urethroplasty. Optilume is cost-saving when compared with endoscopic management in the base case analysis and urethroplasty within a scenario analysis (savings of £2,502 and £243 respectively). The use of the OPEN RCT micro costing approach presents cost savings of £3,690 and £1,089 when Optilume is compared to endoscopic management and urethroplasty respectively. Optilume is also cost-saving when compared to endoscopic management and when using recurrence transition probabilities informed from the OPEN trial (savings of £988 and £1,663 when NHS reference costs and the OPEN RCT micro costs are used respectively), or from the ROBUST I study (savings of £384 per patient).

One-way and two-way sensitivity analysis

As shown in the tornado plot, use of Optilume remained the cost saving treatment strategy across all but one of the parameters that were changed individually within plausible ranges. The only parameter that included cases where the Optilume was found to be cost incurring is the monthly probability of symptom recurrence associated with endoscopic management, which was included with a wide range from 1.9% to 20.3% in the sensitivity analysis. However, this scenario is particularly uncertain due to the differences in endoscopic management recurrence rates reported in the literature. When the relative benefit of Optilume that was observed in ROBUST III is utilized to define the recurrence rate for Optilume in the model (Scenario 1 above), Optilume remains significantly cost beneficial. Literature reports on stricture recurrence vary after standard endoscopic management, with the ROBUST III trial showing recurrence rates for endoscopic management in line with those reported for subjects with multiple prior interventions (Pickard et al., 2020, Heyns et al., 1998, Santucci and Eisenberg, 2010, Jordan et al., 2013, Elliott et al., 2021a). This is explored further using two-way sensitivity analysis because the variation in recurrence rates is likely to impact both endoscopic management and Optilume. The threshold value for monthly probability of recurrence with endoscopic management is 4.1% which would equate to a relative risk of 0.62 for recurrence with Optilume vs endoscopic management. This is double the estimated relative risk from the ROBUST III study and likely falls outside the estimated difference confidence intervals (difference of 28.7% to 66.9% 95% CI reported in Figure 1 of unpublished manuscript).

Figures 2, 3 and 4 show the results of the model are highly robust to the two-way sensitivity analyses.

Figure 2 is a two-way sensitivity analysis showing as the monthly probability of recurrence associated with Optilume increases, the monthly probability of recurrence associated with urethrotomy must also increase for Optilume to remain cost saving. These values were varied based on the uncertainty surrounding recurrence rates. As described, the rates reported in the ROBUST III study used in the base case were generally similar to those reported in the literature for recurrent strictures, the rates of recurrence reporting in the OPEN RCT for endoscopic management were lower than those reported in ROBUST III. Some combinations of recurrence rates do lead to Optilume becoming cost incurring. However, these are typically where the monthly probability of Optilume is equal to or higher than the monthly probability with endoscopic management which the ROBUST III study has indicated is not the case. In some cases small differences between the two treatments with Optilume still having a lower recurrence rate does lead to cost increases, however, these are all expected to be outside of the confidence intervals presented for the difference between Optilume and standard care in the ROBUST

III study. The study reports a 95% CI for difference in treatment failure at 6 months between 28.7% and 66.9%.

Figure 3 is a two-way sensitivity analysis showing that Optilume remained cost saving when the price of Optilume (excluding device) was raised to its highest range of £1,200 and the price of endoscopic management was at its lowest range of £900. These costs were varied based on the uncertainty in using NHS reference costs for the costing of endoscopic management. The lowest costing of endoscopic treatment was found from the NICE MIB, which reported £1,067 (when updated to the latest NHS reference costs). The price of the Optilume procedure (excluding device) price ranged dependent on if it is an outpatient or day case procedure, the highest cost from NHS reference costs was £1,067, assuming it is a day case procedure. Therefore the ranges used in the sensitivity analysis are considered plausible. Even where the cost of the procedure is equal between Optilume and endoscopic management i.e. assuming no procedures can be performed as outpatient procedures and there is no resource saving from an Optilume procedure, the introduction of Optilume is still estimated to be cost saving.

Figure 4 is a two-way sensitivity analysis showing that Optilume remains cost saving for all % variations of using urethroplasty as the follow up treatment in both the intervention and comparator arms of the model. This model is therefore highly robust to changes in the choice of follow up treatment given to patients after their initial treatment for a urethral stricture. ***Threshold analysis***

Probabilistic sensitivity analysis

The PSA demonstrates that the results are robust to joint parameter uncertainty. All parameters were varied in the PSA with the majority of distributions based on confidence intervals reported in the literature, particularly for those parameters that are key drivers of results (probability of recurrence). Optilume was cost saving in 93.4% of 1,000 iterations, as shown in Figure 5.

What are the main sources of uncertainty about the model's conclusions?

The results of the model are robust to the sensitivity analyses conducted providing confidence in the model's conclusions. The only input parameter that lead Optilume to become cost-incurring at the edge of the ranges within the deterministic sensitivity analysis was the monthly probability of recurrence associated with endoscopic management. However, as aforementioned, this input is particularly uncertain due to the differences in endoscopic management recurrence rates observed between the ROBUST III and OPEN RCT and it is unlikely to vary on its own without changes also occurring to probability of recurrence with Optilume. Provided the relative risk between the two treatment arms remains below around 0.6 it is estimated that Optilume would remain cost saving.

Miscellaneous results

Include any other relevant results here.

Tables displaying the number of repeat procedures throughout the model five year time horizon are presented below. Please note that the results are based upon 100 patients unless labelled otherwise.

Clinical outcome	Optilume	Endoscopic management	Incremental
Total number of repeat procedures (endoscopic)	51	109	**-59**
Total number of repeat procedures (surgical)	60	122	**-62**
Total number of repeat procedures	111	231	**-120**
Number per patient	1.11	2.31	**-1.20**

Number of repeat procedures	Year 1	Year 2	Year 3	Year 4	Year 5
Optilume	19.9	45.7	69.1	90.7	111.0
Endoscopic management	85.4	144.1	178.9	206.3	231.2
Incremental	**-65.5**	**-98.3**	**-109.8**	**-115.6**	**-120.3**

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

The economic model was built in Microsoft Excel in house by one health economist at York Health Economics Consortium. The model underwent quality assurance processes and review of all inputs by an intendent health economist at York Health Economics Consortium. Most of the input parameters were validated by an independent UK clinician. Key inputs, where possible, were based on robust sources that were applicable to a UK setting.

No previous economic evidence of Optilume was identified in the systematic review. One study, Pickard et al., (2020), completed an economic evaluation alongside the OPEN RCT which compared the cost-effectiveness of urethroplasty to endoscopic management. The results within Pickard (2020) where presented over a ten-year time horizon and, therefore are not directly comparable to the results presented in this model. As discussed previously the risk of recurrence in the OPEN RCT was reported to be much lower than that in the ROBUST III study. However, the results of the OPEN study could be used to validate the results of the economic model. The model developed alongside the OPEN RCT reported costs of £6,553 and £8,026 for urethrotomy and urethroplasty respectively (incremental difference of £1,473. In order to compare the results of this model to the OPEN RCT model the following changes were made:

- Probability of recurrence for endoscopic management and urethroplasty were based on the OPEN RCT
- Procedure costs for endoscopic management and urethroplasty based on those used in the OPEN study (£1,543 for urethrotomy and £6,001 for urethroplasty, both including the healthcare and patient related costs)
- Removal of adverse events costs because they were not included in the OPEN model
- Removal of costs associated with cured and recurrence health states because they did not appear to be included in the OPEN model.

As a result of these changes our model estimated costs associated with urethrotomy and urethroplasty over 10 years of £7,011 and £9,007 respectively (incremental difference of £1,996). Therefore, the results from our model when using the OPEN data are similar to that reported by the OPEN study which gives confidence in the results of the model. It was not possible to ascertain the reasons for the slightly higher costs estimated in this model from the reporting by Pickard etc al. However, it is noted that it is not clear from Pickard et al what cycle length was used and also what resulting probability of recurrence was used, so these may differ between the two models.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

No clinical experts contributed to the development of the model.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The economic review and cost-consequence model indicate that the use of Optilume results in estimated cost savings of £2,502 per patient if introduced in the NHS for recurrent anterior urethral strictures. Cost savings result from a reduction in recurrence (as demonstrated in the clinical submission) and therefore a reduction in the health care related costs and resources associated with repeat procedures (both surgical and endoscopic). As demonstrated by the cost-consequence model, the increase in costs of initially using Optilume compared with endoscopic management is outweighed by the costs saved from a reduction in procedure recurrence. This was estimated to remain the case in 93.4% of model iterations when running 1,000 iterations of the model as part of PSA for the base case analysis. Results were also robust to changes in individual input parameters as demonstrated in sensitivity analyses, with the probability of recurrence associated with endoscopic management as the only exception. There may also be additional costs associated with treating recurrent anterior urethral strictures that would not be captured in the model, and therefore potentially further underestimating the potential cost savings of introducing Optilume.

Briefly discuss the relevance of the evidence base to the scope.

As discussed in the clinical submission dossier, the clinical evidence demonstrating a reduction in the recurrence of strictures with Optilume was robust and well aligned with the scope.

The cost-consequence model was from the perspective of the NHS and Personal Social Services and all parameters used in the model were aligned with the UK setting and the patient population outlined within the scope. Furthermore, the cost model includes the comparators outlined in the scope and incorporates the following outcome measures: stricture free rate, rate of reintervention procedures, time to treatment failure (i.e. recurrence) and device-related adverse events.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

No previous evidence of Optilume was identified in the systematic review and, therefore, it was not possible to directly compare the cost-effectiveness results against published literature. However, Pickard (2020) reported the cost-effectiveness results of urethrotomy compared with urethroplasty, with the conclusion that urethroplasty is unlikely to be considered cost-effective due to the high initial cost of treatment. As discussed previously the results of this model align well with the results reported in Pickard et al when using similar inputs giving confidence in the model's structure and underlying calculations. However, the recurrence probabilities used in the base case are considerably higher in this model when comparing with Pickard et al and so therefore are the estimated costs. The monthly probabilities in this model are based on the ROBUST III study (Elliott et al., 2021a) because it is the only direct comparative evidence available for Optilume. It is expected that this study is generalisable

to a UK setting, however, it is acknowledged that this may represent a harder to treat population due to the stricter inclusion criteria, and therefore shows higher recurrence rates. However, the results of this study for the Optilume arm align well with the ROBUST I study which has less strict inclusion criteria and is therefore judged to be more likely to align with the wider recurrent stricture population (Mann et al., 2021). However, the ROBUST I study is only a single arm study so it is not possible to observe the recurrence rates for those patients undergoing standard of care. Various scenarios were conducted in order to address this area of uncertainty in the model. Other literature reports on the cost-effectiveness of urethroplasty vs endoscopic management found a slight benefit of urethroplasty in a US setting ($16,093 vs $17,748 total cost), which was similarly driven by the recurrence rate of endoscopic management leading to secondary management with urethroplasty (Rourke et al, 2004).

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis is relevant to all groups included in the scope. Although some parameters such as the risk of recurrence and the treatments received following recurrence are all likely to vary across patients, these inputs were tested in sensitivity analysis and the results were robust to variations in these input parameters (see Figures 2,3 and4).

The ROBUST III study, based in the US, was used for the base case recurrence probabilities (Elliott et al., 2021a). The population used in the ROBUST III, due to being US based and enrolling a more difficult patient population than that studied in the OPEN RCT. To explore this we used sensitivity analysis, (Scenario 1), which looked at the alternative monthly recurrence probabilities from the OPEN RCT, a UK study which reported lower recurrence rates. As seen in Table 10, the results were robust to this variation in the parameter and Optilume was still estimated to be cost saving.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths

Where possible, robust data sources were adopted for model input parameters to ensure appropriate values were applied within the analysis. In terms of unit costs, this meant the utilisation of national databases that are widely adopted for economic evaluations undertaken from a UK perspective.NICE, such as the British National Formulary and NHS Reference Costs.

The base case probability of recurrence was informed from a randomised controlled trial with 127 subjects (ROBUST III) that estimated the efficacy and safety of Optilume compared to endoscopic management (Elliott et al., 2021a). The probability of recurrence with Optilume has also been confirmed with a single arm study reporting results at 3 years (ROBUST I). This study also provides reassurance that the efficacy of Optilume is likely to continue and for those that respond to the treatment the effects are likely to continue.

Extensive sensitivity analysis has been conducted and the results of the model appear robust to plausible changes in input parameters.

Limitations

The ROBUST III trial was US based rather than UK based and, therefore, is not directly generalisable to the NICE scope (Elliott et al., 2021a). However, the results of ROBUST III (Elliott et al., 2021a) study align with ROBUST I (Mann et al., 2021), which had a less strict inclusion criteria (monthly Optilume recurrence probabilities of 2.6% and 0.9% accordingly). Therefore, this suggests the recurrence rates within ROBUST III reflect a wider study population.

The recurrence probabilities associated with endoscopic management are considerably higher within ROBUST III than the OPEN RCT, although the probabilities reported for endoscopic management in ROBUST III were largely in line with other studies evaluating treatment of recurrent strictures (Pickard et al., 2020, Heyns et al., 1998, Santucci and Eisenberg, 2010, Jordan et al., 2013, Elliott et al., 2021a).(Pickard et al., 2020)Therefore, data from the urethrotomy arm of the OPEN RCT has been used as a proxy for endoscopic management within a scenario analyses as a conservative estimate. However, Optilume remained cost saving within this scenario. Furthermore, no head to head data were available comparing Optilume to urethroplasty. Therefore, an indirect comparison was conducted to estimate the relative risk of recurrence between the two treatment options due to an absence of alternative information (as explained further in Section 3).

Quality of life was not considered in the model (in line with the NICE scope), however, a reduction in the incidence of recurrent anterior urethral strictures is likely to impact substantially on patient's quality of life. Therefore, the model is unlikely to capture the full benefits of Optilume.

Detail any further analyses that could be done to improve the reliability of the results.

The results of the cost analysis are likely to provide a good reflection of the impact of introducing Optilume into routine care in the NHS. However, a comparative trial in the UK in a wider population would confirm these results. Further research could be conducted into the monthly probability of recurrence, in a UK setting with a wider population group and looking specifically at Optilume as a comparator. Further research could also be conducted on the true cost of Endoscopic procedures in the UK NHS through a micro costing methodology.

Further research could provide more accurate estimates to use in the model, however, the results of the model appeared robust when tested using conservative values both for risk of recurrence and cost of interventions in sensitivity analyses and therefore would be unlikely to change the direction of the results.

5 References

Please include all references below using NICE's standard referencing style.

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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	03Dec21
Date span of search:	01Jan1900 to 03Dec21

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Search terms were developed by concept utilizing the PICO approach (Population, Intervention, Comparator, Outcome). The population under study included male urethral stricture, the intervention of interest was drug coated balloons, the comparator of interest was standard of care endoscopic treatments or urethroplasty, and the outcomes of interest were stricture recurrence.

The search was conducted the MEDLINE library via PubMed utilizing the search terms and Boolean operators as listed in Table A-1. Search #31 and #33, returned large numbers of results and were further filtered for 'Clinical Trial' and 'Randomized Controlled Trial'.

Table A-1. MEDLINE Search terms and operators

Search	Search Terms	Search	Search Terms
1	Urethral Stricture [mh]	16	Urethral Dilation [tiab]
2	Urethral Stenosis [mh]	17	S-curve dilator [tiab]
3	Urethral Stricture [tiab]	18	s-curve dilator [tiab][all]
4	Urethral Stenosis [tiab]	19	Bougie Dilation [tiab]
5	#1 OR #2 OR #3 OR #4	20	Urethrotomy [tiab]
6	Drug Coated Balloon [tiab]	21	Optical Urethrotomy [tiab]
7	Drug Eluting Balloon [tiab]	22	DVIU [tiab]
8	Paclitaxel Coated Balloon [tiab]	23	Urethroplasty [tiab]
9	Optilume [tiab]	24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
10	In.Pact Admiral [tiab]	25	Stricture Recurrence [tiab]
11	Lutonix [tiab]	26	Redilation [tiab]
12	Ranger Drug Coated Balloon [tiab]	27	Revision Urethroplasty [tiab]
13	Stellarex [tiab]	28	Repeat Urethrotomy [tiab]
14	Biolux [tiab]	29	#24 OR #25 OR #26 OR #27
15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	30	#5 AND #15
		31	#5 AND #24
		32	#5 AND #15 AND #29
		33	#5 AND #24 AND #29

	34	#5 AND #15 AND #24 AND #29

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional searches were conducted to identify ongoing studies that may report results in the near future. Two clinical trial registration databases were searched (US National Library of Medicine registry [clinicaltrials.gov/ct2/home] and EU Clinical Trials Register [https://www.clinicaltrialsregister.eu/ctr-search/search]) using the keyword 'Urethral Stricture'.

Inclusion and exclusion criteria:

Inclusions:

- Male urethral stricture
- Outcomes after endoscopic treatment, single arm
- Outcomes after open surgical treatment (urethroplasty), single arm
- Randomized comparative studies
- Included cost analysis

Exclusions:

- Preclinical/animal studies
- In-vitro studies
- Pediatric studies
- Case reports or early experimental techniques
- Editorials, commentary, technology assessments
- Posterior or membranous strictures
- Hypospadia repair, meatal/glans stricture repair
- Studies of adjunct therapies (e.g. steroids, mitomycin C)
- Diagnostic assessments
- Female strictures
- Cost effectiveness or other non-recurrence outcome measures
- Clean intermittent catheterization or home dilation
- Study protocol or design discussion

Non-comparable population (e.g. length >5cm, urethral dislocation)

Data abstraction strategy:

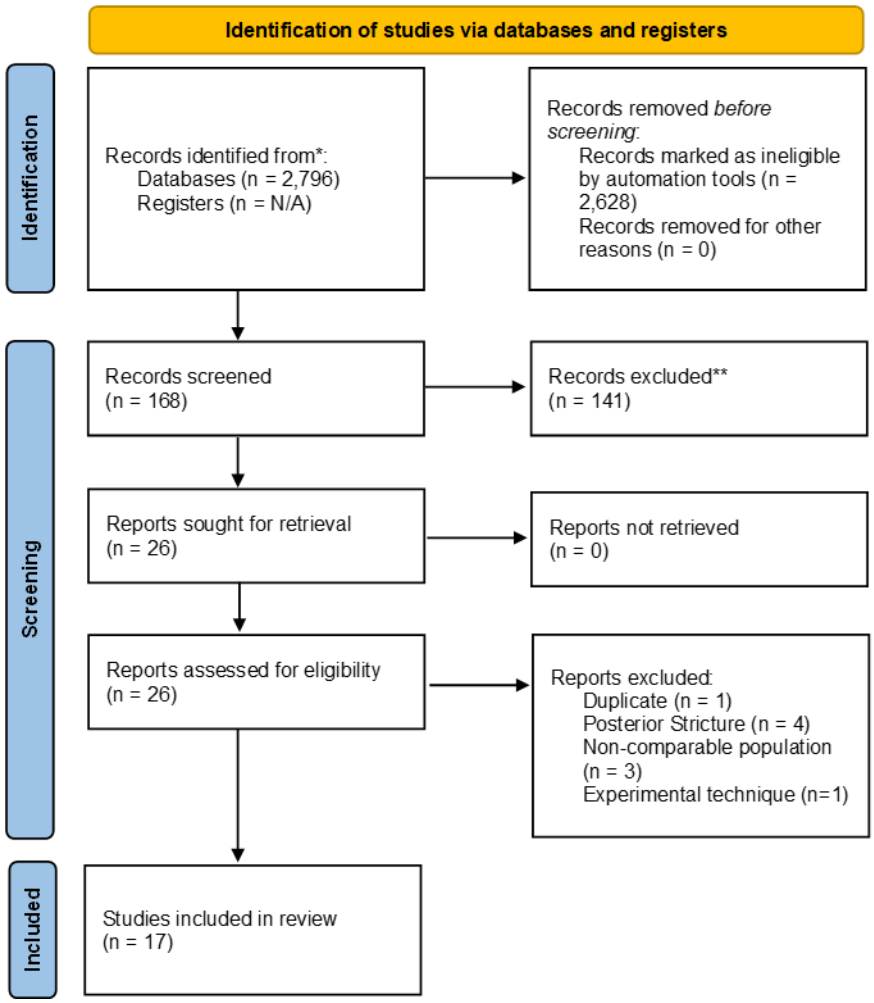
Summary search results (title, brief description) for Search 30-34 were reviewed for relevant articles (P&I, P&C, P&I&O, P&C&O, P&I&C&O). Articles possibly meeting inclusion were identified and abstracts were reviewed for exclusion criteria. Articles continuing to meet criteria after abstract review were given full text review and final determination for inclusion was made.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Guolao B, Eur Urol, 2020	OPEN randomized clinical trial	Duplicate	This was an abbreviated publication of results for the OPEN RCT. The Pickard reference included in the summary represented a more comprehensive reporting of study results.
Atak M, Kaohsiung Med, 2011	Randomized laser vs. cold-knife DVIU	Posterior urethral stricture	The Optilume DCB has not been evaluated in posterior strictures
Mehrsai A, Urology, 2007	Urethroplasty	Posterior urethral strictures	Text
Cai W, Clinics (Sao Paulo), 2016	Laser vs cold knife DVIU	Posterior urethral stricture	Text
Jablonowski Z, Photomed Laser Surg, 2010	Laser vs cold knife DVIU	Posterior urethral stricture	Text
Vasudeva P, Int J Urol, 2015	Dorsal vs ventral buccal graft urethroplasty	Non-comparable population (>5cm)	The Optilume DCB is limited to short urethral strictures that can be treated with a single DCB (<4cm max length)
Dubey D, J Urol, 2007	Dorsal vs penile skin graft urethroplasty	Non-comparable population (>5cm)	Text
Soliman MG, Scand J Urol, 2014	Dorsal vs penile skin graft	Non-comparable population (>5cm)	
Pansadoro V, J Urol, 1999	Buccal mucosal graft urethroplasty	Experimental technique	This was an initial reporting of outcomes from early experience with the buccal grafting technique.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

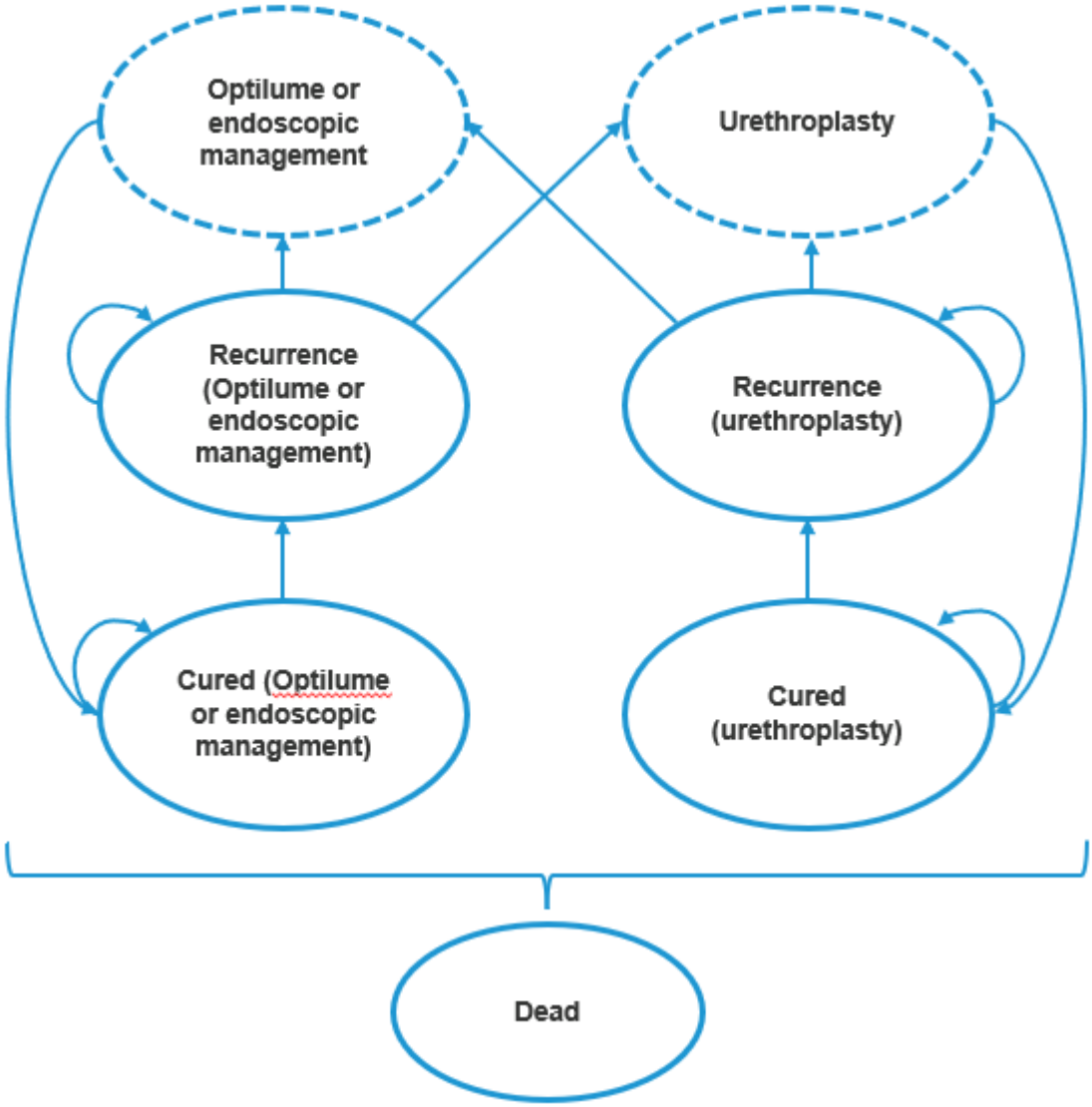


Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*:
** Must be Medical Director or equivalent*

Date: 11Jan22

Print: Ian Schorn

Role / organisation: Vice President Clinical Affairs, Urotronic Inc

Contact email: [redacted]

GID-MT565 Optilume for recurrent bulbar urethral strictures

Addendum 1: Paclitaxel Safety Results

One of the innovative aspects of the Optilume device is the paclitaxel coated balloon. It has been observed that during infusion studies of paclitaxel in treating cancer subjects, there have been adverse reactions and drug-related side effects including neurotoxicity and myelosuppression (Virasoro et al., 2020) and this may lead to queries around the safety of paclitaxel use with Optilume. The EAC considered therefore, that the committee would benefit from a review of the information regarding the safety of paclitaxel in this setting. The company has shared some of the data on this, however due to the confidential nature of the data, it cannot be shared widely and therefore cannot be included in the main Assessment Report. The EAC note there are some minor discrepancies between results published and results provided by the company. This addendum has been prepared by the EAC as a supplement to the Assessment Report.

1 Paclitaxel Safety Results

Although there have been drug related side effects and adverse reaction when using paclitaxel to treat cancer, the concentration of paclitaxel delivered locally during the Optilume DCB procedure is much lower than a single dose of systemic chemotherapy provided to cancer patients. Result from the ROBUST I study reported that the urine concentration immediately post-procedure in ROBUST I was about six times lower than in chemotherapy patients, and dropped significantly by five days. Serum levels were also very low in pharmacokinetic studies of the drug by the company in both ROBUST I and III trials, demonstrating an elimination profile as expected (Elliott et al., 2022a; Elliott et al., 2021a; Mann et al., 2021; Virasoro et al., 2020).

<u>ROBUST I</u>

The concentration of paclitaxel in the urine, blood and semen were a secondary endpoint in the ROBUST I trial (table 1). [redacted]

From the published literature, mean urinary paclitaxel concentration was 184.3±179.1 ng/ ml immediately post-procedure (n=52) and 2.6±4.8 ng/mL at five days (n=21) (Virasoro et al., 2020). Mean urinary concentration provided by the company is [redacted] (table 1) [redacted] (Post-procedure mean urinary concentration was [redacted] but decreased at 5-days post-procedure to 2.6±4.8, and to [redacted].

Published data reported that plasma paclitaxel concentration was very low, as it was near the limit of quantification immediately post-procedure (low=0.1 ng/ml) (Virasoro et al., 2020). More detailed study results provided by the company reported that plasma paclitaxel concentration was [redacted], and [redacted]. The plasma concentration [redacted]. Plasma concentrations were [redacted].

Semen paclitaxel concentration, measured in 31 participants, was low (2.5±2.9 ng/mL) at 14 days ([redacted]) and 1.0±1.6 ([redacted]) at 30 days post procedure (Virasoro et al., 2020).

Table 1: Summary of Paclitaxel Pharmacokinetic (PK) results in ROBUST I trial (Table taken from company 4-year report of ROBUST I results – Elliott et al., 2022a).

Time	PTX Conc.	Optilume DCB PTX (ng/mL)		
		Plasma	Urine	Semen
-1.00 (Baseline)	M±SD Range (N)	[redacted]	[redacted]	NR
0 hour (Post-procedure)	M±SD Range Median (N)	[redacted]	[redacted]	NR
1 hour	M±SD (N)	[redacted]	NR	NR
3 hours	M±SD (N)	[redacted]	NR	NR
5 hours	M±SD (N)	[redacted]	NR	NR
10 hours	M±SD Range (N)	[redacted]	NR	NR
24 hours	M±SD (N)	[redacted]	NR	NR
5 days	M±SD Range Median (N)	[redacted]	[redacted]	NR
14 days	M±SD Range Median (N)	NR	[redacted]	[redacted]
30 days	M±SD Range	NR	[redacted]	[redacted]

Time	PTX Conc.	Optilume DCB PTX (ng/mL)		
		Plasma	Urine	Semen
	Median (N)		[redacted]	[redacted]
	NR = Not required; BLQ = Below level of quantification			

[redacted]

[redacted]

[redacted]

Overall, pharmacokinetic studies in ROBUST I demonstrate that paclitaxel was eliminated as expected, and concurrent biochemical and haematological investigations performed during ROBUST I indicated that the Optilume device and the procedure [redacted] Therefore, the EAC has no concerns around safety of the device in regards to sperm quality and potential teratogenicity.

Table 2: Results for Sperm Quality in ROBUST I trial (table taken from company 4-year report of ROBUST I results – Elliott et al., 2022a).

Category (Reference for normal range)	Baseline	14 Days	6 Month
Semen volume, mL M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]
Density/Concentration, (> 20 million/mL) M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]
Total Sperm Number, (40 to 300 million/mL) M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]
Sperm Motility, (≥40 %) M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]
Sperm Progressive motility, (≥32 %) M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]
Morphology, (≥4 %) M ± SD (n) Range Median	[redacted]	[redacted]	[redacted]

ROBUST II

Pharmacokinetic, biochemical and serological tests were not reported in the ROBUST II trial.

ROBUST III

ROBUST III (Elliott et al., 2021a) included a nonrandomized arm of 15 participants for paclitaxel pharmacokinetic assessments, including samples of plasma, semen and urine taken at baseline and various time points post-procedure through 6-months. Systemic exposure to paclitaxel was minimal, with average plasma concentration rising above the limit of quantification at 1-hour post-procedure (0.12 ng/mL) and 3 hours (0.11 ng/mL).

Average paclitaxel concentration in the urine was highest immediately post-procedure (414.4 ng/mL) and decreased to 13.8 ng/mL at Foley removal. At 30-days post-procedure, the paclitaxel was below the limit of quantification (Elliott et al., 2021a).

The paclitaxel concentration in semen was not reported at baseline, but was 2.99 ng/mL at 30 days, 0.48 ng/mL at 3 months and 0.12 ng/mL at 6 months, and was

detectable in 9/15 (60%), 5/13 (39%), and just 1/12 (8.3%) of subjects respectively (Elliott et al., 2021a).

National Institute for Health and Care Excellence

Collated comments table

MTG: GID-MT565 Optilume

Expert contact details and declarations of interest:

Expert #1	Prof Christopher Chapple, Consultant Urologist, Sheffield Teaching Hospitals NHS Foundation Trust
	Nominated by: Company
	DOI: None
Expert #2	Amr Emara, Consultant Urologist, Hampshire Hospital FT
	Nominated by: Company
	DOI: None
Expert #3	Katie Moore, Consultant Urological Surgeon, Manchester Foundation Trust
	Nominated by: Company
	DOI: None
Expert #4	Miss Louise Olson, Consultant Urological Surgeon, Salford Royal NHS Foundation Trust
	Nominated by: Company
	DOI: None
Expert #5	Mr Trevor J Dorkin, Consultant Urologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust
	Nominated by: Company
	DOI: None
Expert #6	Miss Pareeta Patel, Consultant Urologist, Epsom and St Helier, NHS Trust
	Nominated by: Company
	DOI: None
Expert #7	Majed Shabbir, Consultant Urological Surgeon, Guy's & St. Thomas' NHS Trust
	Nominated by: Company
	DOI: None
Expert #8	Ian Eardley, Consultant Urological Surgeon, Leeds Teaching Hospital Trust
	Nominated by: NICE
	DOI: NONE
Expert #9	Christian Seipp, Consultant Urological Surgeon, Betsi Cadwaladr University Healthboard – Wrexham Maelor Hospital

	Nominated by: Company
	DOI: NONE

			Response
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	Expert #1: I have experience and I am involved in a tertiary centre for the management of urethral stricture disease in Sheffield. I am familiar with the technology. I have not used it yet. It may have a role and it needs to be discussed further.	
	Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #2 I am familiar with the procedure and technology. I am not currently using Optilume but we are in the process of starting it soon. This technique is not widely used in NHS, to date at least one NHS hospital has started using this technique.	

		This technique is developed to deal with male urethral stricture and therefore not used by another speciality. It will be performed instead of the routine cases - urethral dilation or optical urethrotomy - that can be done as a core urological procedure with no need to refer to subspecialised centre.	
		Expert #3 I am familiar with the technology of balloon dilatation of strictures though have not yet used the Optilume device in vivo. This is a new device on has only been approved for use in a few centres within the NHS so far but I understand a number of other centres have business cases in hand to use the device. I suspect the speed of uptake will be high given that Optilume can be used in the outpatient setting and the pressures that the Covid pandemic has put on theatre waiting lists. Balloon dilatation of strictures is performed in specialities such as vascular and upper GI. Patients are referred to urology for management of their strictures. Urology would not need to refer them on.	

	–	Expert #4 I have had video calls with James Wright & Paul Burns from Optilume regarding what the technology is and what is involved with the application. I have no experience using or seeing optilume in action.	
	–	Expert #5 I have not used the technology myself but have seen video demonstrations and read the literature regarding the product/device. I specialise in genito-urethral surgery and am very familiar with the treatment of urethral stricture disease. No – I have not used Optilume to date. As far as I am aware, it is not currently used in the NHS. However, I would expect it to be used widely in the urology community once it became available and after appropriate training. No – as far as I am aware. Not applicable.	
	–	Expert #6 I am familiar with this technology and have used it on a small number of patients in our trust and am continuing to use it on selected patients with recurrent bulbar urethral strictures.	

		I am aware of a number of trusts planning on offering optilume to patients and have also received referrals from trusts that are not yet performing the procedure. I would anticipate it would not take long for NHS trusts to start using it more widely as it does not require any additional skill or equipment to that already used by a General Urologist. Urethral stricture management falls under the remit of a Urologist and would not generally involve any other clinical speciality. I have received referrals and selected patients suitable for the procedure, and do not refer on to any other speciality. To date we have performed the procedure on 6 patients in our trust and have a further 8 patients selected to undergo the procedure in the near future.	
	–	Expert #7 Yes, I am familiar with the procedure and have lectured on its use. I have not personally used it yet, but we have just received approval to use it in our Trust	

		At present it is not widely used, but has the potential for considerable uptake across the NHS (both in teaching and district general hospitals) The basis of the technology is a drug coated balloons used in cardiac procedures This technology would be suitable for patients with urethral strictures. At present it has been used for recurrent strictures only, but could potentially be used for primary strictures as well	
	–	Expert #8 I regularly undertake Urethral dilatation, optical urethrotomy and open urethroplasty. I am familiar with the technology I have never used this technology It is not being undertaken widely within the NHS at present The technology is used purely by urologists	
	–	Expert #9 A) I am familiar with the procedure B) We are currently running regular clinics with Optilume procedures both in my NHS and my private practice. C) Based on my current experience, and given the advantages of the procedure both in terms of feasibility, ease of administration, and efficacy I would expect it to be taken up by more units around the country within a short period of time.	

		D) As far as I am aware, Optilume urethral dilatations are and will only be performed by urologists. Patients are not referred to other specialities	
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have not done any research in this area, but am well aware of the technology, the principles and the results.	
		Expert #2 I had no involvement in research on this procedure however I attended relative webinars with the current updates in outcomes of research and trials.	
		Expert #3 I have done bibliographic research on this procedure.	
		Expert #4 I have had no involvement with research on this proceedure	
		Expert #5 I have reviewed the data that is available (Robust I with 2 years follow-up)	

		Expert #6 Although I have read the published trial research, I have not personally had any involvement in the research of this procedure. I am auditing my outcomes with its use locally.	
		Expert #7 I have done bibliographic research on this procedure.	
		Expert #8 I AM FAMILIAR WITH THE PUBLISHED LITERATURE IN RELATION TO THIS TECHNOLOGY	
		Expert #9 I have done bibliographic research on this procedure.	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: This is the transfer of a technology used for endovascular treatment to the urethra using principles which have already been established with mitomycin. It is the first in a new class of procedures and should probably be confined to use after failed initial urethrotomy in view of costs, etc. It is only applicable to short strictures of 22 mm or less	

		Expert #2 Novel with early studies showing better efficacy with no safety concerns.	
		Expert #3 This is a variation on a design used for strictures in other organs. The addition of the Paclitaxel coating to prevent stricture recurrence is novel. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	
		Expert #4 This is a novel procedure/concept in treating recurrent strictures	
		Expert #5 The current standard of care for endoscopic management of urethral strictures is either optical urethrotomy (using a knife through a cystoscope) or urethral dilation using serial metal or plastic dilators. Balloon dilation of the ureter is a well-recognised technique for certain endourological procedures,	

		and this is an extension of it. The novel aspect with Optilume is the drug-coating of the balloon, designed to inhibit fibrosis and therefore reduce stricture recurrence. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	
		Expert #6 Although balloon dilatation and separate administration of drugs into the urethra (usually by injecting), to prevent recurrent stricture formation have been used in the management of urethral strictures for many years; optilume technology is an innovative way of being able to both dilate the stricture and easily administer a drug topically and therefore potentially more safely, with a more predictable and unified dose absorption and response. The use of paclitaxel in the urinary tract for prevention of stricture recurrence is however novel, with limited data. Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. *Although the use of paclitaxel is novel* Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	

		Expert #7 Novel approach	
		Expert #8 IT IS SIMILAR TO URETHRAL DILATATION AND URETHROTOMY IN THAT IT IS ENDOSCOPIC AND MINIALLY INVASIVE THE DIFFERENCE IS THAT THE BALLOON COATING IS THEORISED TO ENHANCE THE DURABILITY OF THE RESPONSE TO DILATATION IT IS FIRST IN CLASS AND DEFINITIELY NOVEL	
		Expert #9 Definitely novel and of uncertain safety and efficacy.	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: There is potential for replacing urethroplasty for some recurrent short strictures, to be used prior to urethroplasty in recurrent cases after failed urethrotomy.	
		Expert #2 Provisionally it will be used as addition to standard of care but if longer term studies confirm durability of outcomes, then it could replace the current endoscopic standard of care.	

		Expert #3 It has the potential to replace urethral dilatation + self dilatation for recurrent male urethral stricture disease.	
		Expert #4 In addition to and would likely replace optical urethrotomy and possibly urethral dilatation	
		Expert #5 It has the potential to replace urethral dilation and optical urethrotomy for the majority of strictures should there be proven superior efficacy.	
		Expert #6 I think this technology would be a good addition to the existing standard care. Currently, the management of recurrent urethral strictures includes repeated dilatation procedures or reconstructive urethroplasty surgery. In my opinion, those patients that have short lived responses to standard dilatation procedures but are not able or willing to undergo more invasive reconstructive surgery are likely to most benefit from this technology.	
		Expert #7 It has the potential to replace standard of care in the NHS, or to be an additional treatment in the armamentarium of the surgeon treating urethral strictures.	

		Expert #8 IT HAS THE POTENTIAL TO REPLACE CURRENT STANDARD CARE	
		Expert #9 Under normal circumstances, I would have expected it to be seen as an addition to existing standard of care. However, in the current climate of long waiting times for procedures carried out under general anaesthetic, any procedure that allows treatment under local anaesthesia in an outpatient clinic setting with excellent postinterventional results is likely to replace current standard of care.	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Optical urethrotomy, which can be repeated followed by intermittent self-dilatation if first urethrotomy unsuccessful followed by urethroplasty.	
		Expert #2 For anterior urethral strictures < 3 cm optical urethrotomy/ urethral dilation or urethroplasty are the current standard of care.	
		Expert #3 Current standard of care for management of a recurrent urethral stricture is a dilatation. This carries a 60% stricture recurrence risk and therefore the patient is taught to self dilate to prevent this. This	

		is usually done 2-3 times per week by the man. The operation is performed as a daycase under general or regional anaesthetic with the immediate risks of infection, bleeding and urethral injury. The alternative is an anastomotic or augmented urethroplasty. These require a general anaesthetic with a 1-2 night stay in hospital. There is a 15% stricture recurrence rate risks of infection, bleeding, erectile dysfunction (15%), discomfort, fistula formation and perioral numbness if a graft is required for augmentation. Men with recurrent strictures need to be referred to tertiary centres to discuss management of their recurrent problem.	
		Expert #4 The current management of patients is either optical urethrotomy, urethral dilation or urethroplasty	
		Expert #5 The current standard of care for endoscopic management of urethral strictures is either optical urethrotomy (using a knife through a cystoscope) or urethral dilation using serial metal or plastic dilators. These operations can be performed within all urology units by general urologists. An alternative procedure is urethroplasty – urethral reconstruction – which sometimes involves harvesting a buccal graft from the inner cheek. This is highly specialised surgery that is performed by 30-40 urological surgeons in tertiary centres in the UK.	
		Expert #6 As mentioned above. Patients being diagnosed with a stricture will undergo a dilatation procedure by their local urology service (commonly using graduated dilators, optical urethrotomy or a balloon dilator). In recurrent urethral strictures, the options are for repeated dilatation procedures including intermittent self-dilatation or referral to a specialist centre for potential urethroplasty as the long term curative option.	

		Guidelines on the management of urethral strictures include BAGURS professional practice recommendations (2017), AUA guidelines 2016, ICUD consensus, 2010, NICE clinical commissioning policy 2016 and more recently *EAU guidelines?* Optilume may provide a more durable response than standard dilatation for the management of recurrent urethral strictures and can be delivered locally by any Urologist.	
		Expert #7 Current standard is endoscopic surgery (urethral dilatation or optical urethrotomy for primary strictures), and urethroplasty for recurrent strictures	
		Expert #8 FOR NEW BULBAR URETHRAL STRICTURE URETHROTOMY IS THE CURRENT STANDARD OF CARE FOR RECURRENT URETHRAL STRICTURES, PATIENTS CHOOSE BETWEEN OPTICAL URETHROTOMY WITH CONTINUED INTERMITTENT SELF DILATATION OR URETHROPLASTY	
		Expert #9 Urethral strictures are either treated through endoscopic urethrotomy (optical urethrotomy), urethral dilatation or through open surgery (open urethroplasty with or without grafting).	
6	Are you aware of any other competing or alternative procedure/technology	Expert #1: No, none that are licensed for use or recommended.	

	available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?		
		Expert #2 Not to my knowledge.	
		Expert #3 Urethral stents are an alternative technology. They have been tried in the past but were a disaster. I understand that they have been 'reinvented' in the last few years but there will be a hesitancy to use them due to previous issues with the stents blocking and then being unable to be removed. Men that had these are now left with permanent suprapubic catheters or alternative urinary diversions. The stent differs in that it is a permanent indwelling stent to mechanically hold open the stricture compared to Optilume which is a device to dilate the stricture and then deliver a drug in to the urothelium to prevent the stricture recurring.	
		Expert #4 no	
		Expert #5 No	
		Expert #6 Use of drugs to prevent urethral stricture recurrence has been reported. However I am not aware of another drug coated balloon to allow ease and unified administration of a drug into a urethral stricture.	
		Expert #7 This system uses a balloon to dilate the stricture – the drug coating aims to improve the longevity of the dilatation, and has had impressive results in the phase 1 and subsequent RCT's. The	

		technology is the same as drug coated balloons used in treating cardiac atherosclerosis, but being used in a different part of the body for a different type of stenosis.	
		Expert #8 NO	
		Expert #9 There is obviously the option of urethral dilatation – however, this does not have the added benefit of applying medication to the dilated part of the urethra in an attempt to prevent or reduce the likelihood of further scarring and stricture recurrence. Open surgery with or without grafting (e.g. buccal mucosal graft) is far more invasive and requires hospitalisation, a prolonged catheterisation and a significant recovery period.	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Improve efficacy of existing treatment (urethrotomy/dilatation)	
		Expert #2 Less risk of recurrence and avoiding continuation of intermittent self-catheterisation, that will eventually reduce risk or UTIs and re-hospitalisation for same procedure.	
		Expert #3 It avoids the risks particularly erectile dysfunction and hospital stay with urethroplasty. It avoids the need to self dilate (which has a poor compliance) with standard urethral dilatation.	
		Expert #4 Reduced reoccurrence of stricture formation & repeated hospital attendances	

		Reduced need to self-catheterise	
		Expert #5 The initial results are promising with stricture-free rates of 70% at 2 years. This compares favourably with standard endoscopic management. If the benefit is proven in the current ROBUST III RCT, then this treatment will be a game-changer in stricture management. Patients will require fewer interventions at reduced frequency.	
		Expert #6 More durable response than current standard dilatation procedures for recurrent urethral strictures, as well as still being a day case procedure, without the need for a catheter and that can be easily performed by a local urologist.	
		Expert #7 Potential for improved outcome compared to standard of care for primary and recurrent strictures. Less costly and morbid than urethroplasty. Potentially more cost effective for primary strictures if data for recurrent stricture treatment holds true in the primary setting.	
		Expert #8 POTENTIAL IMPROVED DURABILITY OF URETHRAL DILATATION	
		Expert #9 Treatment under local anaesthesia Shorter waiting times and flexible booking of procedure (independent of theatre availability and general anaesthesia) Cost efficacy	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Yes, patients who have failed an initial urethrotomy with a short stricture	
		Expert #2 Patient with recurrent anterior/bulbar stricture < 3 cm.	
		Expert #3 Those with recurrent strictures who are not fit for anaesthetic, who wish to avoid erectile dysfunction risk with urethroplasty, those who do not want to perform self dilatation.	
		Expert #4 Patients unfit or unwilling to have urethroplasty	
		Expert #5 Men with urethral strictures, especially those who do not want to undergo urethroplasty which is a more morbid operation with more time away from work and involves having a catheter in place for several weeks.	
		Expert #6 Recurrent bulbar urethral strictures, up to 4cm in length, with short lived response to standard dilatation procedures, or who are ISC (intermittent self catheterisation) dependent but either not suitable or willing to undergo more	

		invasive reconstructive surgery in a specialist centre.	
		Expert #7 Patients with recurrent strictures, those unwilling or unable to undergo urethroplasty, strictures in difficult to treat locations (bladder neck, membraneous urethral strictures)	
		Expert #8 RECURRENT BULBAR URETHRAL STRICTURES	
		Expert #9 Patients with risk factors for general anaesthesia Patients unsuitable for open urethroplasty	
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: Yes, as an alternative to proceeding straight on to urethroplasty from failed urethral dilatation/urethrotomy.	
		Expert #2 The current literature is suggestive of significant reduction in the stricture recurrence rate which will reduce re-do procedure for same pathology and requirement for long term ISC.	
		Expert #3 Optilume can be performed in the outpatient setting as opposed to urethroplasty which requires theatre, anaesthetic, is more invasive and 1-2 night hospital stay.	

		Avoids the need for the patient to perform self dilatation meaning less hospital visits, less environmental impact with the disposable catheters used and could improve outcomes as we know compliance with self dilatation can be poor and hence the stricture recurs.	
		Expert #4 Yes. It is likely to lead to improved outcomes, fewer hospital visits or less invasive treatments	
		Expert #5 Yes, the potential is there. If the RCT proves superior outcomes this will mean fewer invasive procedures and hospital visits.	
		Expert #6 The current success rate of standard dilatation procedures for the first treatment of a stricture is <50% at 2 years. The success with repeated procedures rapidly declines to virtually no success at 2 years (J Urol 1998, Heyns). The potential benefit from optilume DCB dilatation, is less frequent recurrence rates than standard dilatation procedures. This will result in a related cost benefit of reduced repeat procedures and emergency admissions from stricture complications. Although it is unlikely in the long term that optilume will be as durable as reconstructive surgery, it is cheaper with a shorter hospital stay and does not require specialist centre expertise.	

		Expert #7 Yes, it could lead to improved outcomes, reduced recurrence, less need for self catheterisation, less need for urethroplasty, fewer hospital visits and more invasive open operations (based on the latest available ROBUST III data)	
		Expert #8 YES TO BOTH QUESTIONS	
		Expert #9 Yes – treatment can be delivered safely in outpatient department under local anaesthesia (thus offering more flexibility, shorter waiting times for treatment and potential cost savings) - given current efficacy data it seems realistic to expect fewer stricture recurrences and therefore better clinical outcomes with need for fewer re-interventions	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: This will cost more than urethrotomy alone, but less than urethroplasty if it avoids the need for that in a proportion of patients, therefore a significant cost saving.	
		Expert #2 There is no capital cost involved in this procedure, only cost of disposables and although the initial cost is higher than current standard of care but with less risk of same pathology recurrence and need for re-do, I	

		assume the overall cost could be in favour of this procedure especially if we factor in the cost of the long-term catheterisation and the possible UTIs treatment costs.	
		Expert #3 It will probably cost less in the long run.	
		Expert #4 I cannot comment on financial implications	
		Expert #5 This is difficult to judge, but overall, I think there is a potential cost saving given that over time there may be few hospital admissions	
		Expert #6 By reducing the frequency of stricture recurrence (50% for urethrotomy at 5 years following a first dilatation, *Pansodoro 1996*) and therefore need for repeat treatments, it should be cost beneficial. The cost of the optilume balloon itself is only slightly more than that of standard dilatation procedures and significantly less than that of reconstructive surgery.	
		Expert #7 Would cost less in the long term	
		Expert #8 DEVICE COST IS THE DIFFERENCE, SO WOULD BE MORE EXPENSIVE THAN URETHROTOMY, BUT LESS EXPENSIVE THAN URETHROPLASTY	

		THE CRUCIAL (UNDETERMINED) ISSUE IS WHETHER THE DEVICE DOES OFFER BETTER DURABILITY OF RESPONSE AND IF IT DOES, HOW LONG THAT DURABILITY IS	
		Expert #9 Considering the entire treatment pathway, I would expect the procedure to be less expensive than optical urethrotomy under GA and definitively less expensive than open urethroplasty.	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: Additional costs, but less than urethroplasty, therefore cost benefit potentially. This needs a clinical study though to confirm the previous results, and this is currently being planned by a group that we are leading to look at a randomised study against standard of care.	
		Expert #2 Initially marginally higher cost but less cost on the intermediate/long term.	
		Expert #3 As this will ultimately be done in the outpatient setting, it will be less in terms of staffing resources, space, bed hours etc.	
		Expert #4 It is likely to cost less because it can be delivered in an outpatient setting without the need for anesthetic	
		Expert #5	

		Minimal effect on resources.	
		Expert #6 I would expect the cost to be more or less the same as a standard dilatation procedure, requiring the same staffing, set up and basic equipment. The additional cost would be that of the optilume balloon over standard dilators, which in most UK stricture centres would be the Cook S-Dilators.	
		Expert #7 Initial outlay for the device will be more than the standard of care, but based on the multi-centre RCT data, the significantly lower recurrence rate would lead to a cost saving based on lower re-interventions	
		Expert #8 THE CRUCIAL (UNDETERMINED) ISSUE IS WHETHER THE DEVICE DOES OFFER BETTER DURABILITY OF RESPONSE AND IF IT DOES, HOW LONG THAT DURABILITY IS	
		Expert #9 I would expect cost savings due to the nature of the treatment (treatment in outpatients under LA) and the expected reduction in need for re-interventions.	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Standard urological practice setting and equipment.	
		Expert #2	

		No change to current facilities required for adopting this technique, however chemotherapy disposable equipment may be required, and this is already used as routine practice in all urology treatment centres in their daily procedures (e.g. TURBT followed by mytomycin c bladder instillation)	
		Expert #3 Clinic room, treatment chair, surgeon, HCA, time and area to recover	
		Expert #4 Can be given in outpatients	
		Expert #5 No changes needed.	
		Expert #6 I would use X-ray guidance during the procedure to place the balloon accurately, which I do not routinely use for standard dilatation procedures, but this requires no change to existing facilities for performing dilatation procedures.	
		Expert #7 No additional technology or devices past the drug coated balloon, which can be used in standard cystoscope equipment which is widely available. Has the advantage of potentially being done under local anaesthetic	
		Expert #8	

		NONE	
		Expert #9 Establishment of treatment units in outpatient facilities	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: Yes, there will need to be training and mentoring with regard to the results with the use of this technology.	
		Expert #2 Yes – standard training provided by the technology provider/manufacturer – and on attending relative meetings this is apparently simple intuitive procedure.	
		Expert #3 Surgeon and assisting team will need training in deploying the device safely and effectively. Team will need to be aware of their local policies of managing any potential emergencies in a post procedure patient from a simple vaso-vagal to a cardiac arrest.	
		Expert #4 Yes	
		Expert #5 It is important that any surgeon undergoes training to do this procedure. It is an endoscopic procedure and online training with video	

		demonstrations should suffice. However, it will be important for a company representative to be in theatre for the first few cases until the surgeon and theatre staff are familiar with the equipment.	
		Expert #6 Not really, but a thoughtful approach by a urologist interested in stricture management. The procedure of balloon urethral dilatation is straight forward enough for all urologists to perform, making it easy to adopt in correctly selected patients.	
		Expert #7 Minimal training, past mentorship visit and being signed off on how to use the drug coated balloon safely	
		Expert #8 TRAINED TO USE THE DEVICE	
		Expert #9 The treatment is a modification of existing urological therapy and should be mastered easily by all urologists and trainees within a brief period of training with very short learning curve.	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon)	Expert #1: The risks and adverse events are those associated with any urethrotomy/dilatation and fall with the accepted standard of care.	

	and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	There are theoretical risks with the release of the active agent, although none of significance reported to date.	
		Expert #2 The current 3 years data of relative trials are confirming safe procedure with no major risks, although the technique is novel, but the drugs used are a standard in many other indications with reasonable safety profile for topical/local administration. Possible risks are UTIS/Dysuria/Bleeding. Theoretical adverse effects will be mainly related to systemic absorption of the coated drug (Paclitaxel) with the relative side effects; however, the current data did report any SAEs.	
		Expert #3 Infection 10-50% - equivalent to any cystoscopic procedure Bleeding 10-50% - equivalent to any cystoscopic procedure Urethral trauma – 5-10% Discomfort 10-20%	
		Expert #4 UTI’s, urinary symptoms, pain	
		Expert #5 No difference to the current standard of care – urethral bleeding (10%), urine infection (5%), recurrent stricture (30% at 2 years – this is less than the current standard of 50%+ at 2 years). The balloon is coated with paclitaxel and there is a theoretical risk this could be transmitted in semen.	

		The published study (Robust II) reported no serious adverse events	
		Expert #6 Potential and theoretical adverse events from systemic absorption of paclitaxel. The advantage of application by a coated balloon and not injecting the substance into the urethra is more unified delivery and assured dosing. The research suggests very low levels detectable in blood stream during first hour post procedure with no serious urinary adverse events at 2 years and minor side effects only initially. Theoretical adverse events from drug transmission in semen during sexual intercourse. Researchers have recommended advising patients to use barrier protection during sexual intercourse for up to 3 months post procedure.	
		Expert #7 Based on the multicentre RCT vs standard of care, the Adverse event rate was 39% vs 19%. The most common adverse events (vs standard of care – dilatation) were dysuria (11% vs 2%), Haematuria (11% vs 2%), and pain (5% vs 0%). The risk of infection or incontinence was not notable different between the 2 groups. The serious adverse event rate was 3% vs 4% for standard of care (dilatation). (ROBUST III DATA @ 12months)	
		Expert #8 POTENTIAL ABSORBPTION OF DRUG COATING	
		Expert #9 Potential complications: - urethral bleeding - retention - pain/discomfort - urethral rupture	

		- false passage - stricture recurrence	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Reduction of symptoms and avoidance of a restenosis of the urethra.	
		Expert #2 Simple minimally invasive procedure with data up-to- 3 years of follow up confirming better efficacy and reduced recurrence rate compared to current endoscopic standard of care.	
		Expert #3 ROBUST trials have shown a significant freedom from repeat intervention, improvement in Qmax and IPSS with Optilume compared to controls. The trials also showed anatomical success (able to pass a 16Ch catheter) in 75% of patients at 6 months.	
		Expert #4	
		Expert #5 Stricture-free rate.	
		Expert #6 Patient satisfaction, sustained improvement in urinary symptoms and reduction in need for repeated procedures.	
		Expert #7 Freedom from re-intervention, flow rate, symptoms related to flow	
		Expert #8	

		IMPROVED URINARY SYMPTOMS IMPROVED URINARY FLOW DURATION OF IMPROVEMENT	
		Expert #9 Symptomatic relief (reduction in bothersome LUTS)	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: At present, just limited data with small numbers – further data required before being accepted as the standard of care.	
		Expert #2 NA	
		Expert #3 Uncertainties lie around this being a new device without the longevity of data behind it that the alternatives of dilatation + ISD or urethroplasty have. The data published so far looks very promising and is equivalent to that of the above procedures.	
		Expert #4 Can patients be around pregnant women?	
		Expert #5 As stated above, the data appears promising. RCTs will needed to confirm superior efficacy and the current study (ROBUST III) is due to close to recruitment in December 2020 according to ClinicalTrials.gov	
		Expert #6 The initial early (2year) research data is promising, but data in clinical use and in the longer term (≥ 5years) will give more certainty of potential benefits and aid patient selection.	

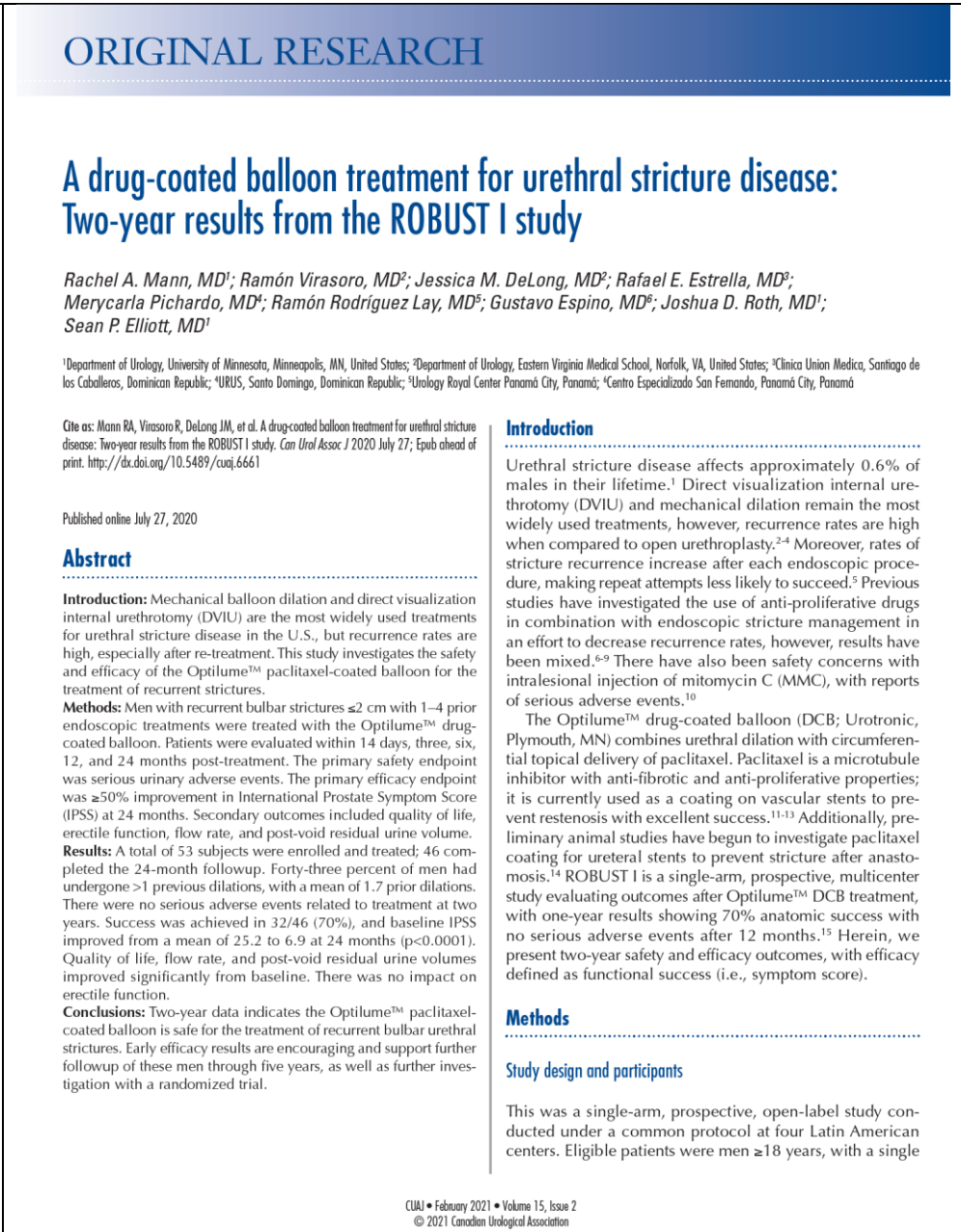
		Expert #7 Unclear how more effective it will be in the primary setting vs standard of care, as all trial data is in the recurrent stricture setting. Unclear how effective it will be for difficult stricture locations (Bladder neck and membranous) as not in trial to date	
		Expert #8 DURATION OF IMPROVEMENT	
		Expert #9 With fairly short observation periods it remains unclear as to whether the rate of stricture recurrence can truly be reduced through this procedure.	
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: This still remains an interesting potential avenue for treatment, but the data is limited at present. The problem is that the underlying pathology is ischemic fibrosis, the question is by preventing fibroblasts producing the scarring, this will improve efficacy. Initial data suggests that's the case	
		Expert #2 NA	
		Expert #3 Controversy about the use of Paclitaxel – this has been associated with a mortality when used intravasculally but in this case will not be used in the vascular system.	
		Expert #4 No	
		Expert #5 No	

		Expert #6 Not yet in widespread clinical use therefore current outcome data is based on limited numbers and experience.	
		Expert #7 Is it better than standard of care (dilatation) and injection of a drug to reduce stricture recurrence (mitomycin C)? This is the potential subject of a trial being considered by BAGURS (British Association of Genito-urethral Reconstructive Surgeons)	
		Expert #8 DURATION OF IMPROVEMENT	
		Expert #9 no	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals.	
		Expert #2 Most or all district general hospitals.	
		Expert #3 A minority of hospitals, but at least 10 in the UK.	
		Expert #4 Most or all district general hospitals	
		Expert #5 Most or all district general hospitals – eventually.	

		Expert #6 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #7 Most or all district general hospitals.	
		Expert #8 Most or all district general hospitals.	
		Expert #9 Most or all district general hospitals.	
19	Please list any abstracts or conference proceedings that you are aware of that have been recently published on this	Expert #1: Ongoing studies	

procedure/technology (this can include your own work).

Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.



ORIGINAL RESEARCH

A drug-coated balloon treatment for urethral stricture disease: Two-year results from the ROBUST I study

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Abstract

Introduction: Mechanical balloon dilation and direct visualization internal urethrotomy (DVIU) are the most widely used treatments for urethral stricture disease in the U.S., but recurrence rates are high, especially after re-treatment. This study investigates the safety and efficacy of the Optilume™ paclitaxel-coated balloon for the treatment of recurrent strictures.

Methods: Men with recurrent bulbar strictures ≤2 cm with 1–4 prior endoscopic treatments were treated with the Optilume™ drug-coated balloon. Patients were evaluated within 14 days, three, six, 12, and 24 months post-treatment. The primary safety endpoint was serious urinary adverse events. The primary efficacy endpoint was ≥50% improvement in International Prostate Symptom Score (IPSS) at 24 months. Secondary outcomes included quality of life, erectile function, flow rate, and post-void residual urine volume.

Results: A total of 53 subjects were enrolled and treated; 46 completed the 24-month followup. Forty-three percent of men had undergone >1 previous dilations, with a mean of 1.7 prior dilations. There were no serious adverse events related to treatment at two years. Success was achieved in 32/46 (70%), and baseline IPSS improved from a mean of 25.2 to 6.9 at 24 months ($p<0.0001$). Quality of life, flow rate, and post-void residual urine volumes improved significantly from baseline. There was no impact on erectile function.

Conclusions: Two-year data indicates the Optilume™ paclitaxel-coated balloon is safe for the treatment of recurrent bulbar urethral strictures. Early efficacy results are encouraging and support further followup of these men through five years, as well as further investigation with a randomized trial.

Introduction

Urethral stricture disease affects approximately 0.6% of males in their lifetime.[1] Direct visualization internal urethrotomy (DVIU) and mechanical dilation remain the most widely used treatments, however, recurrence rates are high when compared to open urethroplasty.[2-4] Moreover, rates of stricture recurrence increase after each endoscopic procedure, making repeat attempts less likely to succeed.[5] Previous studies have investigated the use of anti-proliferative drugs in combination with endoscopic stricture management in an effort to decrease recurrence rates, however, results have been mixed.[6-9] There have also been safety concerns with intralesional injection of mitomycin C (MMC), with reports of serious adverse events.[10]

The Optilume™ drug-coated balloon (DCB; Urotronic, Plymouth, MN) combines urethral dilation with circumferential topical delivery of paclitaxel. Paclitaxel is a microtubule inhibitor with anti-fibrotic and anti-proliferative properties; it is currently used as a coating on vascular stents to prevent restenosis with excellent success.[11-13] Additionally, preliminary animal studies have begun to investigate paclitaxel coating for ureteral stents to prevent stricture after anastomosis.[14] ROBUST I is a single-arm, prospective, multicenter study evaluating outcomes after Optilume™ DCB treatment, with one-year results showing 70% anatomic success with no serious adverse events after 12 months.[15] Herein, we present two-year safety and efficacy outcomes, with efficacy defined as functional success (i.e., symptom score).

Methods

Study design and participants

This was a single-arm, prospective, open-label study conducted under a common protocol at four Latin American centers. Eligible patients were men ≥18 years, with a single

		Expert #2 These two video abstract links with the latest ROBUST III trial outcomes presented in the ICS 2021. https://www.ics.org/2021/abstract/1 https://www.ics.org/2021/abstract/2	
		Expert #3 ROBUST trials Recent poster (prize winning for best in category) at International Continence Meeting	
		Expert #4 ROBUST I study	
		Expert #5 I have no additional literature other than that included in your Medtech innovation briefing.	
		Expert #6 BAUS webinar - Advances in the management of urethral stricture disease (7th May 2021), recording accessible via BAUS website. Session on Optilume DCB, presented by Dr Karl Coutinho.	

		Expert #7 Would recommend review of the ROBUST I, II & III data.	
		Expert #8 Ovid Technologies, Inc. Email Service ---------- Search for: optilume.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] Results: 5 Database: Ovid MEDLINE(R) ALL <1946 to November 24, 2021> Search Strategy: ---------- 1 optilume.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5) ********** 1. One-year outcomes after treatment with a drug-coated balloon catheter system for lower urinary tract symptoms related to benign prostatic hyperplasia. Kaplan SA, Pichardo M, Rijo E, Espino G, Lay RR, Estrella R Prostate Cancer & Prostatic Diseases. 2021 Apr 08. [Journal Article] UI: 33833379 Title Comment Erratum in: Prostate Cancer Prostatic Dis. 2021 Jul 7;:; PMID: 34234311 [https://www.ncbi.nlm.nih.gov/pubmed/34234311] Authors Full Name Kaplan, Steven A, Pichardo, Merycarla, Rijo, Edwin, Espino, Gustavo, Lay, Ramon Rodriguez, Estrella, Rafael Link to the Ovid Full Text or citation: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medp&AN=33833379	

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		Expert #9	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Awaiting the so-called Robust III trial data set which is not yet available – first in man in the States with any significant number.	
		Expert #2 ROBUST III trial was recently presented (see above)	
		Expert #3 Ongoing ROBUST trials.	
		Expert #4	
		Expert #5 YES – ROBUST III	
		Expert #6 Not currently that I am aware of	
		Expert #7 Please see 17. We are also looking to start a trial of primary strictures at Guy's Hospital (currently going through the REC)	

		Expert #8 The robust trials	
		Expert #9	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: More than 5,000.	
		Expert #2 Nearly 8000-12000 cases of bulbar urethral strictures are treated every-year in the UK with estimate of 40-50% of this group can be using this technique.	
		Expert #3 40 per year in my tertiary practice	
		Expert #4	
		Expert #5 Over 90% of the target population would be eligible for this intervention.	
		Expert #6 The incidence of urethral strictures in men is increasingly common in an ageing population, with bulbar urethral strictures being most common. ONS data from 2011 reported 62,000 men were affected in the UK, which corresponded to 17,000 hospital admissions annually and 12,000 operations. HES data 2016-17 coding stricture treatments, suggest 5000 urethrotomy procedures and 5000 urethral dilatation procedures, with 750 urethroplasties took place.	
		Expert #7	

		Approximately ≥ 70% of recurrent anterior strictures, and a similar proportion of primary strictures if shown to be safe in that setting	
		Expert #8 It might replace 50% or urethral dilatations and internal urethrotomy procedures within the HES database	
		Expert #9 ?	
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert #1 The major factor is cost and restricting its use to appropriate cases.	
		Expert #2 According to the manufactures and the current users' description it seems to be a straightforward simple procedure that should be easily adopted.	
		Expert #3 Not that I can think of at the moment.	
		Expert #4 No	
		Expert #5 No	
		Expert #6 Not that I have experienced	
		Expert #7 no	
		Expert #8 THE CRUCIAL (UNDETERMINED) ISSUE IS WHETHER THE DEVICE DOES OFFER BETTER DURABILITY OF RESPONSE AND IF IT DOES, HOW LONG THAT DURABILITY IS	

		Expert #9 No issues	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert #1 No	
		Expert #2 Not to my knowledge.	
		Expert #3 No.	
		Expert #4 No	
		Expert #5 No	
		Expert #6 No	
		Expert #7 Initial outlaw of the device vs standard of care dilators	
		Expert #8 no	
		Expert #9 Not aware of any issues	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert #1 Randomised controlled trial comparing this technique to urethrotomy, which we are planning to submit to the NIHR.	

		Expert #2 More research is always favourable to address new technologies and looking at longer term durability/ efficacy.	
		Expert #3 No.	
		Expert #4 No	
		Expert #5 One RCT is already in progress. A UK-based RCT would add to the evidence base.	
		Expert #6 I think it is important to audit local results and outcomes as longer term data becomes available.	
		Expert #7 Trial of its use in primary urethral strictures, treatment of bladder neck strictures, membranous urethral strictures	
		Expert #8 Medium to long term follow up from a trial randomising between traditional dilatation / urethrotomy and OPTILUME	
		Expert #9 Beneficial outcome measures: Feasibility studies Outcome analysis Patient satisfaction Cost comparison Adverse outcome measures:	

		Efficacy studies (need for re-intervention) measured over at least 5-10 years	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert #1 Beneficial outcome measures: Flow rates and post-voiding residuals, optical urethroscopy. Adverse outcome measures: Restenosis of the urethra.	
		Expert #2 Beneficial outcome measures: (Recurrence rate/ flow-rate- IPSS/QOL) Adverse outcome measures: (Failure rate/ UTIs/bleeding/ toxicity)	
		Expert #3 Beneficial outcome measures: - measure pre and post procedure (3, 6, 12 and 24 months) IPSS, PROM and SHIM Qmax and post void residuals Reassess any infective symptoms Frequency volume chart if frequency was an issue Adverse outcome measures: Reintervention rate over 2 years	

		Deterioration in any of above measures	
		Expert #4 Beneficial outcome measures: IPSS symptom score, QoL Measures	
		Expert #5 Beneficial outcome measures: Stricture-free rate at 12 months/24 months etc Erectile function at 3 months Reduced symptoms – PROMs at 3/12/24 months etc Adverse outcome measures: UTI/sepsis – need for postop antibiotics/hospital readmission – at 30 days	
		Expert #6 Beneficial outcome measures: The validated Urethral Stricture surgery PROM is ideally suited to measuring clinical outcomes, QoL outcomes and patient related outcomes. Objective measures of success with flow rates could also be used. Ideally these would be collected pre-procedure then at subsequent time measures which typically for urethral surgery would be 3 months, 6 months and 12 months initially, then on a 6-12 monthly basis thereafter. Adverse outcome measures:	

		Early complications may commonly include bleeding, infection and discomfort, and less commonly potential urethral injury and drug side effects (headache). In practice we have been recording early adverse events at 1 week post procedure with a baseline flow rate. Late adverse events would be recorded at the above timescales with routine follow-up and maybe related to failure, urethral injury or drug absorption.	
		Expert #7 Beneficial outcome measures: Qmax, IPSS, time to recurrent intervention, ease of passage of flexiscope at 3, 12,24 months, urethral PROM and QoL scores Adverse outcome measures: Urethral PROM & QoL scores, rates of pain (VAS), infection, bleeding, retention, recurrence, stricture progression/ length, impact on subsequent urethroplasty	
		Expert #8 Beneficial outcome measures: Improved symptoms Improved flow Durability of improvement Adverse outcome measures: Drug related side effects Recurrence of symptoms Repeat interventions	

		Expert #9	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert #1 An interesting technique that needs to be restricted in its use relating to cost.	
		Expert #2	
		Expert #3	
		Expert #4	
		Expert #5 No further comments	
		Expert #6	
		Expert #7	
		Expert #8	
		Expert #9	

External Assessment Centre correspondence log

GID-MT565 Optilume for recurrent anterior urethral strictures

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*

1.	17/12/2021	Company start-up meeting to discuss clinical submission	The EAC sent a list of questions in advance of the meeting. The company responded with answers in time for the company start-up meeting on 17/12/22.	Written responses were provided by the company and are reported in Appendix A.
2.		Amended notes back from company start-up meeting verified by company	The company sent back their amended notes from the start-up meeting on 17/12/2021	Company sent back their verified notes from the start-up meeting on 17/12/2021 reported in Appendix A.
3.	11/01/2022	Expert engagement meeting questions	The EAC sent a list of questions in advance of the meeting to the clinical experts.	Questions sent to the Clinical experts prior to the meeting in Appendix C.
4.	21/01/2022	After Clinical expert engagement meeting, meeting notes were sent to all experts for verification with additional questions.	Email sent from EAC to clinical experts with the notes from the clinical expert meeting to be verified. Additional questions asked to clinical experts are below: 1. For patients with recurrent penile/meatal or fossa navicularis strictures, urethroplasty is often first-line therapy. Is Optilume likely to change this recommendation? 2. The company state that Optilume can be used by consultants in urology, urology trainees and urology nurse specialists, compared with just urological surgeons for urethroplasty. In the opinion of the clinical experts, in the U.K, is this the case? 3. What aftercare, if any, is required post-Optilume? 4. What is the preferred method to diagnose a urethral stricture in the UK: urethra-cystoscopy, retrograde urethrography, voiding cystourethrography (VCUG), ultrasound urethrography, or a combination?	Replies from clinical experts have been collated into one final verified set of verified notes which can be found in Appendix C. Answers from clinical experts to the additional questions asked have been collated and can be found in Appendix C.

5.	21/01/2022	Company (Urotronic Inc.) Follow-up questions during draft assessment report writing process.	EAC had additional questions for company: 1. Since the launch of Optilume, have there been any refinements or version numbers that we need to be aware of? If so, which version numbers were used in the ROBUST trials, and which are currently being used across the UK? 2. You had commented on the company engagement start up meeting notes that you had difficulty identifying the Mundy et al, 2010 paper referred to in the meeting. Looking online, I think I have found it (attached). It is less relevant at this stage as it's a review anyway. 3. In the company start-up meeting you briefly mentioned 8 centres that had approved Optilume for use since the MHRA registration in July. Would you be able to send me the list of these hospitals? 4. In the same meeting, you had mentioned that you had some additional user feedback from clinicians using Optilume. Would you be able to share any user feedback with me if possible? 5. In our meeting on Monday, we discussed the 4-year ROBUST I report being marked for academic/commercial in confidence. Are you able to provide me with this? 6. In the ROBUST I trial, the Virasoro et al, 2020 paper states the paclitaxel concentration in the subject's urine to be 199.7 ng/mL±209.9 ng/mL immediately after the procedure, and reduced to 2.6 ng/mL ± 4.8 ng/mL at 5 days post procedure (n=53). However, in the	Response from NICE: Company noted in their email that green has been presented in the public domain, yellow is AiC and red is not likely to be presented. He didn't see any CiC information in the report. He asked that the full report document would NOT be published in any manner. Response from NICE to update EAC that questions regarding expert feedback and centres approved for using Optilume had been asked followed-up to company. Response from Company on 24/01/22: • No device changes since launch

			unpublished Elliott et al, 2022 report of 4-year outcomes, the [redacted]. What is the reason for the difference in both number of patients and paclitaxel concentration immediately after the procedure; and also, the difference in patient number at 5-days post-procedure? Just to note that any answers given will form part of the public correspondence log and will therefore be publicly accessible on the NICE website once the report is finalised.	• In response to Q5, company responded: 'This was provided to NICE, still working on identifying confidentiality applications' • In response to Q6, Company responded: 'Thank you for identifying this discrepancy. The published value reported for Virasoro et al is correct in both respects. One value was not incorporated in the post-procedure sample calculation in the 4y report due to a calculation error, inclusion of that value would have given the same value as Virasoro. The value reported for the 5d samples is correct in the report, best I can tell we just

				forgot to update the same size number.'
6.	24/01/2022	Company (Urotronic Inc.) Additional questions re economic data	Email sent from the EAC to the company for clarification on points pertinent to the economic model of the device: We have a couple of additional queries about the recurrence variables in the economic model and how these are derived from the clinical evidence. My understanding is that they should be reported in Elliot (2021), ROBUST III 1-year data, however I have not been able to find an appropriate result that corresponds. For 6-month data based on the primary outcome of being stricture free (where possible to atraumatically pass a 16Fr flexible cystoscope or a 14Fr catheter through the treated area), the outcomes reported are the same as used in the model (26.8% (11/41) success in comparator, and 74.6% (50/67) for Optilume. However there is a breakdown of results for Endoscopic management between Urethrotomy, balloon dilatation and rigid rod dilatation that does not appear in the published paper. [redacted] The paper reports a 12-month freedom from repeat intervention through 1 year from the Kaplan-Meier calculation of 83.2% vs 21.7%. However the model uses IPSS Responder (≥30% Improvement) and reports [redacted]	Response from Company on 28/01 found in Appendix C.

			Would you be able to give some further explanations as to where the results used in the model come from? We note that there are similar formats of results reported in the 4-year trial report for ROBUST I, is it possible that the numbers in the model are reported in the trial report rather than published paper, and if so, would it be possible to share with us (via NICE docs, with confidential information marked?)	
7.	28/01/2022	Company (Urotronic Inc.) Additional questions	Email sent from EAC to company with additional questions following economic submission: 1. Please could you share the calculations for adverse event costs for: • Wound infection • readmission to hospital 2. Can you confirm that the Urinary retention cost is based on the Accident and Emergency service code 180 (see table at end). Did you look at any other costs given that there is only one procedure listed? 3. Probability of retreatment following recurrence is taken as 90% from the Pickard, 2021 model. Do you have any insight into how they derived this value, given the reported retreatments in table 17 of Pickard 2021? 4. You have provided us with the IPSS responder 'failure carried forward' rate in a previous email, but are you able to provide the non-failure carried forward rate? 5. Further to the previous question, what was the reason for the change in the IPSS responder rate definition from ≥50% improvement used in ROBUST I and II, to ≥30% improvement? If figures for IPSS responder rate ≥50% improvement in ROBUST III are available, are you able to provide the EAC with these?	Response from Company on 28/01: Quite a bit to unpack on a couple of those questions. I'll let the York team answer #1-3 and I'll have to write something up in Word for the other ones… Full response from company on 28/01/22 found in Appendix C Response to Q1-3 from YHEC on 31/01/22 found in Appendix C

6. In ROBUST III, USS-PROM is an outcome but results are not reported in the paper. Are you able to provide these values?
7. VAS pain score was not an efficacy outcome in ROBUST III study but was this measured at all, and if so are you able to provide us with these values?
8. In ROBUST III there is very limited information on the rate of adverse events/SAEs. Are you able to provide the overall AE/SAE figures and a breakdown on the number and type of AEs?

National schedule of NHS costs. OPROC Accident and emergency. LB55A Minor or intermediate, urethra procedures, 19 years and over. Service code 101. Urology

Currency Code	Currency Description	Service Code	Service Description	Procedures	National Average Unit Cost
LB55A	Minor or Intermediate, Urethra Procedures, 19 years and over	180	Accident & Emergency	1	£940.94
LB55A	Minor or Intermediate, Urethra Procedures, 19 years and over	101	Urology	3210	£203.36

<table>
<tr>
<td>8.</td>
<td>28/01/2022</td>
<td>Clinical experts

Additional questions to clinical experts</td>
<td>Email sent from the EAC to Clinical experts on 28/01 with additional questions below:

We would be very grateful if you could answer the below questions as soon as is convenient:
1. If you were to adopt Optilume into normal practice, do you think that:
· You would exclusively use Optilume over other endoscopic procedures, or would you offer both?
· If you offer both, how would that decision be made?
· Would this be different for retreatment?
2. Please could you estimate, for patients requiring re-treatment, what percentage receive which retreatment method? If you do not currently provide Optilume, estimate what you would expect to happen, if possible.

<table>
<tr><td></td><td colspan="3">Re-treatment method used (%)</td></tr>
<tr><td>Most recent procedure</td><td>Optilume</td><td>Endoscopic / Urethrotomy</td><td>Urethroplasty</td></tr>
<tr><td>Optilume</td><td></td><td></td><td></td></tr>
<tr><td>Endoscopic / Urethrotomy</td><td></td><td></td><td></td></tr>
<tr><td>Urethroplasty</td><td></td><td></td><td></td></tr>
</table>

3. Does retreatment method vary with the number of previous treatments?
4. What is the primary consideration in choosing the retreatment method?
5. Approximately how long is there between a recurrence being identified and re-treatment with
· Optilume</td>
<td>Responses from clinical experts have been collated for each question and put in Appendix B.</td>
</tr>
</table>

			· Endoscopic procedures · Urethroplasty 6. Are adverse events likely to happen later than 30 days post procedure? 7. In the ROBUST I trial; self-catheterisation was included in the eligibility criteria as a type of prior treatment. Would you consider self-catheterisation as a form of prior treatment when considering a patient for endoscopic management/Optilume? 8. Across the three ROBUST trials, several objectives (Anatomic success, freedom from repeat intervention, Qmax, PVR) and subjective (IPSS/IPSS QoL/IIEF score/USS-PROM) efficacy outcomes are used. In the management of patients with recurrent urethral strictures, what are the most important of the above outcomes taken into consideration when deciding upon re-treatment?	
9.	28/01/2022	Company (Urotronic Inc.)	Following second company engagement meeting on 17/01/2022, EAC notes were sent to the company for verification	Notes sent by the EAC to the company on 28/01/22 can be found in Appendix B.
10.	02/02/2022	Company (Urotronic Inc.)	Following a virtual meeting with the company on 02/02/2022, the EAC sent the email below requesting the second company engagement meeting notes be verified, and for further clarification on a point regarding training on how to use Optilume: I also wanted to check if you have had the chance to review and verify the second company engagement meeting notes sent at the end of last week on 28th January? We are in the process of updating all correspondence logs to	

			submit with the report on Wednesday and so it would be good to have these notes verified before the weekend. Also during the meeting, I asked the time it takes a clinician wanting to train on how to use Optilume for both the tutorial videos and to learn in person. The company advised that the tutorial videos took ~30 minutes but was unsure of the time the in-person training took. Are you able to give any clarification on this?	

Appendix A: Company start-up meeting

Company answers to EAC questions:

No.	EAC Question	Company response
The technology		
1.	In the algorithm of bulbar urethral stricture treatment by Simsek et al, strictures 1-2cm in length were not treated endoscopically but treated by excision and primary anastomosis. The proposed algorithm recommends treating these patients endoscopically first, then with optilume. What is the justification for changing the pathway here?	Urology Societal (e.g., EAU) guidance on stricture management recommends urethroplasty for recurrence after initial endoscopic treatment or for long (e.g., >2cm) strictures as a primary therapy. The algorithm proposed by Simsek et al take this a step further and recommend EPA for short (1-2cm) strictures due to its excellent long-term outcomes. In practice, the number of physicians trained for urethral reconstruction is a very small proportion of the overall population of urologists, leading to access-to-care issues and long wait lists for urethroplasty procedures. In addition, many patients prefer to avoid more invasive open surgery and prefer to continue with less-effective endoscopic management. The proposed algorithm considers the fact that Optilume has been studied in strictures up to 3cm with similar results, where instead of referring those with strictures 2-3cm directly to urethroplasty they could instead be treated first with the Optilume DCB via a minimally invasive setting.

No.	EAC Question	Company response
The technology		
2.	Do the company envision Optilume removing the eventual need for Urethroplasty completely or just delaying the need for urethroplasty?	From a treatment algorithm perspective, the Optilume DCB will not remove the need for urethroplasty. Urethroplasty remains the most definitive treatment for anatomic resolution of strictures. The Optilume DCB provides a highly efficacious endoscopic treatment for strictures that may obviate the need for a proportion of subjects to receive urethroplasty, however there may still be patients that experience recurrence after treatment with the Optilume DCB as well as those that have stricture characteristics (e.g. >3cm) in which the Optilume DCB has not yet been proven effective.
3.	Company evidence submission states that Optilume can be used as an adjunctive therapy to existing endoscopic management. Is this only the case for strictures <2cm, and then as a standalone or first-line therapy for 2-3cm as a first-line therapy is outside the scope of the NICE guidance?	The statement in the indications for use relating to use as an adjunct is an attempt to incorporate the ability to use pre-dilatation, whereby the pre-dilatation may be considered the primary and the DCB an adjunct. The choice of whether to pre-dilate the stricture is at the discretion of the user and is not driven by stricture length. Consideration for pre-dilatation is driven by evidence (e.g. previous experience) that the stricture may not yield to balloon dilatation.

No.	EAC Question	Company response
The technology		
4.	Are the company aware of any proposed clinical trials looking at Optilume as a first line therapy?	No immediate studies are planned with the Optilume DCB as a primary stricture treatment, however it would be expected that the Optilume DCB would be equally or more effective in these patients as compared to those in the ROBUST series, with no expected difference in safety profile. Optilume DCB was recently approved by the US FDA in which indications for use state 'The Optilume Urethral Drug Coated Balloon is used to treat patients with obstructive urinary symptoms associated with anterior urethral stricture. It is designed to be used in adult males for urethral stricture of ≤3 cm in length' not specifically limiting to 'recurrent anterior urethral stricture'.

No.	EAC Question	Company response
The technology		
5.	What training is required for clinicians and what is the duration of online training?	As non-drug coated balloon dilatation is considered existing practice for the management of urethral stricture, as well as ureteral stricture services offered by Urology departments in the NHS, clinician training can be tailored dependent experience. To clarify the training protocol offered, we ensure each clinician completes a 30-minute online learning program for understanding of existing treatment options and the associated published evidence, existing international guideline review, urethral overview of the Optilume mechanism of action and procedure, review of indications and patient selection and highlights of Optilume clinical evidence available. Following this, a company representative will perform in-person product demonstration via demo device and a clinical model. Should a clinician further request, we offer peer to peer education whereby Urologist's can attend an experienced clinical institute offering Optilume as part of standard practice to witness best practice of the procedure and discuss at a clinical peer level. This is generally a one-day education event where the attendee will witness procedures, be presented with the published evidence and understand further the resources required to perform the procedure in a clinical working environment

No.	EAC Question	Company response
The technology		
6.	Is there a cost for hands-on training?	No. Any formal training required by healthcare professionals is provided by the company at no cost to the Urologist and/or the healthcare provider.
7.	Does the company have any details on the number of clinicians who request hands-on training in addition to online learning?	As non-drug coated balloon dilatation is considered existing practice for the management of urethral stricture, as well as ureteral stricture services offered by Urology departments in the NHS, thus far the request for 'hands-on' training has been minimal (N=2). See the clarification of the training process offered in the answer to question 5.
8.	Could the company provide any feedback from treating clinicians using Optilume?	Yes, feedback can be gained from clinicians in the UK upon request. Previously released press articles contain statements from urologists who have performed Optilume procedures, and these can be provided freely.
Use of the technology		
9.	The device is indicated for use in anterior urethral strictures, but the companies proposed algorithm is for only bulbar urethral strictures. Can Optilume be used for strictures in any part of the anterior urethra including Penile, bulbar and peno-bulbar strictures?	The algorithm figure was adapted from a figure in Simsek et al 2018 that was specific to bulbar strictures. The Optilume DCB has been evaluated in all anterior urethral strictures and is not limited to use in bulbar strictures, this figure in the Clinical submission should be updated.

No.	EAC Question	Company response
The technology		
10.	With patients self-predilating at home, what is the patient compliance rate and failure rate for this?	Intermittent self-dilatation has been evaluated as a tool to prolong time between more definitive treatments (e.g. urethrotomy). Failure is not well defined, as in the setting of urethral stricture the intent is to be more palliative and delay the need for additional endoscopic dilatations and not as a cure. Compliance is also not well defined, as the rate of self-dilatation ranges from 10 times a day (e.g. full clean intermittent catheterization) to once every few weeks and is left more to patient/physician discretion.
11.	Can Optilume be used for strictures in trans men?	The Optilume may be used in patients with male anatomy, existing or remaining.
12.	Company recommends inflating balloon for 5 minutes and NICE MIB recommends up to 10 minutes. Company submission advises longer inflation times may be performed to optimize stricture dilatation. Is this at the discretion of the treating clinician, and what is the evidence to demonstrate longer inflation leads to optimized dilatation?	The length of time the Optilume balloon is inflated in-situ is at the discretion of the clinician. The Optilume instructions for use state 'Inflate the balloon to the rated burst pressure using the inflation device. Do not exceed rated burst pressure (RBP) of the balloon. Maintain pressure for a minimum of 5 minutes, or until desired dilatation is achieved'. There is no evidence to suggest longer inflation times lead to optimized dilatation. The NICE MIB should be corrected to reflect the statement above

No.	EAC Question	Company response
The technology		
13.	Balloon catheter guidewire is 0.97mm (2.91Fr/0.038”) and therefore Optilume cannot be used in lesions that cannot be crossed with a 0.038” guidewire. When does the treating clinician become aware that the lesion cannot be crossed? Is this during pre-dilatation ‘yielding’ of the stricture or beforehand?	To clarify, either a 0.038” OR a 0.035” guidewire is compatible with Optilume. Should a clinician identify a tight stricture either pre-operatively through appropriate diagnostics (e.g., cystoscopy) or intra-operatively that will not allow a guidewire to cross initially, the clinician can and will likely pre-dilate the stricture to a Fr size appropriate, to allow the guidewire to cross the stricture, but less than the 30Fr of Optilume. Pre-dilatation in commercial use to date has been limited as tight strictures not allowing guidewire pass are relatively rare. Also to note, pre-dilatation is not unique to the Optilume procedure for tight urethral strictures but rather any endoscopic procedure.
14.	Pre-dilatation is partly recommended for ‘highly stenosed strictures’ by the company. What diameter or EAU stricture classification is a highly stenosed stricture?	EAU Guidelines state ‘Reduced urethral calibre is variously defined as between <10 Fr to <20 Fr with the majority of series defining <14Fr as diagnostic, compared with a ‘normal’ urethral calibre of 18-30 Fr’ (Page 9). The guidelines continue to state ‘The definition of low- vs. high-grade strictures remains debatable. A urethral plate less than 3 mm is considered a high-grade or tight stricture’ (Page 15). EAU guidelines sub classify degree of urethral narrowing into categories (see below table).

<table>
<tr><th>No.</th><th>EAC Question</th><th>Company response</th></tr>
<tr><td colspan="3">The technology</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><th>Category</th><th>Description</th><th>Urethral Lumen (Fr)</th><th>Degree</th></tr>
<tr><td>0</td><td>Normal urethra on imaging</td><td>-</td><td>-</td></tr>
<tr><td>1</td><td>Subclinical strictures</td><td>Narrow but ≥16Fr</td><td rowspan="2">Low</td></tr>
<tr><td>2</td><td>Low grade strictures</td><td>11-15Fr</td></tr>
<tr><td>3</td><td>High grade or flow significant strictures</td><td>4-10Fr</td><td rowspan="3">High</td></tr>
<tr><td>4</td><td>Nearly obliterative strictures</td><td>1-3Fr</td></tr>
<tr><td>5</td><td>Obliterative strictures</td><td>No lumen (0Fr)</td></tr>
</table>
Page 15, EAU Urethral Stricture Guidelines
</td></tr>
<tr><td>15.</td><td>Do the company have any evidence on whether pre-dilatation before Optilume improves outcome vs. no pre-dilatation?</td><td>This was assessed in the small ROBUST II study, with no difference in anatomic success noted at 6 months post-treatment.</td></tr>
<tr><td>16.</td><td>If there is a loss of pressure within the balloon during inflation or if the balloon ruptures during dilatation, the balloon is deflated and removed. Can a new balloon be reinserted immediately or does the procedure stop completely? If stopped completely, what is the next step in the treatment pathway?</td><td>A new balloon will be opened and used.</td></tr>
<tr><td>17.</td><td>Do the company have any information on how often a loss of pressure within the balloon/balloon rupture occurs?</td><td>Manufacturer complaint records of balloon leak/burst have been noted in 6 of 1,013 units sold (0.6%). These events are a common result of the user inflating the device above its rated burst pressure.</td></tr>
<tr><td>18.</td><td>If Urinary tract infection (UTI) is present at time of treatment, the patient must be treated until cured. Why is this and do the company recommend testing for the presence of a UTI prior to intervention?</td><td>This is included as a recommendation in all relevant Urology societal (e.g. EAU) guidelines for LUTS treatments.</td></tr>
</table>

No.	EAC Question	Company response
The technology		
19.	Is there a minimum length of stricture requirement for Optilume to be used. For example, could it be used in strictures <0.5cm?	There is no minimal sizing, strictures can be very short (<0.5cm) and create voiding issues. Optilume can be used for any size of stricture up to, and equal to, 3cm.
20.	Do the company have any findings on patient compliance with Optilume?	Patient compliance is not a relevant metric for the Optilume, as it is a single use device administered by a physician and has no patient administration component.
21.	Are any parts of the device reusable?	No
22.	What is the 'shelf-life' of Optilume balloon?	18 months – to be 24 months from Q2 2022
Evidence and benefits		
23.	Why was ROBUST IV stopped by the company?	ROBUST IV was contemplated as a method of quickly generating pharmacokinetic data in a post-market setting in Canada. Further dialogue with US regulatory authorities led to the inclusion of a PK sub-study in the ROBUST III study rather than in a separate study in Canada.
24.	Do the company have any information on whether a patient's stricture aetiology is known before selecting for Optilume? Is it known whether Optilume is more/less effective for any particular cause?	Aetiology is something typically defined prior to treatment and will likely be known from a patient's medical record/history. Subgroup analyses from both ROBUST I and ROBUST III did not identify aetiology as having an impact on outcomes after treatment with the Optilume DCB.

No.	EAC Question	Company response
The technology		
25.	Safety and effectiveness data has not been established during clinical studies to support the treatment of strictures in patients with bacterial urethritis, gonorrhoea, or lichen Sclerosus. Is Optilume still appropriate for these patients?	These patients were excluded from the studies due to the fact that the 'stressors' leading to stricture formation (e.g. infection) were still present and would likely lead to disparate results in the way of faster recurrence compared to other aetiologies, leading to potential for imbalance and uncertainty in results. Nothing in the aetiology would preclude treatment with the Optilume DCB, but outcomes after treatment are not well understood.
26.	Are one-year outcomes of the ROBUST II study (DeLong, 2022) study available to be shared?	Yes, the accepted manuscript was included in the literature submitted as part of the original review. Full publication of these results is expected in January 2022.
27.	Are there any academic in confidence data available for the longer-term impact on stricture recurrence?	4-year results from the ROBUST I study are expected to be finalized by the end of this month and shall be available to share confidentially prior to publication.
28.	Will the company be submitting Optilume for UK conformity assessment (UKCA) in addition to CE marking?	Yes, before the 30th June 2023 deadline
29.	What will be the model for economic submission by YHEC? Will it be submitted via excel?	Yes
30.	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	No
The technology		

No.	EAC Question	Company response
The technology		
31.	Are the pharmacokinetics of Paclitaxel when absorbed urethrally known?	Yes, they have been previously published for ROBUST I (Virasoro et al) and ROBUST III (Elliott et al). Systemic absorption is minimal and peaks at 1-hour post-treatment and is not detectable after 3-hours.
32.	Manufacturers state that the drug appears to be localized in the urethra and not systemically absorbed, but there is also warning to consider potential for systemic drug absorption. What is the evidence surrounding systemic absorption of paclitaxel from the urethra?	See above. The warnings are included out of an abundance of caution.
33.	Are drug-drug interactions (incl. patients considering having live vaccines) with paclitaxel taken into consideration during patient selection?	No drug-drug interactions are known or expected with the Optilume DCB, systemic absorption is very limited and not expected to result in systemic adverse effects.
34.	Paclitaxel is a known genotoxin and teratogen with company recommendations to have protected sex for 30 days post-treatment and 90 days for those with sexual partners of childbearing age. What is the justification for the difference in recommendation?	To clarify the warnings, all subjects are counselled to abstain or use a condom for 30 days to prevent exposure of sexual partner to paclitaxel during intercourse. In addition, subjects with a female partner of child-bearing potential are advised to utilize effective contraceptive for at least 90 days due to the presence of a small amount of paclitaxel in semen in some men treated with the Optilume DCB; the effect of these low concentrations on foetal development are unknown.

No.	EAC Question	Company response
The technology		
35.	In the 'Proposed algorithm of bulbar urethral stricture treatment Inc. Optilume', Optilume is only used prior to pre-excision/anastomosis or onlay graft. Is there no role for Optilume after this point, and are the company aware of any other countries using Optilume after/alongside excision/anastomosis?	This algorithm is contemplated in the setting of typical management of strictures, whereby urethroplasty (EPA or graft) is typically a definitive treatment. The Optilume DCB has been used to treat post-urethroplasty failures in a commercial setting, with physicians in the Netherlands expecting to publish a case series when sufficient follow-up has been obtained.

Appendix A: Company start-up meeting notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Start-up Meeting

MTG 565 Optilume for Recurrent Anterior Urethral Strictures

This document summarises the discussions that took place at the company post clinical submission meeting for MTG 565 Optilume, which took place on Friday 17th December 2021,13:00 to 14:00pm.

Welcome and introductions

The EAC and NICE had provided the list of queries to the company and the company provided detailed responses in advance of the meeting and these are reported in table 1. The questions provided to the company centred around some key themes including:

- The clinical pathway
- Training and user feedback
- Population
- Implementation
- Contraindications for use
- General device queries
- Evidence and Benefits

Due to the comprehensive nature of the company's written responses, there were only short clarifications to be discussed during the face-to-face meeting.

The Clinical Pathway (table 1, questions 1-4)

1. Following up on the query around whether the company think that Optilume might remove the need to urethroplasty, the EAC queried whether the company could provide any estimate of patient numbers (Question 2).

   Company response: that these figures are given in ROBUST 1, and if patient has a stricture that recurs several times they are likely to be a candidate for urethroplasty, usually after 2 prior endoscopic procedures.
   The company notes that approximately 23% of patients moved to urethroplasty in ROBUST 1, with ~70% not requiring urethroplasty after Optilume.

2. As follow up to the information provided in response to the questions around the clinical pathway, the EAC sought clarity on the proportion of urologists trained in urethral reconstruction compared with those able to use Optilume (Question 1).

   Company response: the company reiterated the information provided in their written response noting that ~2% of urologists are able to perform urethral reconstruction and therefore this causes waiting lists to be several years long (anecdotally, one consultant in the UK has a 2-year waiting list). Patients have recurrence in this time and this is potentially where Optilume, the company consider, may be helpful.
   The company noted that there are guidelines which push for urethroplasty after 1st recurrence but this rarely happens.

   EAC: the EAC noted that the company quoted Mundy et al, 2010 paper on urethroplasty and had requested to have this reference sent to them. The company will send this information.

3. The EAC queried whether there was any evidence for Optilume's effectiveness in strictures >3cm? (Question 3)

   Company Response: Theoretically need to extend the balloon 0.5 cm past the stricture on either side, so the 5cm balloons could treat up to 4cm.
   We are aware that some physicians in UK treating larger strictures (using 2 balloons) but we can't make this claim as there are no data for this yet.

4. The EAC requested further clarification on the potential place in the clinical pathway for Optilume, specifically use post excision/anastomosis (Question 4)?

   Company response: advised that it is early days but data likely available middle of next year for this.

   EAC: queried previous treatment pathway for these patients and whether it involved Optilume?

   Company response: unsure of previous treatment but added that secondary urethroplasty was not favourable and default post-urethroplasty failure would be endoscopic management.

   EAC: some patients may have been treated with Optilume prior to their urethroplasty so may be having a second treatment after a 'failed' urethroplasty. Repeat surgery after failed urethroplasty surgery not something that clinicians are keen on so Optilume may be a better option for this group of patients.

Training and User Feedback (Questions 5-8)

5. The EAC noted that the company stated that they “offer peer to peer education whereby Urologist’s can attend an experienced clinical institute offering Optilume as part of standard practice to witness best practice of the procedure and discuss at a clinical peer level”. The EAC queried the location of such centres? (Question 5)

   Company response: 7/8 centres approved for use since MHRA registration in July – August time. Some of these centres included:

   [redacted]

   These hospitals are taking up Optilume company has agreed to will email Cedar the list

6. The EAC had asked whether the company could provide user feedback and the company response was that this could be provided on request. The EAC requested this information be shared if possible. (Question 8)

   Company response: will email back Cedar with all the clinician’s comments/feedback.

Population (questions 9-12)

7. Relating to the question around the type of strictures for which Optilume can be used, the EAC noted that the algorithm on company submission is titled “Proposed algorithm of Bulbar Urethral Stricture (BUS) treatment included Optilume”, yet indication is for anterior urethral strictures? (Question 9).

   Company response: confirmed that Optilume is not restricted to BUS and can be used in Penile strictures.

   NICE: commented that this may be the case, but there may be a discrepancy between the device’s indication and the clinical appetite to be used in penile strictures.

   Company: advised that the proportion of BUS strictures is substantially higher than penile strictures 60% and 20% respectively. The primary target market for the device is bulbar, but ROBUST III RCT, 8 patients (10% - 15%) had penile strictures; 5 of which were successful. Generally, recurrence rate is more likely in penile structures due to smaller urethral diameter vs. bulbar portion of urethra. This is true for standard endoscopic management (0 successes in ROBUST III) as well as urethroplasty.

8. The EAC and NICE queried the generalisability evidence relating to use of Optilume for bulbar strictures to penile strictures (Question 9)

   Company Response: Healthy diameter of Bulbar is larger than for penile therefore penile more at risk of recurrence. The main population is bulbar, but there are limited data for use with penile.

9. The EAC queried whether both penile and bulbar strictures are managed in the same way? (Question 9)

   Company Response: The clinical pathway would be the same initially but urethroplasty would be considered much sooner and in some cases as initial treatment for penile strictures.

10. The EAC followed up on their query around whether Optilume could be used for strictures in trans men to further clarify whether the device could be used in people who had undergone female – male gender reassignment, specifically in patients post-phalloplasty? (Question 11)

    Company response: advised that the stricture rate for this population is quite high but not studied in that population yet. This burgeoning area of interest for devices such as Optilume is one which may be explored in the future, but target problem is niche. There is a lot of excitement in this application regarding Optilume.

    EAC: this needs to be noted as a potential equalities issue.

Implementation (table 1, questions 13-17)

11. The EAC asked for further clarification on diagnostic identification of narrow or unsuitable strictures pre-Optilume? (Question 14)

    Company response: unsuitable strictures are usually identified during cystoscopy and if the stricture is unsuitable, pre-dilatation will be done prior to Optilume. This will be part of the pre-work when diagnosing stricture. If total or obliterative stricture, pre-dilatation with rigid-rod or flexible-rod cystoscopy would be done to open up the lumen to ~20Fr minimum. Objective of pre-dilatation is to widen lumen but not over-dilate lumen due to requirements for Optilume to stretch lumenal endothelial cells, forming channels in the lumen, enabling paclitaxel absorption (Question 14).

Contraindications for use (table 1, questions 18-19)

12. The EAC requested clarification on whether Optilume candidates are tested for UTI before procedure? (Question 18)

    Company response: the company advised that this is part of the pre-op and is routine for any endoscopic treatment. Any dilatation is checked for a UTI so there are no infections, this is general urology practice.

    EAC: all patients would be tested for UTI prior to any treatment and this will be a consideration for the economic analysis.

General Device Queries (table 1, questions 20-26)

13. The EAC queried whether pharmacokinetic data was available? (Question 28)

    Company response: Pharmacokinetic data are available in ROBUST (Elliot et al 2021; Virasoro et al, 2020).

Evidence and Benefits (Table 1, questions 27-35)

14. The EAC followed up on their query around one-year outcome data from ROBUST II and long-term follow-up data (Question31 & 32)

    Company Response: The one-year outcome data is available in a manuscript which has been accepted for publication (DeLong) which has been provided to the EAC. In relation to long-term follow-up data, the company is currently looking at 4-year follow-up data for ROBUST 1 and to EAC for assessment report (provided Academic in Confidence) as soon as it is available.

    The company queried the timelines for getting these results to the EAC.

    NICE: data for ROBUST 1 to be available as soon as possible so it can be passed by the NICE team, and the long-term follow data will be required by early 2022 if possible.

15. The EAC and company discussed the Economic Submission further (question 34). The EAC confirmed with the company that the economic model will be submitted in Excel format.

Company response: Yes, the model will be in Excel. Currently we are working on a number of possible scenarios as there are a number of factors which can have an impact on the costs such as choice of data for the model (e.g. using data from specialist centres vs non-specialist centres). Company advised that Optilume over a period of time is cost effective vs retreatment. Using OPEN trial as a reference, centres were specialised reconstruction centres and therefore this data does not mimic real-world access to reconstruction and evidence. Also looking at what suitable cost (NHS reference costs), the company commented that NHS reference costs are quite conservative, but YHEC economic submission will likely include several good informative sensitivity analyses as part of submission.

Concluding comments

The EAC will email company if there are any further questions to be asked and clarified contacts for company related questions – company confirmed James and Ian were contact for EAC.

The company requested deadlines for next company involvement in NICE MTEP process. NICE gave several deadlines and will follow-up directly with the company.

Appendix B: Company engagement meeting

NATIONAL INSTITUTE AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Engagement Meeting

MTG 565 Optilume for Recurrent Anterior Urethral Strictures

This document summarises the discussions that took place at the company Engagement meeting for MTG 565 Optilume, which took place on Monday 17th January,14:00 to 15:30.

Attendees:

Company:

- James Wright
- Kyle Knauf
- Ian Schorn

YHEC:

- Judith Shore
- Hayden Holmes

NICE:

- Lizzy Latimer
- Victoria Fitton
- Chris Chesters
- Lirije Hyseni
- Ivan Maslyankov

EAC:

- Susan O'Connell
- Megan Dale
- Michael Beddard
- Ann Morris

1. Welcome and Introductions

NICE briefly introduced everyone on the call and outlined the format for the meeting.

2 EAC Clinical Evidence Review Update

2 EAC clinical evidence review update

EAC gave a short update of where the clinical evidence summary is currently, noting that there was nothing contentious at this time.
EAC noted there are 5 papers included in the evidence base – including just 1 RCT (ROBUST III) and no additional studies to the ROBUST trials. The EAC has excluded some papers that were included in the company submission as although they included relevant treatments, they did not compare with Optilume.

3 ROBUST 1 – confidential information

The company has provided the EAC and NICE with the year 4 trial report for ROBUST 1. The company noted that there are some details such as technical details in the document that they would not want made public in any way, however most of the outcomes data will eventually be publicly available.

Company noted that an abstract of ROBUST I 4-year outcomes will be presented at a conference on 18th to 21st March. This will be treated as academic in confidence for now. However, the company also noted that the conference may not go ahead in which case it may still be AiC. The company will keep us in the loop on the developments and whether the abstract will be presented.

NICE provided an explanation on academic in confidence (AiC) and commercial in confidence (CiC) data and how they differ in terms of who the information is made available to and when.

- AiC information is information provided in confidence where disclosure could prejudice future publication of the information in a scientific publication. It is expected that AiC information is going to be published at some stage. AiC information will be discussed in part 1 of the committee where the public can see it but will be redacted at consultation
- CiC information relates to the commercial interests of the owner of the information. It will not be published and therefore not discussed in part 1 of the committee meeting.

NICE noted that it would be helpful if the company could go through the report and highlight what they consider confidential before the assessment report is submitted.
Also, reminded the company they will have time to fact check to confirm or query anything in the assessment report.
The company agreed to have a look at the report and get back to NICE with details on what information cannot be shared.

4 Questions on the economic evidence submission:

EAC question: The model takes a mean of day case and outpatient procedure costs for Optilume. Could you give us any information on how widespread the use of Optilume is in an outpatient setting in the NHS, and what equipment and staffing would need to be present?

Response: The company notes that in the NHS, Optilume is currently only being used in a day-case setting, performing it within their existing setting as it is in the early adoption phase. They noted that one hospital in Wales is about to introduce the procedure in an outpatient setting. A number of hospitals in NHS are just about to start with first procedures in Jan/Feb.

The company reported that hospitals in the US and Canada already performing Optilume procedures in day case scenario under local anaesthesia. The company reported that there are a handful of cases so far in the US that have been done under minimal anaesthesia (e.g. lidocaine) and that it is a procedure that any urologist could do in any setting that dilatation is currently done. Already have hospitals in the UK moving forward and after implementation are moving towards an outpatient setting.

The company stated that the procedure aligns well to the local anaesthetic regimen for Urolift.

The EAC queried levels of anaesthesia/sedation required as well as staff and room requirements.

In terms of the Optilume procedure specifically, the company noted that in the UK 10-15 minutes prior to procedure, an initial tube of cold instillagel anaesthetic gel is inserted into the urethra, the patient is put into position and penis clamped or held in place and a 2nd tube of gel is inserted before advancing scope down the urethra itself.

NICE noted that the clinical experts have highlighted that the level of pain might be a problem in an outpatient setting when the balloon is inflated.

The company noted that you are not cutting the urethra with Optilume so not creating trauma, the balloon is slowly dilated, stretching the urethra so although patients will feel some level of discomfort but this is mostly due to the flexible cystoscope going through the urethra around the U bend rather than with the balloon.
When a procedure is done under minimal sedation/anaesthesia a flexible scope can be used which is tolerated better than the rigid scope.
The company further clarified the difference in using cold/hot blade to make an incision in the scar tissue itself which is potential trauma and is managed differently.

The company noted that staffing requirements are minimal. In terms of staff it's similar to the shared learning from NHS Fife, for Urolift - there's a urologist who performs the procedure, nurse scrub tech and a runner in the flexible cystoscopy room.

EAC raised a query why the NHS Reference costs are different for endoscopic procedures and Optilume?

YHEC noted that for endoscopic procedures, the model included day case and inpatient reference costs (based on OPEN trial) which showed a short length of stay for endoscopic management and so there may be some patients who require impatient stay. These are deliberately different costs as it includes a small amount of inpatient costs for endoscopic treatment.

The EAC noted that in the model, patients waiting for re-treatment are assumed to have 4 follow up appointments per year.

YHEC responded that there is minimal data for this, however an NHS England report suggest following up every 3 months for a year. They also stated that this would cover resource use for ongoing complications such as UTIs, which are not included separately.

EAC noted that in the model, patients treated with Optilume are further treated with Optilume and patients treated endoscopically are further treated endoscopically and queried how this reflects reality?

YHEC noted that the assumption in the base case is that a patient on Optilume would stay on Optilume rather than have a different endoscopic treatment. It is assumed that this is the most effective treatment so people would opt for this. However, there is an option in the model to look at endoscopic treatment after Optilume. Recommendations are that after failed endoscopic/Optilume should go on to urethroplasty but there are waiting lists for this and some patients may have further endoscopic treatments while on the waiting list for urethroplasty.

5 Additional questions:

NICE queried why the model used a 5-year base case time horizon?

YHEC responded that there is limited long-term data so considering a longer time horizon would introduce excessive uncertainty to the model/results.
There is some limited data that most of the recurrences would occur within the first year with limited recurrences in the following year, so 5 years captures the key impact. YHEC also noted that 2-3 years would understate the benefits.

NICE noted: with the sensitivity analysis, it looks at up to 10 years, but was a lifetime time horizon considered?

YHEC noted: a lifetime horizon was not considered as it would be unlikely that Optilume would be the last ever treatment that a patient receives, but there isn't the life-long evidence for this, so it was preferable to keep the model simple.

EAC queried recurrence being different in the different years which is not in the model. Is this a general observation for this type of procedure, or is it Optilume specific?

Company response: There is not a lot of hard data we can base the model off of. It would overcomplicate the model if we added that and so kept it at a flat monthly rate.

Appendix C: Clinical expert engagement meeting:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Clinical Expert Engagement Meeting

MTG 565 Optilume for Recurrent Anterior Urethral Strictures

This document summarises the discussions that took place during the clinical expert engagement meeting for MTG 565 Optilume, which took place on Tuesday 11th January 2022,13:00 to 14:30pm. A list of questions was shared with clinical experts in advance of the meeting to allow them to prepare some responses where appropriate. Any questions which were not addressed during the course of the meeting have been noted at the end of this document and responses will be sought via e-mail.

Attendees

Clinical experts:

- Mr Trevor Dorkin (TD)
- Miss Katie Moore (KM)
- Miss Louise Olsen (LO)
- Miss Pareeta Patel (PP)
- Mr Ian Eardley (IE)
- Prof Nick Watkin (NW)

NICE:

- Tara Chernick (TC)
- Lirije Hyseni (LH)
- Lizzy Latimer (LL)
- Ivan Maslyankov (IM)
- Chris Chesters (CC)

EAC

- Michael Beddard (MB)
- Megan Dale (MD)
- Ann Morris (AM)
- Susan O'Connell (SOC)

1. Welcome and Introductions

NICE briefly introduced everyone on the call and outlined the format for the meeting.

Discussion centred around some key topic areas including

1. Clinical Experience
2. Population
3. Comparators
4. Clinical Pathway
5. Resources, Staffing and Setting
6. Additional Questions

Clinical Experience

NICE asked the clinical experts to briefly describe their experience with Optilume with specific questions including:

Do you anticipate Optilume being more widely used in the NHS in the future?

One expert stated they were not willing to adopt Optilume without any longer term RCT data. A second expert noted they have a few cases lined up next month but having funding issues although the company are supplying the device free of charge. A third expert noted they are wanting to use Optilume but having are difficulties with the device approvals process within their trust partly because of new management.

NICE added that within the adoption report, 7 clinicians have been interviewed across 6 institutes who were in the process of submitting a business case for Optilume or were waiting to hear back. Some had delays with governance.

What additional evidence do you think may be needed to facilitate adoption?

All experts agreed that more randomised trial data would be helpful and in particular, long-term follow up data.

What are the characteristics of people currently being identified for treatment with Optilume? With wider adoption would these selection criteria expand?

One expert who is using Optilume noted that their patient cohort is also being kept as homogenous as possible at the moment due to a lack of evidence, therefore, patients with strictures in the Penobulbar region are the only ones being considered which represents the typical patient.

Experts who have experience using the Optilume device provide an overview of the device.

Only one expert and their team are currently using the device and described how this worked within their team including comments on safety, tolerability, setting and efficacy.

The clinical expert reported they have treated 10 patients so far and there are another 5 booked in next few weeks. Patients seem enthusiastic and are motivated to be involved in a pilot study. Patients understand the concept very clearly and the procedure as a whole is for patients who

have recurrent urethral strictures and so these patients will have had experience with at least 1 similar type of procedure before.

The clinical expert noted that from early experience, the procedure, which is done as a day-case procedure is very well tolerated. A move from a general anaesthetic to sedation has also been done and well tolerated. However, the clinical expert was sceptical about local anaesthesia alone as it will be painful during inflation of the balloon for a period of 7 minutes and so considers a move to outpatient setting unlikely.

Side effects are minimal. All patients remained un-catheterised post-treatment. Urinary testing afterwards. Patients are going home without catheter as it is not standard of care to put catheters in post-procedure, clinicians just make sure the bladders are empty at the start of the procedure and afterwards.

To identify stricture, image intensification (II) is used together with direct visualisation using a ureteroscope or cystoscope and guidewire. The balloon is positioned at the bottom and top end of structure over a guide wire, using II and the bottom end is visualised and pushed through with a fine calibre ureteroscope or cystoscope. One expert confirmed that he does not predilate patients routinely with standard of care and did not predilate these 10 Optilume patients.

All results are very short term and so unable to give any information around long-term outcomes at the moment, but the clinical expert reported they are optimistic that Optilume is a good technique in principle.

The clinical expert highlighted that due to covid-19, there are a lot of patients waiting for urethroplasty (up to two year waiting list) and these patients were keen to have an intervention that might be better than previous, and so are willing to have Optilume if it will improve symptoms.

Population

1. **Optilume is recommended for treatment of anterior urethral strictures; including penile/meatal and fossa navicularis strictures. Do the clinical experts have any experience in using Optilume for strictures other than those in the bulbar region?**

One expert stated that he would not use Optilume in penile strictures as open surgery is much more effective for these patients.

One expert stated that the patients they had been treating had strictures between 1.5-3 cm in length. As the balloons are 5 cm, and there is a need for 1 cm on either side to straddle the stricture, the limited factor is the length of the balloon.

A second expert queried this further and asked if they would consider using Optilume close to the sphincter. The clinical expert confirmed that he would be happy to put Optilume into high bulbar strictures and that even if it is close to the sphincter, it will cope if it is stretched as it would be with standard dilators or cystoscopes that enter the bladder and with a high bulbar stricture, this is inevitable.

Further to the problem of generalising the care pathway and evidence for bulbar to penile strictures, one expert added that dilatation doesn't seem to do well in penile strictures.

The experts agreed that the company's evidence is in bulbar strictures and they don't have evidence beyond that, therefore the device should only be used in bulbar strictures.

2. **The company states that Optilume can be used in single, tandem or diffuse anterior urethral strictures. Do the clinical experts agree with these indications?**

One expert clarified that it would be used in tandem or for two discreet strictures, providing the balloon will cover the entire length of the strictures. A second clinical expert stated that this terminology used in the scope is not common amongst clinicians and should be clarified in the Assessment Report.

3. **Does the cause of a urethral stricture impact the likelihood of Optilume being considered for a patient? For example, is a clinician more likely to recommend Optilume if a patient has a urethral stricture caused by a sexually transmitted infection rather than trauma?**
   One expert commented that in patients with BXO, they have dense scarring tissue which is not suitable for Optilume. A second expert added that this very dense scarring stricture makes dilatation with a balloon very difficult, and therefore would not consider using Optilume in BXO patients as urethrotomy would be more suitable.

   Experts commented that trauma patients probably wouldn't be candidates for Optilume either. The experts agreed that patients for whom Optilume may not be suitable are infrequent and would be discussed in a multidisciplinary meeting setting. For example, in a patient that had a contraindication for open surgery (urethroplasty), perhaps Optilume would change things but it would be a case of discussing with the patient on a case-by-case basis.

4. **In the ROBUST trials, patients were excluded if their stricture was due to bacterial urethritis, untreated gonorrhoea or had a history of Lichen Sclerosus or Balanitis Xerotica Obliterans (BXO). In routine clinical practice, what would be the standard care for these patients, and would they be eligible for Optilume?**

NICE asked if the above aetiologies would be something we need to be aware of when considering the generalisability of Optilume.
One clinical expert added that bacterial urethritis and untreated gonorrhoea are very uncommonly seen and not an issue in his experience. The clinical expert added that the bacterial infection would be treated before the stricture. Lichen sclerosis and BXO are usually at the distal urethra and rarely or never cause isolated bulbar strictures. The clinical expert noted that it is likely that in the clinical trials using Optilume, these patients (those with gonorrhoea or bacterial urethritis) were excluded to avoid the risk of sepsis if left untreated in these patients.

5. **Are there any comorbidities/contraindications that would exclude a patient from Optilume treatment?**

One expert noted that immunosuppressed patients would probably be the patients of concern. Also, would exclude patients with known adverse reactions to paclitaxel as stated in the device instructions for use.

Comparators

6. **In a previous NICE MIB for Optilume, clinical experts noted that it has the potential to replace urethroplasty and/or urethrotomy. Do the clinical experts anticipate Optilume replacing either procedure completely, or just delaying the procedures?**

One expert sees Optilume as an alternative to endoscopic management or for someone that wants to delay a urethroplasty but does not think that it would necessarily replace either. A second expert, commented that they are hoping Optilume might delay urethroplasty. They are hoping that Optilume may bridge the gap, and while it may not avoid urethroplasty completely, if it were to delay it for a couple of years, this would be a good outcome.

A third expert commented that Optilume is not going to replace urethrotomy or urethral dilatation, but it really depends upon the frequency of urethral dilatation. When given the option, men are choosing Optilume rather than urethroplasty as it is less invasive than surgery.

One expert added that the initial results with Optilume in trials may be more efficacious as they are predilating up to 30F, which is not standard of care.

NICE noted there is no evidence that a balloon is used in any other method of treating/managing strictures and asked the experts to comment on this?

One expert added that the urethrotomy works well and uses reusable knives rather than a one-time use consumable, so it is likely more a cost issue.

A second expert noted that the balloon is a consumable and has limitations in terms of length and numbers of strictures that need treating. It also has a cost associated and this is why it is not used routinely instead of graduated dilators or DVIU. In terms of the Optilume, the balloon is a mechanism of delivery for the paclitaxel and it is the paclitaxel that is key and that the addition of the paclitaxel is what impacts recurrence.

NICE asked how common it is for patients to self-dilate.

One expert noted that it depends upon where you're working with some centres/settings offering the option of self-dilatation. The expert noted that patient choice is important with some patients choosing self-dilatation and others not. Further away from equipoise when there is no better option than endoscopic management before surgery, patients may be encouraged to do self-dilatation as this may be the only option. The younger your patient, the more future time they're self-dilating for in their life and so this is not practical. It is all about having equitable access to all the different treatments.

A second expert added that some patients you may offer self-dilatation to, will try it for some time and change their mind.

Urethral Stricture Clinical pathway

7. Figure 1 below is a simplified proposed clinical pathway for urethral stricture management without Optilume and figure 2 is the same pathway including Optilume. These are based upon on current guidelines and pathways proposed by the company. Do clinical experts agree that this pathway is accurate?

The EAC explained that the pathway is a streamlined pathway based on guidelines available and the pathway provided by the company.

Clinical experts gave opinion on clinical pathway – many disagreed with the diagnosis section and would recommend removing this, but largely agreed with the addition of Optilume in the proposed pathway in figure 2.

One clinical expert added that Optilume would be considered after just one failed dilatation and this is where it would fit in the clinical pathway. However, 50% of people can be treated successfully on first dilatation. The evidence base currently is simply for recurrent strictures and the clinical expert noted anything up to 3 cm would likely be treated with Optilume if it is a recurrent bulbar urethral stricture. One clinical expert reiterated that if a patient fails dilatation and Optilume, then they should be referred for urethroplasty.

One clinical expert added that the bottom section of the pathway with urethroplasty/grafting is not correct. Patients would not have two separate surgeries, if grafting were needed it would be done as part of the initial urethroplasty.

After a failed urethroplasty, 1 expert noted that Optilume has a role, although some may go to dilatation. One expert noted that after failed urethroplasty, you should go back to MDT for discussion.

A second expert added that the diagnosis section and conservative management is not representative of all cases as younger patients would not generally be catheterised with an indwelling catheter.

One clinical expert also added that ‘anterior urethral stricture’ needs to be taken out of the pathway, and it should be amended to ‘bulbar urethral stricture’ to avoid clinicians misinterpreting the recommendation and using the device on penile strictures, to which it is not indicated. A second clinical expert also emphasised that this device would be used in bulbar strictures and not anterior urethral strictures. All other clinicians commented in agreement.

NICE asked if any clinicians would consider doing a second Optilume at any point?

One expert stated they would use it again but the decision would be based upon timeframe of stricture recurrence as some patients do not remain stricture free for long. Patients are less likely to want to have these procedures if recurring within weeks/months but might be happy if recurrence is years apart.

One expert noted the pathway is quite flexible – not an 'either-or' when it comes to treatment options and choice of treatment is likely to be patient driven (choice, co-morbidities, bladder function etc). This was reiterated by a second clinical expert who noted there is no rigid pathway. One expert added that, for example elderly patients with complex medical conditions are managed in the context of performance and their bladder function.

Following on from the comments from experts that the first part of the pathway is not relevant, the EAC questioned current pathway of getting to the point of treating a patient with a urethral stricture in terms of clinical diagnosis.

One expert noted that in younger men a stricture may be the top of the list and therefore confirmatory diagnosis will happen quite quickly whereas with an older man, a stricture may not be considered immediately therefore the early part of the pathway would be more relevant.

The expert noted that in an elderly patient, something such as prostate enlargement would be considered first, and management would be taken through a flowchart similar to the one suggested.

The clinical expert added that patients are often diagnosed from either a urethrogram showing a stricture, urethroscopy or when catheterisation is attempted but prevented due to stricture.

NICE commented that it seems as though there is an age driven approach to the clinical pathway which was confirmed by the experts.

The EAC requested clarification on whether there is an existing clinical pathway that clinicians follow currently?

One clinical expert confirmed that there is not a recognised pathway that exists as patients would come from multiple routes, for example patients would perhaps undergo investigations for benign prostatic hyperplasia (BPH) and managed using the appropriate care pathway.

8. **Company state that Optilume can be used as an adjunctive therapy with other dilatation devices and/or procedures. Where in the treatment pathway (figure 1) would the clinical experts suggest Optilume can be used adjunctively?**

One expert indicated there is not the evidence for adjunctive use of Optilume with other therapies and so this would not be adopted. Other clinical experts agreed with this.

Figure 1: Urethral stricture pathway without Optilume

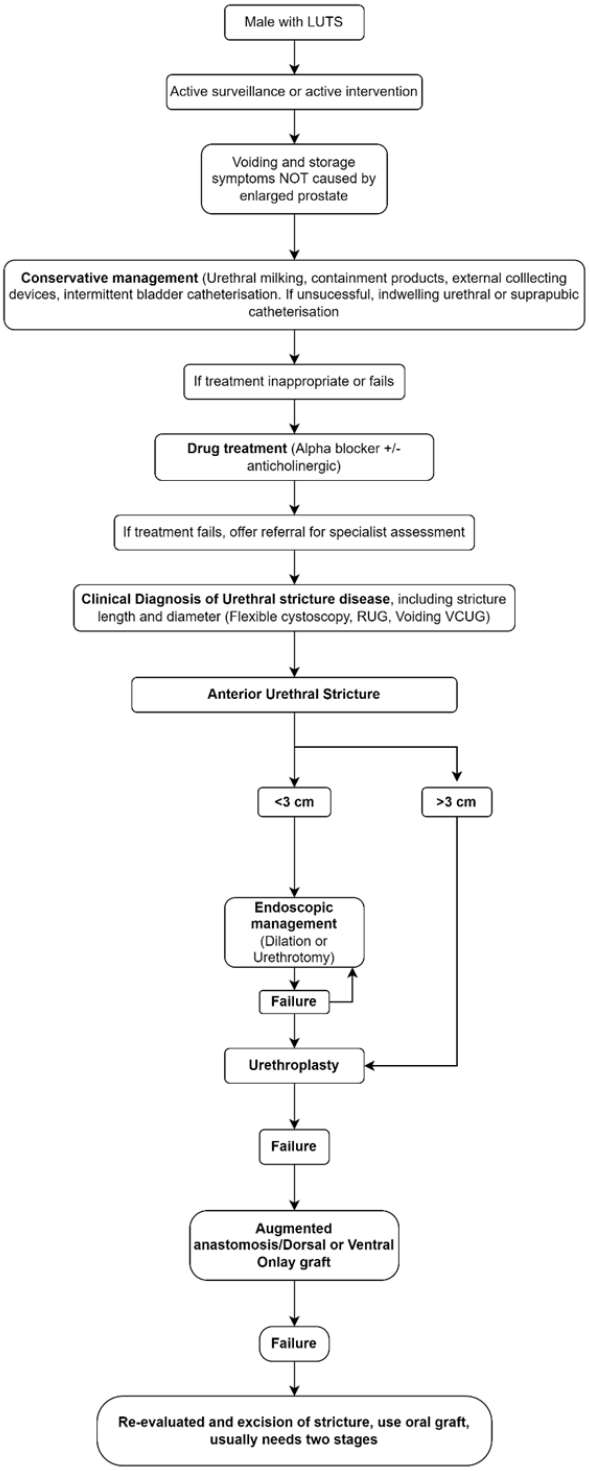
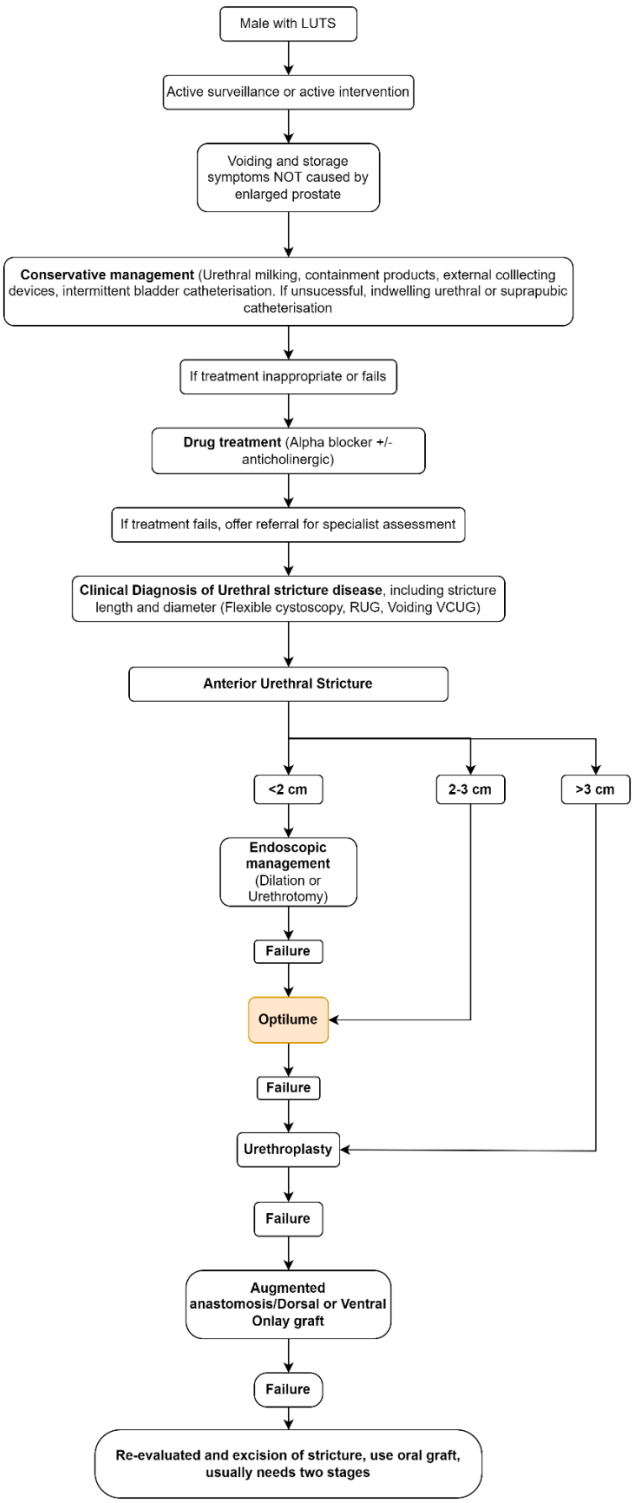


Figure 2: Urethral stricture clinical pathway including Optilume



Resources, Staffing and Setting

9. **The company state that Optilume can be performed in an outpatient setting under local anaesthesia; therefore, removing the requirement for inpatient stay, general anaesthesia and theatre time. Do the clinical experts agree that this is the case?**

Two clinical experts were not convinced about this. One expert noted that the likelihood is company have stated outpatient use of Optilume as it becomes more affordable if you're talking about outpatient treatments with no need for inpatient care. The problem is that patients have to be very still which is difficult during an uncomfortable/painful procedure. The procedure also requires a great degree of precision and the balloon can be difficult to place accurately without image intensifier which is not standard to have available in an outpatient setting, other than a lithotripsy suite.

A third expert added that he struggles to realistically see someone sitting still for ~7 minutes to enable precise and accurate placement of a balloon in the outpatient suite.

One expert added that their patients are sedated and it is good as they sleep through the procedure. The expert added that with even with I.V sedation, there is a patient reaction of pain during balloon inflation and the I.V sedation dose may need to be increased during this period. The recovery time for Optilume tends to be a couple of hours. No side effects reported in first 10 patients treated. Most patients wake up, have something to eat and drink and need to urinate, before being discharged. In their opinion, to move it to outpatient clinic would be cost incurring in some way to actually set it up but the main issue in terms of feasibility is the pain during the procedure.

An additional expert added that the company are possibly stating outpatient setting is possible to reflect the countries in which the device may be used and to account for places where procedure might be done in urology office settings, however he agrees with the other experts that it is not really possible and would be quite cruel, so he also would not perform the procedure in an outpatient setting.

10. **Optilume is intended to be used without predilatation, however predilatation was used in the ROBUST trials. Would the clinical experts predilate prior to intervention, and if so, does this require any additional resources? Would using predilatation be expected to impact the clinical outcomes?**

One expert commented that in a solitary stricture, predilatation should not make a difference. The only scenario where they suspect it would be an issue is where someone has multiple strictures, but either way it wouldn't necessarily alter the clinical outcome.

Additional questions

A number of questions were not discussed during the meeting due to time constraints. These were circulated to the clinical experts for additional information and feedback.

11. **For patients with recurrent penile/meatal or fossa navicularis strictures, urethroplasty is often first-line therapy. Is Optilume likely to change this recommendation?**
12. **The company state that Optilume can be used by consultants in urology, urology trainees and urology nurse specialists, compared with just urological surgeons for urethroplasty. In the opinion of the clinical experts, in the U.K, is this the case?**
13. **What aftercare, if any, is required post-Optilume?**
14. **What is the preferred method to diagnose a urethral stricture in the UK: urethra-cystoscopy, retrograde urethrography, voiding cystourethrography (VCUG), ultrasound urethrography, or a combination?**

Collated expert responses from Q4

Additional Questions

A number of questions were not discussed during the meeting due to time constraints. These were circulated to the clinical experts for additional information and feedback.

For patients with recurrent penile/meatal or fossa navicularis strictures, urethroplasty is often first-line therapy. Is Optilume likely to change this recommendation?
One expert said no, as previously stated Optilume would be considered for use in recurrent bulbar strictures, and not in pendulous penile or meatal strictures. A second expert said possibly but trials are required.

The company state that Optilume can be used by consultants in urology, urology trainees and urology nurse specialists, compared with just urological surgeons for urethroplasty. In the opinion of the clinical experts, in the U.K, is this the case?
One expert stated that anyone who is competent in endourology procedures and in endoscopic stricture management would be able to use Optilume.
A second expert stated that Optilume will be able to be used by core urology consultant as trainees though I doubt urology nurse specialists would use it as they don't tend to perform procedures other than flexible cystoscopies and prostate biopsies. Urology nurse specialists do not perform standard urethral dilatations. Urethroplasties should only be performed in tertiary centres by urology consultants with a sub-speciality interest in them.

What aftercare, if any, is required post-Optilume?
Response from one expert stated that it would be standard follow-up as for any patient that has undergone endoscopic management for their stricture.
While a second expert stated that they personally would conduct an outpatient review with flow rate, post void residual and PROM and SHIM assessment at 3, 12 and 24 months and then put the man on PIFU pathway for 2 years.

What is the preferred method to diagnose a urethral stricture in the UK: urethra-cystoscopy, retrograde urethrography, voiding cystourethrography (VCUG), ultrasound urethrography, or a combination?
Two experts stated retrograde urethrography and/or urethroscopy. One expert noted that neither VCUG or US urethrography is standard practice for stricture diagnosis.

Collated expert responses to Q8:

1. **If you were to adopt Optilume into normal practice, do you think that:**

You would exclusively use Optilume over other endoscopic procedures, or would you offer both?

Three experts reported they would not use Optilume exclusively, with two experts stating they would offer it alongside other endoscopic procedures.

A fourth expert noted they would prefer to see some longer-term data before using Optilume. If that data was ok (say 2 year follow up) they would use Optimum as an additional choice for patients with recurrent short urethral strictures in the bulbar urethra

If you offer both, how would that decision be made?

One expert would offer it to those with recurrent Bulbar strictures, <3cm in length, and had failed other endoscopic treatments. A second expert would consider Optilume for re-treatments, not for first stricture treatment.

A third expert said the decision would be based on the patient's stricture (location & size), general health, patient's wishes

A fourth expert would offer urethrotomy plus self-dilatation versus urethroplasty versus Optilume, explaining the differences and allowing the patient to choose.

Would this be different for retreatment?

One expert responded that retreatment with Optilume would only be offered to those that had had a good response (perhaps of 2 years) to an initial Optilume procedure. A second expert said they would more likely to offer Optilume but would depend on length of time since previous treatment. A third clinical expert would still offer both for a recurrent stricture given that Optilume is a new technology without the long-term data. The expert noted that based on feedback from patients, most patients however will go for Optilume as they do not want to perform self-dilatation which would be a requirement post endoscopic procedure to prevent recurrence. It will be patient choice. For a primary presentation they would just offer endoscopic treatment.

A fourth expert noted that there wouldn't necessarily be any difference in their decision making for retreatments.

2. **Please could you estimate, for patients requiring re-treatment, what percentage receive which retreatment method? If you do not currently provide Optilume, estimate what you would expect to happen, if possible.**

	Re-treatment method used (%)		
Most recent procedure	**Optilume**	**Endoscopic / Urethrotomy**	**Urethroplasty**
Optilume	30*	10*	60*

Endoscopic / Urethrotomy	50* 30Δ	30* 10Δ	20* 60Δ
Urethroplasty	90*	5*	5*

*Clinical expert 3 responses; ΔClinical expert 5 responses

One expert reported that there are too many variables not able to answer this while a second expert has not yet used Optilume so was unsure. One expert noted there is no data for repeating Optilume, so they wouldn't outside the context of a clinical trial.

3. **Does retreatment method vary with the number of previous treatments?**

One expert stated that if you continue to fail with endoscopic treatments, with short lived responses, you would ideally offer a urethroplasty

Three experts said no, with one expert additionally noting that multiple treatments usually result in long strictures and they aren't currently an option for Optilume.

4. **What is the primary consideration in choosing the retreatment method?**

Four experts agree that patient choice was a key consideration with one expert noting that patients choose for different reasons with chance of long term cure the most common and important driver. One expert added that some men do not want to perform ISD therefore won't have a repeated endoscopic procedure. Some men to not want the erectile dysfunction risk that comes with urethroplasty therefore choose endoscopic management. Some men just aren't fit enough to undergo a urethroplasty but don't want to do ISD. There isn't an overarching factor.

Additional considerations include stricture location and length, patient co-morbidities/age, time since previous treatment

5. **Approximately how long is there between a recurrence being identified and re-treatment with Optilume**

One expert stated that if available can be offered a date within 4 weeks while a second expert stated 4-6 months.

One expert is not using Optilume yet so unable to answer

One expert was not certain what was being asked but noted that in a recurrent stricture of the right length and location, all treatments are on the table.

Endoscopic procedures

One expert stated that if available can be offered a date within 4 weeks while a second expert stated 4-6 months.

Urethroplasty

One expert stated this is dependent on waiting list and urgency (2-6 months) and a second expert stated 12-24 months

A third expert stated that for both endoscopic procedures and urethroplasty waiting times for retreatment after identification of a recurrence vary between 6 and 104 weeks due to the current Covid situation. If a patient just has LUTS then they have a long wait. If they have gone in to retention, have infective episodes or high residuals then their surgery can be expedited.

6. **Are adverse events likely to happen later than 30 days post procedure?**

Four experts agreed that this was would not happen/was unlikely.

7. **In the ROBUST I trial; self-catheterisation was included in the eligibility criteria as a type of prior treatment. Would you consider self-catheterisation as a form of prior treatment when considering a patient for endoscopic management/Optilume?**

Three experts stated yes. One expert added that those performing self-dilatation would be the considered (the expert additionally noted that it was important to understand that self-catheterisation may be performed for reasons other than stricture management). A second expert added self-catheterisation/dilatation is an adjunct for either urethrotomy or urethral dilatation. The introduction of self-dilatation is not possible unless there's been a prior primary treatment such as urethrotomy or dilatation.

8. **Across the three ROBUST trials, several objectives (Anatomic success, freedom from repeat intervention, Qmax, PVR) and subjective (IPSS/IPSS QoL/IIEF score/USS-PROM) efficacy outcomes are used. In the management of patients with recurrent urethral strictures, what are the most important of the above outcomes taken into consideration when deciding upon re-treatment?**

One expert stated that there is no right or wrong answer here. The primary motivation for patients with symptoms.

- If you have a patient with symptoms, then you can demonstrate a recurrent structure either by cystoscopy or urethrogram and treatment for that recurrent structure is indicated.
- If the patient has no symptoms it's difficult to justify treatment on the basis of imaging or endoscopy alone

Two experts reported that Patient reported symptoms/bother (USS PROM or IPSS) would be most important and both experts also reported that Qmax was important. One expert stated that it was possible that IPSS score can be affected by other things as well as the stricture. Other important outcomes included flow rate, PVR and freedom from repeat intervention.

Appendix D: Company/YHEC email correspondence

Company response to Q6:

On the breakdown of outcomes by standard-of-care treatment type, they will be reported as part of a response to a letter to the editor. See attached. This document is academic in confidence, it will be published alongside the full manuscript (which is currently just an ePub) in an upcoming issue of Journal of Urology.

You are correct that the responder rate definition is not included in the 12m manuscript; the primary outcome for the entire study was the 'stricture free rate' at 6 months as you describe, the responder rate definition is utilized for longer term follow up and will be utilized for future (e.g. 2y) manuscripts where cystoscopy is not part of the follow-up program. I'm hesitant to send the full report given the burden of having to mark up the confidentiality pieces like we did for RB1. The relevant table is below, let me know if you need the full report to be able to utilize. The below table would be considered academic in confidence.

Table 9-28. IPSS Responder (≥30% Improvement) Over Time (Failure Carried Forward)

Study Arm	30-Day	3-Month	6-Month	1-Year
Control n/N (%) 90% CI [1]	[redacted]	[redacted]	[redacted]	[redacted]
Optilume® DCB n/N (%) 90% CI [1]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Confidence intervals (CI) are estimated using the Clopper-Pearson (exact) approach.
[2] Improvement from baseline is calculated by subtracting post-baseline values from baseline values.

YHEC answers to Q7:

1. Please could you share the calculations for adverse event costs for:

   - Wound infection
   - readmission to hospital

   YHEC response: Excel file attached.

2. Can you confirm that the Urinary retention cost is based on the Accident and Emergency service code 180 (see table at end). Did you look at any other costs given that there is only one procedure listed?

   YHEC response: I can confirm that is the code we used. We didn't think the outpatient one was appropriate as this was thought to just reflect a procedure cost/standard outpatient appointment and wouldn't include potential admission etc. The A&E costs in NHS reference costs seemed very broad so this was the only cost I could see that might reflect emergency urinary retention.

3. Probability of retreatment following recurrence is taken as 90% from the Pickard, 2021 model. Do you have any insight into how they derived this value, given the reported retreatments in table 17 of Pickard 2021?

   YHEC response: I haven't had any contact with the author so my only insight is what is reported in the study but I wonder if it's based on the number of people receiving treatment initially rather than as part of the retreatments which may not be fully captured due to the length of the study period? It looks like a total of 23 patients didn't have treatment after randomisation to urethroplasty or urethrotomy out of the 222 that were randomised which works out to around 10% not receiving treatment (Figure 6 in the paper)?

Company response to Q7

1. You have provided us with the IPSS responder 'failure carried forward' rate in a previous email, but are you able to provide the non-failure carried forward rate?

This is a bit of a quirk in how responder was defined in the ROBUST III protocol; patients receiving additional treatment weren't automatically considered failures. So the 'failure carried forward' method corresponds to the definition of ≥30% improvement without repeat intervention (i.e. failures at previous timepoints were carried forward as would be expected).

2. Further to the previous question, what was the reason for the change in the IPSS responder rate definition from ≥50% improvement used in ROBUST I and II, to ≥30% improvement? If figures for IPSS responder rate ≥50% improvement in ROBUST III are available, are you able to provide the EAC with these?

This was driven by a recently (mid 2020) released FDA Guidance document that defines a 30% improvement as an appropriate minimum clinically significant difference when utilizing the IPSS questionnaire in studies evaluating devices for BPH. Prior to this guidance, the MCD for the IPSS was not clearly articulated in the literature and varied from a fixed improvement (e.g. improvement of 3, 8, etc) to a % improvement. Urotronic chose a definition including a 50% improvement as a conservative approach for the single arm study of ROBUST I, however this definition is overly stringent when compared to other definitions of recurrence (e.g. 'return to baseline' symptoms in OPEN trial). Interestingly, the responder rates in ROBUST I tended to be very similar regardless of definition used.

Both definitions were reported in ROBUST I and ROBUST III, see below. Urotronic is working to harmonize definitions for future analyses across studies utilizing the ≥30% improvement without reintervention definition.

ROBUST III

1. **Table 0-1. IPSS Responder (≥50% Improvement) Over Time (Failure Carried Forward)**

Study Arm	30-Day	3-Month	6-Month	1-Year
Control n/N (%) 90% CI [1]	[redacted]	[redacted]	[redacted]	[redacted]
Optilume® DCB n/N (%) 90% CI [1]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Confidence intervals (CI) are estimated using the Clopper-Pearson (exact) approach.
[2] Improvement from baseline is calculated by subtracting post-baseline values from baseline values.

ROBUST I

2. **Table 0-2. Subjects who experienced ≥50% Improvement in IPSS from Baseline**

Category	3 Month	6 Month	Year 1	Year 2	Year 3	Year 4
Success	43	41	37	32	29	[redacted]
Failure	8	9	11	15	14	[redacted]
Evaluable	**51**	**50**	**48**	**47**	**43**	[redacted]
Responder Rate	**84%**	**82%**	**77%**	**68%**	**67%**	[redacted]

3. **Table 0-3. Subjects who experienced ≥30% Improvement in IPSS from Baseline**

Category	3 Month	6 Month	Year 1	Year 2	Year 3	Year 4
Success	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3. In ROBUST III, USS-PROM is an outcome but results are not reported in the paper. Are you able to provide these values?

ROBUST III did not incorporate the USS-PROM tool into the follow-up protocol.

4. VAS pain score was not an efficacy outcome in ROBUST III study but was this measured at all, and if so are you able to provide us with these values?

Table 9-9. Peri-operative VAS Pain Scores

Treatment Group	Baseline	Pre-Discharge	Foley Removal	30 Day
Control Arm (N=48)				
n	47	47	48	47
Mean ± SD	1.9 ± 2.3	2.1 ± 2.2	1.5 ± 2.0	0.2 ± 0.6
Median	1.0	2.0	1.0	0.0
Min, Max	0, 8	0, 8	0, 7	0, 2
Optilume Arm (N=79)				
n	78	77	78	78
Mean ± SD	1.6 ± 2.2	2.5 ± 2.2	1.4 ± 1.7	0.6 ± 1.0
Median	1.0	2.0	1.0	0.0
Min, Max	0, 8	0, 9	0, 8	0, 6

5. In ROBUST III there is very limited information on the rate of adverse events/SAEs. Are you able to provide the overall AE/SAE figures and a breakdown on the number

See below for device/procedure related AEs and ALL SAEs. Of note, the hematuria AEs were grade 1 i.e. observational only and didn't require treatment (in both arms) so weren't reflected in the model.

Table 13. Renal/Urinary Device/Procedure Related Adverse Events by MedDRA SOC and PT.

System Organ Class/ Preferred Term	Control Arm		Optilume Arm	
	Events	Subjects (N=48)	Events	Subjects (N=79)
Renal and Urinary Disorders	5	4/48 (8.3%)	19	16/79 (20.3%)
Dysuria	0	0/48 (0.0%)	5	5/79 (6.3%)
Bladder Spasm	2	1/48 (2.1%)	2	2/79 (2.5%)
Hematuria	0	0/48 (0.0%)	3	3/79 (3.8%)
Urethral Stenosis	1	1/48 (2.1%)	1	1/79 (1.3%)
Urinary Incontinence	0	0/48 (0.0%)	2	2/79 (2.5%)
Urinary Retention	0	0/48 (0.0%)	2	2/79 (2.5%)
Urine Flow Decreased	1	1/48 (2.1%)	1	1/79 (1.3%)
Lower Urinary Tract Symptoms	1	1/48 (2.1%)	0	0/79 (0.0%)
Terminal Dribbling	0	0/48 (0.0%)	1	1/79 (1.3%)
Urethral Hemorrhage	0	0/48 (0.0%)	1	1/79 (1.3%)
Urethritis	0	0/48 (0.0%)	1	1/79 (1.3%)

Table 9-33. Rate of Acute Urinary Retention Requiring Catheterization Through 6 Months

Endpoint	Control Arm (N=48)	Optilume Arm (N=79)	Difference (95% CI)
Rate of acute urinary retention requiring catheterization by 6 months	3/48 (6.3%)	1/79 (1.3%)	-5.0% (-22.7%, 12.9%)
Confidence Intervals (CI) for the difference are estimated using the exact approach.			

Table 10-6. Summary of Serious Adverse Events by Term (Adjudicated)

System Organ Class/ Preferred Term	Control Arm		Optilume Arm	
	Events	Subjects (N=48)	Events	Subjects (N=79)
Renal and Urinary Disorders	**2**	**2/48 (4.2%)**	**1**	**1/79 (1.3%)**
Urinary Retention	*2*	*2/48 (4.2%)*	*0*	*0/79 (0.0%)*
Urethral Cancer	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Infections and Infestations	**2**	**2/48 (4.2%)**	**2**	**2/79 (2.5%)**
COVID-19	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
COVID-19 Pneumonia	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Sepsis	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Urinary Tract Infection	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0/48 (0.0%)**	**3**	**3/79 (3.8%)**
Pulmonary Embolism	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Lung Adenocarcinoma	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*

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 Report factual check

Optilume for recurrent bulbar urethral strictures

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 to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **14 February 2022** 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.

09/02/2022

NICE National Institute for Health and Care Excellence

Issue 1 Registered Trade Name

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
15	1	Missing word	The Optilume® Urethral Drug Coated Balloon (Optilume DCB) CE marked medical Device	To reflect the registered trade name of the device, only needs ® on first use To complete the sentence	These changes have been made.

Issue 2 Paclitaxel Mechanism of Action

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
15	4	Extra Word	…proprietary circumferential coating of the ~~microtubule~~ anti-fibrotic and anti-proliferative…"	Should either elaborate on paclitaxel's action to stabilize microtubules or delete and maintain existing general references to mechanism of action	'Microtubule' has been removed to keep description of mechanism of action more general.

NICE National Institute for Health and Care Excellence

Issue 3 Optilume DCB Indication vs Recommended Use

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
15	17	Inaccurate indication statement	…with recurrent anterior ~~bulbar~~ urethral strictures.	Indications for use in the applicable IFU (1111-002rD) for the UK includes recurrent anterior strictures ≤3cm in length. See IFU (1111-002rD) supplied alongside this factual check pro-forma for reference. Understanding that NICE recommendations may be limited to use in bulbar strictures, factual evidence exists that the device has been studied in penile strictures and includes all anterior strictures in its indications for use. The report should clearly delineate between what is an indication statement, what has factually been studied, and what is part of the problem statement and is a	The EAC has made the suggested changes to specify the indication statement as per the IFU.
16	17	Incorrect statement of evidence on stricture location	…men aged ≥18 years with recurrent ~~bulbar~~ anterior urethral stricture…		
16	27	Incorrect statement of evidence on stricture location	…is ~~a lack of~~ limited clinical evidence…		The EAC has made the suggested changes to clarify the limited and not lack of evidence in penile strictures.
17	Table 1	Incorrect statement of evidence on stricture location	…as the evidence base is limited ~~to~~ in all but bulbar urethral strictures…		The EAC has made the suggested change to reflect the limited evidence base in anterior strictures other than those in the bulbar region.

				recommended patient population for use by NICE.	

Issue 4 ROBUST Studies Geographical Location

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
15	20	ROBUST study geographies	…three ~~U.S.~~ North American studies…	ROBUST I conducted in Panama and Dominican Republic, ROBUST III conducted in the US and Canada	The EAC has made the suggested change to indicate that the ROBUST trials are in North America and not just the U.S.

Issue 5 Optilume procedure treatment setting

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
16	4	All procedures assumed to take place as a day-case	There are now NHS Trusts performing procedures as outpatient treatments	To highlight transfer from day-case treatment to outpatient treatment	A comment to address these three points has been added to the 'integration into the NHS' section of the report stating 'the company has noted that there is 1 trust that is using Optilume in an outpatient setting under local anaesthesia'.
24/25	46-49/1-10	Clinical experts' opinion of not being able to be performed under	Recommend you contact Mr. Christian Seipp for additional clinical input as he has now performed numerous	The treatment has already been adopted by one expert, Mr. Christian Seipp (Betsi Cadwaladr University Health	

		local anaesthesia in outpatients	procedures under local anaesthesia in an outpatient setting	Board) using local anaesthesia in an outpatient setting without compromising precision of the procedure	
85	14-22	Clinical experts' opinion of not being able to be performed under local anaesthesia in outpatients	Recommend you contact Mr. Christian Seipp for additional clinical input as he has now performed numerous procedures under local anaesthesia in an outpatient setting	The treatment has already been adopted by one expert, Mr. Christian Seipp (Betsi Cadwaladr University Health Board) using local anaesthesia in an outpatient setting without compromising precision of the procedure	

Issue 6 Optilume DCB Contraindications

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
20	4	Incorrect statement on contraindications	…contraindicated for use in people with ~~Balanitis Xerotica Obliterans (BXO),~~ known hypersensitivity…	Balanitis Xerotica Obliterans (BXO) is not a contraindication for the Optilume DCB per the device IFU (1111-002rD). See IFU (1111-002rD) supplied alongside this factual check pro-forma for reference.	The EAC has removed the contraindication for use in people with BXO from paragraph 1 of page 20. A comment has also been added to line 12 of page 29 to clarify that safety and effectiveness data has not been established in patients with BXO.

Issue 7 Optilume Intended Use

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
24	20	Assumed to only delay further invasive treatment	The indication for Optilume is not to replace any of the currently available treatments but to add to the existing armamentarium in an effort to delay or prevent the need for the more invasive urethroplasty surgery.	The original statement only refers to Optilume as a potential delaying tactic to Urethroplasty, the likelihood is some if not most patients will have a lasting result as a result of treatment with Optilume thus preventing the need for Urethroplasty.	The EAC have amended the comment on page 24 and also page 87 to highlight that Optilume may be used to delay or prevent the need for further invasive urethroplasty surgery.

Issue 8 Guidelines for Treatment – Urethral Stents

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
24	31-32	Assumed that Optilume is considered similar to a urethral stent, it isn't. A stent remains in situ, for a prolonged period of time. Optilume is	Additionally, European Association of Urology (EAU) guidelines recommend against the use of endoscopic treatment methods such as DVIU for penile strictures,	If commenting on non-feasibility for penile strictures, reference the guidelines statement for endoscopic treatment of penile strictures, not urethral stents.	As per the EAU guidelines, the suggested change has been made by the EAC to include the advice against the use of DVIU for penile strictures.

		removed. Also, stents are not recommended for use in the EAU guidelines	and instead recommends augmentation urethroplasty.		

Issue 9 Recovery time following Optilume treatment

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
25	11-12	Recovery time	As above Issue 10, when performed in outpatients, recovery time has been significantly reduced to 30-45 mins. Contact Mr. Christian Seipp for clinical expert opinion	Recovery time is reduced when performed in Outpatients as it is currently being performed in an NHS hospital	Thank you for your comment, the EAC has noted in the report (Integration to the NHS) that there is one clinician using Optilume in an outpatient setting.

Issue 10 Intended Population

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
38, 40 & 41	Tables	EAC comments that 'patient cohort had mostly undergone 1	Delete sentence	As per scope, this is the exact patient cohort for Optilume having undergone	The EAC have removed the first comment concerning 1-2 prior endoscopic procedures

		or two endoscopic procedures which may not be representative of typical patients requiring Optilume.' EAC later comments for DeLong 2022 'patients were not eligible unless they had ≥2 prior endoscopic procedures which does not fit with where the Optilume would be considered by clinicials		previous endoscopic treatment but failed. Having failed one or two endoscopic treatments, would be considered recurring thus is the effective patient cohort that Optilume has been studied in and is indicated for use.	not being representative of typical patients for Optilume. The second comment regarding the DeLong 2022 study has not been changed as patients are eligible for Optilume after 1 prior endoscopic procedure, and DeLong recruited patients who had ≥2 procedures.

Issue 11 Reported Endpoints for ROBUST I

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
51	22-35	Bias in outcome definitions	The primary efficacy outcome of the study was improvement in IPSS at 90 days. Efficacy	The primary efficacy outcome for the overall study did not change from the inception of	Thank you for clarifying the reasons behind the change in outcomes emphasised throughout the ROBUST trial publications.

			outcome measures reported in the 1 and 2 year publications included anatomic success at 1 year and 'functional success' at 2 years, which was defined as a 50% improvement in IPSS compared to baseline.	the protocol, but the outcomes emphasized in the publications changed from anatomic success at 1 year to functional success at 2 years due to the lack of planned cystoscopy at long-term follow-up. Authors chose anatomic success as the primary reported outcome at 1 year as this is the 'gold standard' for measuring success post-urethroplasty. Since cystoscopy was not conducted at later timepoints, the emphasized endpoint was improvement in subjective symptoms without repeat intervention. This does not represent a bias in outcome measure choice, rather emphasis on the available data and most appropriate measure at the timepoint being reported, and represents real world practices.	Taking this into consideration, the EAC has amended the paragraph in the report to highlight that what may appear to be a risk of bias in selecting outcomes, is a difference in emphasis on available data. Comment in the EAC comments section of Table 6 has also been amended.
51		Outcomes in both years one and two were different.	Delete current first line of last paragraph and replace with: Paclitaxel concentration and VAS pain scores were	Paclitaxel concentration and VAS pain scales were evaluated at early timepoints to evaluate peri-procedural	The suggested changes have been made by the EAC.

			evaluated at early timepoints and reported in the one year manuscript.	pain and paclitaxel pharmacokinetics. These outcomes were reported with the 1 year data and were not relevant to be repeated for the 2 year report, as no new data had been collected.	
52		Changes to outcomes across the 4-year trial introduces bias	Delete reference to changes in outcome definitions	No definitions were changed during the study, rather the emphasized endpoints in publications varied based on available outcome measures at the specific timepoint for which the publication was written	Thank you for clarifying the reasons behind the change in outcomes emphasised throughout the ROBUST trial publications. Taking this into consideration, the EAC has amended the paragraph in the report to highlight that what may appear to be a risk of bias in selecting outcomes, is a difference in emphasis on available data. Comment in the EAC comments section of Table 6 has also been amended.
52		Reference made to no grading of events, and only 49% of AEs accounted for in the 1 year outcomes paper”	Delete this paragraph	Virasoro et al included all adverse events reported through 1 year, and provided mild/moderate/severe grading per CTCAE in Figure 1 of the publication.	The wording of the paragraph has been amended slightly to explain that of the 52 AEs reported in Virasoro 2020, 49% were categorised by event type (UTI, fever etc), and the rest were not. Similarly in the two-year outcomes (Mann 2021), 71 AEs were reported, 44% of which were categorised by event type, and 56% not reported.

					The EAC has however added that all AEs were categorised and accounted for in the 4-year report.
52		Reference to utilizing DVIU when pre-dilation did not yield the stricture is incorrectly conveyed	…and if pre-dilation did not yield the stricture, DVIU was recommended prior to application of the Optilume DCB. ~~This could have introduced selection bias to trial design as those most likely to have stricture recurrence may not have been included in the trial.~~	Fundamental misunderstanding of study design. Subjects were not excluded if pre-dilation with an uncoated balloon failed to dilate the stricture, rather they were recommended to undergo further DVIU followed by treatment with the Optilume DCB within the same operative period.	Thank you for your comment, the EAC has made these amendments to the report. A comment has been added to specify that it is unclear whether outcomes may differ for the 26% of participants who received a combination of pre-dilation types.

Issue 12 ROBUST III Critical Appraisal

Page No.	**Line. No**	**Description of factual inaccuracy**	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
53		Sample size mis-stated	The sample size was 127 randomized patients; 48 in the control group and 79 in the Optilume group. An additional 15 ~~of which were~~	The non-randomized PK sub-study enrolled 15 patients, while the randomized study enrolled 127.	The EAC have amended this point and also in table 8 (page 46) to reflect a sample size of 127 + an additional 15 subjects enrolled to PK for paclitaxel. This was correctly stated on page 71 of the report and in the Paclitaxel Addendum.

			non-randomized subjects were enrolled for paclitaxel…		
53		Randomization approach not clearly stated	…with patients randomized in a 2:1 ratio via centralized electronic system and stratified…	Randomization was conducted centrally through an electronic database system just prior to treatment so that concealment of allocation could be maintained, possibly changing EACs judgement of the risk of bias in the randomization schema	Thank you for providing this clarity. This randomisation process is not stated in the Elliott 2021a paper but has been added to the report.
53		Statement that participants were not treated by an intent-to-treat method is factually false	~~Patients randomized to the intervention arm were randomized through treatment up to 6-months, at which point they were unblinded and were given the choice to cross-over to treatment with the Optilume…~~ Patients were blinded to treatment assignment through 6 months post-treatment after which they were unblinded. This unblinding could have biased some secondary outcomes at follow-up including the IIEF and PROMS scoring. Subjects randomized to the control	All endpoints were assessed utilizing Intent-to-Treat methodology, where all subjects randomized to control were assessed in the control group. Those undergoing repeat intervention, including cross-over to receive Optilume after confirmed stricture recurrence, were considered failures for categorical endpoints or assigned the worst observed value for continuous endpoints for timepoints after the intervention, as described in Elliott et al 2021. Crossover	Thank you for your comments. Some of the changes have been made to the report to clarify that patients could only cross-over if they had stricture recurrence.

			group were allowed to cross over only if stricture recurrence was confirmed via recurrent symptoms, decreased flow, and stricture diameter <12F as measured by retrograde urethrogram.	was not 'offered' to every control patient, rather it was a treatment option available if their stricture recurred and further intervention was necessary.	
54		USS-PROM scoring was not included as an outcome in the ROBUST III trial	~~Of note, USS=PROMs scoring is specified as an outcome in the ROBUST III trial but no results are reported~~	USS-PROM is not listed as an outcome measure in the ROBUST III study in any study documentation	The USS-PROM results and overall results sections have been updated to indicate that USS-PROM was not a reported outcome. A comment on page 54 has also been removed and a comment regarding USS-PROM in table 8 has also been changed.
54		Statement that only 7 in the control group and 12 in the Optilume group had anatomic success reported at 6 months.	Delete sentence	Table 2 in Elliot SP et al 2021 shows anatomic success is 26.8% (11/41) in the Control arm and 74.6% (50/67) in the Optilume arm. Cystoscopy outcomes were missing in 7 and 12 patients, respectively	This sentence has been deleted from page 55 of the report as anatomic success was reported. Comment regarding cystoscopy outcomes missing has been added to the anatomical success results section (page 57, line 4).

Issue 13 **Inaccurate Endpoint Definition**

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response

55, 71		ULT tested ability to pass 16F cystoscope or 14F catheter	…ability to pass a flexible cystoscope into the bladder (≥16F) or the…	In the description of the endpoint in Virasoro et al, mention is made that various sized cystoscopes are available (15-20F), however the endpoint definition in the protocol only referenced cystoscopes ≥16F. The statement in Virasoro et al was intending to explain why a 14F catheter was included as a final assessment if a cystoscope could not be passed.	This minor change to cystoscope diameter has been made to page 56.

Issue 14 Inaccurate Endpoint Reporting – ROBUST I Anatomic Success

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
56, 71, 74	Table 11, Line 8-9, Table 19	ROBUST I only reported anatomic success at 6 months and 1 year	Table 11 cells for ROBUST I should reflect 'N/R' for years 2, 3, and 4 Sentence on page 71, line 8-9 should be deleted. Table 19 cell for 4 year anatomic success should reflect 'N/R'	Anatomic success was measured by cystoscopy and/or catheter passage, this was only conducted at the 6 month and 12-month visit. 'Functional Success' reported at years 2-4 was defined as improvement of ≥50% from baseline in IPSS without repeat intervention.	Thank you for your comments. Anatomical success was misinterpreted in the 4-year report and so these results have been removed from Table 11 and Table 19, and replaced with N/R. The comment on page 72 regarding anatomical success through to 4-years in ROBUST I on page 72 has also been removed.

Issue 15 Listing of USS-PROM as an Outcome for ROBUST III

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
66		ROBUST III did not include USS-PROM as an outcome measure	Replace current sentence with “The ROBUST III study did not include USS-PROM as an outcome measure”	No study documentation exists that references USS-PROM as an outcome for ROBUST III	

Issue 16 Future Clinical Trials in the UK

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
84	33-34	No proposed clinical trials for the UK that the EAC are aware of	[redacted]	[redacted]	Comment added to report on page 88.

Issue 17 Number of NHS Organisations Utilizing Optilume

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
85	6-9	Optilume is currently used in [redacted] NHS organisation in England and [redacted]	Optilume is currently used in four NHS organisations in England and [redacted] and approved for use in a further [redacted] in the UK	Since writing this assessment report a number of NHS hospitals have begun performing procedures, this includes three clinical experts who contributed to the report (Mr. Dorkin, Ms. Patel and Prof. Watkin)	The EAC has amended the text on page 86 for clarity.

Issue 18 Costs associated with Optilume procedure

Page No.	Line. No	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
100	1	Cost of procedure	This would incur a cost reduction if performed in an outpatient setting versus daycase/inpatient	The treatment has already been adopted by one expert, Mr. Christian Seipp (Betsi Cadwaladr University Health Board) using local anaesthesia in an outpatient setting without compromising precision of the procedure. This will be written in an	The EAC has amended the text on p. 101 to read: Expert advice was that it is unlikely in the NHS that Optilume would be adopted as an outpatient procedure, as it requires sedation in addition to local anaesthesia, however the company have provided information that 1 centre is now offering the procedure in an outpatient setting. The EAC have used only the day case costs,

				eventual single centre study from Betsi Cadwaladr University Health Board	changing the procedure cost from £635 to £1,067 to reflect current use, but this may change in the future. The EAC added an additional sentence on p.103: If an outpatient setting were widely used there would be an increase in the cost saving due to Optilume.