

# Open urethroplasty versus endoscopic urethrotomy for recurrent urethral stricture in men: the OPEN RCT

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†In memoriam

**Declared competing interests of authors:** Robert Pickard, Graeme MacLennan, John Norrie, Luke Vale, Tim Rapley, Elaine McColl, Daniela Andrich and Jonathan Cook report grants from the NHS [National Institute for Health Research (NIHR)] during the conduct of the study. John Norrie reports membership of the following NIHR boards: Commissioning Priority Review Decision-making committee (2015); Health Technology Assessment (HTA) Commissioning Board (2010–16); HTA Commissioning Sub-Board (Expression of Interest) (2014); HTA Funding Boards Policy Group (2016–19); HTA General Board (2014–18); HTA Post-Board funding teleconference (2016–19); NIHR Clinical Trials Unit Standing Advisory Committee (2018–present); NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board (2014–19); Pre-exposure Prophylaxis Impact Review Panel (2017). Luke Vale reports membership of NIHR HTA Clinical Evaluation and Trials panel from 2015 to March 2018. Elaine McColl reports grants from the NIHR Journals Library outside the submitted work. In addition, from 2013 to 2016 Elaine McColl was a member of the NIHR Journals Library Editorial Group. Jonathan Cook was a member of the HTA Efficient Study Designs Board (2014–16) during part of this study’s duration. James N’Dow was a member of the HTA General Board (2016 to March 2018).

**Disclaimer:** This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published November 2020

DOI: 10.3310/hta24610

## Scientific summary

### The OPEN RCT

Health Technology Assessment 2020; Vol. 24: No. 61

DOI: 10.3310/hta24610

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## Scientific summary

**B**ulbar urethral stricture is a common cause of urinary symptoms in men (typically difficulty in passing urine). Initial treatment is usually by endoscopic urethrotomy which widens the narrowed segment by incising the stricture internally under vision. In about half the cases the stricture will recur requiring retreatment. Retreatment can be by repeat endoscopic urethrotomy or more complex surgery, open urethroplasty, to reconstruct the urethra using a graft of oral mucosa. Evidence to help guide men with recurrent bulbar urethral stricture and their clinicians in choosing which management strategy to follow is limited. The OPEN study compared outcomes and costs of the two procedures in a randomised controlled trial (RCT).

### Objectives

The hypothesis was that the use of open urethroplasty for men with recurrent bulbar stricture would reduce the voiding urinary symptom score over a 24-month trial period by at least 10% compared with endoscopic urethrotomy. We addressed the following main research questions:

- Does open urethroplasty offer superior symptom control?
- What is the difference in reintervention rate?
- What is the relative cost-effectiveness of urethroplasty over 24 months?

### Methods

#### Design

A 38-site, patient-randomised, two-arm superiority trial comparing, in parallel groups, open urethroplasty (experimental) with endoscopic urethrotomy (control) for men with recurrent bulbar urethral stricture. Participants and surgeons could not be blinded to the allocated procedure. Central trial research staff managing trial data were blinded to allocated group. We performed within-trial cost–utility analysis and a qualitative process evaluation of feasibility. The design, conduct and reporting of the trial was informed by patients either as co-applicants or as a member of an independent Trial Steering Committee.

#### Setting and participants

Eligible men were recruited through urology departments of NHS hospitals throughout the UK. The original plan to randomise 500 participants over a 24-month period was not feasible. The trial was modified, aiming to recruit 210 men over a 35-month period and to complete follow-up and analysis over a total trial duration of 62 months. Follow-up continued for at least 24 months after randomisation.

#### Inclusion criteria

- Men aged  $\geq 16$  years.
- Stricture located predominantly in the bulbar urethra.
- Undergone at least one previous intervention for bulbar urethral stricture.
- Clinician and patient agreement that further intervention was required.
- Suitable for general or regional anaesthesia of up to 3 hours' duration.
- Willingness to have up to a 2-week period of urethral catheterisation.

#### Exclusion criteria

- Perineal sepsis.
- Previous participation in the study.

## Measurement of outcomes

### Clinical

Clinical outcomes were measured by repeated participant completion of the urethral stricture surgery – patient-reported outcome measure (USS-PROM) over at least 24 months following randomisation. Specific time points were baseline prior to randomisation, prior to intervention, 1 week after catheter removal, at 3, 6, 9, 12 and 24 months post intervention, at 18 and 24 months post randomisation, before and after any reintervention and at the end of the trial in December 2017. The USS-PROM included a six-item urinary voiding symptoms questionnaire as the primary outcome measure, each item being scored from 0 (no symptoms) to 4 (symptoms all of the time), giving a total score of 0–24 and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire assessing health state. The EQ-5D-5L comprised mobility, self-care, usual activities, pain/discomfort and anxiety/depression domains each with five levels describing increasing severity. EuroQol-5 Dimensions responses were converted into utilities using a standard scoring approach. It also included a visual analogue in which health is self-rated from 0 (worst possible) to 100 (best possible) health. Further interventions were documented.

### Harms

Harms arising from trial participation were documented at the time of, and shortly after, the trial intervention and at 3 and 24 months after intervention. The severity of consequences arising from postoperative complications was categorised using the Clavien–Dindo system from 1 (no deviation from routine care) to 5 (death).

### Health economic outcomes

EuroQol-5 Dimensions, five-level version utility values were used to derive quality-adjusted life-years (QALYs). Within-trial cost–utility was assessed as the incremental cost per QALY over the 24 months after randomisation. Health-care costs were calculated from resource use data and participant completion of a bespoke cost questionnaire covering the 24 months post randomisation.

### Qualitative study of feasibility

Semistructured interviews were conducted with men who accepted randomisation, those men who declined participation and urologists who routinely treated stricture patients. Interviews were audio-recorded, transcribed verbatim and analysed qualitatively.

### Statistical analysis

#### Randomisation

Consented participants were randomised to one of the two intervention groups using a telephone interactive voice response system or via a web-based randomisation application. The randomisation algorithm used recruitment site and time since last procedure (< 12 months or ≥ 12 months) as minimisation covariates to allocate treatment to intervention and control groups in a 1 : 1 ratio. A random element was incorporated.

#### Sample size

Assessment of recruitment rate during the first year of the study showed that the original estimated sample size of 500 was unlikely to be feasible in a fundable time period and was reassessed. Three parameters informed the revised sample size calculation: (1) the minimum clinically important difference, defined as a > 10% difference in effect estimate; (2) power to detect any difference set at 90%; and (3) the standard deviation (SD) of the primary outcome measure. This was calculated from the 220 measurements of post-intervention USS-PROM voiding score submitted by the first 69 participants, scaled from 0 to 1. The observed SD was 0.15, which was increased to 0.21 to allow for subsequent changes over trial duration. This gave a revised sample size of 170 men with complete follow-up, inflated to 210 men in total to allow for 19% attrition. The trial was also powered to determine whether or not the use of urethroplasty would result in a 30% reduction in the need for further intervention at 24 months,

relative to urethrotomy. To detect this difference with 90% power required 104 men. Statistical significance was defined at the two-sided 5% level, with corresponding 95% confidence intervals (CIs) derived.

### Statistical methods

The trial protocol, trial questionnaires, statistical analysis plan (SAP) and additional SAP are available at [www.journalslibrary.nihr.ac.uk/programmes/hta/105723#/](http://www.journalslibrary.nihr.ac.uk/programmes/hta/105723#/) (accessed 8 July 2019).

All of the main analyses were performed on a complete-case intention-to-treat (ITT) basis according to allocated group, including all participants with required follow-up data. Sensitivity analyses on the primary outcome to assess the robustness of the measured treatment effect were also performed. These analyses compared trial groups by ITT using imputation to estimate missing values for groups who underwent the intervention they were allocated (per protocol).

### Primary outcome

The primary outcome measure, area under the curve (AUC) for the USS-PROM voiding symptom questionnaire over 24 months following randomisation, was analysed using linear regression, adjusted for minimisation covariates. All available measurements were used to construct the curve using the trapezoid rule.

The primary analysis was on observed data. To be included in this analysis participants had to submit at least three measurements of voiding score: (1) a baseline measure, (2) an early measurement up to 12 months after intervention and (3) a later measurement up to 24 months post randomisation. We explored differences between responders and non-responders to inform our missing data model.

Subgroup analyses explored the possible modification of treatment effect by clinically important factors: time since last procedure (< 12 months or  $\geq$  12 months) as a proxy measure of stricture severity, stricture length, number of previous interventions and age. These were done as exploratory analyses, including treatment-by-factor interactions in the model. Reintervention was analysed as a time-to-event outcome using Cox regression.

### Safety data

Postoperative complications were categorised according to the Clavien–Dindo scale.

### Statistical software

Analyses were carried out in Stata<sup>®</sup> version 14 (StataCorp LP, College Station, TX, USA). The study was overseen by an independent Trial Steering Committee (TSC) and a Data Monitoring Committee.

### Health economic analysis

Effectiveness was measured by QALYs derived using an AUC approach. Costs (2017 GB pounds) to the NHS were summed from trial and NHS sources, and means calculated for each group. Cost–utility was expressed as the incremental cost per QALY gained.

### Qualitative study

For the qualitative process evaluation, semistructured interviews were conducted with men suffering urethral stricture who accepted randomisation, those men who declined participation and urologists who routinely treated men with urethral stricture. Interviews were audio-recorded, transcribed and analysed using rigorous qualitative methods.

## Results

### Clinical effectiveness

A total of 109 men were randomised to urethroplasty and 113 men to urethrotomy. In the complete-case ITT analysis the AUC over 24 months for urinary voiding symptoms, on a scale of 0 (no symptoms) to 24 (symptoms all the time), was 7.4 (SD 3.8) in the group allocated to urethroplasty and 7.8 (SD 4.2) for

those men allocated to urethrotomy, giving an effect size of  $-0.36$  (95% CI  $-1.74$  to  $1.02$ ) in favour of urethroplasty. Sensitivity analysis using multiple imputation gave a mean difference of  $-0.33$  (95% CI  $-1.74$  to  $1.09$ ). Including only participants who underwent the intervention they were allocated showed a mean difference of  $-1.02$  (95% CI  $-2.12$  to  $0.07$ ). Both procedures resulted in substantial symptom improvement at 3 months post intervention, with the mean voiding score falling from  $13.4$  (SD  $4.5$ ) to  $6.0$  (SD  $5.5$ ) in the urethroplasty group and from  $13.2$  (SD  $4.7$ ) to  $6.4$  (SD  $5.3$ ) in the urethrotomy group.

During the follow-up period, 15 of 93 (16%) men in the urethroplasty group had at least one reintervention for urethral stricture compared with 29 of 104 (28%) men in the urethrotomy group, giving a hazard ratio for time to reintervention of  $0.52$  (95% CI  $0.31$  to  $0.89$ ); 48% lower risk for urethroplasty. A per-protocol analysis including only men who underwent the intervention they were originally allocated to found a hazard ratio of  $0.28$  (95% CI  $0.15$  to  $0.55$ ) in favour of urethroplasty. Severe postoperative complications (Clavien–Dindo grade  $\geq 3$ ) were few, with two in the group that received urethroplasty and five, including one death from pulmonary embolism, in the group that received urethrotomy.

### Cost-effectiveness

The mean cost to the NHS and participants over 24 months post randomisation for the urethroplasty group was  $\pounds 4869$  (95% CI  $\pounds 4123$  to  $\pounds 5614$ ) compared with  $\pounds 2721$  (95% CI  $\pounds 1444$  to  $\pounds 3999$ ) 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%.

### Qualitative study

Interviews with patients ( $n = 19$ ) showed that some men held strong preferences for a particular management option, but others felt able to accept randomisation. Participation in the OPEN trial needed to be discussed at initial presentation to general urology clinics prior to specialist referral when strong preferences were established. Extra general urology units were therefore set up as study sites. Interviews with urologists ( $n = 15$ ) showed specific preconceived expectations about how men would react to the recruitment discussion. Clinicians may be potentially selective about the men who they decided to approach for participation in the trial and so were given additional support and training, emphasising the appropriateness of offering trial participation to all men who were eligible.

### Conclusions

The primary trial result showed no evidence that symptom control was better following urethroplasty. Uncertainty surrounding the point estimate included no difference and a greater improvement after urethrotomy. Our result was consistent with the null hypothesis of no difference. Analysis with imputation of missing data gave a similar result. We found a 57% relative reduction in the rate of reintervention in the urethroplasty group, which was statistically significant and exceeded the hypothesised reduction. Urethroplasty cost more on average than urethrotomy and the gain in QALYs was similar. Urethroplasty was unlikely to be considered cost-effective over 24 months.

A systematic literature review, including trial registration databases, found no other completed trials or trials in progress in this clinical area. Comparison with recent cohort studies of men undergoing urethroplasty reporting the same outcome measure showed similar baseline characteristics and improvement after surgery in USS-PROM voiding score to the OPEN trial population. Earlier cohort studies of urethrotomy tended to show a shorter time to reintervention than that seen in the OPEN trial. We believe that our findings are generalisable to the wider population of men with recurrent bulbar urethral stricture and to populations of men in other countries.

As predicted by our qualitative feasibility study, recruitment of sufficient participants was problematic owing to the difficulty in identifying men early enough to ensure that they had not already formed a strong preference for a particular intervention. This was also evident by the higher than expected proportion of randomised participants who chose to undergo the alternative intervention, rather than the allocated one. Confidence in the primary trial results was also somewhat undermined by the relatively lower rate of USS-PROM completion in the urethroplasty group. However, alternative analysis using multiple imputation did not materially change the primary result. The strong preferences men may hold and the tendency of urologists to recommend particular procedures to men who consult go some way to explain the findings from registry studies, indicating that urethrotomy is the predominantly used option for management of recurrent stricture. Our results, particularly the lower risk of reintervention after urethroplasty, to an extent support the opinion of current guideline panellists, that urethroplasty should be considered as the preferred treatment option for recurrent stricture. This requires access to specialist urology services that may be variable in some health-care settings, including the UK NHS, although, in terms of cost-effectiveness over 24 months, urethroplasty is likely to be more costly and result in similar QALYs.

For men with recurrent bulbar urethral stricture considering options for further treatment, it would appear that there is no clear winner between urethroplasty and urethrotomy. Both options offer safe and effective symptom control, although urethroplasty has a greater duration of benefit with fewer further interventions required after the initial surgery but does require a longer period of indwelling catheterisation. Men will continue to need to weigh up the pros and cons of each option, considering their own values and preferences. Urologists caring for and counselling such patients could use the results of the OPEN trial to provide impartial advice regarding the options and ensure that both procedures are accessible to the men concerned.

### Recommendations for research (in priority order)

- Determine the most efficient pathway of care for men seeking urethroplasty, including enhanced recovery and follow-up.
- Identify factors driving choice of treatment in men with bulbar urethral stricture.
- Identify adjunctive interventions that decrease recurrence after urethrotomy.
- A RCT to compare outcomes from non-transecting with transecting anastomotic urethroplasty.

### Trial registration

This trial is registered as ISRCTN98009168.

### Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.





ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/57/23. The contractual start date was in November 2012. The draft report began editorial review in May 2018 and was accepted for publication in May 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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