



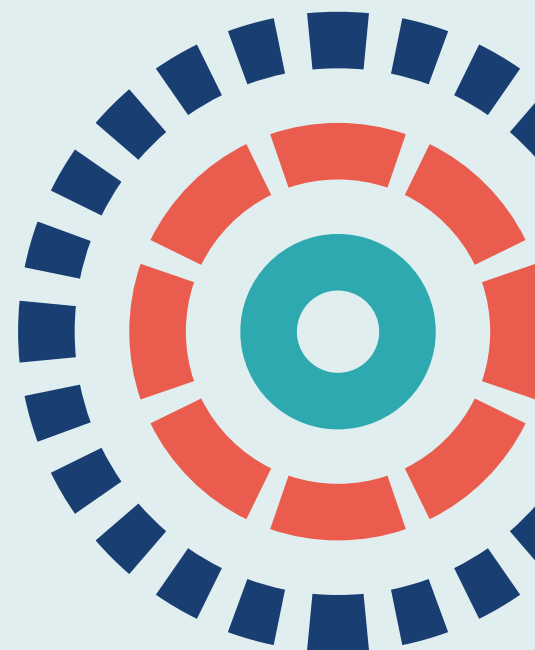
Health Technology Assessment

Volume 24 • Issue 61 • November 2020

ISSN 1366-5278

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

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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

This report should be referenced as follows:

Pickard R, Goulao B, Carnell S, Shen J, MacLennan G, Norrie J, *et al.* Open urethroplasty versus endoscopic urethrotomy for recurrent urethral stricture in men: the OPEN RCT. *Health Technol Assess* 2020;**24**(61).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nhr.ac.uk

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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.

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Abstract

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

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Background: Men who suffer recurrence of bulbar urethral stricture have to decide between endoscopic urethrotomy and open urethroplasty to manage their urinary symptoms. Evidence of relative clinical effectiveness and cost-effectiveness is lacking.

Objectives: To assess benefit, harms and cost-effectiveness of open urethroplasty compared with endoscopic urethrotomy as treatment for recurrent urethral stricture in men.

Design: Parallel-group, open-label, patient-randomised trial of allocated intervention with 6-monthly follow-ups over 24 months. Target sample size was 210 participants providing outcome data. Participants, clinicians and local research staff could not be blinded to allocation. Central trial staff were blinded when needed.

Setting: UK NHS with recruitment from 38 hospital sites.

Participants: A total of 222 men requiring operative treatment for recurrence of bulbar urethral stricture who had received at least one previous intervention for stricture.

Interventions: A centralised randomisation system using random blocks allocated participants 1 : 1 to open urethroplasty (experimental group) or endoscopic urethrotomy (control group).

Main outcome measures: The primary clinical outcome was control of urinary symptoms. Cost-effectiveness was assessed by cost per quality-adjusted life-year (QALY) gained over 24 months. The main secondary outcome was the need for reintervention for stricture recurrence.

Results: The mean difference in the area under the curve of repeated measurement of voiding symptoms scored from 0 (no symptoms) to 24 (severe symptoms) between the two groups was -0.36 [95% confidence interval (CI) -1.78 to 1.02 ; $p = 0.6$]. Mean voiding symptom scores improved between baseline and 24 months after randomisation from 13.4 [standard deviation (SD) 4.5] to 6 (SD 5.5) for urethroplasty group and from 13.2 (SD 4.7) to 6.4 (SD 5.3) for urethrotomy. Reintervention was less frequent and occurred earlier in the urethroplasty group (hazard ratio 0.52 , 95% CI 0.31 to 0.89 ; $p = 0.02$). There were two postoperative complications requiring reinterventions in the group that received urethroplasty and five, including one death from pulmonary embolism, in the group that received urethrotomy. Over 24 months, urethroplasty cost on average more than urethrotomy (cost difference $\pounds 2148$, 95% CI $\pounds 689$ to $\pounds 3606$) and resulted in a similar number of QALYs (QALY difference -0.01 , 95% CI -0.17 to 0.14). Therefore, based on current evidence, urethrotomy is considered to be cost-effective.

Limitations: We were able to include only 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.

Conclusions: 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 had a higher cost over the 24 months of follow-up and was unlikely to be considered cost-effective.

Future work: Formulate methods to incorporate short-term disutility data into cost-effectiveness analysis. Survey pathways of care for men with urethral stricture, including the use of enhanced recovery after urethroplasty. Establish a pragmatic follow-up schedule to allow national audit of outcomes following urethral surgery with linkage to NHS Hospital Episode Statistics.

Trial registration: Current Controlled Trials ISRCTN98009168.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 61. See the NIHR Journals Library website for further project information.

Contents

List of tables	xiii
List of figures	xv
List of abbreviations	xvii
Plain English summary	xix
Scientific summary	xxi
Chapter 1 Introduction: background and objectives	1
Scientific background	1
<i>Urethral stricture disease</i>	1
<i>Treatment options for bulbar urethral stricture</i>	2
<i>Interventions under study</i>	3
<i>Current management guidance</i>	3
<i>Evidence regarding choice of urethrotomy and urethroplasty</i>	4
Summary with implications for trial design	4
Aims and objectives	5
<i>Primary objectives</i>	5
<i>Secondary objectives</i>	5
Chapter 2 Methods	7
Summary of study design	7
<i>Sites</i>	7
<i>Trial management</i>	7
<i>Participants</i>	7
<i>Consent procedures</i>	9
<i>Randomisation</i>	9
<i>Progress on study</i>	10
<i>Participant expenses</i>	11
<i>Withdrawal</i>	11
<i>Patient and public involvement</i>	11
Outcome measurement	11
<i>Primary effectiveness outcome</i>	11
<i>Secondary effectiveness outcomes</i>	12
<i>Harms</i>	12
<i>Primary cost-effectiveness outcome</i>	12
<i>Secondary cost-effectiveness outcome</i>	13
Data collection	13
<i>Summary</i>	13
<i>Trial events</i>	13
Details of study interventions	14
<i>General</i>	14
<i>Urethroplasty (experimental)</i>	14
<i>Endoscopic urethrotomy (control)</i>	15
<i>Delivery of interventions</i>	15

Changes to study design	15
<i>Sample size calculation</i>	15
<i>Statistical analysis</i>	17
<i>Qualitative substudy</i>	20
<i>Trial progress and monitoring</i>	20
<i>Sources of bias</i>	20
Definition and end of study	21
Compliance and withdrawal	21
Data monitoring, quality control and assurance	21
Ethics and governance	22
Trial registration and protocol availability	22
Chapter 3 Results	23
Recruitment	23
Participant flow	23
Numbers analysed	23
<i>Primary analysis</i>	23
<i>Outcomes</i>	29
<i>Adverse events</i>	37
<i>Serious adverse events</i>	40
Chapter 4 Qualitative substudy	41
Introduction	41
Methods	41
<i>Interviews with men eligible for participation</i>	41
<i>Interviews with clinicians</i>	42
<i>Data management and analysis</i>	42
Results	42
<i>Interviews with men</i>	43
<i>Clinician interviews</i>	48
<i>The clinical organisation of referrals</i>	51
Discussion	53
<i>Shaping trial recruitment and design</i>	54
<i>Enabling more recruitment discussions</i>	55
<i>Enabling different recruitment discussions</i>	55
Chapter 5 Health economic evaluation	57
Introduction	57
Within-trial analysis	57
Results	57
<i>Analysis of resource use and cost</i>	57
<i>Total cost</i>	60
<i>Quality-adjusted life-years</i>	60
<i>Cost-utility analysis</i>	61
<i>Results</i>	62
Long-term modelling	65
<i>Methods</i>	65
<i>Results</i>	68
Time trade-off exercise	70
<i>Development of time trade-off materials</i>	70
<i>Data analysis</i>	71
<i>Results</i>	71
<i>Discussion</i>	72
<i>Conclusion</i>	73

Chapter 6 Discussion	75
Statement and interpretation of results	75
Strengths and limitations	77
Generalisability	78
Future work	78
Chapter 7 Conclusions	79
Recommendations for research	79
Acknowledgements	81
References	85
Appendix 1 Time trade-off protocol	93
Appendix 2 Interview schedule: men who accepted randomisation	97
Appendix 3 Interview schedule: men who declined randomisation	99
Appendix 4 Interview schedule: clinicians	101
Appendix 5 Recruitment vignettes	103
Appendix 6 Consolidated Health Economic Evaluation Reporting Standards checklist	105
Appendix 7 Health state profiles	109

List of tables

TABLE 1 Schedule of study interventions and outcome data collection	8
TABLE 2 Changes to the protocol requiring regulatory approval	16
TABLE 3 Recruitment sites	25
TABLE 4 Reasons for non-participation	27
TABLE 5 Reasons for withdrawal	27
TABLE 6 Inclusion in primary analysis and intervention carried out in those men excluded	28
TABLE 7 Clinical characteristics at baseline by randomised group	28
TABLE 8 Participant-reported symptoms at baseline by randomised group	29
TABLE 9 Treatment received in the trial by randomised group	30
TABLE 10 Reason for not undergoing allocated intervention	30
TABLE 11 Time interval between randomisation and intervention	30
TABLE 12 Trial questionnaire return rates	31
TABLE 13 Sensitivity analyses for primary result	31
TABLE 14 Interaction terms for the subgroups	32
TABLE 15 Number of reinterventions according to randomised group	33
TABLE 16 Maximum flow rate (≥ 10 ml/second) increase from baseline	35
TABLE 17 Recurrence (for those participants who had surgery)	36
TABLE 18 Changes in participant-reported outcomes measured on the trial questionnaire at baseline and 24 months	36
TABLE 19 Adverse events by event and randomised allocation and intervention received	37
TABLE 20 Clavien–Dindo classification of postoperative SAEs by event and randomised allocation and intervention received	38
TABLE 21 Clavien–Dindo classification of postoperative AEs in participants undergoing an intervention	39
TABLE 22 Details of men eligible for inclusion in the trial who participated in interviews	39

TABLE 23 Summary of men's accounts of their treatment preferences	48
TABLE 24 Comparison of clinicians' expectations and recruitment practices	50
TABLE 25 Key problems mapped against Powell <i>et al.</i> 's compilation of implementation strategies	55
TABLE 26 Resource use for each trial intervention	58
TABLE 27 NHS cost (£) for each trial intervention	59
TABLE 28 Resource use and cost (£) to the NHS and patients for each trial intervention during follow-up (24 months)	59
TABLE 29 Cost (£) of reintervention occurring in each allocated group	60
TABLE 30 Total cost (£) for each trial group	60
TABLE 31 Utility values at each time point and QALYs over the trial follow-up	62
TABLE 32 Cost-effectiveness analysis	64
TABLE 33 Model parameters	67
TABLE 34 Markov model result over 10 years: base case and deterministic sensitivity analyses	69
TABLE 35 Estimated utility values	72
TABLE 36 List of consequences for each procedure that are used to design the health profiles	94

List of figures

FIGURE 1 Pictorial representation of male urethra	1
FIGURE 2 Ascending urethrogram showing 2-cm bulbar urethral stricture	2
FIGURE 3 Uroflowmetry record of man with bulbar urethral stricture	2
FIGURE 4 Chart showing flow of participants through the trial	10
FIGURE 5 Planned and actual recruitment trajectory for the OPEN trial	24
FIGURE 6 Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing progress of participants through the study	26
FIGURE 7 Mean (standard error of the mean) for total voiding score at each nominal time point	31
FIGURE 8 Subgroup analyses for the USS-PROM voiding score AUC	32
FIGURE 9 Hazard curves for reintervention by randomised or treatment received group up to 4 years after initial intervention	34
FIGURE 10 Subgroup analyses for time to reintervention	35
FIGURE 11 Different points of recruitment to the OPEN trial	51
FIGURE 12 Utility values at each time point and QALYs over the trial follow-up with corresponding number of observations	63
FIGURE 13 Cost-effectiveness acceptability curve (base case)	65
FIGURE 14 Incremental cost and QALY plots (base case)	65
FIGURE 15 Markov model structure	66
FIGURE 16 Cost-effectiveness acceptability curve (Markov model – base case)	69
FIGURE 17 Incremental costs and QALY plots (model base case)	70

List of abbreviations

AE	adverse event	NIHR	National Institute for Health Research
AUC	area under the curve		
BAUS	British Association of Urological Surgeons	OPCS-4	OPCS Classification of Interventions and Procedures version 4
CHaRT	Centre for Healthcare Randomised Trials	PCQ	participant costs questionnaire
CI	confidence interval	PI	principal investigator
CRF	case report form	QALY	quality-adjusted life-year
DMC	Data Monitoring Committee	Q _{max}	maximum urinary flow rate
EQ-5D	EuroQol-5 Dimensions	RCT	randomised controlled trial
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	SAE	serious adverse event
GCP	Good Clinical Practice	SAP	statistical analysis plan
GP	general practitioner	SD	standard deviation
HRQoL	health-related quality of life	TMG	Trial Management Group
ICER	incremental cost-effectiveness ratio	TSC	Trial Steering Committee
IQR	interquartile range	TTO	time trade-off
ITT	intention to treat	USS-PROM	urethral stricture surgery – patient-reported outcome measure
NCTU	Newcastle Clinical Trials Unit	VAS	visual analogue scale

Plain English summary

The urethra carries urine from the bladder to the tip of the penis. Men can develop a condition called urethral stricture when part of the urethra narrows due to scarring. This can lead to difficulties in passing urine and can recur. There are two operations for urethral stricture. The standard approach is endoscopic urethrotomy. The alternative is open urethroplasty. This study wanted to find out which operation was preferable in terms of symptom control, time before further surgery and which operation was best value for the NHS. All aspects of the study were informed by patients.

Two hundred and twenty-two men who had received at least one previous operation for stricture took part. The choice of operation was decided by chance (randomisation). Of these men, 113 were randomised to urethrotomy and 109 were randomised to urethroplasty. Following their operation, the men filled in questionnaires every 3–6 months for 2 years about their symptoms and if any further surgery was needed. The two groups were then compared.

Of the 222 men who took part, 159 provided enough information for inclusion in the comparison (90 were in the urethrotomy group and 69 were in the urethroplasty group). The improvement over time in urinary symptoms was similar for the two groups. Men in the urethrotomy group were twice as likely to need a further operation over the 2-year study period. Very few men experienced serious complications.

This study showed that both operations led to symptom improvement for men with recurrent urethral stricture. Urethroplasty, however, appears unlikely to offer good value for money for the NHS.

Men needing treatment for recurrent urethral stricture can use this information to weigh up the pros and cons of each operation to decide with their clinical team which one to undergo.

Scientific summary

Bulbar 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 ≥ 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#/ (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[®] 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 ≥ 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.

Chapter 1 Introduction: background and objectives

Material from Stephenson *et al.*¹ 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* 2015;**16**:600; Whybrow *et al.*² Equipose across the patient population: optimising recruitment to a randomised controlled trial. *Trials* 2017;**18**:140; and Whybrow *et al.*³ How men manage bulbar urethral stricture by concealing urinary symptoms. *Qual Health Res* 2015;**25**:1435–42 have been used within this report under Creative Commons Licenses.

Scientific background

Urethral stricture disease

The male urethra is an epithelium-lined tube enveloped by smooth muscle erectile tissue (corpus spongiosum) and an outer layer of striated muscle (bulbospongiosus). It runs from the bladder outlet (neck), through the prostate gland, perineum and the ventral (under) aspect of the penis, opening at the fossa navicularis at the penile tip (external urethral meatus). It is anatomically divided (from proximal to distal) into prostatic, membranous, bulbous and penile segments (*Figure 1*).

It functions as an active conduit to void urine and thereby empty the urinary bladder when desired.⁵ It is also the conduit for ejaculation and emission of semen, which enters the urethra from ejaculatory ducts running through the prostate.

Urethral stricture is caused by annular scar formation in the epithelium and underlying smooth muscle layers, resulting in narrowing of the lumen, loss of propulsive muscle action and restriction of urine flow. Published estimates of the prevalence of urethral stricture disease among adult men derived from hospital activity registries in the USA include 0.6%⁶ and 0.9%.⁷ Urethral stricture disease (OPCS Classification of Interventions and Procedures version 3 – character primary diagnosis code N35) resulted in > 17,000 admissions of men to NHS hospitals in England during 2016–17.⁸ Men notice a reduction in the strength of urinary stream, prolonged voiding time and slow emptying of the urethra, often with dribbling of urine

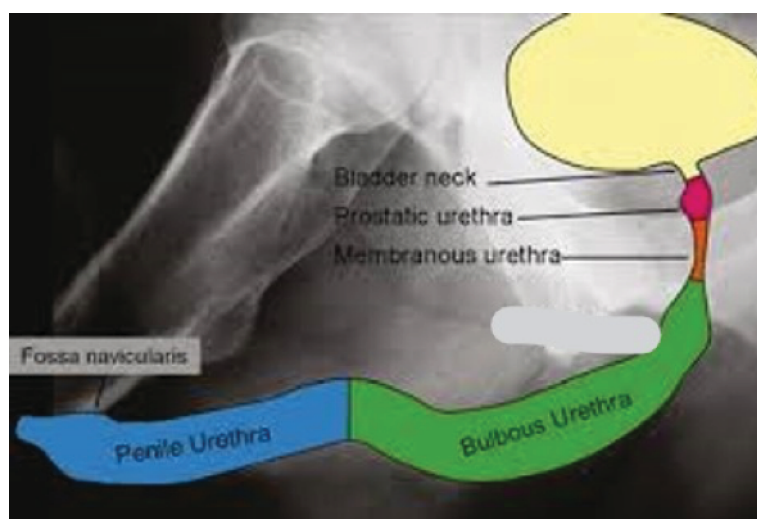


FIGURE 1 Pictorial representation of male urethra. This figure was published in *Surgery*, Vol. 35, Watkin and Patel,⁴ The diagnosis and management of acquired urethral stricture disease, pp. 313–23, © Elsevier 2017. Reproduced with permission.

after micturition. When these symptoms become intolerable men seek medical help and are generally assessed by a urology specialist. Stricture site and length are evaluated by performing either a telescopic (urethroscopy) or radiological (urethrography) examination of the urethra or both (*Figure 2*). Severity of urinary obstruction is assessed by measurement of maximum urinary flow rate (Q_{max}) and residual urine after voiding (*Figure 3*). Most strictures are located in the bulbar segment of the urethra between the pelvic floor and penoscrotal junction. The cause of stricture formation is most often unknown, but it may result from previous injury or infection (urethritis).

Treatment options for bulbar urethral stricture

Men with bulbar urethral stricture have two management options: (1) endoluminal treatment, in which the stricture is disrupted from within the urethral lumen (urethrotomy or dilatation); or (2) open surgery (urethroplasty), in which the stricture is approached through an incision in the perineal skin and excised or bridged by interposition of a healthy tissue graft. Unless there are complicating factors, men with a first stricture occurrence generally choose to undergo an endoscopic urethrotomy, as it is a straightforward

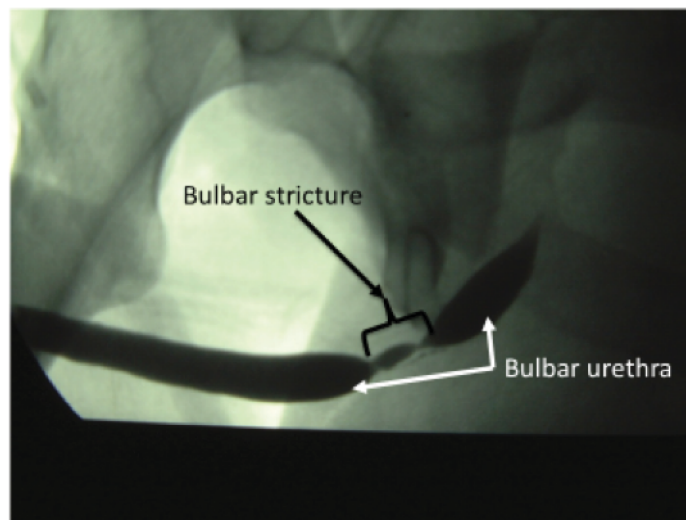


FIGURE 2 Ascending urethrogram showing 2-cm bulbar urethral stricture. Courtesy of Nick Watkin, St George's University Hospitals NHS Foundation Trust.

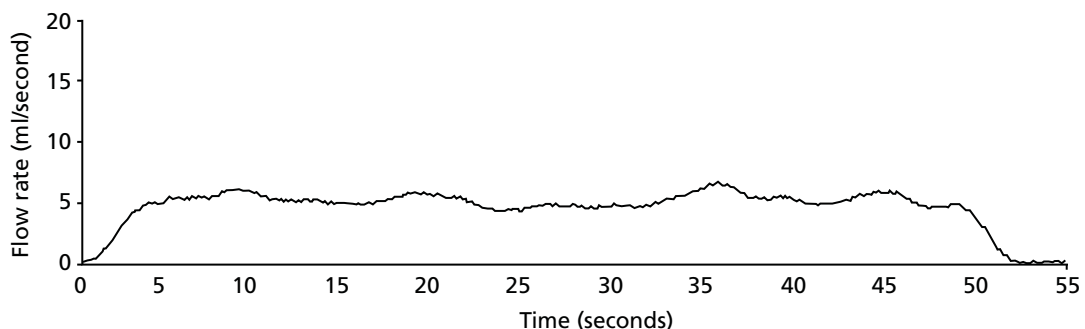


FIGURE 3 Uroflowmetry record of man with bulbar urethral stricture. The flow is slow up to a maximum of 6 ml/second (normal ≥ 15 ml/second) and prolonged. Courtesy of Alison Bray, Newcastle upon Tyne Hospitals NHS Foundation Trust.

procedure and can be carried out under the same anaesthetic following diagnostic urethroscopy. A review of case series suggested that following this first urethrotomy the rate of recurrence at 2 years was 40% and 60% at 8 years.⁹ For those men whose stricture recurs, the choice is between further urethrotomy (or simple dilatation for short flimsy strictures) and open urethroplasty. Urethroplasty is a more complex procedure, but case series suggest a lower stricture recurrence rate of around 15% at 2 years and 20% at 6 years.^{10–12} Management discussions between urologists and men with recurrent bulbar stricture centre around the choice between these two strategies: (1) planning and carrying out urethroplasty surgery with a view to longer-term freedom from recurrent stricture, or (2) further urethrotomy repeated as needed at stricture recurrence. The relative efficiency of these two strategies for the management of recurrent bulbar urethral stricture in men is the focus of this trial.

Interventions under study

The experimental intervention strategy is open urethroplasty.¹³ The bulbar urethra is approached through a longitudinal incision in the perineal skin behind the undersurface of the scrotum. The bulbar urethra is dissected free and the strictured segment incised in either the dorsal or ventral surface. The area of the stricture is then either removed and the cut ends rejoined (anastomotic urethroplasty) or augmented by insertion of a tissue graft.¹⁴ The tissue graft (typical dimensions 5 × 2 cm) is harvested from the mucosa of the mouth. The urethra is then retubularised and the repaired area protected by passage of a urethral catheter to drain urine. Urethroplasty requires a general anaesthetic, takes 2–3 hours to perform and is followed by a 2-week period of urethral catheterisation postoperatively. Median hospital stay in the UK NHS is 2 days.⁸

The control intervention strategy is endoscopic urethrotomy (also known as direct visual internal urethrotomy, internal urethrotomy or optical urethrotomy).¹⁵ This procedure involves passing an endoscope under direct vision down to the distal end of the stricture.¹⁶ The narrowed area is then progressively incised from distal to proximal with a straight longitudinal cut, either using a steel blade ('cold knife') mounted on the endoscope¹⁷ or under endoscopic control with a diathermy needle or laser fibre ('hot knife'). Once the lumen has been incised sufficiently to restore a normal calibre (approximately 6 mm diameter) the endoscope is withdrawn and a urethral catheter passed to tamponade bleeding from the cut area and provide reliable urine drainage during the postoperative period. If the stricture is short and flimsy, simple dilatation with the endoscope or graduated dilators may suffice without incising the urethral mucosa and underlying corpus spongiosum. Endoscopic urethrotomy requires a general anaesthetic and takes approximately 45 minutes to perform. The median hospital stay in the UK NHS is 1 day.⁸ The urethral catheter is typically removed 24–48 hours postoperatively. Men having repeated urethrotomy may be offered training for a programme of intermittent self-dilatation, using an appropriately sized soft plastic catheter. This adjunctive intervention appears to lessen the risk of recurrence over the subsequent 12 months.¹⁸

Both procedures have a similar spectrum of complications, predominantly bleeding from the wound site and urinary infection. If an oral mucosal graft is used to augment the urethra, then there are specific complications related to the donor site in the mouth.

Current management guidance

Evidence for effectiveness of optical urethrotomy and open urethroplasty for treatment of bulbar urethral stricture has been summarised in four systematic reviews.^{13,15,19,20} The Cochrane review,¹⁹ up to June 2012, found no randomised trials comparing outcomes after urethrotomy and urethroplasty and could not make any conclusion regarding comparative effectiveness. An updated Cochrane search performed to August 2017 found no more recent relevant completed randomised controlled trials (RCTs) or any other RCTs in progress. Reviews underpinning published guidelines, sponsored jointly by the Société Internationale d'Urologie, the International Consultation on Urologic Disease^{13,15} and by the American Urological Association,²⁰ included non-randomised studies, predominantly of retrospective cohort design. Guideline formulation subsequent to these reviews was predominantly based on expert opinion and panel consensus. Guidance from the Société Internationale d'Urologie¹⁵ suggests that optical urethrotomy is an appropriate management option for initial

treatment of bulbar urethral stricture, with an overall long-term success rate of about 50%. The guidance also states that the first recurrence of bulbar stricture could be treated with urethrotomy as long as no adverse factors, such as recurrence at < 3 months post surgery, are present. Success rates in terms of up to 2 years freedom from recurrence in the case series varied from 53% to 95%. Buckley *et al.*¹⁵ recommended that urethrotomy should not be used for second or subsequent recurrences. Urethroplasty with scar excision and primary mucosal anastomosis or use of an interposition graft of oral mucosa was recommended for complex or recurrent bulbar stricture.¹³ The more recent systematic review and guideline from the American Urological Association also did not find any robust evidence on which to base clinical practice recommendations.²⁰ Wessells *et al.*²⁰ suggested that both optical urethrotomy and urethroplasty were appropriate initial procedures for men with bulbar urethral stricture. For those men with recurrent stricture, they considered that only urethroplasty would potentially give long-term symptom control. Further recurrence after repeat urethrotomy was regarded as highly likely and therefore should be considered only as a palliative management option. There is little published qualitative research on patient experience of living with and managing the condition. Patients do appear most concerned regarding the impact of their urinary symptoms, particularly difficulty voiding and post-micturition dribbling, on their daily activities.²¹ Agreement between patients and specialist clinicians regarding ranking of importance of particular symptoms is poor.²¹

Evidence regarding choice of urethrotomy and urethroplasty

Guidance from two professional urologist organisations, the Société Internationale d'Urologie and the American Urological Association, is clear that open urethroplasty is the recommended option for men with recurrent bulbar stricture. However, this recommendation is based on low-level evidence and expert opinion. Both guideline panels were predominantly made up of urologists specialising in urethroplasty, without general physician or patient representation. Registry studies suggest that optical urethrotomy is more frequently used than urethroplasty for recurrent strictures.²² Case series from a number of health-care systems also suggest that repeated urethrotomy is preferred in practice for recurrent bulbar strictures,^{23–26} with urethroplasty reserved for complex strictures. Reasons for the more frequent choice of urethrotomy for treatment of recurrent bulbar stricture may include patient and clinician preference, restricted availability of urethroplasty, health service organisational issues and lower cost to the patient and health-care provider. Information regarding management of men with urethral stricture disease and costs in the UK, derived from NHS England hospital activity and tariff data⁸ from April 2016 to March 2017, showed a total cost of £17.8M, comprising 742 urethroplasty procedures [OPCS Classification of Interventions and Procedures version 4 (OPCS-4) M73.6], with a mean tariff cost of £4157 (Healthcare Resource Group code LB29A), 5074 endoscopic urethrotomy procedures (OPCS-4 M76.3) and 5838 male urethral dilatation procedures (OPCS-4 M76.4/M79.2), both with a mean tariff cost of £1468 (Healthcare Resource Group code LB55A). A number of studies have made cost comparisons between the two procedures accounting for procedure costs derived from personally funded health-care provision and risk of recurrence derived from cohort studies. A UK-based cost comparison suggested that a strategy of initial urethrotomy followed by urethroplasty at first recurrence was least costly.²⁷ US decision-analytic models, using cost minimisation²⁸ and cost-effectiveness²⁹ methodology, suggest that initial urethrotomy (providing a success rate of > 40%) followed by urethroplasty on recurrence is the most efficient treatment strategy for men with bulbar urethral stricture, although utility weights were not used and parameter estimates were from non-comparative studies.

Summary with implications for trial design

Decisions for men and their clinicians regarding how to best manage recurrent bulbar stricture continue to be based on low-level evidence with no robust comparative studies of clinical effectiveness or cost-effectiveness. A strategy of urethrotomy repeated as necessary has the attraction of being a straightforward, widely available procedure practised by 95% of urologists.²⁴ It is characterised by a short hospital stay and rapid recovery. It does not appear to be a curative procedure, meaning that multiple subsequent interventions may be needed during the man's lifetime. A strategy of open urethroplasty, on the other hand, requires longer

operating time and the need for specific expertise, restricting availability. However, it appears to be associated with lower recurrence rate and longer duration of symptom relief. At present, men with recurrent bulbar stricture are guided by clinician experience and preference, together with their own past experience of interventions and their individual values and preferences. Decisions by health-care providers regarding investment in, and provision of, specialist urethroplasty services are also made difficult by this evidence gap.

Aims and objectives

This trial aimed to determine whether or not a strategy of urethroplasty is superior to one of urethrotomy for alleviation of urinary symptoms in men with recurrent bulbar stricture over 24 months and whether or not it is cost-effective for the UK NHS. The trial hypothesis was that the difference in the control of voiding symptoms over 24 months after randomisation was > 10%. To achieve these aims we set the following objectives.

Primary objectives

- Determine the relative impact on symptoms over 24 months.
- Determine the incremental cost per quality-adjusted life-year (QALY) over 24 months.

Secondary objectives

- Determine the relative rate of need for reintervention.
- Determine the relative change in Q_{\max} at 24 months.
- Establish the safety profile of each procedure.
- Model the incremental cost per QALY of the most effective treatment over 10 years.
- Qualitatively assess the views of men with urethral stricture and their clinicians regarding the disease, the available treatment interventions and participation in the trial.
- Determine the factors that men trade-off in deciding between the two strategies.

Chapter 2 Methods

This chapter covers trial design and methods, statistical analysis and governance. Details of the methods and findings of the parallel qualitative study and economic evaluation are provided in *Chapters 4* and *5*, respectively.

Summary of study design

We designed an open-label, patient-randomised, parallel-group superiority trial comparing an experimental strategy of open urethroplasty against a control strategy of endoscopic urethrotomy in men with recurrent bulbar stricture, primarily in terms of symptom control over 24 months. Both strategies are in routine use in the UK NHS. For urethroplasty, there is a need for specialist referral for further assessment and counselling regarding harvesting of an oral mucosal graft. Because of this complex and variable care pathway, we chose a pragmatic design without blinding of clinicians or participants. Clinical trials unit staff entering and managing trial data were blinded to participant allocation. Men in both groups received standard perioperative care, including consent for the surgical intervention that they were allocated to and/or underwent. Inclusion criteria were made as broad as possible within the constraint of subjects having to be able and willing to undergo either procedure and agreeing to random allocation. The trial was set in the UK – England, Wales and Scotland – recruiting participants from NHS hospitals providing operative urological procedures for men with urethral stricture.

Sites

From 18 February 2013 to 5 March 2015 we progressively established 53 research sites (38 recruited at least one participant), all being NHS secondary care providers affiliated to the National Institute for Health Research (NIHR) Clinical Research Network in England and equivalent organisations in Scotland and Wales, which agreed to host the study locally. We initially concentrated on sites that could undertake both urethrotomy and urethroplasty. Subsequently, we set up sites that offered only urethrotomy. Those sites required delineation of routine referral pathways to a previously established trial site that offered urethroplasty (*Table 1*).

Additionally, four participant identification centres were opened between August and September 2014 to support recruitment to the trial.

Trial management

The central trial office was established at the Newcastle Clinical Trials Unit (NCTU), Newcastle University, Newcastle upon Tyne, UK. The NCTU was responsible for obtaining approvals, trial registration, trial management and organising the collection of outcome measures. The health economic evaluation and qualitative research teams were also based in Newcastle. The randomisation service, database construction and management, and statistical analysis were based in the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen, Aberdeen, UK.

Participants

Adult men with a history of urethral stricture disease having previously undergone at least one intervention for bulbar urethral stricture were identified at the time of clinic presentation with recurrent symptoms and from health-care records at each site. Clinicians were encouraged, through the NIHR Clinical Research Network, local and national meetings, and relevant professional organisations, including the British Association of Urological Surgeons (BAUS) and the British Association of Genito-urethral Surgeons, to introduce the study to men under their care. Patients were approached and introduced to the study by

TABLE 1 Schedule of study interventions and outcome data collection

Study intervention and outcome data collection component	Visit 2		Visit 3: intervention (according to site processes)	Visit 4: 3-month clinical follow-up ^a	Remote: 12 months follow-up ^a	Postal: 18 months ^a	Visit 5: 24-month follow-up ^a	Postal: 24 months after surgery	End of study (November 2017)	Pre and post reintervention
	Consent	Baseline								
Eligibility checklist	✓									
Trial discussed and patient information sheet provided	✓									
Informed consent	✓									
USS-PROM ^b	✓		✓	✓	✓	✓	✓	✓	✓	✓
Resource use questionnaire			✓		✓	✓	✓			
Further intervention questionnaire								✓	✓	
Uroflowmetry	✓			✓			✓			
Randomisation		✓								
Process of care			✓	✓	✓	✓	✓	✓	✓	✓
AEs			✓	✓	✓	✓	✓	✓	✓	✓

AE, adverse event; USS-PROM, urethral stricture surgery – patient-reported outcome measure.

^a 18- and 24-month time points timed from date of randomisation; all other time points timed from date of intervention.

clinical staff at site. If men were interested, an eligibility check was carried out by local research staff at each site according to the following criteria:

Inclusion criteria

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

Exclusion criteria

- Current perineal sepsis and/or urethrocutaneous fistula.
- No previous intervention for bulbar stricture.
- Inability to adhere to the trial protocol.
- Previous participation in the study.

Consent procedures

Men who were eligible and in provisional agreement for participation were seen by local research staff and given trial information. Trial eligibility was checked for each potential subject using information from the prospective participant and from his clinical record. Sites kept a screening log documenting non-identifiable information and reasons for non-participation. The right to refuse to participate without giving reasons was respected.

Following a period of at least 48 hours post provision of trial information, interested and eligible patients were then contacted using their preferred means of communication (surface mail, e-mail, telephone or text) and reviewed by local research staff to explain fully the purpose and conduct of the study, including the need for randomisation to allocate them to either procedure. If they agreed to take part they gave written consent to be randomised to either open urethroplasty or endoscopic urethrotomy by signing and dating the study consent form, which was witnessed and dated by a member of the research team with documented, delegated responsibility to do so. The timing of randomisation was usually at the time of trial consent, provided that there was agreement between patient and clinician that intervention for recurrent bulbar stricture was required. Standard local arrangements concerning preoperative assessment, hospital admission, consent for surgery, conduct of surgery and after care continued unaffected by study participation. Men eligible for the study who were not willing to consider randomisation were asked to consent to being approached by a qualitative researcher, regarding participation in an interview-based study. Urologists participating in trial recruitment were also asked to give expressions of interest in participating in this qualitative study. The recruitment timetable is shown in *Figure 4*.

Randomisation

Participant allocation

Consented men were allocated to urethroplasty or urethrotomy using a centralised, automated, randomisation application hosted by CHaRT and accessed by telephone or through the internet. The algorithm allocated participants to urethroplasty or urethrotomy in a 1 : 1 ratio, with recruitment site and time since last procedure (< 12 months or ≥ 12 months) as minimisation covariates. The final allocation algorithm was set by a statistician not involved in trial planning or analysis and included a random component. Participants were informed of their allocated treatment group immediately following randomisation.

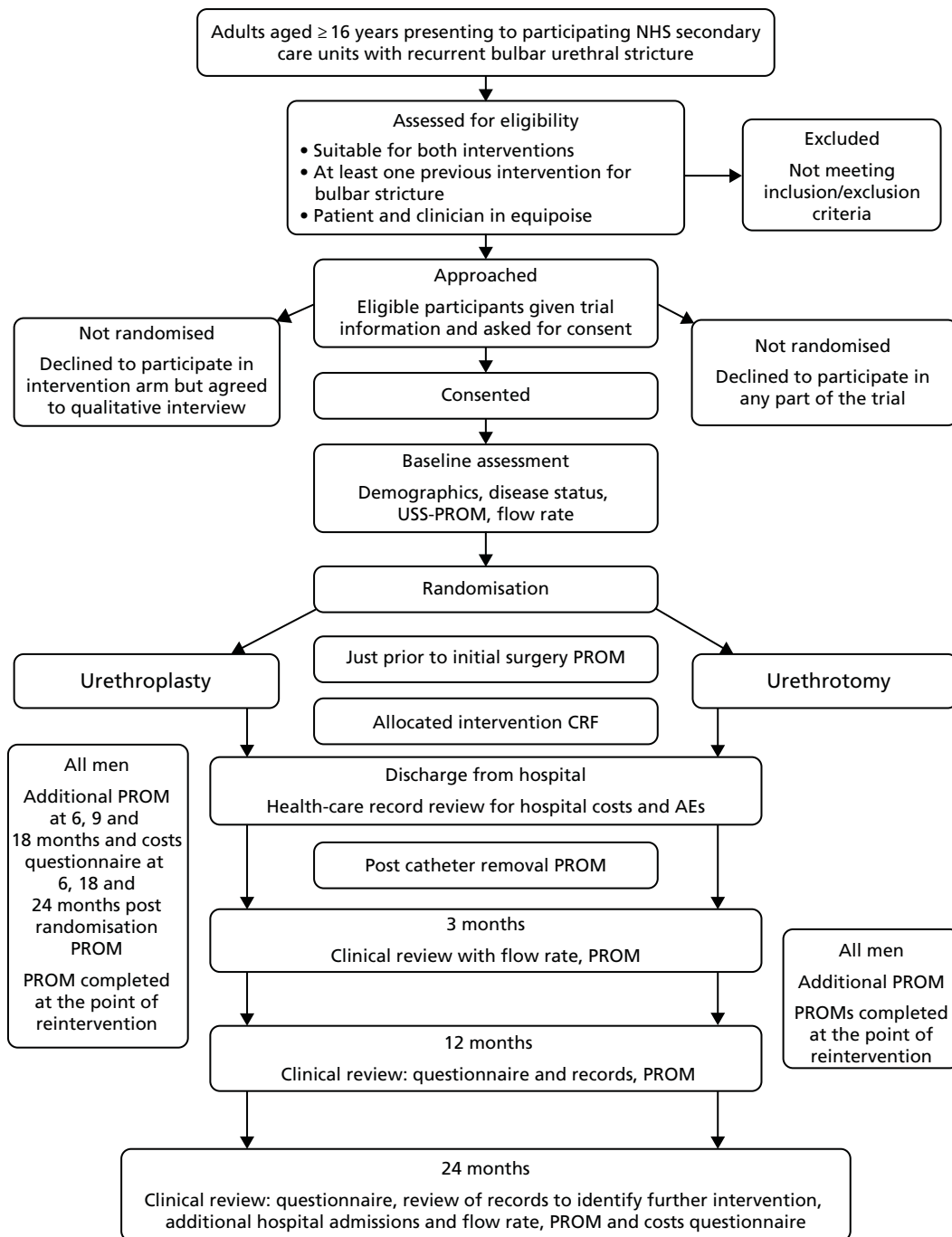


FIGURE 4 Chart showing flow of participants through the trial. AE, adverse event; CRF, case report form; PROM, patient-reported outcome measure; USS-PROM, urethral stricture surgery – patient-reported outcome measure.

Progress on study

The schedule of events for trial participants is shown in *Table 1*. Baseline data were collected by site research staff just prior to randomisation to minimise any biases that might result from knowledge of the allocated intervention. We aimed for participants to undergo their allocated procedure as soon as possible and preferably no longer than 12 weeks after randomisation, subject to participant and clinician preference and health-care provider service constraints. At 3, 12 and 24 months post intervention, research staff at site contacted participants for a follow-up to complete case report forms (CRFs), face to face or by telephone, with supplementation by health-care record review.

Participant expenses

Expenses incurred by participants as a result of extra attendances outside standard local NHS care were reimbursed. Participants were given £25 thank-you gift vouchers to cover any unforeseen additional costs at the time of randomisation, 24 months after randomisation and on receipt of a completed end-of-trial questionnaire in December 2017.

Withdrawal

Consented participants remained on study unless they withdrew their consent or trial staff deemed that further participation by an individual was not appropriate. Participants who declined their allocated procedure after randomisation were kept on study, including those men who underwent the alternative procedure and those men who did not undergo an intervention. The reason for withdrawal was recorded if the participant agreed.

Patient and public involvement

Prior to funding application, we discussed the rationale of the trial with a patient with urethral stricture who had experienced both urethrotomy and urethroplasty. He agreed to be a co-investigator and reviewed the funding application from a patient perspective. Subsequently, he reviewed and commented on trial documents relevant to patients prior to submission for ethics approval. He contributed to discussions at trial management meetings, particularly at the start of recruitment and at the end of the study. As part of governance of the trial, we recruited a member of the public through the Northern Regional Public Involvement in Medical Research Network to act as a lay member of the Trial Steering Committee (TSC). He attended and contributed to TSC meetings throughout the trial, offering very helpful lay input into trial oversight and management. Both individuals critically appraised the final report from a lay perspective.

Outcome measurement

Participant-reported outcomes for the OPEN trial were collected through a specific trial questionnaire completed by participants. The questionnaire, urethral stricture surgery – patient-reported outcome measure (USS-PROM), has been validated in this patient group in English,³⁰ German,³¹ Turkish,³² Russian,³³ Spanish³⁴ and Portuguese.³⁵ It comprised six questions on voiding symptoms and their impact on daily activities, self-rating of urine flow strength (using a pictorial guide) and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), questionnaire measuring health status. For the purposes of this trial, a single-item question, overall satisfaction with sexual function, was added from the validated International Index of Erectile Function questionnaire.³⁶ Participant completion of trial questionnaires at baseline, prior to allocated intervention and 1 week after catheter removal following intervention were prompted and overseen by local research staff at site. Subsequently, participants were automatically sent a letter enclosing a questionnaire and instruction for completion at 3, 6, 9, 12 and 24 months following the date of allocated intervention and at 18 and 24 months after the date of randomisation. A final questionnaire was sent out to all randomised participants for completion at the end of the study in November 2017. Participants also had the option to complete the questionnaires online with automatic upload to the trial database, or by telephone call with trial management staff. Need for completion was prompted by letter from the trial office at NCTU. We scheduled additional collections of outcome measures just prior to and at 1 month subsequent to any further surgical procedure for bulbar urethral stricture.

Primary effectiveness outcome

The primary outcome for the OPEN trial was the area under the curve (AUC) of the urinary voiding symptom score component of the USS-PROM, repeatedly measured over 24 months following randomisation. The voiding symptom measure comprised six questions each scored from 0 (symptom not present) to 4 (symptom present all of the time), giving a range of total score of 0–24. The completed questionnaires were returned to the trial office at NCTU for data entry.

Secondary effectiveness outcomes

Patient reported

The USS-PROM questionnaire also included measurements assessing the outcomes of urine stream strength, impact of urinary symptoms on daily activity and overall health status. The single-item visual scale of urinary stream strength was scored from 1 (strong stream) to 4 (weak stream). The question regarding impact of urinary symptoms on daily activities was scored from 0 (not at all) to 3 (a lot). The USS-PROM questionnaire measured health status using the EQ-5D-5L questionnaire.³⁷ Each domain was scored 0 (no problem) to 4 (extreme or incapacitating problem), giving a total ranging from 0 to 20. This measure was accompanied by the EQ-5D visual analogue scale (VAS), on which participants rated their overall health between 0 (the worst health imaginable) and 100 (the best health imaginable). An additional single-item question, overall satisfaction with sexual function, was scored from 1 (very dissatisfied) to 5 (very satisfied).³⁶ All measures included in the USS-PROM were self-completed by participants at the same multiple time points as the primary outcome.

Clinical

Maximum urinary flow rate was measured for each participant by asking them to void at least 150 ml of urine into a commercial, calibrated uroflowmeter available at site. This measurement was scheduled to take place at baseline, at 3 months post intervention, and between the 12 and 24 months' post-intervention visits. An increase in Q_{\max} of ≥ 10 ml/second compared with baseline was categorised as a successful outcome.³⁸ If participants underwent a further intervention for bulbar urethral stricture subsequent to the allocated trial procedure (excluding self-dilatation), this was documented at the 3-, 12- or 24-month follow-up, completed by research staff at site. Additionally, site staff were asked to complete a reintervention CRF. Participants were asked to provide information regarding any further interventions for recurrent bulbar stricture in the further intervention questionnaire sent to all participants at 24 months post surgery and at the end of the study (November 2017). Recurrence of bulbar stricture but without a planned or completed further intervention was recorded in the 24-month follow-up CRF, using information from symptom report, urine flow rate and documentation in the health-care record. We considered that a stricture was likely to have recurred if at least one of the following conditions were met during the 24 months after intervention: a reintervention had occurred or was scheduled, the Q_{\max} had deteriorated to the preintervention value or the voiding score had deteriorated to baseline value.

Harms

Harms arising from trial participation, principally related to the procedure undergone, were collected through CRFs completed by research staff at site at the time of, and shortly after, the trial intervention, at 3, 12 and 24 months after intervention, and at the time of, and shortly after, reintervention. They were categorised as being expected adverse events (AEs), as listed in the trial protocol, or unexpected AEs. The trial office were notified of any AE deemed serious [i.e. a serious adverse event (SAE)] via an e-mail alert originating from the CHaRT database, triggered by data entry at site. The SAEs were then adjudicated by the chief investigator in discussion with other members of the trial team and, when required, by the site principal investigator (PI), to decide if the SAE was indeed serious and whether it was related or unrelated to participation in the OPEN trial.

Primary cost-effectiveness outcome

The primary outcome of the health economic evaluation was cost-utility, assessed as the incremental cost per QALY at 24 months after randomisation. Health-care costs were calculated from hospital visits recorded by research staff at site on CRFs completed at 3 and 24 months, and from use of primary care services as reported by participants on a patient's cost questionnaire completed at 6 and 12 months after allocated intervention and at 18 and 24 months after randomisation. Patient costs were collected through a questionnaire completed at 6 months after allocated intervention. Responses to the EQ-5D-5L health status questionnaire were transformed using UK population tariffs³⁹ to produce a health state utility score for each participant.

Secondary cost-effectiveness outcome

To complement the primary cost–utility analysis, the health economic evaluation included a time trade-off (TTO) experiment to better understand choices made by men with urethral stricture and assess the likely short-term disutility of the procedures that would not be measured at the EQ-5D-5L time points, and also a Markov model to project observed differences in outcome and their impact on cost-effectiveness over a 10-year time horizon. The health economic evaluation carried out as part of the OPEN trial is fully described in *Chapter 5*.

Data collection

Summary

Data from trial CRFs were entered by research staff at site through a password-protected portal onto the internet-based data management system developed, set up, hosted and maintained by CHaRT. Participant-completed questionnaires from catheter removal post intervention onwards were collated at the central trial office and entered into the trial database by NCTU staff, whereas patient-reported outcomes at baseline and just prior to intervention were entered at site by research staff. Staff in the NCTU trial office in Newcastle worked closely with the local research teams at site and the trial team at CHaRT in Aberdeen to ensure that data were complete and accurate. We made concerted efforts to chase and complete any missing data entries through contact with the sites. Participants' details were stored securely in the CHaRT study database under the guidelines of the Data Protection Act 1998.⁴⁰ Participants were allocated an individual specific trial number and all data, other than personal data, were identified only by this unique study number. Data collected during the course of the research were kept strictly confidential and accessed only by members of the trial team.

Trial events

The schedule of events for the OPEN trial is shown in *Table 1*.

Screening

After identification by clinical staff, men potentially eligible for the trial and who were willing to consider participating were introduced to research staff at site. General demographics and eligibility were checked and anonymised data entered on a screening log. Trial Information was provided and potential participants were given at least 48 hours to consider participation in the study. Following review, at a mutually convenient time, those men who wanted to take part, who fulfilled the entry criteria and who understood the rationale and conduct of the trial provided written consent witnessed by research staff at site with delegated approval to do so. The participant and local research staff then completed baseline data collection.

Randomisation

Randomisation was performed as close as possible to the date of consent (normally immediately thereafter) and the participant and clinical staff responsible for their care informed. For participants allocated to urethroplasty, recruited at urethrotomy-only sites, onward referral to the appropriate specialist centre was organised by the responsible clinician and the trial office informed. Details of baseline assessment and allocated intervention were entered on the web-based data management system baseline and randomisation CRF.

Intervention

Research staff at site liaised with the clinical team caring for the individual participant regarding arrangements for undergoing the allocated intervention (urethroplasty or urethrotomy). The protocol anticipated a maximum 12-week delay between randomisation and surgery. A more extended time awaiting allocated intervention was nonetheless allowed. This resulted from uncertainty regarding assessment required prior to anaesthesia and surgery, clinical prioritisation, need for onward referral for some men allocated to urethroplasty and time waiting for surgery. Just prior to intervention, participants were asked to again complete the trial questionnaire.

Research staff at site recorded details of the intervention given, together with any AEs during surgery, the subsequent postoperative hospital stay and during the period of postoperative catheterisation in the allocated intervention CRF. Participants completed a further trial questionnaire 1 week after catheter removal, which was generally performed in hospital.

Follow-up

When possible, the 3-monthly trial follow-up visits carried out by research staff at site coincided with routine or extra clinical visits. If appropriate, the trial participant reviews could be completed by telephone in conjunction with the review of health-care records. Local research staff recorded any deviations in standard care, such as reinterventions for bulbar urethral stricture, AEs, unscheduled outpatient visits and any hospital stays. Owing to slower than planned recruitment, longer than anticipated waiting times for surgery and the need to complete the trial within the funded period, a final review of all participants was arranged at the end of the study during November and December 2017, 24 months after the date of the last randomisation. This consisted of participant completion of a trial questionnaire and a further intervention questionnaire. Uroflowmetry was carried out at baseline and at 3 and 24 months after surgery.

Data handling and record keeping

Data were recorded by site staff on electronic CRFs in a bespoke electronic database within a software package designed and maintained by CHaRT in Aberdeen. In certain cases, data were initially recorded on paper CRFs prior to transfer to the study database. The database was accessed by research staff at site through a password-protected portal unique to that site. Participant questionnaires returned by post to the trial office in NCTU were entered by NCTU staff who remained blind to participant allocation. Participants had the option of completing the questionnaire online with immediate electronic transfer to the database. Participants who chose this option at baseline were sent the web address to the participant area and a unique login identifier for that participant to gain access to the area. Once logged in, the participant would then be able to complete the questionnaire for the relevant time point. Participant data collected under a unique identifier were kept confidential and accessed only by members of the trial team. Extensive efforts were made to ensure completion and collection of trial questionnaires at each time point. Regular checks were carried out and missing data pursued with research and clinical staff at site and with participants through their preferred means of communication. Up to three reminders to complete questionnaires were sent at each scheduled time point. Essential data will be retained for a period of at least 10 years following close of study, in line with sponsor policy and the latest European Directive on Good Clinical Practice (GCP) (2005/28/EC). Data were handled, digitalised and stored in accordance with the Data Protection Act 1998.⁴⁰

Details of study interventions

General

Study design was pragmatic, in that, apart from randomised allocation of intervention and outcome data collection, standard care pathways for each procedure at individual sites were followed. These included type of anaesthesia, use and regimen of antibiotic prophylaxis, surgical instrumentation, closure or non-closure of oral mucosal graft donor site, duration of postoperative urethral catheterisation and clinical follow-up schedule, including use of investigations to detect stricture recurrence. The interventions were funded by the NHS in accordance with local contracting mechanisms. The NHS excess treatment costs were approved by the sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK) and the host NHS organisation at each participating site.

Urethroplasty (experimental)

For urethroplasty, men were positioned supine on the operating table with hips and knees held in an abducted and flexed position by suitable leg supports. A longitudinal skin incision was made in the perineum above the anus and towards the base of the scrotum. The bulbar urethra was localised and mobilised from its attachments. The stricture segment was incised longitudinally on the dorsal or ventral surface according to surgeon preference. The surgeon then decided if the stricture could be excised with or without transection of

the corpus spongiosum and a primary anastomosis made (typically, proximal strictures < 2 cm in length with limited fibrosis) or if an oral mucosal graft should be placed without stricture excision in an augmented repair (typically, fibrotic strictures \geq 2 cm in length). The oral mucosal graft was harvested from the inner cheek, defatted and sutured to the cut urethral edges, then stabilised against the corpora cavernosa if dorsally placed or the corpus spongiosum if ventrally placed. A 16-French silicone Foley urethral catheter was then placed and left in situ for free drainage of urine for a postoperative period of approximately 2 weeks. Once recovered, the patient was discharged home to return at a planned later date for a urethrogram to check that there was no leakage from the area of repair, catheter removal and trial of voiding. The median stay from NHS England hospital activity data at the time of the trial was 2 days.⁸ Clinical follow-up was usually by wound and symptom review at 3 months and urinary flow rate measured at 3 and 24 months post intervention.

Endoscopic urethrotomy (control)

For urethrotomy, men were positioned supine on the operating table with legs supported in an abducted and flexed position. The endoscope (Sachse urethrotome) was passed retrogradely through the urethral lumen under direct vision until the distal end of the stricture segment was encountered. A fine-calibre guidewire was placed through the stricture into the bladder to aid incision planning. The stricture was progressively incised longitudinally under vision using the steel blade ('cold knife') mounted on the endoscope until healthy mucosa signalling the proximal end of the stricture was reached. Alternatively, a diathermy needle mounted on the endoscope or a laser fibre passed through the endoscope was used to make the incision ('hot knife'). For short flimsy strictures, dilatation with the endoscope or graduated dilators could be used rather than formal urethrotomy. A 16-French silicone Foley catheter was then placed for free drainage of urine during the postoperative period. It was typically removed at 24–48 hours postoperatively, with a trial of voiding prior to discharge or following hospital reattendance after discharge. Follow-up was by outpatient review and urinary flow measurement 3 and 24 months postoperatively. According to patient and clinician decision, a standardised programme of intermittent self-dilatation could be initiated 1 week after catheter removal, as this can delay time to recurrence.¹⁸

Delivery of interventions

All procedures were carried out by accredited consultant urologists or senior trainees in urology. Competency in performing endoscopic urethrotomy is a mandatory component of training as urologists and is regularly performed by approximately 95% of practising urologists.²⁴ Urethroplasty is a specialised technique requiring extra training. Specialist surgeons with recognised expertise working in specific UK centres were identified through BAUS and acted as PIs for the trial at these sites. The precise technique of urethroplasty used for each participant was decided by the operating surgeon. Details of each intervention were recorded by research staff at site on a CRF.

Changes to study design

Changes made to the protocol during the trial are listed in *Table 2*. Owing to slow recruitment, the trial protocol was adjusted over the period October 2014 to February 2015. The sample size required to detect a 10% difference in voiding symptom score was recalculated using primary outcome data collected up to September 2014, without unblinding of allocated groups. This gave a revised target recruitment of 210 men. To take into account the prolonged recruitment period and differing waiting times for surgery, we reprofiled timing of collection of the primary outcome, anchoring the timing of participant completion of trial questionnaire completed during the last 6 months of the study to the date of randomisation, rather than the date of allocated intervention. In line with these changes, the end of recruitment period was put back to December 2015 and the end of study to December 2017.

Sample size calculation

We aimed to detect at least a 0.1 (10%) difference in the AUC of the voiding symptom score calculated from the plotting of repeated measurements over 24 months for both trial groups and using a 0–1 utility scale. This conservatively assumed a standard deviation (SD) score of < 0.33 based on the finding of a SD of

TABLE 2 Changes to the protocol requiring regulatory approval

Description	Protocol version	Date
Justification of sample size for the secondary outcome of need for further intervention in case of poor recruitment (104 rather than 500 men)	1.1	15 November 2012
Inclusion of two extra trial questionnaire completions (just prior to the procedure and at 1 week after catheter removal)		
Addition of validated single-item global sexual function question to the PROM		
Protocol contacts page updated	1.2	15 February 2013
Emergency contact details updated		
Removal of SF-12 and clarification of the time points that the resource use questionnaires will be completed		
Clarification of what participant data will be stored on the trial database		
AE reporting had been written according to the regulations for CTIMP studies. As trial is not a CTIMP, amended with guidance from the National Research Ethics Service website		
Amended protocol appendix (with no changes to the main protocol) to include the second qualitative phase, a TTO evaluation	1.3	12 January 2014
Addition of site monitoring centrally when possible		
Amended protocol and consent form to ask site to fax a copy of the consent form to the central trial office		
Changes to members of the health economics team	1.4	20 February 2014
Change of trial manager		
Typographical changes		
Addition of online advertisement URL: www.trialreach.com , which feeds information to URL: www.patient.co.uk . Basic trial information to be advertised online	1.5	16 July 2014
Addition of video demonstrating a model trial consultation on the OPEN trial electronic CRF website		
Clarification in the protocol and patient information sheet that there is a limit to the amount of patient travel expenses that can be claimed: £25 per visit, when the visit occurs outside routine care		
Length of archiving altered to 10 years in line with the clinical trial agreement and sponsor practice		
Alteration of the number of recruiting sites and locations within the UK		
Change to end of recruitment date from 31 October 2014 to 27 February 2015 to reflect the delayed opening of the study	1.6	22 October 2014
Change to the length of recruitment period. Recruitment to close 31 December 2015. End of follow-up therefore December 2017	1.7	17 February 2015
Reduction in the sample size required from 500 to 210		
Change of the timing of 18- and 24-month post-surgery questionnaires to be 18 and 24 months after randomisation to mitigate bias from different waiting times for surgery		
Addition of two secondary objectives: (1) looking at the symptom control and quality of life over the study period and (2) need for reintervention over the study period (median time from intervention)		

TABLE 2 Changes to the protocol requiring regulatory approval (*continued*)

Description	Protocol version	Date
Participant follow-up by questionnaires will be increased with two additional time points: 24 months after surgery and at the end of study (December 2017)		
Introduction of a reintervention questionnaire for participants to complete at 24 months post surgery and at the end of study (December 2017)		
Addition of a third 'thank you' voucher at trial end		
Update to the TTO substudy protocol (see <i>Appendix 1</i>)		
Change to trial manager contact details		
Typographical changes		
Clarification of study procedures and analysis for participants who did not receive their randomised allocated intervention	1.8	3 October 2016
Update to SAE reporting procedure (introduction of paper SAE form)		
Administrative changes		
CTIMP, Clinical Trial of an Investigational Medicinal Product; PROM, patient-reported outcome measure; SF-12, Short Form questionnaire-12 items.		

0.15 in a previous shorter-term study among men undergoing bulbar urethroplasty.³⁰ For 90% power this would require 500 men to be randomised. Following the trial feasibility phase, it was clear that this sample size was not achievable in a fundable time frame. We therefore recalculated the SD of the symptom score in August 2014, using trial data collected from the first 69 men randomised who had completed at least one score following intervention (220 measurements in total), while maintaining blinding of allocated intervention. This recalculation gave a SD of 0.165, which reduced to 0.15 when adjusted for baseline score and trial site. Using these data we updated our sample size estimate assuming a reduced SD of ≤ 0.21 . This indicated a requirement of 170 men to be randomised to have 90% power for detection of a 10% difference at a two-sided 5% level. We inflated the figure to 210 to allow an up to 19% loss to follow-up rate. When interpreting actual trial data we found results more straightforward to consider by scaling the AUC to the USS-PROM scale minimum and maximum over 24 months, in which a score of 0 indicated a complete lack of symptoms over the trial and a score of 24 indicated full symptoms throughout the trial. Rescaling the AUC did not change the assumptions of the sample calculation.

Statistical analysis

Primary outcome

The primary analysis was based on the intention-to-treat (ITT) principle, with participant groups compared according to randomly allocated intervention using available data in a complete-case 'modified' ITT analysis. Details of the planned analyses were documented prior to the end of the trial in a statistical analysis plan (SAP) [see www.journalslibrary.nihr.ac.uk/programmes/hta/105723# (accessed 26 June 2019)].

Additional planned analyses using a per-protocol definition and inclusion of more men enabled by data imputation in a further ITT sensitivity analysis were detailed in an additional SAP [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/105723#/ (accessed 26 June 2019)].

Baseline and follow-up data were summarised using mean (SD) or median [interquartile range (IQR)] when appropriate for continuous variables. Discrete variables were summarised with numbers and percentages. Treatment effects were presented with 95% confidence intervals (CIs).

The primary outcome measure, AUC for the repeated measurement of voiding symptom score contained in the USS-PROM trial questionnaire over 24 months following randomisation, was analysed using linear regression adjusted for the minimisation covariates of site and stricture severity, defined as the time duration between the last previous intervention for bulbar stricture and the date of randomisation (< 12 months or ≥ 12 months). Voiding score was measured at baseline; prior to intervention; 1 week after catheter removal; 3, 6, 9 and 12 months after intervention; and 18 and 24 months after randomisation. Additionally, participants were asked to complete the trial questionnaire 24 months after intervention and at the end of study (November 2017). Trial questionnaires were also completed before and after any reintervention for stricture recurrence. The AUC was constructed using the trapezoidal rule, which assumes a constant increment (or decrement) in score between two points when outcome is measured. The AUC was divided by total duration of the trial for each participant up to 24 months post randomisation to facilitate interpretation. The original sample size calculation introduced the AUC in its usual format, 0–1 utility; however, in our results we decided to multiply the scale by 24 in order to present it in the same scale as the voiding score (0–24) and therefore facilitate interpretation.

For the primary analysis, all participants who had surgery and completed at least three voiding scores, comprising one baseline measure prior to trial intervention, one early measure up to 12 months after intervention and one later measure up to 24 months post randomisation, were included. Participants who did not have a late measure but had returned an end of study or a 24 months post intervention measure were included if this measure was collected within 6 months after their 24 months post randomisation time point. For the two participants without a baseline or preintervention measure, we used imputation based on the mean score observed at that site.

Sensitivity analyses detailed in the additional SAP were conducted to assess the robustness of the primary treatment effect estimate. This was done by relaxing and tightening the minimum number of measures needed to be included in the analysis. When available, all observed data were used across all time points. However, for many participants, data were missing at various time points. The assumptions of the data inclusion for the primary analysis and proposed sensitivity strategies are outlined below for each group of measurement time points.

Baseline

If either of the baseline and prior to surgery measurements were missing but the other was available, we assumed a constant score between these two time points and imputed one with the other. If both were missing, we imputed the site mean for each time point to allow calculation of the AUC for the primary analysis.

Early

If the 1 week after catheter removal measure was missing we did not impute a value; in these circumstances the AUC calculation was made between the baseline and first available early measure. As the 1 week after catheter removal measure could occur at any real time point throughout the trial, we used real time (in months) to incorporate this into the relevant time section of the AUC. Only one of the 3-, 6-, 9- and 12-month post-surgery measures was required. The AUC calculation used the notional time, in weeks, between the last available time point prior to 3 months and the first of these time points. If one or two time points were missing, we did not impute a value for those missing time points, but assumed constant increment (or decrement) in score between those points where outcomes were measured.

Late

Only one of the 18- and 24-month post-randomisation time points was required to calculate the AUC. If the 18-month time point was missing but the 24-month time point was measured, we did not impute a value for 18 months. Rather, the AUC calculation used the notional time (in months) between the last available measurement prior to 18 months and assumed constant increment (or decrement) in score between these two time points. If the 18-month time point was measured but the 24-month time point was missing, we carried the 18-month measurement forward to 24 months to allow calculation of the AUC. If there was a 24-month post-intervention or end of study measurement closer in time to the 24-month post-randomisation measure than the 18-month time point, we used that rather than the 18-month measure.

Accounting for occurrence of reintervention

For participants who underwent reintervention and submitted outcome measures prior to or following this intervention, we incorporated these into the relevant time section of the AUC by inserting the extra observations between notional time point measures. When reintervention clashed with a scheduled outcome measurement, the reintervention reported measurements were used. If a reintervention took place but the associated outcome measures were missing, we used index intervention outcome data for that participant. We assessed the appropriateness of this assumption empirically with observed data.

Secondary outcomes

The following secondary outcomes were recorded:

- difference in condition-specific quality-of-life trajectory, measured from 0 to 3 by the AUC for the single item on the USS-PROM
- difference in global sexual functioning trajectory, measured from 1 to 5 by the AUC for the single-item male sexual satisfaction score from Index of Erectile Function questionnaire
- difference in generic quality-of-life trajectory, measured by the AUC for the EQ-5D-5L total score based on responses to 5-dimension items and using UK population valuations (0 death to 1 full health)³⁹ and VAS score (0 worse possible health state to 100 best possible health state)
- difference in rate of improvement of Q_{max} , measured at baseline, 3 months, and between 12 and 24 months with an increase in $Q_{max} \geq 10$ ml/second from baseline taken to signify a successful outcome
- difference in rate of need for further intervention, recorded from the clinical record for those participants returning to the care of their original specialist with recurrent stricture, by patient questionnaire for participants seeking care elsewhere and checked by the local trial research staff at the final 24-month assessment.

Secondary outcomes were analysed using generalised linear models appropriate for the distribution of the outcome, with adjustment for minimisation and baseline variables as appropriate. Reintervention was analysed as a time-to-event outcome using Cox regression and adjusting for minimisation variables and centre. Hazard ratios and 95% CI were calculated with the model. Kaplan–Meier curves were generated. Participants were included in the analysis using the observation time available until database closure (at least 2 years and up to 4 years). Box regression with multiple failure time data used the Andersen–Gill model.

For assessment of the primary outcome, missing follow-up data were estimated in sensitivity analysis using multiple imputation models for participants who had missing time points. We explored differences between responders and non-responders to inform our missing data model. We calculated an AUC for each imputation and combined these using Rubin's rules under a missing at random assumption.^{41,42} We also explored, using pattern mixture models, imputation of a range of values estimated from observed data using different missing not at random scenarios. Measures of the primary outcome collected at 24 months post intervention and at the end of the study were also included, when applicable, as a sensitivity analysis of the calculation of the AUC.

There were no planned or requested interim outcome analyses. The analyses were performed in Stata® version 14 (StataCorp LP, College Station, TX, USA).

Subgroup analysis

Subgroup analyses explored the possible modification of treatment effect by clinically important factors: time since last procedure (< 12 months or ≥ 12 months) as a global measure of stricture severity, age, stricture length and number of previous interventions. This was done by including treatment-by-factor interactions in the model and they were classified as exploratory analyses. No adjustment of the significance level was applied and findings should not be considered definitive but require replication.

Adverse events

An AE may be defined as any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention.

For the purposes of this trial:

- all AEs were recorded at time of initial or reintervention surgery, and at 3, 12 and 24 months after initial intervention, and categorised by trial staff according to expectedness, relatedness, severity and for postoperative complications, according to the Clavien–Dindo classification.⁴³

Please refer to the protocol [see www.journalslibrary.nihr.ac.uk/programmes/hta/105723/#/documentation (accessed 26 June 2019)] for more information about AE classification and reporting.

Qualitative substudy

Qualitative work was undertaken to establish factors determining willingness of patients and support of their clinicians to consider participation. Timely and successful completion of the planned qualitative study first established that the aims of the trial were important to men eligible to participate, given the troublesome and chronic nature of their symptoms, and to both general and specialist clinicians; these findings reinforced the rationale and need for the trial. As part of this work, we found that men eligible for inclusion were most likely to be willing to participate when their symptoms had first recurred and this was the point at which they expressed most uncertainty as to which option would be best for them as individuals. Both general and specialist clinicians were also very supportive of the aims of the trial given the uncertainty of guidance on best treatment, but expressed concerns regarding delivery of balanced information to men eligible for participation. To assist men eligible for participation in making a decision about participation, appropriate written guidance and an example video were provided, supported by personal contact from the trial team.

Trial progress and monitoring

The study initially set out to progressively build to a target of 500 participants over 24 months. This included an initial 12-month feasibility study, during which recruitment and patient adherence to the intervention were evaluated. Feasibility of recruitment was analysed after 9 months of active recruitment (trial month 12) and reported in August 2014 to the TSC and the funder, with an additional safety report reviewed by the Data Monitoring Committee (DMC). Recruitment continued to be monitored by the Trial Management Group (TMG) through returns to the randomisation website. The funder and TSC requested a recovery plan to mitigate the slow recruitment and ensure that the trial was completed over a fundable period of time. The recovery plan, which principally involved a re-estimation of required sample size using early observed data to 210 randomised participants, opening of additional sites and the recruitment window increasing from 24 months to 35 months, was submitted and approved by the TSC and funder in December 2014.

Sources of bias

To allow randomisation, both the eligible participant and the responsible clinician needed to be sufficiently uncertain whether the experimental or control strategy was best for management of the individual's recurrent urethral stricture. Given the lack of high-level evidence as to which was the more effective intervention, trial information was provided illustrating the uncertainty and the need for a definitive trial. This aimed to ensure that any selection bias in terms of differing characteristics of men with recurrent bulbar urethral stricture willing to be randomised compared with those men who were eligible but not willing to participate was minimised. As far as possible and within the limits of data protection legislation, we recorded reasons for declining randomisation, but patients were free to decline participation and randomisation without giving a reason.

Trial literature for men eligible for participation or who were participating in the trial included the following: the OPEN trial participant information sheet and consent form v1.5 (main trial), the OPEN trial participant information sheet and consent form interview study v1.3, the OPEN trial website synopsis v1.1, the OPEN trial patient end of study questionnaire letter v1.0, the OPEN trial patient questionnaire letter v1.2, the OPEN trial patient invitation letter main study v1.0, the OPEN trial contact card v1.0 and participant flowchart v1.0. These documents are available at www.journalslibrary.nihr.ac.uk/programmes/hta/105723/#/ (accessed 26 June 2019).

Definition and end of study

The end of study, defined as the 24-month post-randomisation follow-up for the last recruited participant, was originally planned for 28 February 2017. Owing to slow recruitment, an extension was granted in December 2014 by the funder and approved by the TSC to a new end date of 31 January 2018. A further extension to 30 April 2018 was approved in December 2017 by the funder and TSC in consultation with the DMC to allow more time to consider the primary result of the trial in the light of additional analyses prior to report submission. Active participation in the trial ended on 23 December 2017.

Compliance and withdrawal

Outcome data were collected remotely whenever feasible by participant completion of the trial questionnaires. Local research staff made use of planned routine clinical visits to check completion of trial documentation, with reference to the trial database and participants' health-care record. Adherence to the allocated group (urethroplasty or urethrotomy) was checked by completion of an intervention CRF at the time of surgery. Reasons why participants chose not to have their allocated intervention but underwent the alternative procedure instead or who did not have any intervention were recorded. These participants continued to complete trial questionnaires and trial visits according to protocol to allow them to be included in the complete-case ITT primary analysis. The trial statistician monitored attrition rate against the anticipated maximum of 19% and reported to the TMG, TSC and DMC as appropriate.

Data monitoring, quality control and assurance

Quality control was maintained through adherence to standard operating procedures governing the work of sponsor (Research and Development Directorate, Newcastle upon Tyne Hospitals NHS Foundation Trust), NCTU, CHaRT and local research teams, and in accordance with the study protocol, the principles of GCP, research governance and clinical trial regulations. An independent DMC was set up comprising one methodologist, one clinician not connected to the trial and one statistician (chairperson). The purpose of this committee was to monitor efficacy and safety end points. It operated in accordance with written terms of reference linked to the DMC's lessons, ethics, statistics charter.⁴⁴ Only the DMC and the trial statistician preparing reports to the DMC had access, prior to completion of the trial, to data separated by allocated group. The DMC met at the start and completion and four times during the study. The DMC meetings were also attended by the trial statistician.

A TSC was established to provide overall supervision of the trial. The TSC consisted of an independent clinician who acted as chairperson, two further independent clinicians, an independent statistician, a lay representative and the chief investigator. Other members of the TMG attended as required or as requested by the chairperson. The committee met approximately every 6 months during recruitment and annually thereafter for the duration of the trial.

Monitoring of study conduct and collected data followed a written monitoring plan, informed by a risk assessment and agreed with sponsor. It was performed by a combination of central review and site monitoring visits to ensure that the study was conducted in accordance with GCP. Study site monitoring was undertaken by appropriately trained members of the NCTU. The main areas of focus were consent, eligibility, SAEs and completeness of the investigator site file at each site and the trial master file held at NCTU. Audit of data entry using a random 10% sample of trial questionnaires showed a 3% error rate, below the threshold of 5% that would have triggered a full audit.

Ethics and governance

The Newcastle upon Tyne Hospitals NHS Foundation Trust Research and Development Directorate sponsored the trial (reference 6332). Favourable ethics opinion for the trial was obtained on 16 October 2012 from the NHS Research Ethics Service Committee North East – Newcastle and North Tyneside 1 (reference 12/NE/0343) and subsequent research and development and Caldicott Guardian approvals were granted by each participating site. Approval was sought and obtained for all substantive protocol amendments (see *Table 2*).

Trial registration and protocol availability

The trial was registered as ISRCTN98009168 on 29 November 2012 and in the UK NIHR Portfolio (reference 13507). The latest version (1.8) of the full protocol is available at www.journalslibrary.nihr.ac.uk/programmes/hta/105723/#/ (accessed 14 February 2017) and a published version is also available.¹

Chapter 3 Results

Recruitment

The trial recruited from 38 NHS hospital sites across the UK (England, Scotland and Wales). The first participant was randomised on 27 February 2013 and the last on 23 December 2015. The planned recruitment window was extended by 12 months to 35 months to allow the opening of further sites and to achieve the revised recruitment target (*Figure 5*). Participants were identified when attending hospital urology clinics. The recruitment strategy was first to open specialist sites where both urethroplasty and urethrotomy were carried out and subsequently to open general urology sites where only urethrotomy was provided, with urethroplasty accessed by referral to a previously established specialist site. Overall, 222 participants were recruited and randomised [58 (26%) from general sites and 164 (74%) from specialist sites] (*Table 3*).

Participant flow

The flow of participants enrolled in the study is shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (*Figure 6*). A total of 1249 men were identified by study sites (83% of the target of 1500 men) and screened for eligibility. Of these men, 1027 (82%) were either deemed ineligible to take part by local research staff or declined to participate in the trial (*Tables 4 and 5*). Following completion of written consent and collection of baseline data, 222 participants (106% of revised target) were randomised, with 109 men allocated to open urethroplasty and 113 men to endoscopic urethrotomy.

Numbers analysed

Primary analysis

In the primary complete-case ITT analysis we included 159 (72%) of the randomised participants using the criteria of having completed primary outcome questionnaires on a minimum of three occasions: at baseline, during the first year after intervention and at 18–24 months after randomisation. This was 94% of the pre-set target of 170 participants providing data on the primary outcome in our revised sample size calculation. The total of 159 men comprised 69 men (63% of those men randomised) allocated to the urethroplasty group and 90 men (81% of those men randomised) allocated to urethrotomy. A total of 25 men allocated to urethroplasty had urethrotomy and a further 15 men had no intervention. From the urethrotomy group, 11 men had urethroplasty and 8 men did not have any intervention. Accordingly, 19 men (17%) allocated to urethrotomy did not receive urethrotomy and 40 men (37%) allocated to urethroplasty did not receive urethroplasty. All participants who 'crossed over' or did not have any intervention but who remained in active follow-up and provided sufficient completed trial questionnaires were analysed according to allocated group (complete-case ITT analysis). Reasons for exclusion from the primary analysis are detailed in *Table 6*.

Of 222 randomised participants, 109 were allocated to the urethroplasty group and 113 allocated to the urethrotomy group. Two randomised participants, one from each group, were excluded soon after randomisation because further assessment showed them to be ineligible and they were classified as post-randomisation withdrawals, excluding them from the primary analysis. One man (allocated to urethroplasty) was unfit for prolonged anaesthesia and one (allocated to urethrotomy) had a stricture that, following urethrography, was deemed unsuitable for endoscopic management. Accordingly, at baseline, there were 108 participants in the urethroplasty group and 112 in the urethrotomy group. Baseline characteristics were well balanced between the two groups (*Tables 7 and 8*). Twenty-two participants allocated to urethroplasty underwent urethrotomy and 15 participants did not have either procedure. In the urethrotomy group,

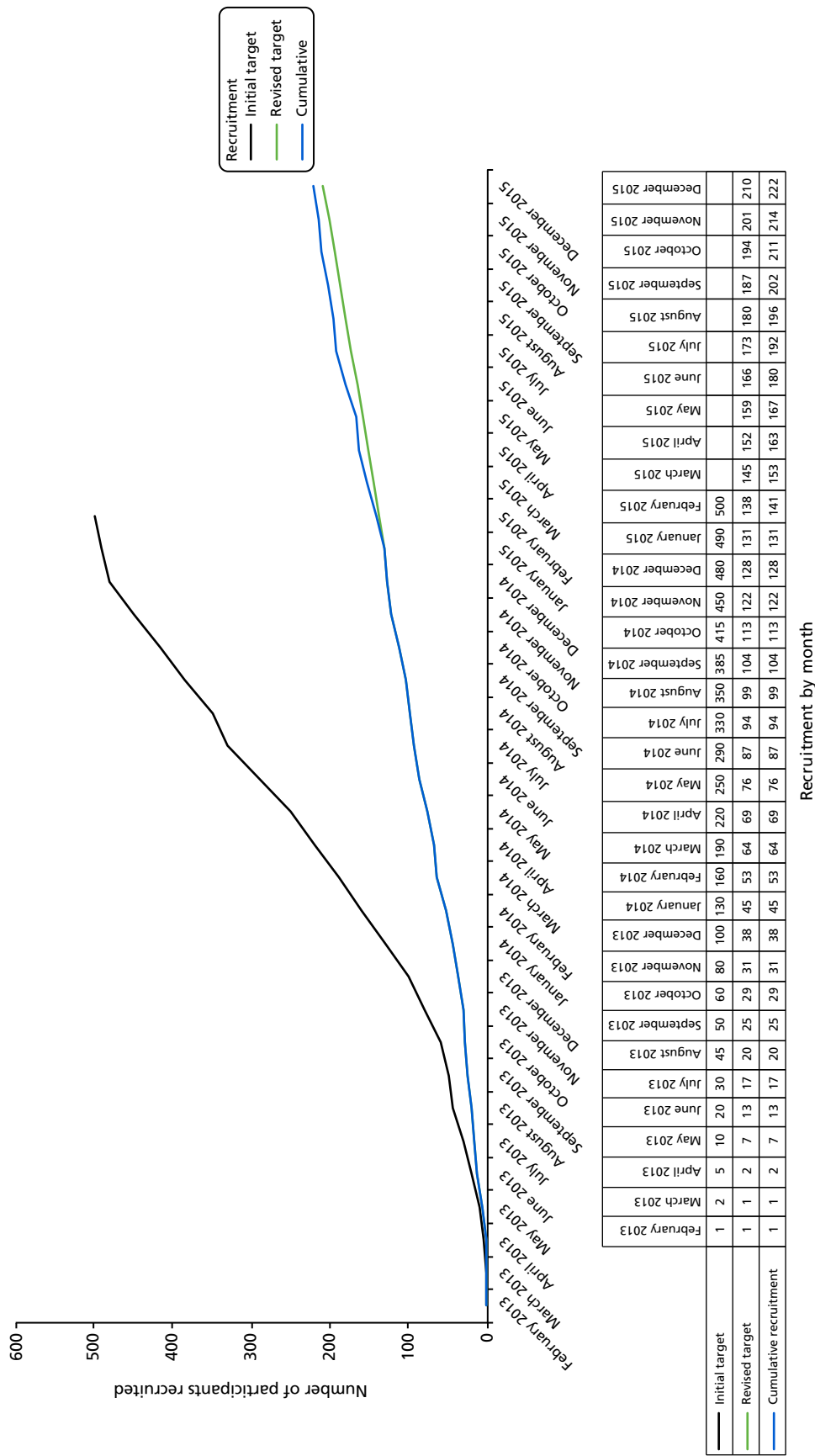


FIGURE 5 Planned and actual recruitment trajectory for the OPEN trial.

TABLE 3 Recruitment sites

Site of recruitment ^a	Number of participants randomised at site
<i>Freeman Hospital, Newcastle upon Tyne</i>	21
• James Cook University Hospital, Middlesbrough	1
• York Hospital, York	5
<i>St George's Hospital, London</i>	12
• Frimley Park Hospital, Surrey	3
• East Surrey Hospital, Surrey	2
<i>University College London Hospitals NHS Foundation Trust, London</i>	4
• Maidstone Hospital, Kent	1
• Darent Valley Hospital, Kent	9
• Basildon University Hospital, Essex	6
• Bedford Hospital, Bedfordshire	6
• Whittington Hospital, London	2
<i>Russells Hall Hospital, West Midlands</i>	17
<i>Queen Alexandra Hospital, Portsmouth</i>	11
<i>St Richard's Hospital, Chichester</i>	4
<i>Manchester Royal Infirmary, Manchester</i>	0
• Royal Blackburn Hospital, Blackburn	5
<i>St James's University Hospital, Leeds</i>	3
• Airedale General Hospital, West Yorkshire	3
<i>Weston General Hospital, Weston-super-Mare</i>	2
• Torbay Hospital, Torquay	2
• Cheltenham General Hospital, Cheltenham	3
• Royal Devon and Exeter Hospital, Exeter	1
• Yeovil District Hospital, Yeovil	1
• Musgrove Park Hospital, Taunton	2
<i>Addenbrooke's Hospital, Cambridge</i>	31
<i>Royal Hallamshire Hospital, Sheffield</i>	1
<i>Aintree University Hospital, Liverpool</i>	8
<i>Stepping Hill Hospital, Stockport</i>	2
• Royal Albert Edward Infirmary, Wigan	1
<i>Kent and Canterbury Hospital, Canterbury</i>	13
<i>Southampton General Hospital, Southampton</i>	12
<i>Aberdeen Royal Infirmary, Aberdeen</i>	5
<i>Sunderland Royal Hospital, Sunderland</i>	9

continued

TABLE 3 Recruitment sites (continued)

Site of recruitment ^a	Number of participants randomised at site
<i>Guy's Hospital, London</i>	5
<i>Charing Cross Hospital, London</i>	1
<i>Princess of Wales Hospital, Bridgend</i>	2
• University Hospital of Wales, Cardiff	1
<i>Western General Hospital, Edinburgh</i>	5
Total randomised	222

a Sites performing urethroplasty and urethrotomy in italics, sites performing only urethrotomy in plain text listed below their referral centre for urethroplasty.

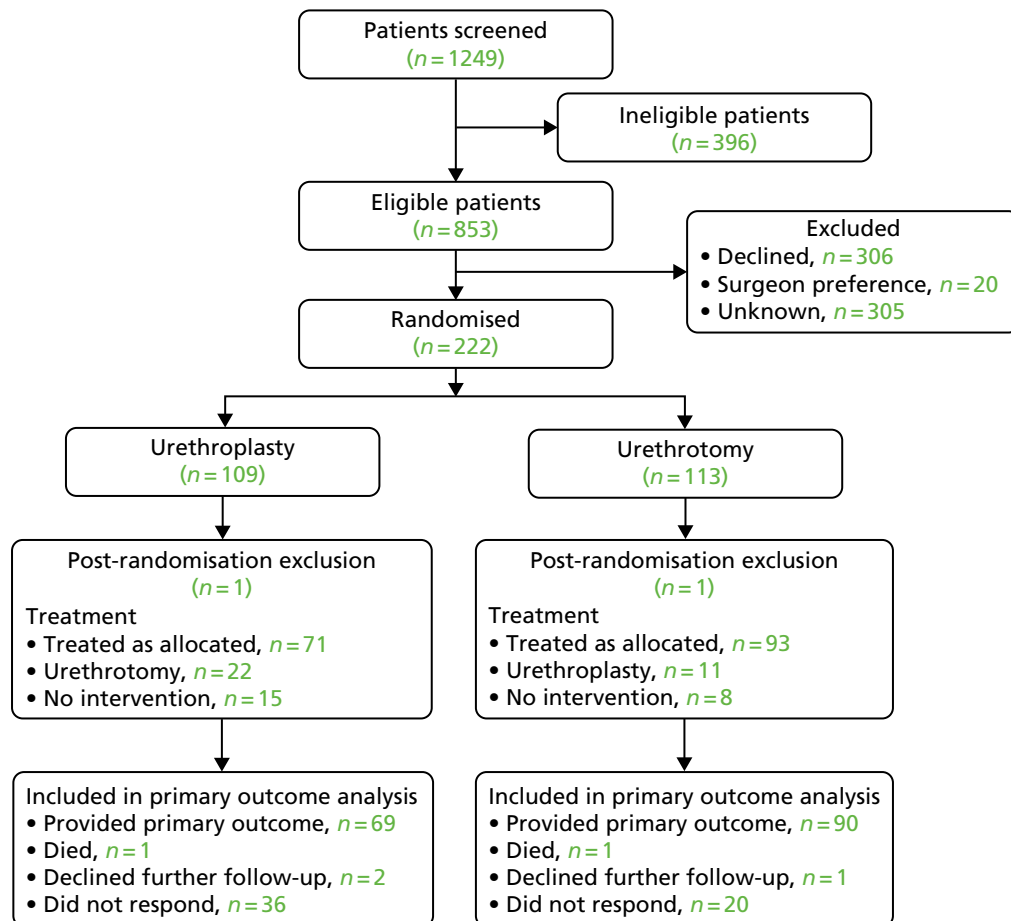


FIGURE 6 Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing progress of participants through the study. Reprinted from *European Urology*, vol. 78, Goulao B, Carnell S, Shen S, MacLennan G, Norrie J, Cook J, *et al.*, Surgical treatment for recurrent bulbar urethral stricture: a randomised open-label superiority trial of open urethroplasty versus endoscopic urethrotomy (the OPEN trial), pp. 572–80,⁴⁵ Copyright 2020, with permission from Elsevier.

TABLE 4 Reasons for non-participation

Participants approached	Total (N = 1249; 100.0%), n (%)
Ineligible	396 (32)
Age < 16 years	4 (0.3)
Stricture in penile urethra	66 (5.3)
No previous intervention for stricture	101 (8.1)
Intervention not required	65 (5.2)
Unwilling to have 2-week catheterisation	1 (0.1)
Unable to give consent	13 (1.0)
Perineal sepsis or fistula	7 (0.6)
Previous participation in the OPEN trial	5 (0.4)
Unable to have 3-hour anaesthetic	22 (1.8)
Inability to adhere to trial protocol	11 (0.9)
Ineligible, no reason stated	101 (8.1)
Patient declined participation	306 (24.5)
Preference for open urethroplasty	185 (14.8), 60% of those men who declined
Preference for endoscopic urethrotomy	79 (6.3), 26% of those men who declined
Potential adverse effects of urethroplasty	6 (0.5)
Potential adverse effects of urethrotomy	1 (0.1)
Need for urethrogram for urethroplasty	2 (0.2)
Unable to fulfil protocol commitments	19 (1.5), 6% of those men who declined
Patient did not attend follow-up	14 (1.1)
Surgeon preference	20 (1.6), 7% of those men who declined
Unknown	305 (24.4)

TABLE 5 Reasons for withdrawal

Reason for withdrawal	Intervention (n)		Total
	Urethroplasty (N = 109)	Endoscopic urethrotomy (N = 113)	
Withdrawal by participant	5		5
No longer requires treatment	1		1
Withdrawn by clinician	1		1
Participant did not accept allocation and wished to have alternative (crossover)	1	1	1
Participant referred to specialist site where urologist was not available to perform procedure	2		2
Participant not suitable for surgery		1	1
Participant deceased	1	1	2
No reason recorded/given	1	3	4
Total	12	6	18

TABLE 6 Inclusion in primary analysis and intervention carried out in those men excluded

	Intervention (<i>n</i>)	
	Urethroplasty (<i>N</i> = 108)	Urethrotomy (<i>N</i> = 112)
Included		
All three required questionnaires received	69	90
Excluded		
At least one required questionnaire missing	39	22
Intervention performed in those men excluded		
Allocated intervention	17	13
Alternative intervention (crossover)	7	1
No intervention performed	15	8

TABLE 7 Clinical characteristics at baseline by randomised group

Variable	Urethroplasty (<i>N</i> = 108)	Number of participants providing data	Urethrotomy (<i>N</i> = 112)	Number of participants providing data
Age (years), mean (SD)	49.4 (14.3)	108	48.5 (15.4)	112
Length of stricture (cm), mean (SD)	2.0 (1.4)	67	1.7 (1.1)	63
Duration of disease (years), mean (SD)	7.3 (9.7)	78	9.9 (11.7)	80
Previous interventions, mean (SD)	1.9 (2.0)	108	1.8 (1.7)	112
Time (months) since last intervention, <i>n</i> (%)				
< 12	36 (33.3)		36 (32.1)	
≥ 12	72 (66.7)		76 (67.9)	
Predominant site of stricture in bulbar urethra, <i>n</i> (%)				
Proximal	30 (27.8)		24 (21.4)	
Mid	34 (31.5)		41 (36.6)	
Distal	17 (15.7)		17 (15.2)	
Unknown	6 (5.6)		14 (12.5)	
Missing	21 (19.4)		16 (14.3)	
Cause of stricture, <i>n</i> (%)				
Unknown	76 (70.4)		81 (72.3)	
Trauma	11 (10.2)		11 (9.8)	
Infection	5 (4.6)		6 (5.4)	
Other	12 (11.1)		7 (6.3)	
Missing	4 (3.7)		7 (6.3)	
Use of intermittent self-dilatation, <i>n</i> (%)				
Never	60 (55.6)		66 (58.9)	
Previously	25 (23.1)		31 (27.7)	
Currently	23 (21.3)		14 (12.5)	
Missing	0 (0)		1 (0.9)	
Q _{max} (ml/second), mean (SD)	10.0 (6.0)	83	9.7 (5.2)	90
Urethrogram performed, <i>n</i> (%)	70 (64.8)		62 (55.4)	
Urethroscopy performed, <i>n</i> (%)	34 (31.5)		42 (37.5)	

TABLE 8 Participant-reported symptoms at baseline by randomised group

Patient-reported symptoms measure	Urethroplasty (N = 108)	Number of participants providing data	Urethrotomy (N = 112)	Number of participants providing data
USS-PROM				
Total voiding score (0 = no symptoms, 24 = symptoms all the time), mean (SD)	13.4 (4.5)	105	13.2 (4.7)	109
Impact of urinary symptoms on daily activities (0 = none, 3 = a lot), median (P25–P75)	2.0 (1.0–3.0)	107	2.0 (1.0–3.0)	110
Satisfaction with sexual function (1 = very satisfied, 5 = very dissatisfied), median (P25–P75)	2.0 (1.0–3.0)	97	2.0 (1.0–3.0)	100
Urinary stream picture score (1 = strong, 4 = weak), median (P25–P75)	3.0 (3.0–4.0)	103	3.0 (3.0–4.0)	108
Voiding score component questions ^a				
Delay before starting to urinate, median (P25–P75)	2.0 (1.0–3.0)	105	2.0 (1.0–3.0)	110
Poor strength of urinary stream, median (P25–P75)	3.0 (3.0–4.0)	105	3.0 (3.0–4.0)	109
Having to strain before urinating, median (P25–P75)	2.0 (1.0–3.0)	105	2.0 (1.0–3.0)	110
Intermittent urinary stream, median (P25–P75)	2.0 (1.0–3.0)	104	2.0 (1.0–3.0)	110
Feeling of incomplete bladder emptying, median (P25–P75)	2.0 (1.0–3.0)	105	2.0 (1.0–3.0)	110
Post-micturition dribbling, median (P25–P75)	2.0 (1.0–3.0)	105	2.0 (1.0–3.0)	110
Overall health status on VAS, rating from 0 (worst possible health) to 100 (best health imaginable), mean (SD)	72.4 (19.8)	104	76.7 (17.3)	105
P25, 25th percentile; P75, 75th percentile.				
a Component questions each scored 0 (symptom not present) to 4 (symptom present all the time).				

11 men underwent urethroplasty and eight men no procedure. These protocol deviations and their reasons are given in *Tables 9* and *10*. The median time between randomisations and interventions was 92 days, compared with 47.5 days for urethrotomy (*Table 11*). The rate of trial questionnaire return by each group for each time point is given in *Table 12*. The attrition rate for inclusion in the primary analysis was 30 of 109 (27%) men in the urethroplasty group, 23 of 113 (20%) men in the urethrotomy group and 53 of 222 (24%) men in the randomised population as a whole.

Outcomes

Primary

Area under the curve for USS-PROM total voiding score

Figure 7 shows the mean total USS-PROM voiding score for each randomised group by time point. 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 (a mean difference of -0.36 , 95% CI -1.74 to 1.02 ; $p = 0.60$ in favour of the urethroplasty group). To assess whether or not the primary outcome was biased by the exclusion of participants with fewer than the required three measures, we undertook as sensitivity analyses an ITT calculation using the predefined methods of data imputation to replace missing values and a per-protocol analysis using data only from participants eligible for the primary analysis who underwent

TABLE 9 Treatment received in the trial by randomised group

Allocated intervention	Intervention, <i>n</i> (%)	
	Urethroplasty (<i>N</i> = 108)	Urethrotomy (<i>N</i> = 112)
Urethroplasty	71 (66)	11 (9.8)
• Anastomotic without transection	9 (8.3)	4 (3.6)
• Anastomotic with transection	9 (8.3)	1 (0.89)
• Ventral graft urethroplasty	7 (6.5)	2 (1.8)
• Dorsal graft urethroplasty	45 (42)	4 (3.6)
• Perineal urethrostomy	1 (0.93)	0 (0)
Urethrotomy	22 (20)	93 (83.0)
• Optical urethrotomy cold knife	15 (14)	90 (80)
• Optical urethrotomy hot knife	0 (0)	1 (0.89)
• Dilatation	7 (6.5)	2 (1.8)
Commenced regimen of intermittent self-dilatation	9 (8.3) ^a	29 (26)
No intervention performed	15 (13.9)	8 (7.1)

a All had crossed over and received urethrotomy.

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TABLE 10 Reason for not undergoing allocated intervention

Reason	Intervention, <i>n</i> (%)	
	Urethroplasty (<i>N</i> = 108)	Urethrotomy (<i>N</i> = 112)
Reason for crossing over		
Patient decision	16 (14.8)	8 (7.1)
Patient unsuitable/ineligible	6 (5.6)	0 (0)
Unknown	0 (0)	3 (2.7)
Reasons for not having surgery		
Unknown	15 (13.9)	8 (7.1)

TABLE 11 Time interval between randomisation and intervention

Allocated intervention	Number of participants providing data	Median (IQR) days
Urethroplasty (<i>N</i> = 108)	93	90 (53–157)
Urethrotomy (<i>N</i> = 112)	104	47.5 (28–88)

the intervention to which they were randomly allocated. The results of these three analyses are presented in *Table 13*. The estimate of the primary outcome was robust to sensitivity analyses using pattern-mixture models for missing data for all but unrealistic scenarios (e.g. missing observations in one arm of the trial staying at baseline levels for all 24 months, whereas in the other arm all missing observations were consistent with observed scores).

TABLE 12 Trial questionnaire return rates

Study time point	Intervention (n)	
	Urethroplasty (N = 108)	Urethrotomy (N = 112)
Baseline	107 (99.1)	110 (98.2)
Pre intervention	107 (99.1)	110 (98.2)
1 week post intervention	56 (51.9)	70 (62.5)
3 months post intervention	73 (67.6)	88 (78.6)
6 months post intervention	61 (56.5)	78 (69.6)
9 months post intervention	65 (60.2)	82 (73.2)
12 months post intervention	66 (61.1)	81 (72.3)
18 months post randomisation	64 (59.3)	82 (73.2)
24 months post randomisation	58 (53.7)	58 (51.8)
24 months post intervention	51 (47.2)	57 (50.9)
End of study	51 (47.2)	57 (50.9)

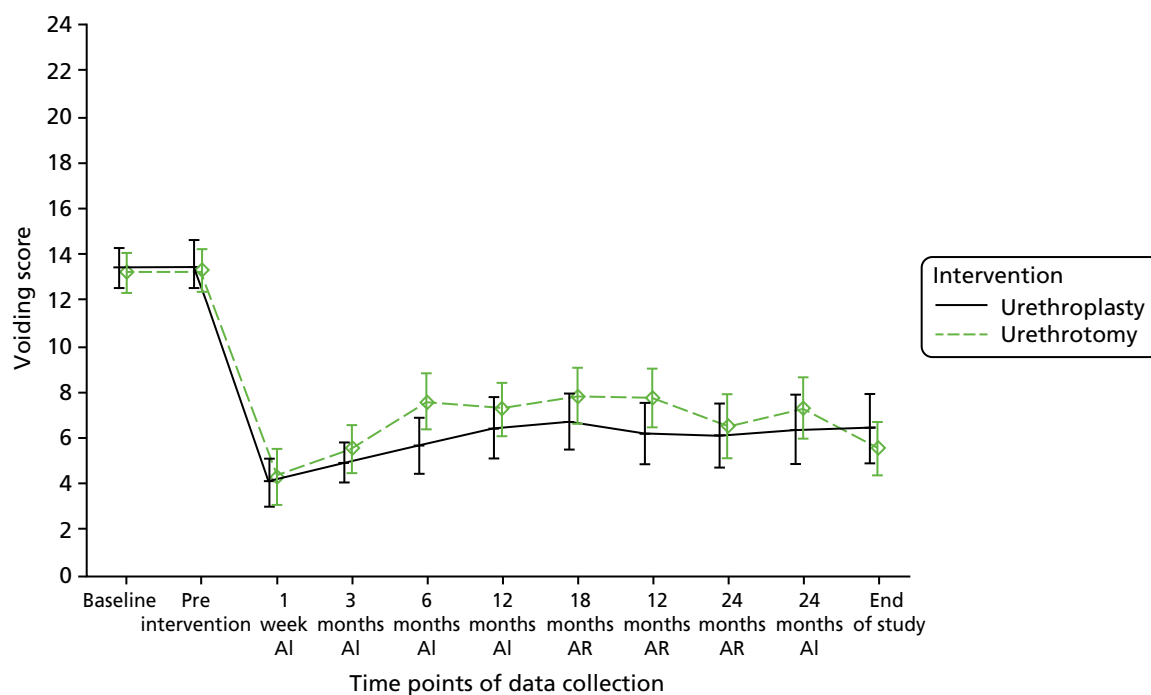


FIGURE 7 Mean (standard error of the mean) for total voiding score at each nominal time point. AI, after intervention; AR, after randomisation.

TABLE 13 Sensitivity analyses for primary result

Analysis	AUC (primary outcome) in each sensitivity analysis		
	Urethroplasty (N = 108), mean (SD); n	Urethrotomy (N = 112), mean (SD); n	Effect size (95% CI); p-value
Complete-case ITT analysis (primary analysis)	7.4 (3.8); 69	7.8 (4.2); 90	-0.36 (-1.74 to 1.02); 0.60
Sensitivity analysis with multiple imputation (ITT)	7.7 (3.9); 93	7.9 (4.2); 104	-0.33 (-1.74 to 1.09); 0.64
Per protocol (underwent allocated intervention)	6.8 (2.9); 54	7.8 (4.2); 80	-1.02 (-2.12 to 0.07); 0.07

Subgroup analyses

We identified number of previous interventions, length of stricture, time since last intervention prior to randomisation and age as risk factors with potential to increase the risk of failure to control symptoms. *Figure 8* presents subgroup analyses for the AUC of the voiding score. *Table 14* presents the interaction term for each subgroup. The results show no evidence that the treatment effect of the different subgroups varies significantly from the main effect.

Secondary outcomes

Area under the curve for impact of urinary symptoms on daily activities: assessing condition-specific quality of life

Sufficient data were available to calculate this outcome for 69 participants in the urethroplasty group and 90 participants in the urethrotomy group. The urethroplasty group had a mean score at 24 months of 1.1 (SD 0.8), compared with 1.0 (SD 0.7) in the urethrotomy group. The mean difference between treatments adjusting for minimisation variables was 0.06 (95% CI -0.19 to 0.30).

Area under the curve for satisfaction with sexual function

Sufficient data were available to calculate this outcome for 63 participants in the urethroplasty group and 87 participants in the urethrotomy group. The urethroplasty group had a mean AUC of 2.9 (SD 1.2), compared with a mean of 2.5 (SD 1.2) in the urethrotomy group. The mean difference between treatments adjusting for minimisation variables was 0.35 (95% CI -0.06 to 0.75).

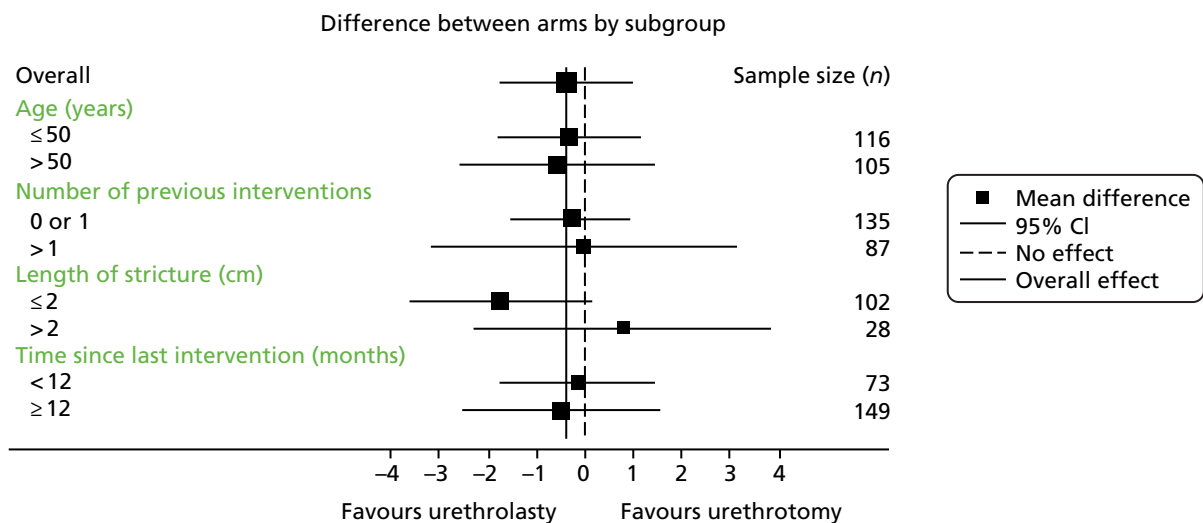


FIGURE 8 Subgroup analyses for the USS-PROM voiding score AUC.

TABLE 14 Interaction terms for the subgroups

Interaction term	Effect size (95% CI); p-value
Overall	-0.36 (-1.74 to 1.02); 0.60
Time since last intervention	-0.36 (-3.19 to 2.46); 0.79
Length of stricture	2.54 (-1.42 to 6.50); 0.20
Number of previous interventions	0.56 (-2.89 to 4.02); 0.74
Age	-0.25 (-2.58 to 2.08); 0.83

Reintervention

In total, 44 participants had at least one reintervention and there were 52 reinterventions overall (Table 15). During the trial observation period for each participant (up to 4 years), 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 hazard ratio for time until first reintervention was 0.52 (95% CI 0.31 to 0.89; $p = 0.02$) (Figure 9), representing a 48% lower risk of reintervention with urethroplasty. Calculation including multiple events gave a similar hazard ratio of 0.49 (95% CI 0.30 to 0.82). A secondary analysis involving only men who underwent the allocated intervention (per protocol) showed a hazard ratio for time to reintervention of 0.28 (95% CI 0.15 to 0.55; $p < 0.001$) (see Figure 9). Subgroup analyses showed no evidence of heterogeneity around the ITT treatment effect (Figure 10). For men undergoing urethrotomy, commencement of intermittent self-dilatation did not lengthen the time to recurrence. Median time until first reintervention was 384 (IQR 214–555) days for 21 participants who did not commence dilatation and 308 (IQR 171–399) days for seven participants who did.

Improvement in maximum flow rate

A successful outcome in terms of Q_{\max} was defined as an increase of ≥ 10 ml/second from baseline at 3 months, and between 12 and 24 months. Data allowing calculation of this outcome were available from 64 men in the urethroplasty group and from 68 men in the urethrotomy group at 3 months. Participants in the urethroplasty group had twice the odds of experiencing an improvement ≥ 10 ml/second in their maximum flow rate at 3 months compared with participants in the urethrotomy arm. 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 ≥ 10 ml/second in their maximum flow rate (Table 16).

Recurrence

Stricture recurrence was observed in 19 (20%) participants in the urethroplasty group and 39 (38%) participants in the urethrotomy group. The difference was significant in favour of urethroplasty, with a mean odds ratio of 0.43 (95% CI 0.24 to 0.76) (Table 17).

Urinary stream picture score

Median stream score was lower at 24 months post randomisation than at baseline in both randomised groups. A total of 24 out of 59 (41%) participants reported an improvement of at least two grades in their urinary stream score in the urethroplasty group compared with 18 out of 59 (31%) participants in the urethrotomy group. There was a significant association between self-reported urinary stream improvement at 24 months and improved Q_{\max} at 24 months ($n = 66$; $p = 0.02$).

TABLE 15 Number of reinterventions according to randomised group

	Intervention, n (%)	
	Urethroplasty	Urethrotomy
Total participants randomised	108	112
Participants with data available	93	104
Number of reinterventions received		
0	78 (83.9)	75 (72.1)
1	13 (14.0)	26 (25.0)
2	1 (1.1)	2 (1.9)
3	1 (1.1)	0 (0)
4	0 (0)	1 (1.0)

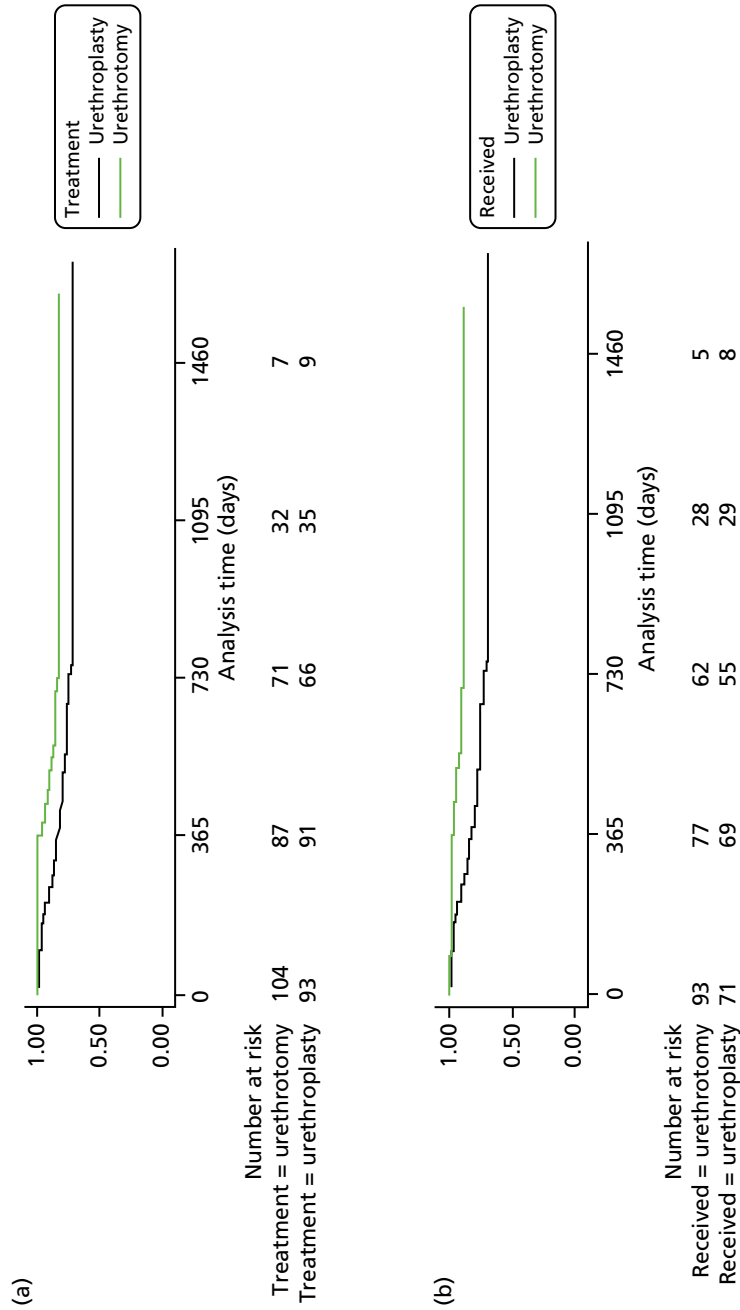


FIGURE 9 Hazard curves for reintervention by randomised or treatment received group up to 4 years after initial intervention. (a) Analysis of participants who had surgery according to their randomised allocation (modified ITT); and (b) restricted to men who underwent procedure allocated at randomisation (per protocol). Reprinted from *European Urology*, vol. 78, Goulao B, Carnell S, Shen S, MacLennan G, Norrie J, Cook J, et al., Surgical treatment for recurrent bulbar urethral stricture: a randomised open-label superiority trial of open urethroplasty versus endoscopic urethrotomy (the OPEN trial), pp. 572–80, 45 Copyright 2020, with permission from Elsevier.

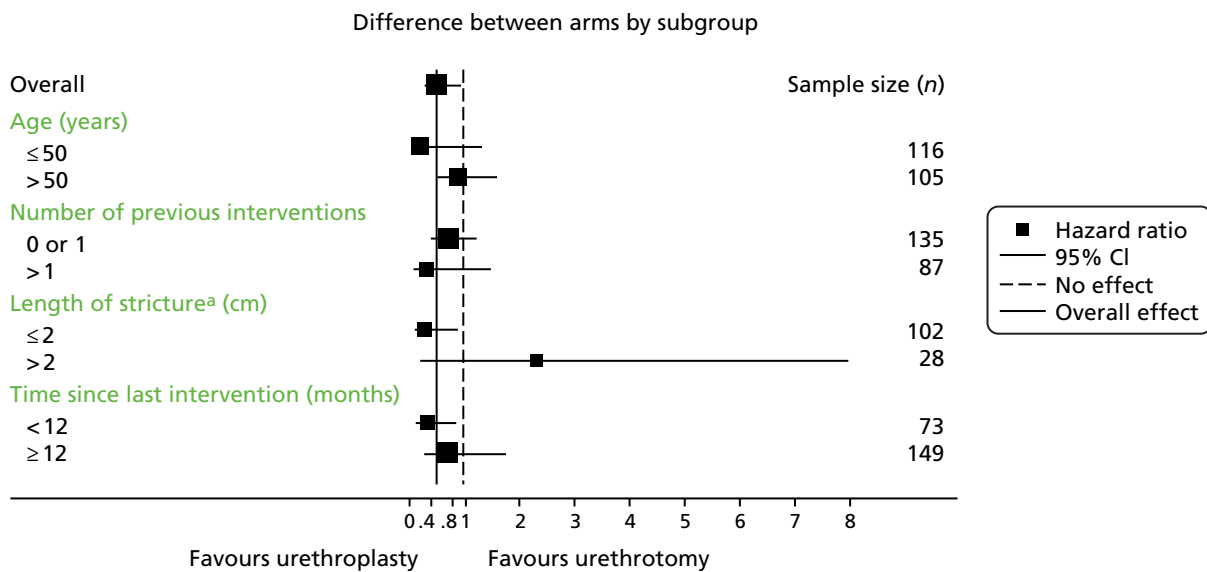


FIGURE 10 Subgroup analyses for time to reintervention. a, Upper limit of the CI truncated to fit the graph (95% CI 0.19 to 28.4).

TABLE 16 Maximum flow rate (≥ 10 ml/second) increase from baseline

Maximum flow rate	Urethroplasty (N = 93)	Number of participants providing data	Urethrotomy (N = 104)	Number of participants providing data	Odds ratio (95% CI); p-value ^a (urethroplasty vs. urethrotomy)
Flow rate baseline, mean (SD)	13.2 (15.5)	75	10.5 (6.7)	89	
Flow rate at 3 months, mean (SD)	22.3 (11.4)	64	17.6 (11.1)	68	
Flow rate at 12 months, mean (SD)	22.3 (12.2)	41	16.8 (11.5)	55	
Flow rate at 24 months, mean (SD)	21.7 (13.7)	29	19.1 (11.8)	49	
Improved at 3 months from baseline, ^b n (%)					2.08 (1.05 to 4.12); 0.035
Not improved	28 (30.1)		42 (40.4)		
Improved	29 (31.2)		21 (20.2)		
Missing	36 (38.7)		41 (39.4)		
Improved at 12 or 24 months from baseline, ^b n (%)					2.64 (1.14 to 6.15); 0.024
Not improved	26 (28.0)		50 (48.1)		
Improved	18 (19.4)		13 (12.5)		
Missing	49 (52.7)		41 (39.4)		

a Odds ratio adjusted for minimisation variables.

b Improvement defined as an increase in the flow rate of ≥ 10 ml/second.

Health status: EuroQol-5 Dimensions

Participants' rating of their state of health at 24 months on the EuroQol-5 Dimensions (EQ-5D) VAS from 0 (worst health imaginable) to 100 (best health imaginable) was a mean of 81.9 (SD 19.5) in the urethroplasty group and a mean of 79.4 (SD 17.5) in the urethrotomy group.

TABLE 17 Recurrence (for those participants who had surgery)

	Intervention, <i>n</i> (%)		Odds ratio (95% CI); <i>p</i> -value (urethroplasty vs. urethrotomy)
	Urethroplasty (<i>N</i> = 93)	Urethrotomy (<i>N</i> = 104)	
Any recurrence	19 (20.4)	39 (37.5)	0.43 (0.24 to 0.76); < 0.001
Reintervention	15 (16.1)	29 (27.9)	
Stricture recurrence at 12 months	4 (4.3)	14 (13.5)	
Stricture recurrence at 24 months	6 (6.5)	8 (7.7)	
Deterioration in flow rate	5 (5.4)	7 (6.7)	
Deterioration in voiding score	1 (1.1)	1 (1.0)	

Absolute changes in outcomes between baseline and 24 months

Changes in the absolute values of participant-reported outcomes between baseline and 24 months were similar between the urethroplasty and urethrotomy groups (Table 18).

TABLE 18 Changes in participant-reported outcomes measured on the trial questionnaire at baseline and 24 months

USS-PROM domain	Intervention							
	Urethroplasty (<i>N</i> = 108)				Urethrotomy (<i>N</i> = 112)			
	Baseline (USS-PROM score)	<i>n</i>	24 months (USS-PROM score)	<i>n</i>	Baseline (USS-PROM score)	<i>n</i>	24 months (USS-PROM score)	<i>n</i>
Total voiding score (0 = no symptoms to 24 = symptoms all the time), mean (SD)	13.4 (4.5)	104	6.0 (5.5)	58	13.2 (4.7)	109	6.4 (5.3)	59
Delay before starting to urinate (0–4), median (P25–P75)	2.0 (1.0–3.0)	105	0.0 (0.0–1.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–2.0)	59
Poor strength of urinary stream (0–4), median (P25–P75)	3.0 (3.0–4.0)	105	1.0 (0.0–2.0)	58	3.0 (3.0–4.0)	109	1.0 (0.0–2.0)	59
Having to strain before urinating (0–4), median (P25–P75)	2.0 (1.0–3.0)	105	0.0 (0.0–1.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–1.0)	59
Intermittent urinary stream (0–4), median (P25–P75)	2.0 (1.0–3.0)	104	1.0 (0.0–1.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–1.0)	59
Feeling of incomplete bladder emptying (0–4), median (P25–P75)	2.0 (1.0–3.0)	105	1.0 (0.0–2.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–2.0)	59
Post-micturition dribbling (0–4), median (P25–P75)	2.0 (1.0–3.0)	105	1.0 (0.0–2.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–2.0)	59
Impact of urinary symptoms (0 = no impact to 3 = a lot of impact), median (P25–P75)	2.0 (1.0–3.0)	107	0.0 (0.0–1.0)	58	2.0 (1.0–3.0)	110	1.0 (0.0–1.0)	59
Satisfaction with sexual function (0 = very satisfied to 4 = very dissatisfied), median (P25–P75)	3.0 (2.0–4.0)	97	1.0 (0.0–3.0)	53	3.0 (2.0–4.0)	100	1.0 (0.0–2.0)	56
Urine stream strength picture (1 = weak to 5 = strong), median (P25–P75)	3.0 (3.0–4.0)	103	2.0 (1.0–3.0)	58	3.0 (3.0–4.0)	108	2.0 (2.0–3.0)	58
Overall health state (0 = worst health imaginable to 100 = best health imaginable), mean (SD)	72 (20)	104	81.9 (19.5)	58	77 (17)	105	79.4 (17.5)	59

P25, 25th percentile; P75, 75th percentile.

Adverse events

At least one AE was reported for 89 of the trial participants (81 participants had one AE, seven participants had two AEs and one participant had three AEs). The reported AEs and SAEs are tabulated according to allocated group and treatment received (Tables 19–22). Postoperative complications categorised by the Clavien–Dindo grade are also tabulated by allocated group and intervention received (see Table 21).

TABLE 19 Adverse events by event and randomised allocation and intervention received

AE	Intervention, n (%)	
	Urethroplasty	Urethrotomy
Participants undergoing an intervention (allocated group)	(N = 101)	(N = 104)
AEs during the perioperative period		
Mouth pain	12 (11.9)	4 (3.8)
Wound infection	4 (4.0)	0 (0)
Bladder 'spasm' requiring treatment	2 (2.0)	1 (1.0)
Urinary tract infection	3 (3.0)	0 (0)
Initial failed trial without catheter	0 (0)	1 (1.0)
AEs during follow-up		
Erectile dysfunction	5 (5.0)	2 (1.9)
Mouth pain	2 (2.0)	2 (1.9)
Urinary tract infection	5 (5.0)	6 (5.8)
New urinary symptom	9 (8.9)	5 (4.8)
Wound infection	0 (0)	2 (1.9)
Wound pain	5 (5.0)	1 (1.0)
Numb testicles	2 (2.0)	0 (0)
Issues related to sexual climax	2 (2.0)	0 (0)
Other ^a	1 (1.0)	3 (2.9)
Erectile dysfunction and wound infection	1 (1.0)	0 (0)
Erectile dysfunction and wound pain	1 (1.0)	0 (0)
Wound infection, urinary tract infection and fistula	1 (1.0)	0 (0)
Participants undergoing an intervention (treatment received)	(N = 90)	(N = 115)
AEs during the perioperative period		
Mouth pain	14 (15.6)	2 (1.7)
Wound infection	4 (4.4)	0 (0)
Bladder 'spasm' requiring treatment	2 (2.2)	1 (0.9)
Urinary tract infection	3 (3.3)	0 (0)
Initial failed trial without catheter	0 (0)	1 (0.9)
AEs during follow-up		
Erectile dysfunction	4 (4.4)	3 (2.6)
Mouth pain	4 (4.4)	0 (0)
Urinary tract infection	5 (5.6)	6 (5.2)
New urinary symptom	8 (8.9)	6 (5.2)
Wound infection	1 (1.1)	1 (0.9)
Wound pain	5 (5.6)	1 (0.9)
Numb testicles	2 (2.2)	0 (0)

continued

TABLE 19 Adverse events by event and randomised allocation and intervention received (*continued*)

AE	Intervention, <i>n</i> (%)	
	Urethroplasty	Urethrotomy
Issues related to sexual climax	2 (2.2)	0 (0)
Other	1 (1.1)	3 (2.6)
Erectile dysfunction and wound infection	1 (1.1)	0 (0)
Erectile dysfunction and wound pain	1 (1.1)	0 (0)
Wound infection, urinary tract infection and fistula	1 (1.1)	0 (0)
Total	58	25

a Upper respiratory tract infection, swollen ankles, haematuria and dysuria, falls.

TABLE 20 Clavien–Dindo classification of postoperative SAEs by event and randomised allocation and intervention received

SAE	Intervention, <i>n</i> (%)	
	Urethroplasty	Urethrotomy
Participants undergoing an intervention (allocated group)	(N = 98)	(N = 104)
Related	0 (0)	2 (1.9)
Expected	3 (3.1)	2 (1.9)
SAEs		
Urinary tract infection	3 (3.1)	1 (1.0)
New urinary symptom	1 (1.0)	0 (0)
Wound infection	1 (1.0)	1 (1.0)
Wound pain	1 (1.0)	0 (0)
Haematuria	2 (2.0)	0 (0)
Readmission to hospital	3 (3.1)	1 (1.0)
Diverticular perforation	0 (0)	1 (1.0)
Death	0 (0)	1 (1.0)
Other ^a	2 (2.0)	2 (1.9)
Wound infection and fistula	1 (1.0)	0 (0)
Participants undergoing an intervention (treatment received)	(N = 84)	(N = 118)
Related	0 (0)	2 (1.7)
Expected	3 (3.6)	2 (1.7)
SAEs		
Urinary tract infection	3 (3.6)	1 (0.8)
New urinary symptom	1 (1.2)	1 (0.8)
Wound infection	1 (1.2)	1 (0.8)
Wound pain	1 (1.2)	0 (0)
Haematuria	1 (1.2)	1 (0.8)
Readmission to hospital	0 (0)	4 (3.4)
Diverticular perforation	0 (0)	1 (0.8)
Death ^b	0 (0)	1 (0.8)
Other	1 (1.2)	3 (2.5)
Wound infection and fistula	1 (1.2)	0 (0)

a Urethral bleeding following a urethrogram, posterior circulation cerebral infarct, left hemianopia, chest pain, cholecystitis.
b Deep-vein thrombosis and pulmonary embolism.

TABLE 21 Clavien–Dindo classification of postoperative AEs in participants undergoing an intervention

Clavien–Dindo classification	Intervention, <i>n</i> (%)	
	Urethroplasty	Urethrotomy
Allocated group undergoing either intervention^a	(N = 98)	(N = 104)
Clavien classification		
Grade I	6 (6.1)	4 (3.8)
Grade II	3 (3.1)	2 (1.9)
Grade III-a	4 (4.1)	0 (0)
Grade III-b	1 (1.0)	0 (0)
Grade IV	0 (0)	1 (1.0)
Grade V	0 (0)	1 (1.0)
Participants undergoing an intervention (treatment received)^b	(N = 84)	(N = 118)
Clavien classification		
Grade I	4 (4.8)	6 (5.1)
Grade II	3 (3.6)	2 (1.7)
Grade III-a	1 (1.2)	3 (2.5)
Grade III-b	1 (1.2)	0 (0)
Grade IV	0 (0)	1 (0.8)
Grade V	0 (0)	1 (0.8)

a According to allocation (for definition, see the BAUS website⁴⁶).
b Received intervention (for definition, see the BAUS website⁴⁶).

TABLE 22 Details of men eligible for inclusion in the trial who participated in interviews

Pseudonym	Age (years)	Site	Agreed to randomisation
Archie	34	Greentown	Agreed
Alexander	39	Greentown	Agreed
Raymon	36	Greentown	Agreed
Aydan	47	Greentown	Agreed
Darren	39	Blacktown	Agreed
Jake	31	Blacktown	Agreed
James	44	Blacktown	Agreed
Terry	48	Goldtown	Agreed
Elliot	62	Silvertown	Agreed
Carl	25	Bronzestown	Declined
Miles	70	Blacktown	Declined
Asif	26	Blacktown	Declined
Richard	45	Blacktown	Declined
Taylor	34	Blacktown	Declined
Stuart	44	Bluetown	Declined
Lucas	27	Goldtown	Declined
Jeremy	27	Goldtown	Declined
Ben	25	Silvertown	Declined
Michael	35	Silvertown	Declined

Mouth pain was the most common perioperative AE and was more frequent in the urethroplasty group, according to both randomised allocation and treatment received.

Serious adverse events

During the trial 22 participants were reported to have experienced at least one SAE (17 participants suffered one SAE, three participants suffered two SAEs and two participants suffered three SAEs).

Chapter 4 Qualitative substudy

Introduction

About half of all RCTs face difficulties in achieving target recruitment.⁴⁷ Surgical RCTs can be particularly challenging, as they involve clinical uncertainty about the relative impact of procedurally different options. In addition, clinicians and patients may have preferences for one type of surgery, informed by past experience and expectations, among other factors. Owing to the complex target population, necessity for multiple sites and relatively different treatment arms, it was anticipated that the OPEN trial would face recruitment challenges. A recent review of qualitative research within and alongside trials shows the range of issues that qualitative work can elucidate, including issues around trial design, conduct and processes.⁴⁸ Embedded qualitative work has been shown to have great potential in helping to improve recruitment and trial design.^{49–51} Qualitative research can be used to highlight organisational barriers, reveal recruiters' discomforts, improve information provision^{52,53} and to understand patients' perspectives and decision-making.^{54–57} Patient and clinician interviews have been used to evaluate trial acceptability as well as inform outcome measures.^{58,59}

This chapter reports on the qualitative process evaluation that was conducted as part of the OPEN trial feasibility phase. This research was conducted during the first 10 months of OPEN trial recruitment (February–December 2013). It had three objectives, to:

1. explore the factors most important to men with bulbar urethral stricture in differentiating between treatments and agreeing to trial participation
2. explore the factors most important to clinicians in recommending treatments and approaching men eligible for the trial about participation
3. contribute to the feasibility assessment by identifying potential barriers to participation and thereby informing recruitment strategy and design.

Methods

Following ethics approval (reference 12/NE/0343), the qualitative team conducted interviews with two groups of participants: (1) men eligible to participate (declined or accepted randomisation) and (2) urological practitioners (general or specialists, active recruiters or non-recruiters).

Interviews with men eligible for participation

Interviews with trial-eligible men were designed to explore their priorities in seeking surgical intervention and deciding whether or not to participate in the OPEN trial (interview schedules can be found in *Appendices 2* and *3*). To be eligible for the OPEN trial, and therefore for the qualitative study, men had to have a diagnosed urethral stricture and be able to undergo both endoscopic management by urethrotomy and reconstructive surgery by urethroplasty. Participating sites were encouraged to ask men if they would be willing to participate in an interview, regardless of their decision to participate in the trial. Men were asked to sign a consent form, separate from trial participation, and the site research nurse then passed the men's contact details onto the qualitative team. All men who were willing to be interviewed were then contacted by the researcher (PW) and offered an interview either face to face or by telephone. For face-to-face interviews the researcher either travelled to the participant's home or preferred location or offered them travel expenses to come to where the qualitative team was based. It was anticipated that interviews with men with bulbar urethral stricture may raise potentially sensitive issues, such as erectile function and urination problems. The researcher (who was male) was provided with guidance and support in how to prepare for, and manage, potentially sensitive topic areas.

Interviews with clinicians

Interviews with urologists were designed to explore clinicians' opinions regarding the management of urethral stricture, their sense of equipoise between the trial groups and the acceptability of approaching men about being randomised (interview schedule can be found in *Appendix 4*). In discussion with the chief investigator and trial team, it was decided that qualitative interviews would be conducted with a broad range of urological practitioners. Criterion sampling was used to include both specialist and general urologists, including those urologists who were not recruiting to the OPEN trial. General urologists are those who perform urethrotomy but would have to refer men elsewhere to receive an urethroplasty procedure. Specialist urologists are those who can perform both procedures. To be eligible for an interview, urologists needed to be currently practising and routinely treating men with urethral stricture, but were not necessarily contributing to the OPEN trial recruitment. The sampling and recruitment of clinicians for interviewing involved a mixture of snowballing and contacting practitioners from a BAUS database. Surgeons were contacted by the researcher either by telephone or by e-mail. Potential interviewees were sent a consent form and information about qualitative substudy. All those clinicians approached were reassured of their anonymity and that their interview data would be managed independently of the OPEN trial team. When a clinician was willing to be interviewed, the researcher arranged for the consent form to be signed and the interview to be conducted either face to face or by telephone. All interviews were audio-recorded, except for one that the clinician requested not be. In this case, a full description of the interview was written by the researcher and discussed with the qualitative research team before informing the analysis.

Data management and analysis

Qualitative analysis is an interpretive process that benefits from interdisciplinary working. Throughout the qualitative substudy, results and findings were discussed with the CI and presented to PIs at the OPEN trial investigators meeting in Newcastle upon Tyne (August 2013). All interviews were audio-recorded, transcribed verbatim, checked and edited to ensure respondents' anonymity. Analysis was conducted in accordance with the standard procedures of rigorous qualitative analysis (Rapley⁶⁰) and aimed to identify, explore and refine emergent patterns. Procedures from first-generation grounded theory – coding, constant comparison, memoing⁶¹ – were used, alongside tables,⁶² diagrams and mapping.⁶³ Proprietary software (NVivo version 10; QSR International, Warrington, UK) was used to support the management and retrieval of data.⁶⁴ Data collection and analysis occurred concurrently, so that issues raised in earlier phases of fieldwork were explored in subsequent ones. Data collection and analysis were also supported by discussion in trial meetings and regular qualitative data clinic sessions, which included health professionals and social scientists from different clinical and academic backgrounds.

Results

The qualitative substudy was conducted in the first 10 months of recruitment (between February and December 2013). During this period, 38 men had agreed to randomisation at 10 different sites. The lead site had recruited 10 of the men (26% of eligible men approached at this site). The qualitative substudy conducted a total of 34 interviews during this time, 19 with men eligible for participation in the trial and 15 with clinicians.

By the end of the qualitative substudy, 25% (40/159) of the men screened for the OPEN trial had said they would be willing to be interviewed. Of these, 19 men were eligible for participation in the OPEN trial and were available for an interview. These participants had been recruited from five sites across the UK. The age of participants ranged from 25 to 70 years (median age 36 years). *Table 22* shows the details of the men who were interviewed. All respondents had a diagnosed bulbar urethral stricture and had received at least one previous urethrotomy. The interviews took place between February and November 2013. Most men opted to be interviewed by telephone, which was found to be beneficial as some respondents said they were more comfortable discussing embarrassing issues by telephone.

To recruit clinicians to the substudy the researchers used (with permission) records from the BAUS database to contact 47 practising urological surgeons. Twenty clinicians responded and 15 agreed to an interview, all based at different UK hospitals. The 15 clinicians interviewed included those clinicians who were actively recruiting to the OPEN trial ($n = 9$), those considering involvement ($n = 4$) and those clinicians who were not involved ($n = 2$). The number of years of urological experience varied from 4 to 30. At the point of being interviewed, some clinicians were approaching men about the OPEN trial and could reflect on their experience of recruitment and how the trial was integrated with their standard treatment practices.

The qualitative findings are divided into five sections. The first focuses on the context of men's experiences of urethral stricture and how this shaped their decision-making in regards to surgery. The second section looks at men's accounts of either declining study participation owing to a preference for one of the procedures or accepting randomisation. The third section focuses on general urologists' views of the OPEN trial and their expectations about recruitment practices. The fourth section deals with specialist urologists' expectations. The final section discusses findings relevant to the organisation of standard care pathway and its alignment with trial recruitment.

Interviews with men

The interviews with men revealed a number of common themes in the experience of living with symptoms of a stricture and seeking medical treatment. The men's accounts revealed some of the practical issues that they faced on a daily basis. Understanding their experiences provides an insight into their help-seeking and priorities in treatment decision-making.

Symptoms

Men repeatedly described their frustration at having a recurrent sense of urgency while not being able to empty their bladder. They struggled to describe the physical sensation giving rise to notions of there being a 'blockage' and of something 'being wrong'. Some of the men described the sensation as 'burning', although for most this was 'uncomfortable' or a 'dull ache', rather than painful. Nonetheless, the sensation of a full bladder was upsetting and frustrating, causing significant distress. One described it as 'horrible . . . it's like a torture' (Terry) and another noted:

Imagine like all the time needing to go to the toilet and eh, not being able to basically, that's what it was and that was horrific.

Ben

Periods of retention were sporadic and could last for hours. Sitting in a hot bath, urethral massage or trying to relax were tactics these men tried to help themselves void. Several participants described trying to structure their work and life so they could carry out symptom management without others knowing. When symptoms occurred, it was typical to stop activities and head home. Such interruption of daily life was described as causing the most distress. Nocturia (waking up in order to pass urine) was common and caused distress because of the interruption to sleep. One participant described having not slept properly in years:

Before the operation I could be waking up anything to six or seven times in 4 hours to go to the toilet. Being constantly tired, it's horrible, it's so draining.

Carl

Nocturia and frequency could be managed privately at home, but during the day many of the men found that symptoms interrupted their work. Several of the men described disruption to their work or not being able to concentrate:

I am doing [. . .] a lot of technical work and things like, you know, I keep on going to the toilet it's really a pain. It just, yeah, especially when I am doing very intricate things in the workplace I get a bit nervous and I get urgency to go to the toilet like it's really [sighs and stops].

Ben

The fact that sensations of urgency could arise unexpectedly meant that men often felt anxious and uneasy. Men were particularly concerned about social embarrassment and reported a fear of being 'caught out'. The fact that this was 'always in the back of your mind' illustrates the wider pervasiveness of symptoms beyond their actual occurrence.

Concealment and routines of self-management

Underpinning the general discomfort described above was the desire to conceal symptoms from others. Most of the men felt that urethral stricture was a condition that could not be shared publicly. Several men described avoiding telling even their closest family about their condition:

No, no I didn't tell anybody. No, nobody could have noticed it not unless I let somebody know. It's not something you want to shout about!

Miles

Taylor described how only his wife knew and that he had pretended to his children that his regular hospital visits were for knee treatments:

It's funny you've got a little secret that you can't tell anybody. Because I can sit there and talk to [. . .] people about a lot of health-related issues, but this is the one thing that I won't let anybody know about and I wouldn't talk about.

Taylor

The desire for privacy is understandable but can mean missing the potential therapeutic benefit of talking to others about their illness. This is evident in how many of the men described concealing their illness and treatment from friends or family:

I think if I told my family, they'll just make a fuss out of things. No, I kept it quiet. [Pause] I didn't have any support from friends and family because I didn't inform anyone.

Alex

Management and concealment of symptoms was achieved through planning and routines. Men described maintaining the appearance of normality through planning daily activities around toilet access:

[I am] so self-conscious about it if it was the case of we're going out to go and do the food shop I would start getting ready half hour before obviously get your shoes on and do whatever you need to do but it was a case of like first thing go to the toilet then I'd go and do something and it would be go back to the toilet and go and do something else and then go back, I would go to the toilet about five times in half an hour and go out every half hour I would have to go to the toilet again.

Carl

A number of tactics were described as being part of a routine to help voiding before going out or meeting others, such as taking a hot shower or using a catheter tube for self-dilatation. Some men also said they used tissue or cloth in the underwear to disguise urine leakage (post-micturition dribble).

Another aspect of planning and routine employed to manage symptoms was restricting fluid intake. Some men said that they preferred to feel thirsty rather than risk urgency. Ben had been living with the stricture for a relatively short amount of time and said that he was starting to avoid liquids in order to both sleep better and keep working:

I am supposed to be drinking a lot of water [according to my doctor] but recently I've been pretty bad but it's only because I am absolutely sick and tired of going to the toilet at night! If I have a lot of work to do I tend to drink less so I don't have to go, you know what I mean? Rather than take me

from my work. Probably it's not the best like in terms of, you know, my health 'cause my doctors tell me I have to drink loads of water but, you know, sometimes it's just not practical.

Ben

For those men who had lived with the condition for decades, tactics for managing their stricture had become second nature. Miles, who was 70 years of age, had experienced stricture symptoms most of his adult life and described developing tactics to avoid people's offers of alcoholic drinks and having become accustomed to not drinking alcohol.

Routines of self-management allow men with urethral stricture to continue their lives without friends or colleagues having to know about their urinary problems. Most of the men were worried that others would notice the time they spent in the toilet or at a urinal. Public toilets were a particular 'danger zone' where urinary problems might be exposed. Bars were discussed by several of the men as somewhere they might be 'caught out' because of the combination of drinking and socialising:

There's times when I've been out and I think 'shit I can't go to piss! I can't go to the toilet! I can't do this: I've got to go!' and everyone says 'what are you doing?' and I say 'oh, I'm just nipping off somewhere' and then just go home.

Terry

Most of the participants described avoiding or limiting social interactions in order to conceal their condition, reflecting how urinary symptoms can significantly impact upon a person's social life.

Help-seeking

Although the symptoms and concealment caused distress, most of the men said that they had delayed for some time before seeking help. Throughout the interviews it was common for the men to downplay the severity of their symptoms as 'not life-threatening' and say that they preferred not to 'make a fuss':

Obviously, it's affecting my life in a lot of ways at the moment . . . obviously my marriage, sexually, the inconvenience, pain, and everything else that I'm going through. So apart from that you know you've just got to get on with things I suppose. Well, I mean it is it's a lot but there's a lot of people worse off than I am that's the way I look at it.

Terry

The men interviewed said that they preferred to 'get on with it' and tolerate symptoms rather than seek curative treatment. This reluctance to present symptoms corresponds to previous research showing that men often delay in seeking medical treatment.⁶⁵ Other men described getting used to the symptoms and having a different sense of what was normal urination and toileting behaviour. This was often because of a gradual onset of symptoms and becoming accustomed to low flow rates:

The symptoms possibly started very more back but I never realised. 'Cos how would you realise? You know, for never been known what is a normal passing flow and what is not normal [. . .] being patient or being an ordinary person? You would never know that this [was] part of some sort of symptoms.

Asif

Previous research suggests that traditional notions of male identity, such as being tough, resilient and independent, can undermine men's health-seeking and acknowledgement of a problem.⁶⁵ In the case of urethral stricture, such delays are likely to be exacerbated by the concealment and self-management of symptoms.

Men's management of urethral stricture is inextricably related to the desire to conceal symptoms from others through routines of self-management. The tendency to hide urinary problems raises issues not just of unseen emotional burdens on these men, but also of significant delays in seeking medical help and

advice. Many of the men interviewed described seeking medical advice only once self-management and concealment were no longer tenable. As discussed in the following section, this has implications for men's decision-making and treatment preferences.

Preference for urethrotomy

Men were supportive of the OPEN trial and wanted to be able to contribute to research for the benefit of future patients. This type of altruism and wanting to 'give back' is common in patients' accounts of trial participation.⁵⁷ Despite wanting to help, 10 of the men we interviewed declined randomisation due to an over-riding preference for one of the procedures; all had prior experience of urethrotomy.

Those men who expressed a preference for urethrotomy said it was to avoid wearing a catheter, taking time off work or undergoing the 'serious' operation necessary for urethroplasty:

You're going to be in hospital for a couple of days you have the catheter in for over 10 days or what not. It's kind of, no it's freaked me out a little bit. I'm quite happy with urethrotomy.

Carl

The shorter recovery period and minimum disruption to work and social life were typical reasons given for opting to have a repeat urethrotomy. The desire to conceal their condition from others contributed to the preference for fast treatment with minimum recovery time.

Most men perceived a trade-off between repeated treatments (urethrotomy) and the possibility of a permanent solution (urethroplasty). Men who chose to have an urethrotomy sometimes included the possibility of further treatment within their decision-making. Although urethral stricture is a burden on these men's lives, it is relatively benign, meaning that men's decision-making can concern long-term management rather than seeking a curative solution. This means that these men could reasonably opt for the 'short-term solution' of urethrotomy and potentially delay curative treatments. As one man outlined, 'The operation I've already had, I'm quite happy with that until it's really necessary to move on'. Delaying what they saw as a more serious operation (urethroplasty) until 'moving on' is necessary or unavoidable was a common justification for having a preference for urethrotomy:

I don't think I could go through that operation unless anything drastic happened [yeah] where I really feel, you know, the pain was getting too much.

Richard

Men who declined trial participation and opted to have a repeat urethrotomy said they were willing to risk having only short-term relief from their stricture symptoms rather than commit to the time and recovery trajectory of the more complex urethroplasty. The fact that men would be able to have a urethroplasty at a later date was an important aspect of choosing to have a repeat urethrotomy:

Nobody really fancies surgery but [the clinician] says I should have [urethroplasty] done and I said 'well I will next time and I will make the time for it'. I'll have to because if you add up all the time I've had for [urethrotomy] that I've lost I could have been sorted by now.

Raymond

Preference for urethroplasty

Other interviewees declined randomisation because of an over-riding preference for urethroplasty. The common account of this decision was seeking a curative solution because the recurring symptoms, following a previous urethrotomy, were no longer tolerable. These men felt unwilling to accept the possibility of being randomised to a repeat urethrotomy. As one man explained, 'but it's like I've already had it [urethrotomy] done, you don't want to go through that again' (Jeremy). There was no threshold number of previous urethrotomies that shaped this decision. Some men were unwilling to have a second whereas others were willing to receive a third or fourth.

The need to travel and referral to specialist sites were key factors in a preference for urethroplasty. Some men described that they had already actively sought an alternative to urethrotomy at the point when they were approached about the OPEN trial. They felt that they had already made a practical commitment to reconstructive surgery by seeking referral to a specialist and, in some cases, already arranging for time off work for the recovery period. These men saw themselves as being at a point at which urethrotomy was not an acceptable treatment option and this could be understood as being past a point of equipoise:

I don't see the sense in sitting here in 6 months' time going in for regular dilation because, you know, there has to come an end to it somewhere. So that's the route I went down. And I said [to the consultant], 'look you know, I'm very happy to help in any way that I can [with the trial] but eh I'd rather go for the sort of bigger op on the basis that there's a good chance that will sort it out and make life more comfortable for a longer period of time'. And that's where I'm at.

Elliot

Men's accounts of treatment preferences often included aspects of temporality in their decision-making. This can also be seen in the interviews with men who agreed to be randomised.

Accepting randomisation

The nine men interviewed who had accepted randomisation described being at a point at which the differences in cost and benefits of each treatment were negligible. Three of the men expressed a weak preference but were still willing to 'help out'. The other six said that they were undecided as to which treatment would be best for them at that point in time. These men can be understood as being at a point of equipoise as they were fully informed and had balanced the comparative costs and benefits of the two alternative treatments. The following quote is an example of being equally poised in the desires for a shorter recovery time and the possibility of a curative solution:

[With urethroplasty] I'm not so worried about the catheter. I would take the time off and just sit that out [. . .] But it's, obviously, [worrying] that you will make a full recovery afterwards and you won't be having to look after your wounds forever, essentially. That's the worry on that. [Consultant] got a very good reputation for this sort of thing. So, it's not this actual procedure that bothers me, it's the recovery afterwards and affecting your ability in later life. [. . .] As for concerns about the urethrotomy, my main concern with that is that I don't want to keep having that every 2 years. It was a relatively painless operation. I was in and out during the same day. But I don't want to keep going back every 2 years or so to have that repeatedly done.

Archie

This man decided to have his treatment randomised and is a good example of a point of equipoise within the OPEN trial. Having had two previous urethrotomies, he was willing to have another but also ready to try the more invasive alternative. Archie describes being worried both about recovering from urethroplasty and needing repeat surgery following urethrotomy, which are the uncertainties underpinning the OPEN trial. This balance of factors illustrates the necessary uncertainty for accepting randomisation. It is also the uncertainty that clinicians needed to allow for in order to recruit to the OPEN trial.

The relevance of being at the right point in time could be seen in the accounts of men who accepted randomisation. For example, Jake went on to say that if there was to be a 'next time', he would no longer be indifferent:

Interviewer: *Would you feel disappointed at all if you were randomised to the urethrotomy?*

Jake: *I'm not disappointed at this stage, no. I think, obviously, the next time, I would probably be heavily in favour of the other.*

The recurrent theme of temporality for decision-making and preferences suggests that there is a particular window of opportunity in which men with recurrent bulbar urethral stricture are in equipoise and willing to accept randomisation.

Throughout men’s accounts there was a common theme of a perceived trade-off between potentially worsening symptoms and commitment to ‘serious surgery’. Men balanced the immediate inconvenience of a long recovery period with better chances of a curative solution. *Table 23* illustrates how treatment decisions were closely related to men’s perception of the severity and manageability of their symptoms. Those men with an over-riding preference understood their own urethral stricture symptoms to be at a particular point: either too slight to consider a serious operation or too severe not to.

The results highlight how the decision to accept or decline randomisation was made in the context of an overall trajectory of treatment and worsening symptoms. Generally, the longer a man has had urethral stricture, the more likely it is that his symptoms will return and the more willing he will be to commit the time necessary for the curative solution anticipated from urethroplasty. Men who felt that their symptoms were tolerable were less likely to commit to the recovery and more likely to opt for urethrotomy. There is a window within men’s treatment pathway in which they are willing to receive either treatment. Recruiters could allow for uncertainty by answering concerns about the acceptability of symptom recurrence and the commitment needed for reconstructive surgery.

Clinician interviews

To place these interviews in context, it is important to note that there are two types of clinicians participating in the trial: specialist urologists and general urologists. Specialist urological surgeons are able to offer both of the OPEN trial treatment options as they are trained to carry out urethroplasty, whereas general urologists are able to deliver only urethrotomy and have to refer patients to a specialist if they feel urethroplasty is required. Regardless of their participation in the trial, the clinicians who were interviewed were generally supportive of OPEN trial, with one exception. The exception, a general urologist who asked not to be audio-recorded, said that they felt that the OPEN trial was a promotion of urethroplasty and therefore not to the benefit of general urologists. All other clinicians supported the OPEN trial and felt that there existed a genuine uncertainty in the management of urethral stricture patients:

We know that urethroplasty lasts for quite a while but we don’t know really how they compare in the same patients or group, because classically they’ve been different lots of patients.

Specialist urologist 3

TABLE 23 Summary of men’s accounts of their treatment preferences

Decision	Preference	Symptoms	Operation
Declined randomisation	Preference for urethrotomy	Symptom recurrence and severity is tolerable	Symptom recurrence sufficiently tolerable to not want to endure serious operation and recovery time
	Preference for urethroplasty	Symptom recurrence and severity no longer tolerable. Patient desires a permanent solution	Desire for long-term solution over-rides immediate symptom relief. Unwilling to risk further recurrence
Accepted randomisation	No preference	Symptoms tolerable but considering serious operation	Willing to commit to recovery time. An additional repeated urethrotomy is also acceptable

A less experienced specialist had decided not to participate in the OPEN trial because it would mean reducing the opportunity to practise urethroplasty and potentially having their 'learning curve' contained within the study results:

The last thing I want, from a personal perspective, is to see a great little stricture and think 'perfect, that will do nicely' only to have him randomised to a [urethrotomy] – do you see what I mean? . . . Obviously we all support research but I don't think [we are a] busy centre and do I want my result – my learning curve results in a trial?

Specialist urologist 3

Despite general support for the study, when asked about their expectations or experience of recruiting to the OPEN trial, most clinicians felt that it already was, or would be, difficult. Some of the general urologists felt concerned that they would see only a small number of eligible patients at their clinic. However, the most prominent concern about recruitment was dealing with men's preferences.

General urologists

Most general urologists anticipated that eligible patients would prefer urethrotomy and that this preference would be a barrier to recruitment. Their account focused on the 'easy' option that patients would 'obviously' prefer:

Most patients are going to opt for a urethrotomy and not a urethroplasty but you can either have daycase operation and go home with a catheter for a day or two or you can have a major procedure and be in hospital for a few days and I think it's just going to be hard, why would I want to be randomised? I'd rather just have the easy one.

General urologist 1

These expectations were related to ideas about the average types of eligible patient. General urologists described men with recurrent stricture as being older or with relatively minor symptoms. These men were typically treated by repeated urethrotomies and self-management using the adjunctive technique of intermittent self-dilatation. They felt that putting these patients forward for randomisation would be challenging:

I think the work [of the OPEN trial] needs doing, it's a good study to do. I think we will have a few issues with people opting to have an operation that we may not have recommended in the normal situation.

General urologist 3

Although eligible, general urologists felt that randomising these patients proved, or would prove, difficult when at odds with their routine clinical practice. This difficulty can be tied to the clinician's feeling around the severity of the problem:

If somebody has a very simple urethral stricture and then you will think oh why should I subject this person to an open procedure rather than just an optical urethrotomy.

General urologist 4

The following quote also suggests a blurred line between what the 'old guys' want and what the general urologist is comfortable offering:

There are few guys, old guys, who really don't want to have an urethroplasty that keep getting urethrotomy. You know most of them, after I have seen them, will go with the urethrotomy and then send him home generally.

General urologist 5

The perceived expectations of the ‘older patients’ or those with ‘relatively minor symptoms’ underlie the clinician’s temptation to be selective in identifying potential participants:

I think we do treat the different age groups slightly differently so the young guys are more likely to go for a urethroplasty [. . .] whereas your elderly guy, you’re trying to avoid operations, [. . .] I think there is a lot of individual basis that we are going to make these decisions on.

General urologist 3

Uneven representation of the treatment arms can be seen to be an extension of what the clinicians felt their patients wanted or needed. The perceived expectation of the ‘typical’ patient with recurrent stricture led to a tendency to recommend urethrotomy:

Patients who would like to take the chance [with urethroplasty] if you tell them that with the urethrotomy there is a certain chance that you’ll be fine you won’t need the reconstruction so they might go for that.

General urologist 1

The findings therefore highlight a preference, a potential source of selection bias among general urologists (Table 24). However, it is important to note how this preference is underpinned by consideration of patients who tend to be older or with relatively minor symptoms.

Specialist urological surgeons

Specialist urologists anticipated the opposite: that few patients would be willing to consider another urethrotomy and that over-riding preference for urethroplasty would be a barrier to recruitment (see Table 24):

I would imagine for somebody who’s had two urethrotomies, of average – of typical age, probably 75% of them definitely are happy to proceed to the urethroplasty.

Specialist urologist 5

Specialists see a large proportion of referrals with either severe or complicated strictures referred specifically with the intention of discussing urethroplasty as a treatment option:

One of [my] concerns with the OPEN trial is that the guys I’m seeing are generally those who have been referred to me with a view to doing an urethroplasty.

Specialist urologist 1

Those men who had received such referrals found it hard ‘selling’ the trial to patients and felt compelled to guide them towards urethroplasty, especially patients with severe or complex strictures. Here a specialist describes an encounter with a man who has been tolerating severe symptoms:

He said ‘oh that’s about normal!’ I said, ‘Well if I told you that was less than 10% of the flow of a normal person and that you’re leaving behind more than half a bladder full of urine, how would you react to that?’ And he said, ‘oh that’s terrible!’ I said ‘Yes, well you really should have an [urethroplasty] operation!’

Specialist urologist 2

TABLE 24 Comparison of clinicians’ expectations and recruitment practices

Clinician	Patient population	Clinicians’ expectation	Recruitment practice
General urologist	Older, history of self-management	Men will opt for urethrotomy	Older patients excluded, reluctance to refer
Specialist urologist	Younger, complex referrals	Men will opt for urethroplasty	Reluctance to suggest repeat urethrotomy

In this case, despite the patient's eligibility and uncertainty, the surgeon could not remain neutral and felt compelled to recommend urethroplasty. Another specialist outlined how, with some men, he felt he could not offer the trial:

I think the hardest thing which I find is to er, try and explain, and get someone whose had say five urethrotomies, whose chances of a urethrotomy actually working is zero . . . and then trying to get him to consider having a urethrotomy done when it's not something that I would advise to a friend or a relative . . . I find it very difficult and in fact I don't really bother trying to get them into the OPEN trial.

Specialist urologist 3

Such accounts are evidence of a lack of clinical equipoise at the limits of the eligibility criteria.⁵³ Many specialists described difficulty in staying neutral. Even if they would not explicitly recommend urethroplasty, they reported producing language and terminology representing treatment arms unevenly:

If you say to them you can have a more complicated operation you've got a 95% chance of being cured versus we can keep doing this [urethrotomy] every couple of years and you'll end up urethral cripple, most of them will take the option [of urethroplasty].

Specialist urologist 6

The eligibility criteria for the OPEN trial had no upper age limit. Neither was the severity of the stricture symptoms a reason for exclusion. However, interviews revealed these factors as potential grounds for selectivity. Previous nested qualitative studies have highlighted clinician 'selection bias' as a distinct barrier to recruitment.⁵³ Similarly, we found that, despite supporting the trial, general and specialist urological surgeons found, or felt that they would find, discussing the trial with certain types of patient a struggle, or they struggled to represent the arms of the trial evenly. It is important to note that these differences in clinicians' expectations of men's preferences reflect their relative position within the overall organisation of care for urethral stricture.

The clinical organisation of referrals

Interview data from both clinicians and men were used to map the standard care pathways for bulbar stricture patients in the UK. *Figure 11* is a simplistic representation of a standard patient pathway to treatment and the two potential points of recruitment. Typically, a man will present his symptoms to a general practitioner (GP) before being referred to a local urology clinic. Most men will be initially treated at a general urology clinic and receive their first urethrotomy. If the man's stricture symptoms return, he tends to return to the same clinic, either directly or through his GP. At this point, the man is now eligible to receive either a repeat urethrotomy or a reconstructive urethroplasty, making him potentially eligible for inclusion in the OPEN trial. In standard practice, the urologist can either recommend another repeat urethrotomy or refer the man to a specialist to discuss reconstructive options. There is no precedent for how many repeated urethrotomies a man should have had prior to referral for urethroplasty; indeed, this is part of the uncertainty about how to manage the condition. If the man is interested in urethroplasty,

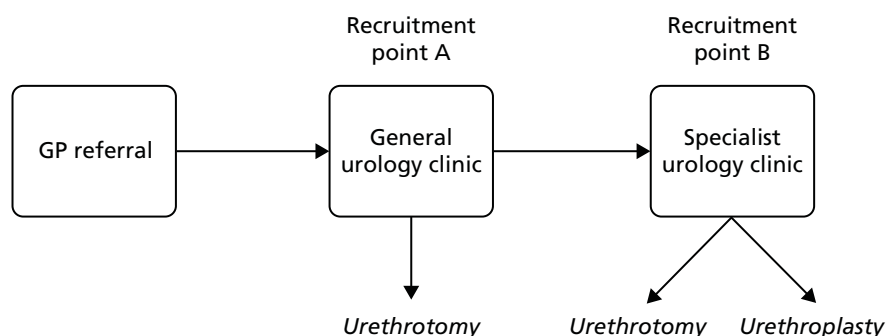


FIGURE 11 Different points of recruitment to the OPEN trial.

or the clinician feels that the patient's case is severe enough, the clinician may recommend referral to a specialist centre to discuss urethroplasty.

In practice, this means that younger patients and more complex cases tend to be referred to specialists more readily than older patients or those with relatively simple strictures:

You know the 18-, 20-, 30-year-olds, it just seems to me that consultants around the region acknowledge the fact that they're facing a lifetime of self-catheterisation and they tend to get referred younger, whereas the people in the seventies or what have you, may well get pushed towards intermittent self-dilatation and referred to me only when they've had complications.

Specialist urologist 5

As outlined above, specialist urologists felt reluctant to randomise patients whose symptoms were severe, whereas general urologists felt that it was difficult to refer patients whose symptoms were manageable with a repeat urethrotomy. These differing perspectives correspond with the types of stricture patient they typically treat. General urologists see patients with moderate symptoms, whereas specialists see more complex and severe cases. In this way, the difficulty recruiters have in achieving clinical equipoise is not adequately explained as individual bias, but is partly a result of the relative positions of general and specialist urologists in the organisation and division of urethral stricture care.

The differences in clinicians' expectations of patient preferences reflect their relative position within the overall organisation of care for urethral stricture. Intersite referrals were a key factor and underpinned the expectations of men's willingness to be randomised. In particular, there was concern that men who were approached post referral would be expecting to discuss urethroplasty and therefore less willing to be randomised. Echoing some of the interviews with men, a specialist urologist said that speaking to men about randomisation would be difficult where the man was already anticipating discussion of urethroplasty, as 'a lot of the men are already primed' (specialist urologist 3). Specialists were concerned that men who had already been told by the referring clinician that they would be having urethroplasty would make recruitment harder:

The referring urologist says, 'Oh, what you need is an urethroplasty, I'll send you to [consultant's name]'. And then I try and talk them back into randomisation! It'll be more difficult for us. If they come to me [without preconceptions] it'll be easier for me . . . what you need really [is] the guy who's not quite sure what to do.

Specialist urologist 3

A few of the specialists said that they had spoken to or were planning to speak with referring centres and to try and involve them in the recruitment process and in keeping patients open to both procedures. One of the clinicians outlined that this was more feasible when there was already a good network of communication between urological sites. Related to this, a few urologists expressed concern about having to refer patients to consultants whom they did not know personally. One remarked that, had trial recruitment involved referring a patient to a clinician they did not know, they would not have agreed to become a recruiting centre.

When asked in the interview about the referral process, many of the specialist urologists said that men were not referred frequently or early enough. Some complained that the men who were referred to them from general clinics were severe or complex cases and felt that the men may have benefited from an urethroplasty sooner. On the other hand, some general urologists reported that the patients often wanted to be treated simply and locally if possible:

You know you're talking about a 2.5-hour journey each way, you know. Plus, if it's a consultation and surgery, that's two stages. Some men will go for it and some won't.

General urologist 2

Other general urologists admitted that they may try and 'hold on to' a patient if they could reasonably be treated locally. They were concerned that early referral, and therefore trial participation, might not be in the interest of their patients who wanted local care. General urologists also felt that referrals could potentially undermine recruitment. This is because patients would have to agree to potentially travel between sites before they could agree to be randomised. This would be particularly burdensome for patients when the nearest specialist was some distance away:

You tell [men] that in this arm of the trial, I mean this part, will be done locally but if you, for the reconstruction you might have to go to another hospital, and then that might influence. They might say 'OK I don't want to take part in the trial because I'd rather stay local'.

General urologist 4

Relatedly, another issue raised by some was the need for men to take time off work and inform friends and family. As discussed earlier, many men with urethral stricture prefer to conceal and self-manage the condition. Several of the clinicians anticipated that it might not be easy for patients to agree to potentially take time off work and add to the recovery time, as this would usually require some personal preparation.

Discussion

There is a growing body of literature concerning the use of qualitative studies in order to inform RCT recruitment strategies. Although the majority of this literature focuses on the activities of recruiters and the need to improve information provision to patients, qualitative research can also provide valuable insights into the experiences and opinions of the eligible patients. Patient preferences are often the primary reason for declining trial participation,^{57,66–68} although they are not always well understood and do not always receive detailed attention. For the purposes of this study, patient preferences were conceived as being complex and trial specific.² Living with bulbar urethral stricture can be a distressing experience for men. The condition can interrupt daily life, leaving them feeling frustrated, anxious and uneasy. They can attempt, through generating plans and formulating routines, to conceal symptoms from others. Although the symptoms and the concealment can cause significant distress, most of the men had delayed seeking help. Many described seeking medical advice only once symptoms, attempts at self-management and concealment were no longer tenable. Importantly, any discussion about treatment options, including taking part in the OPEN trial, happens within this broader trajectory of living with stricture.

As with many trials, patients demonstrated conditional altruism,^{57,69} in that they were supportive of the idea of the OPEN trial. However, given the context of an evolving symptom experience that leads to a decision to seek help, and a prior experience of at least one urethrotomy, some men had developed clear preferences for a specific treatment, which meant that they felt they could not take part. Those men with a preference for urethrotomy felt that symptom recurrence was, at this point in time, sufficiently tolerable to not want to endure what they saw as a serious operation with longer recovery time. They were also aware that in the future, if or when necessary, they could always opt for urethroplasty. In contrast, those men with a preference for urethroplasty felt that symptom recurrence was no longer tolerable and they wanted a more permanent solution, so could not risk randomisation to repeat urethrotomy. Notably, they felt that they had already made a practical commitment to reconstructive surgery by being referred to a specialist. Finally, for those men who were willing to be randomised, the difference in cost and benefits of each treatment were relatively negligible at this point in time.

Patient interviews were particularly important in understanding men's subjective experiences and understanding of the care pathways and recruitment process. Previous research has highlighted the importance of understanding the patient pathways for recruitment^{50,70} and focused on understanding and improving the congruence of trial design and standard care pathways.⁵⁴ In the feasibility stage of a multicentre RCT trial, it is important to describe and evaluate the current care pathways, in order to inform

early design decisions and practical choices. There is clearly a specific point in the trajectory of the experience of symptom recurrence, severity and help-seeking when men are willing to consider randomisation. Going forward, the substudy highlighted that the OPEN trial needed to maximise recruitment discussions with men at this point in their trajectories. Those discussions can be initiated only through a clinician's willingness to approach eligible men about trial participation. The OPEN trial sought to work with clinicians to embed those recruitment discussions within specific points in the men's treatment pathways. The standard treatment pathway for the majority of men eligible for trial participation is referral for an initial visit to a general urology clinic. At the general urology clinic, they discuss the options of receiving a repeat urethrotomy or a reconstructive urethroplasty with a general urologist. If men opt for a reconstructive urethroplasty they will then be referred to a specialist urology clinic for discussion with a specialist urologist. At the time of conducting the qualitative substudy, February–December 2013, the majority of recruitment discussions were happening at specialist centres initiated by specialist clinicians.

Multicentred trials have often encountered difficulty in achieving consistent practice across all sites.⁷¹ Previous work has shown that qualitative research can be valuable for exploring the acceptability of a trial among clinicians.⁴⁹ Barriers need to be identified early, so they can be removed or bypassed. A number of studies have reported qualitative research embedded within RCTs as a recruitment intervention.^{53,72,73} Elliott *et al.*⁵⁰ have analysed recruiter and patient interactions in order to understand how trialists are presenting information to patients, including the description of the trial arms and the randomisation process.⁵⁰ They suggest that recruitment is a fragile process and that clinicians may feel uncomfortable approaching patients about trial participation and therefore require training.⁷²

General and specialist clinicians were supportive of the OPEN trial. They felt that there was genuine uncertainty about how to manage men with bulbar urethral stricture. However, they were concerned that recruitment could be difficult. Each group of clinicians outlined a specific set of expectations about how men would react to the recruitment discussion. General urologists felt that eligible men would be more likely to want to have a repeat urethrotomy, to be treated simply and locally. They reported that they themselves might be reluctant to recommend randomisation if the man had had only one previous operation, was old or would need to travel far for an urethroplasty. In contrast, specialist urologists felt that eligible men seeing them would be more likely to want to have a urethroplasty. They reported that they personally might be reluctant to recommend randomisation if the man had complex or severe strictures. They also noted, as did some of the men in their interviews, that a man's preference for urethroplasty is often already established prior to consulting a specialist. The men are primed before arrival: they know that they are being referred to the specialist centre specifically in order to further discuss one option, namely urethroplasty.

Shaping trial recruitment and design

While the qualitative substudy was being conducted during the first 10 months of recruitment, the OPEN trial was not recruiting to target. The findings of the qualitative work suggested specific barriers to recruitment. Clearly, some men have strong preferences, and when recruitment discussion took place with them they declined randomisation. However, some men who took part in recruitment discussions were at a specific point in the trajectory of their experience of symptom recurrence, severity and help-seeking, at which point they were willing to accept randomisation. Given the differing expectations and expressions of reluctance of approaching some men, which both general and specialist urologists raised, some men potentially eligible for the trial may not have had the opportunity to discuss potential trial participation at all.

Following the report of the substudy, the qualitative team collaborated with the chief investigator and Trial Management Group to develop implementation strategies to increase both the number and location of recruitment discussions. It was agreed that the findings would be used to develop an overall approach, as well as relevant tools to help with the initiation of new sites, the training of recruiters and the maintenance of good, consistent recruitment practices. We mapped the key problems we had identified against Powell *et al.*'s⁷⁴ compilation of strategies for implementing clinical innovations in health and mental health care (Table 25). This helped to inform the detail, direction and content of the strategies we suggested to shape the trial recruitment and design going forward. It was important that all discussions and support tools used

TABLE 25 Key problems mapped against Powell *et al.*'s⁴ compilation of implementation strategies

Key problem	Implementation strategies
Clinicians have potential to be selective about the men who they decide to approach	Education strategies: develop effective educational materials; distribute educational materials; conduct educational outreach visits
Men have potential to develop strong treatment preference through referral process to specialist centres	Plan strategies: build a coalition Restructure strategies: change service sites Education strategies: prepare patients/consumers to be active participants

with clinicians reflect the types of concerns that men were likely to have, as well as the discomfort experienced by specialists and general clinicians in approaching different types of men.

Enabling more recruitment discussions

Given that recruiting clinicians can be selective about the men to whom they introduce the trial, it was felt that new and existing recruiters should be provided with support that emphasises the need to offer trial participation to all potentially eligible men. We recommended that, within the OPEN trial, support should include examples of men with different treatment preferences. This should also be sensitive to the different perspectives and biases of specialist and general urologists. Thus, support for general urologists should emphasise how it can be appropriate to refer men to a specialist, even if they are older and their symptoms are relatively minor. Conversely, support for specialist urologists should emphasise how repeat urethrotomy can also be appropriate for younger men or those men with severe or frequently recurring urethral stricture.

In part, the focus needed to be on getting clinicians to explicitly reflect on, and so challenge, their expectations and feeling of discomfort about approaching some potentially eligible men. For example, to encourage recruiters to approach more potentially eligible men, the findings were used to create several illustrative vignettes of urethral stricture patients (see *Appendix 5*). These reflected the types of men who were seen, their concerns, previous treatment history and severity of symptoms. Early versions of the vignettes were designed to look like GP referral letters; however, feedback from clinicians suggested that these were too lengthy and not like typical referrals. Incorporating this feedback, these were revised to be short case studies with explanations of their learning outcome for recruiting clinicians. A video was also made to introduce and promote the OPEN trial. It outlined the trial and then depicted two clinical scenarios, which simulated recruitment discussions around the available treatment options and study participation. The video was publicly available and was designed to target new and potential recruiting clinicians, as well as to be a resource for men who had been informed about the study and were considering trial participation.

Enabling different recruitment discussions

Another focus was on expanding the points at which eligible men could be initially informed about and recruited to the OPEN trial. As noted above, at the time of conducting the qualitative substudy, the majority of recruitment discussion was happening at specialist centres and was undertaken by specialist clinicians. However, findings strongly suggested that recruitment discussions at specialist centres could be too late in the treatment pathway for some men, given that they could be entering those discussions already primed with an expectation that the focus of the consultation would be on one option, namely urethroplasty. However, recruitment discussions with men eligible to participate in the trial could potentially occur at two distinct points in the standard treatment pathway, at both general centres and specialist centres.

One strategy that was suggested was to focus on changing the emphasis of discussions that men have at general sites, prior to referral to specialist sites. When possible, specialist sites and the OPEN trial team could directly engage with their colleagues at general sites to reframe elements of the discussions general clinicians have with men prior to referral. Rather than suggest that the focus of the referral would be to only discuss and then receive urethroplasty, they could outline that both options would be considered. A related strategy was also suggested, to approach men earlier in the pathway by increasing the number of general urology centres participating in the OPEN trial. This could then improve access to eligible men who are yet to develop a strong preference for either procedure. However, a disadvantage of trying to approach men at general clinics is that they would see far fewer men potentially eligible for the OPEN trial than specialist sites. This meant that more general sites would be needed to recruit the same number of participants as specialist sites, albeit with the potential for a better conversion of eligible patients accepting randomisation.

Chapter 5 Health economic evaluation

Introduction

This chapter describes the economic evaluation undertaken as part of the OPEN trial, aiming to provide an analysis of relative cost-effectiveness of open urethroplasty (experimental) against endoscopic urethrotomy (control), for men with recurrent bulbar urethral stricture. It comprises a within-trial cost-effectiveness analysis and a 10-year Markov model. The within-trial analysis examined the relative efficiency of open urethroplasty compared with endoscopic urethrotomy over a 24-month period after randomisation. A sensitivity analysis to assess the robustness of the primary findings compares the interventions over a 24-month period after initial surgery. As open urethroplasty was a priori expected to be both more effective and more costly than endoscopic urethrotomy and its benefits may persist beyond 24 months, Markov modelling was conducted with a 10-year time horizon to compare the costs, QALYs gained and incremental cost per QALY of the interventions.

The study adopted the viewpoint of both the NHS and the patient and collected resource use data, which included the costs of treatments and the use of primary and secondary NHS services, as well as participants' out-of-pocket expenses relating to the condition and its management. All costs and QALYs were appropriately discounted using the recommended discount rate (3.5% per annum) at the time of the data collection.⁷⁵ A completed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist is reported in *Appendix 6*.

Within-trial analysis

Information on NHS resources used to deliver the interventions was collected on the initial intervention CRF. Effectiveness of the intervention was measured by participant completion of the EQ-5D-5L at a number of time points as part of the USS-PROM in the trial questionnaire. Participant' use of health services and out-of-pocket costs during the follow-up period were collected from a bespoke participant costs questionnaire (PCQ). Costs collected from different time points were all converted to the same price year (2017) using the Consumer Price Index.⁷⁶

Results

Analysis of resource use and cost

Cost of the intervention

Costs associated with each of the two trial interventions were micro-costed and estimated on a per-patient basis. The resource use of the interventions included staff time and drugs associated with the performance of the procedures, single-use and reusable equipment utilised during each intervention and duration of use of theatre suites. Information on principal clinical staff present at the procedures and their job title, surgery time and length of hospital stay was obtained from the CRF. Information on additional staff required to be present during the procedures and the drugs used was obtained from study clinicians. Details of single use and reusable equipment required during the procedures and their costs were provided by NHS operating suite staff at the main site (Freeman Hospital, Newcastle upon Tyne, UK). Study clinicians were consulted throughout the micro-costing exercise.

Following the initial surgery, a further urethral catheter removal appointment of variable duration was required for every participant. This did not usually require a hospital bed and it was assumed that NHS resource use for this activity would be the same for both trial groups. The NHS resource use of catheter removal was assumed to be 10 minutes of a qualified nurse's time in a standard treatment room. This was used to derive a uniform cost for every participant who had a catheter removal. Three participants were recorded as having an overnight stay for the catheter removal, the cost of which was added to those participants' overall hospital stay.

Multiple imputation was performed to complete any missing data on length of hospital stay and length of operation theatre time used in the sensitivity analysis. The resource use for each trial intervention is shown in *Table 26*.

Unit costs associated with each resource use were summed to calculate total cost to the NHS. The unit costs were obtained from the following sources: the standard time costs of different grades of staff were based on *Unit Cost of Health and Social Care 2017* documentation from Personal Social Services Research Unit;⁷⁷ theatre suite costs were based on information from the Information Services Division, NHS Scotland;⁷⁸ and the costs of drugs used during the procedure was obtained from manufacturers' price lists from the NHS Dictionary of Medicines and Devices database.⁷⁹

As shown in *Table 27*, in general, urethroplasty had a higher procedure cost than urethrotomy, both in the base-case analysis and in the sensitivity analysis with multiple imputations. This higher cost was mainly driven by longer operating time and hospital stay for urethroplasty relative to urethrotomy.

Cost of health-care service use during follow-up

Data on resource use during the follow-up period were collected retrospectively through the bespoke PCQ. The PCQ had two parts. Part A administered at 6, 12, 18 and 24 months after initial surgery recorded information on the level of the usage of the health services and the costs of any other self-purchased health care required to manage the condition. Part B, administered once only, at 6 months after initial surgery, collected information on the time and travel costs the participant incurred while accessing health services. The role of part B was to calculate the unit costs to the participant of attending each type of health service and was combined with data from part A to derive total costs to the participant. The use of health services recorded in part A included primary (GP and nurse visits) and secondary care (outpatient visits and inpatient stays) resource use. Unit costs associated with the use of these health-care services were from the Personal Social Services Research Unit.⁷⁷ Owing to the relatively small number of patients reporting use of health-care services related to urethral stricture during the follow-up period, it was assumed that participants who did not complete a questionnaire had no urethral stricture-related health service use during the follow-up period.

TABLE 26 Resource use for each trial intervention

Resource type	Intervention		Intervention	
	Urethroplasty		Urethrotomy	
	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>
Base-case analysis				
Theatre suite time (minutes)	159 (84.3)	77	46 (47)	85
Length of hospital stay (days)	1.34 (0.95)	89	0.52 (1)	97
Sensitivity analysis with data imputation				
Theatre suite time (minutes)	158 (81.9)	93	57 (56)	104
Length of hospital stay (days)	1.32 (0.93)	93	0.55 (1)	104

TABLE 27 NHS cost (£) for each trial intervention

Resource type	Intervention			
	Urethroplasty		Urethrotomy	
	Mean (SD) (£)	<i>n</i>	Mean (SD) (£)	<i>n</i>
Base-case analysis				
Theatre suite cost	3096.09 (1639.57)	77	890.35 (924.07)	85
Hospital stay cost	423.42 (274.97)	89	219.27 (157.22)	97
Total NHS intervention cost	4892.83 (2355.48)	74	1540.50 (1300.77)	83
Total NHS intervention cost including those men who did not receive surgery	4068.20 (2827.62)	89	1405.08 (1316.82)	91
Sensitivity analysis with data imputation				
Theatre suite cost	3070.55 (1592.56)	93	1106.49 (1093.39)	104
Hospital stay cost	418.40 (269.98)	93	225.16 (153.37)	104
Total NHS intervention cost	4769.59 (2283.16)	93	1831.87 (1537.73)	104
Total NHS intervention cost including those men who did not receive surgery	4107.15 (2688.54)	108	1701.02 (1555.24)	112

Measures of resource use were combined with unit costs to provide an estimate of the total cost for each participant. All costs were adjusted to the price year 2017 and those costs that occurred in the second follow-up year were discounted by 3.5%. Details of the services used and their costs are reported in *Table 28*.

As indicated by the high SD, the resource use and costs during follow-up were highly variable. This arose because the majority of participants did not report any use of health services following their initial treatment. For those men who did report the use of health services, those men randomised to the urethrotomy group used significantly more than those in the urethroplasty group.

Cost of reintervention

A total of 44 patients had reinterventions during the trial's follow-up period (29 patients in the urethrotomy group and 15 patients in the urethroplasty group). Three patients in the urethrotomy group had more than one reintervention and two patients from the urethroplasty group had more than one reintervention. The same process of micro-costing (see *Cost of the intervention*) was conducted to calculate those reintervention

TABLE 28 Resource use and cost (£) to the NHS and patients for each trial intervention during follow-up (24 months)

NHS resource use and costs during follow-up	Intervention			
	Urethroplasty (<i>N</i> = 108)		Urethrotomy (<i>N</i> = 112)	
	Resource use, mean (SD)	Cost, mean (SD)	Resource use, mean (SD)	Cost, mean (SD)
Inpatient admission	0.06 (0.34)	43.95 (252.67)	0.21 (0.72)	268.91 (2270.90)
Outpatient visit	0.38 (1.02)	40.29 (108.41)	0.86 (1.74)	91.18 (184.37)
GP visit	0.80 (2.70)	29.28 (100.61)	1.04 (2.18)	36.45 (77.22)
Nurse visit	0.16 (0.61)	1.38 (5.50)	0.18 (0.56)	1.92 (6.01)
Total NHS costs	NA	114.90 (375.86)	NA	398.46 (2444.35)
Total patient costs (time and travel costs and out-of-pocket expenses)	NA	29.28 (135.57)	NA	60.66 (305.92)

NA, not applicable.

costs (Table 29). It is worth noting that both types of procedures were used for reinterventions in both groups. The reason why urethrotomy patients used more resources on average than urethroplasty patients was that patients randomised to the urethrotomy group were more likely to have urethroplasty as their reintervention treatment; therefore, the resource use for the urethrotomy group was higher on average for those men who had reinterventions.

Total cost

Taking the perspective of the NHS and patients and their families, total costs combining NHS resource use costs (intervention, reintervention and health service use during follow-up) and patients' out-of-pocket costs are presented in Table 30.

As Table 30 shows, the cost of urethroplasty was higher over the 24 months post randomisation than that of urethrotomy. However, the magnitude of the difference in cost reduced when reintervention and follow-up costs were included.

Quality-adjusted life-years

Effectiveness was measured in terms of utility derived from responses to the EQ-5D-5L collected at baseline, immediately prior to surgery, 1 week after catheter removal, at 3, 6, 9, 12 and 24 months following surgery, at 18 and 24 months after randomisation and at the end of study. Additional EQ-5D-5L questionnaires were intended to be completed at times of participants requiring reintervention; however, very few patients submitted both pre- and post-reintervention EQ-5D-5L data. Among those participants who had both pre- and post-reintervention EQ-5D-5L data, no difference was found between the allocated intervention groups or between pre and post reintervention; therefore, these EQ-5D-5L data were not used in the calculation of total QALYs. The responses to the EQ-5D-5L questionnaire were transformed using UK population tariffs³⁹ to produce a health state utility score for each participant in each of the treatment groups using the AUC method.⁸⁰

TABLE 29 Cost (£) of reintervention occurring in each allocated group

Reintervention cost	Intervention			
	Urethroplasty		Urethrotomy	
	Mean (SD) (£)	<i>n</i>	Mean (SD) (£)	<i>n</i>
Base-case analysis	3896.39 (4606.26)	9	4626.09 (2222.69)	17
Sensitivity analysis with data imputation	3255.86 (3842.12)	15	4674.68 (1997.89)	29

TABLE 30 Total cost (£) for each trial group

Total cost	Intervention			
	Urethroplasty		Urethrotomy	
	Mean (SD) (£)	<i>n</i>	Mean (SD) (£)	<i>n</i>
Base-case analysis				
Total intervention and reintervention cost	4331.51 (3150.60)	89	2209.19 (2368.13)	91
Total NHS cost (intervention and reintervention with follow-up)	4454.55 (3190.76)	89	2657.41 (3475.67)	91
Total societal cost (NHS and patient costs)	4479.94 (3218.47)	89	2729.90 (3712.57)	91
Sensitivity analysis with data imputation				
Total intervention and reintervention cost	4559.35 (3060.64)	108	2911.43 (2712.73)	112
Total NHS cost (intervention and reintervention with follow-up)	4674.25 (3134.93)	108	3309.89 (3552.15)	112
Total societal cost (NHS and patient costs)	4703.53 (3155.05)	108	3370.55 (3755.24)	112

Given the large number of time points for EQ-5D-5L data, and to align with the primary effectiveness analysis, it was decided that, to be included in the AUC analysis without imputation, the participant must have at least three EQ-5D-5L observations with one at the start of the assessment period, one at the mid-range and one at the end, and the specific requirement was dependent on the status of the participants (whether or not they had received surgery) and the type of analysis conducted, as explained below.

For those participants who did not receive an initial surgery, to be included in the AUC analysis without imputation, they must have completed EQ-5D-5L data on the three time points: baseline, 18 months and 24 months after randomisation.

For those participants who received an initial surgery, the base-case analysis examined QALYs over the period from baseline to 24 months after randomisation; therefore, the AUC analysis required complete EQ-5D-5L data at baseline and 24 months after randomisation, and at one of the data collection points of 3, 6, 9 and 12 months following surgery and 18 months following randomisation. Given the differences in the duration of the period between randomisation and undergoing an intervention between urethroplasty and urethrotomy, we also examined QALYs over the period from the time prior to surgery to 24 months post surgery, in which case the AUC analysis required complete EQ-5D-5L data at prior to surgery and 24 months after surgery, and at one of the data collection points of 3, 6, 9 and 12 months following surgery and 18 and 24 months following randomisation.

For all calculations of QALYs the first observation used (either baseline or prior to surgery, depending on the patient groups and analysis type) was set at time point zero and the date on which the EQ-5D-5L was recorded as being completed was used to calculate the number of days from the first observation. This time dimension was initially used in the calculation of QALYs rather than the nominal time point at which the EQ-5D-5L was to be completed. In an alternative analysis, the responses were rescaled to the nominal data collection points (i.e. 730 days; note that cost data did not need to be rescaled in the same way as the recall period was predefined within the data collection tools). Additionally, multiple imputation for EQ-5D-5L at all missing time points was conducted to calculate QALYs for all participants.

A summary of the results of the EQ-5D-5L for each time point by intervention, as well as the estimates of QALYs for both the base-case analysis (QALYs at 24 months after randomisation) and the sensitivity analyses described above, is provided in *Table 31* and in *Figure 12*.

Cost–utility analysis

Method

Although a comparison of cost-effectiveness over a 24-month time horizon from baseline to end of study was intended as described in the study protocol, owing to the unpredictable nature of surgery planning at different sites, there was a considerable difference in time from baseline to having initial surgery between patients, making it an unfair comparison to use baseline as time zero to the end of study. It was, therefore, decided to examine the cost-effectiveness with different time points as time zero. In the base-case analysis, QALY gain was based on QALYs calculated from baseline to 24 months post randomisation. The sensitivity analysis examined QALY gain based on QALYs calculated from the time prior to surgery to 24 months post surgery. For both cases, QALY gain was also rescaled to the nominal time (i.e. 730 days) as additional sensitivity analyses. All of the above used complete cases only. Additionally, multiple imputation was conducted for all the missing observations and sensitivity analyses with imputation were also conducted in the same manner as complete-case analyses.

Costs used in the cost–utility analyses included initial intervention costs and subsequent follow-up costs, as well as patients' out-of-pocket costs. Costs with imputation were used together with QALYs with imputation in the sensitivity analyses. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs for each group. Uncertainty in

TABLE 31 Utility values at each time point and QALYs over the trial follow-up

EQ-5D-5L	Intervention			
	Urethroplasty		Urethrotomy	
	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>
Baseline	0.83 (0.22)	106	0.87 (0.17)	107
Just before surgery	0.84 (0.21)	74	0.86 (0.16)	96
1 week after catheter removal	0.84 (0.17)	53	0.89 (0.13)	70
3 months after surgery	0.88 (0.15)	69	0.89 (0.19)	84
6 months after surgery	0.87 (0.17)	60	0.87 (0.19)	77
9 months after surgery	0.88 (0.17)	63	0.88 (0.19)	81
12 months after surgery	0.87 (0.21)	63	0.87 (0.21)	80
18 months after randomisation	0.85 (0.23)	62	0.87 (0.20)	79
24 months after randomisation	0.87 (0.25)	58	0.90 (0.16)	58
24 months after surgery	0.87 (0.26)	48	0.91 (0.13)	59
QALYs at 24 months after randomisation	1.75 (0.40)	55	1.76 (0.35)	54
QALYs at 24 months after randomisation (rescaled to 730 days)	1.66 (0.34)	55	1.70 (0.34)	54
QALYs at 24 months after surgery	1.73 (0.54)	44	1.77 (0.34)	56
QALYs at 24 months after surgery (rescaled to 730 days)	1.42 (0.40)	44	1.58 (0.30)	56
QALYs at 24 months after randomisation with imputation	1.73 (0.32)	108	1.76 (0.28)	112
QALYs at 24 months after randomisation with imputation (rescaled to 730 days)	1.67 (0.29)	108	1.72 (0.27)	112
QALYs at 24 months after surgery with imputation	1.75 (0.37)	108	1.76 (0.29)	112
QALYs at 24 months after surgery with imputation (rescaled to 730 days)	1.67 (0.30)	108	1.72 (0.26)	112

parameter estimates was addressed through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves, to provide both probabilistic and deterministic sensitivity analyses.

Results

The base-case analysis and all sensitivity analysis results are presented in *Table 32*. In the base case, urethroplasty cost more (cost difference £2148, 95% CI £689 to £3606) than urethrotomy, while generating a lower point estimate of QALY gain (QALY difference -0.01 , 95% CI -0.17 to 0.14). Urethroplasty was therefore dominated by urethrotomy. This suggests that urethrotomy was more cost-effective than urethroplasty in the base-case scenario. The base-case result appears to be robust, as it is seen in all of the sensitivity analyses that urethroplasty cost more and the point estimate of effect was lower. The cost-effectiveness acceptability curve (*Figure 13*) and incremental cost and QALY plots (*Figure 14*) are presented for the base case. As seen in *Figure 13*, the probability of urethroplasty being cost-effective increases as the threshold for society's willingness to pay for a QALY increases; however, urethroplasty never had more than approximately a 20% chance of being considered cost-effective over a 2-year time horizon for the range of cost per QALY thresholds considered. This is supported by the incremental cost and QALY plots (see *Figure 14*), in which the mean incremental cost per QALY falls in the north-east quadrant of the graph, indicating urethroplasty to cost more but to be less effective using the point estimate of benefit.

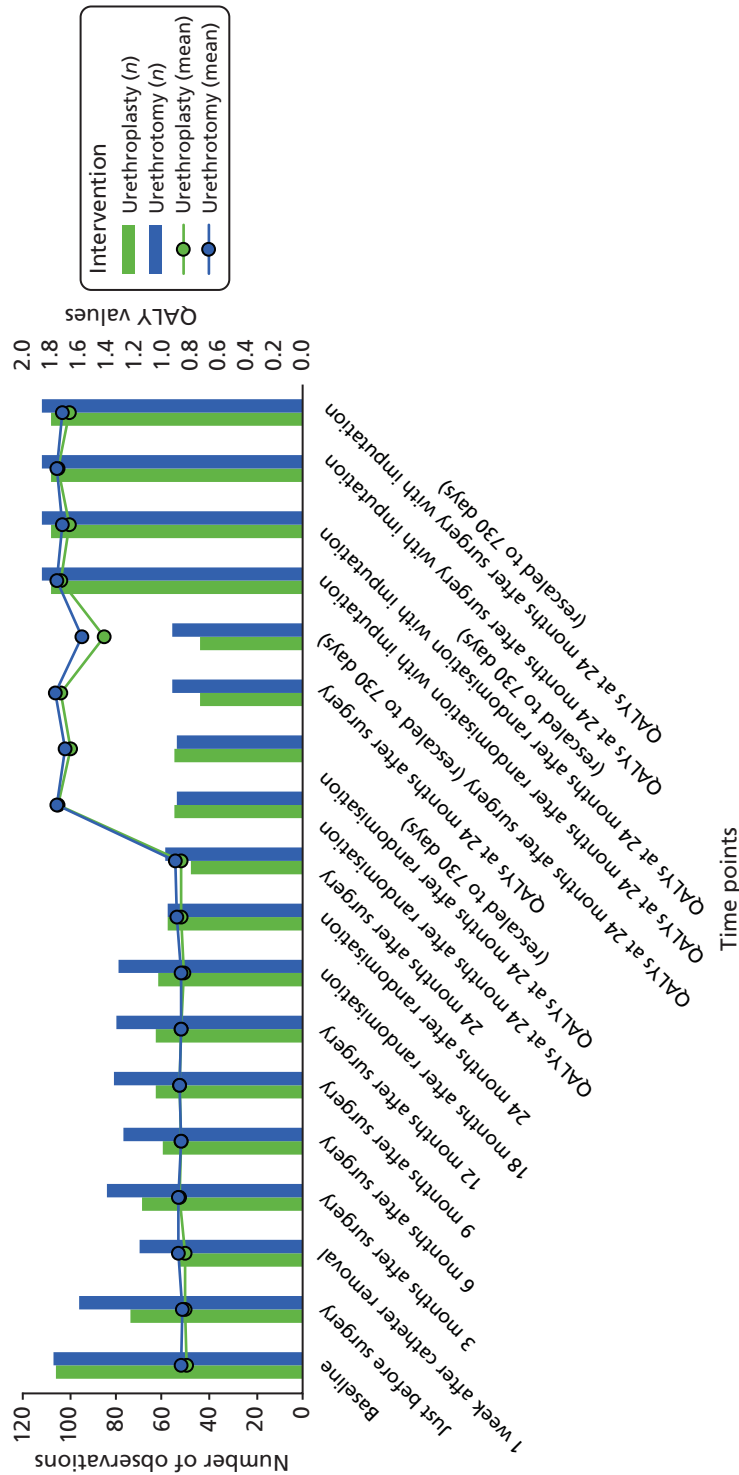


FIGURE 12 Utility values at each time point and QALYs over the trial follow-up with corresponding number of observations.

TABLE 32 Cost-effectiveness analysis

Investigation strategy	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALY mean (95% CI)	Incremental effect mean (95% CI)	ICER (£)	Probability (%) of each treatment strategy being cost-effective for different threshold values for society's willingness to pay				
						£0	£10,000	£20,000	£30,000	£50,000
Base case, 24 months post randomisation										
Urethroplasty (n = 46)	4869 (4123 to 5614)	2148 (689 to 3606)	1.74 (1.61 to 1.86)	-0.01 (-0.17 to 0.14)		0	2	8	14	23
Urethrotomy (n = 46)	2721 (1444 to 3999)		1.75 (1.65 to 1.85)		Dominant	100	98	92	86	77
24 months post randomisation (rescaled QALY)										
Urethroplasty (n = 46)	4869 (4123 to 5614)	2148 (689 to 3606)	1.65 (1.55 to 1.76)	-0.04 (-0.18 to 0.11)		0	1	3	5	10
Urethrotomy (n = 46)	2721 (1444 to 3999)		1.69 (1.59 to 1.79)		Dominant	100	99	93	95	90
24 months post surgery										
Urethroplasty (n = 37)	4963 (3977 to 5949)	1672 (-65 to 3409)	1.73 (1.54 to 1.92)	-0.04 (-0.24 to 0.16)		2	7	14	19	25
Urethrotomy (n = 48)	3291 (1947 to 4636)		1.77 (1.67 to 1.87)		Dominant	98	93	86	81	75
24 months post surgery (rescaled QALY)										
Urethroplasty (n = 37)	4963 (3977 to 5949)	1672 (-65 to 3409)	1.42 (1.28 to 1.56)	-0.16 (-0.31 to -0.01)		2	1	1	1	1
Urethrotomy (n = 48)	3291 (1947 to 4636)		1.58 (1.49 to 1.67)		Dominant	98	99	99	99	99
24 months post randomisation with imputation										
Urethroplasty (n = 108)	4704 (4102 to 5305)	1333 (410 to 2256)	1.73 (1.67 to 1.79)	-0.03 (-0.11 to 0.05)		0	0	2	4	9
Urethrotomy (n = 112)	3371 (2667 to 4074)		1.76 (1.71 to 1.81)		Dominant	100	100	98	96	91
24 months post randomisation with imputation (rescaled QALY)										
Urethroplasty (n = 108)	4704 (4102 to 5305)	1333 (410 to 2256)	1.67 (1.62 to 1.73)	-0.05 (-0.13 to 0.02)		0	0	0	1	2
Urethrotomy (n = 112)	3371 (2667 to 4074)		1.72 (1.67 to 1.77)		Dominant	100	100	100	99	98
24 months post surgery with imputation										
Urethroplasty (n = 108)	4704 (4102 to 5305)	1333 (410 to 2256)	1.75 (1.68 to 1.82)	-0.02 (-0.10 to 0.07)		0	1	5	10	19
Urethrotomy (n = 112)	3371 (2667 to 4074)		1.76 (1.71 to 1.82)		Dominant	100	99	95	90	81
24 months post surgery with imputation (rescaled QALY)										
Urethroplasty (n = 108)	4704 (4102 to 5305)	1333 (410 to 2256)	1.67 (1.61 to 1.73)	-0.05 (-0.12 to 0.02)		0	0	0	1	2
Urethrotomy (n = 112)	3371 (2667 to 4074)		1.72 (1.67 to 1.77)		Dominant	100	100	100	99	98

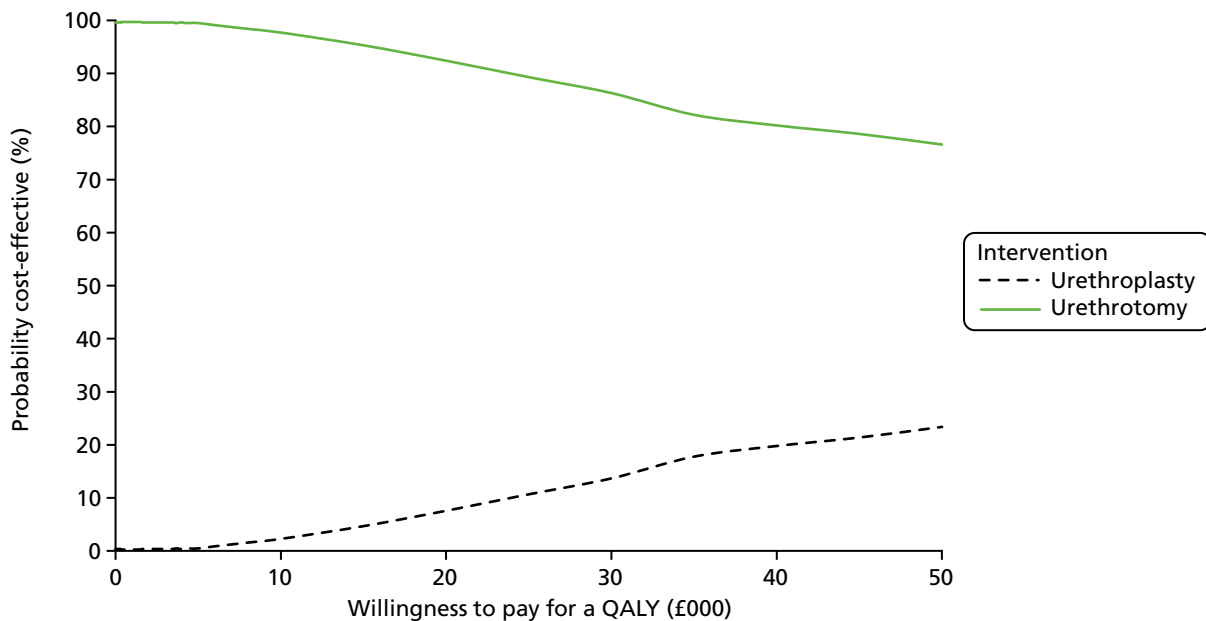


FIGURE 13 Cost-effectiveness acceptability curve (base case).

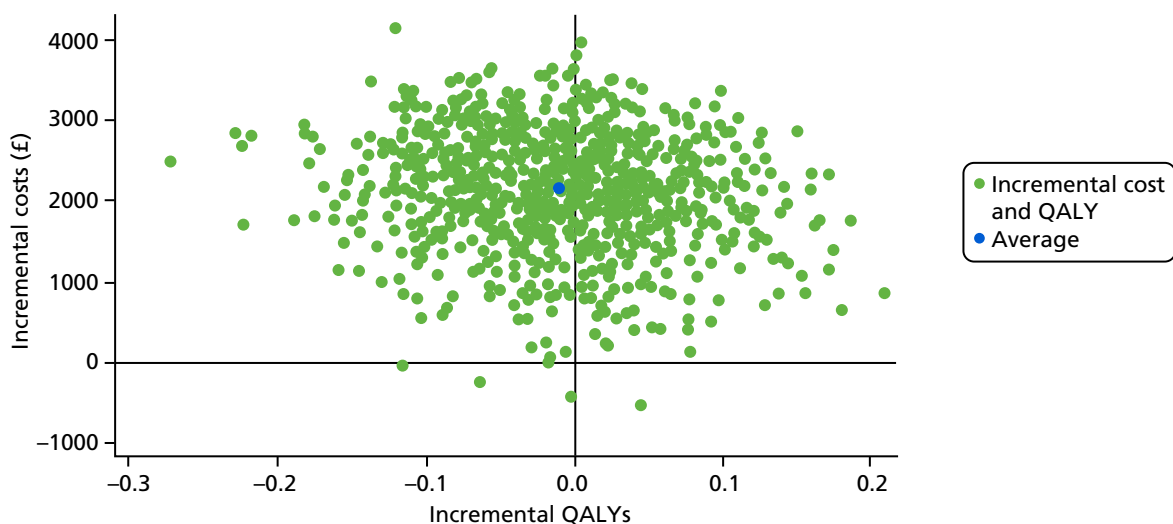


FIGURE 14 Incremental cost and QALY plots (base case).

Long-term modelling

Methods

The Markov model consisted of three health states: (1) cured (symptom free), (2) symptomatic and (3) deceased. The deceased state was included to allow for general population mortality when examining the cohorts over a long-term horizon. In the model, every patient started off receiving one of the two trial interventions. They then moved through the care pathways over time, incurring costs and accruing QALYs. The care pathways followed described the process of care, disease incidence and progression. These features were linked in a logical way, defined by a set of mathematical relationships that dictated how and when an individual might move through the model. The structure of the model is shown in *Figure 15*. The model parameters were based on information derived from the trial and the distribution for each parameter was defined considering the mean, standard error and anticipated shape of the distribution. Model parameters included costs for each intervention and their follow-up; utility for cured (symptom-free) and symptomatic states; probability of surgery success for each intervention; probability

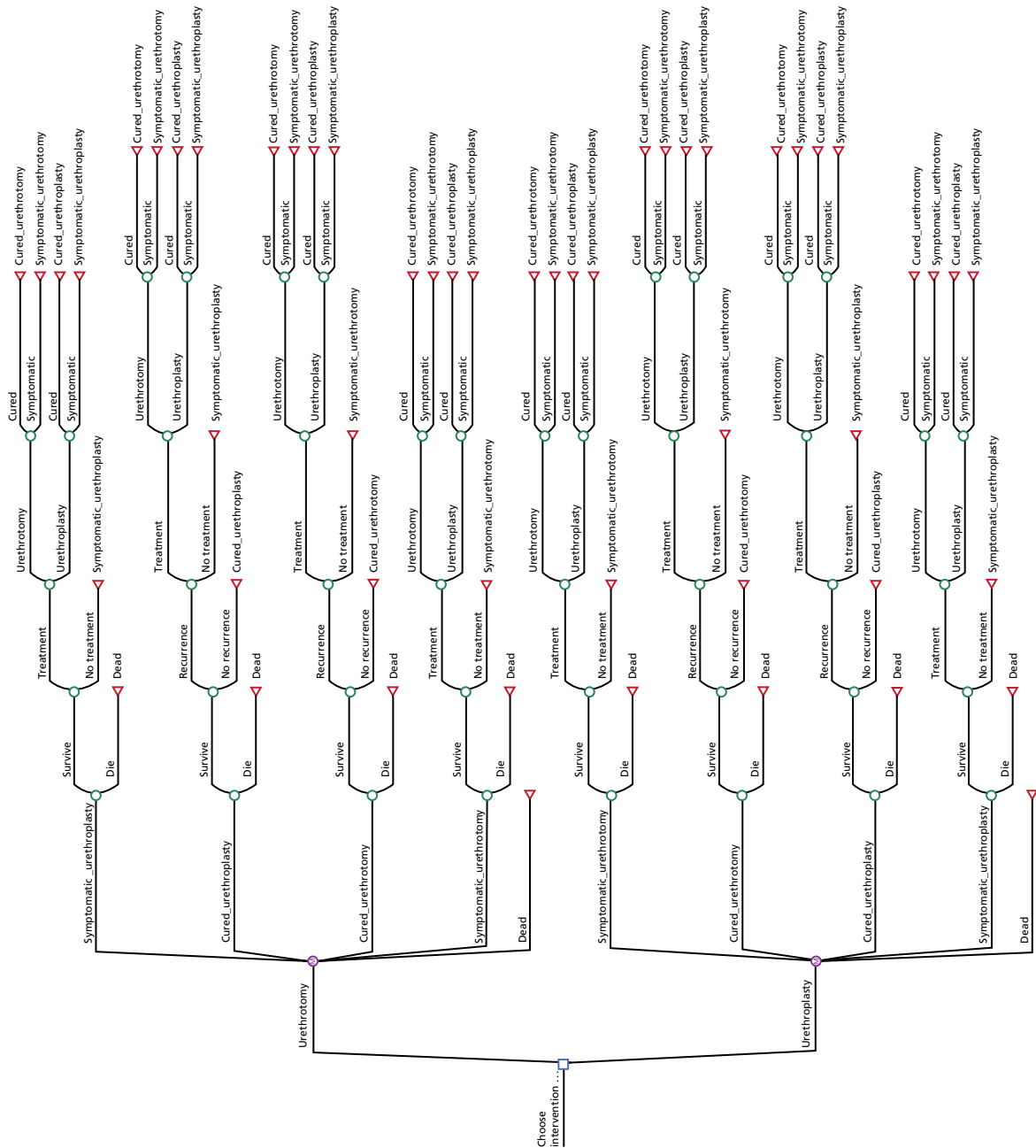


FIGURE 15 Markov model structure.

of receiving treatment when symptomatic; and probability of the type of treatment procedure received conditional on the previous intervention. Survival analysis was used to generate forward transition probabilities of recurrence following each intervention. *Table 33* describes all model parameters. Half-cycle corrections were applied in the model.

TABLE 33 Model parameters

Parameter name	Value, mean (SE)	Source and distribution
Cost of urethroplasty (including initial surgery with catheter removal and hospital stay)	Base case: £5871 (£229)	Based on value from the trial; gamma distribution
	By treatment received: £5808 (£219)	
Cost of urethrotomy (including initial surgery with catheter removal and hospital stay)	Base case: £1316 (£96)	Based on value from the trial; gamma distribution
	By treatment received: £1367 (£90)	
Utility associated with cured (symptom-free) health state	Base case: 0.899 (0.013)	Based on value from the trial; beta distribution; utility values at 3 months after surgery, of those men who showed a significant improvement in voiding scores
	By treatment received: same as base case	
Utility associated with symptomatic health state	Base case: 0.852 (0.014)	Based on value from the trial; beta distribution; utility values at baseline
	By treatment received: same as base case	
Cost of health service use and patient's out-of-pocket expenses following urethroplasty	Base case: £130 (£46)	Based on value from the trial; gamma distribution
	By treatment received: £141 (£45)	
Cost of health service use and patient's out-of-pocket expenses following urethrotomy	Base case: £227 (£42)	Based on value from the trial; gamma distribution
	By treatment received: £210 (£38)	
Surgery success rate for urethroplasty	Base case: 0.95 (0.03)	Based on value from the trial; beta distribution
	By treatment received: 0.94 (0.03)	
Surgery success rate for urethrotomy	Base case: 0.91 (0.03)	Based on value from the trial; beta distribution
	By treatment received: 0.92 (0.03)	
Probability of being treated when symptomatic	Base case: 0.90 (0.02)	Based on value from the trial; beta distribution
	By treatment received: same as base case	
Probability of receiving urethroplasty if the last treatment is urethroplasty	Base case: 0.12 (0.12)	Based on value from the trial; beta distribution
	By treatment received: 0.11 (0.11)	
Probability of receiving urethroplasty if the last treatment is urethrotomy	Base case: 0.70 (0.08)	Based on value from the trial; beta distribution
	By treatment received: 0.63 (0.07)	
Probability of recurrence following urethroplasty	Base case: 0.042	Based on survival analysis from the trial
	By treatment received: 0.041	
Probability of recurrence following urethrotomy	Base case: 0.1497	Based on survival analysis from the trial
	By treatment received: 0.150	

SE, standard error.

The base-case analysis used parameters estimated based on information from study participants who received the intervention to which they had been allocated. Probabilistic sensitivity analysis of the base-case scenario was carried out using Monte Carlo simulation, in which model inputs for each parameter were randomly selected from predefined distributions and the results recorded. This process was repeated for 10,000 iterations to produce a distribution of results from the model.

Deterministic sensitivity analyses were conducted by changing the key parameters in set ways that were determined based on information from those men who received the same intervention, regardless of whether or not it was the intervention they were allocated.

An important model parameter is the choice of the next treatment given the previous treatment the patient had. 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 would receive urethrotomy if the last treatment was urethroplasty. This suggests that a large proportion of patients switch to a treatment different from their previous one every time they have a reintervention. There is no consensus on the treatment choices in reintervention and such choices are often influenced by many non-clinical factors, such as patient choice, waiting time and travel time. Given the high uncertainty around treatment choice in reintervention, deterministic sensitivity analyses also examined the impact of changing the percentages of patients switching treatments.

The costs and effects were combined in an incremental analysis, comparing different treatment strategies, and presented as the point estimates of mean costs, mean QALYs and mean incremental cost per QALY. These results were presented graphically using the incremental cost and QALY plots and a cost-effectiveness acceptability curve.

Results

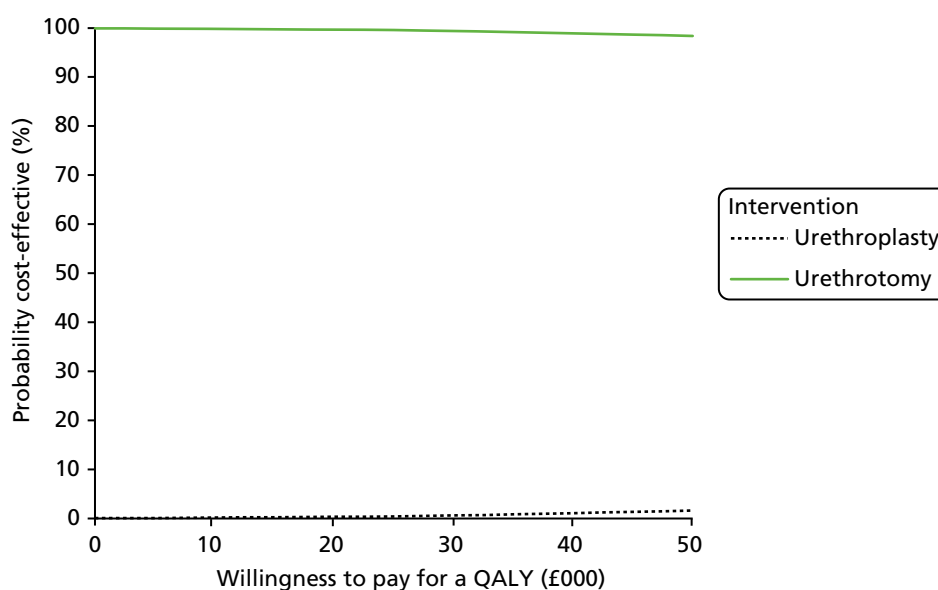
In the base-case analysis, in which model parameters were based on those men who received the intervention they were allocated by randomisation, urethroplasty is unlikely to be considered cost-effective under society's current willingness to pay for a QALY. This is also illustrated by the probabilistic sensitivity analysis in which urethroplasty has almost no chance of being considered cost-effective at any of the threshold values for society's willingness to pay for a QALY considered (*Table 34* and *Figures 16* and *17*).

In the deterministic sensitivity analysis, in which model parameters were based on those men who received the same treatment procedure regardless of their allocated intervention group, a similar trend is observed to the base-case analysis, with urethroplasty being unlikely to be cost-effective under society's current willingness-to-pay threshold for a QALY. The same is observed in the deterministic sensitivity analyses varying the probabilities of the choices of treatments in reintervention.

Both probabilistic and deterministic sensitivity analyses show that urethroplasty is unlikely to be cost-effective over a 10-year time horizon under a number of plausible scenarios. This is mainly driven by the higher cost of urethroplasty than urethrotomy, while both of the treatment procedures produce similar QALY gains, despite those men receiving urethroplasty having a lower chance of recurrence than those men receiving urethrotomy. It could be argued that the EQ-5D-5L may not be a sensitive measure for this group of patients and would, therefore, not capture important changes in quality of life for this condition. Additionally, decrement in quality of life following the procedures were not taken into consideration in the analysis conducted. Given the likelihood of recurrence requiring repeated treatments, this decrement could make a difference in QALY gains between the two treatments. The potential way to measure this decrement was explored using the TTO exercise.

TABLE 34 Markov model result over 10 years: base case and deterministic sensitivity analyses

Treatment strategy	Cost (£)	QALY	ICER (£)	Probability (%) of each treatment strategy is cost-effective for different threshold values for society's willingness to pay for a QALY				
				£0	£10,000	£20,000	£30,000	£50,000
Base case								
Urethroplasty	8026	7.61	301,073	0	0	0	0	2
Urethrotomy	6553	7.60		100	100	100	100	98
Parameters based on treatment received								
Urethroplasty	7987	7.61	307,328	0	0	0	0%	1
Urethrotomy	6490	7.60		100	100	100	10	99
Always receive the same treatment at recurrence								
Urethroplasty	9026	7.61	476,162	0	0	0	0	0
Urethrotomy	4059	7.60		100	100	100	100	100
Always receive the other treatment at recurrence								
Urethroplasty	8076	7.61	263,383	0	0	1	2	4
Urethrotomy	7054	7.60		100	100	99	98	96

**FIGURE 16** Cost-effectiveness acceptability curve (Markov model – base case).

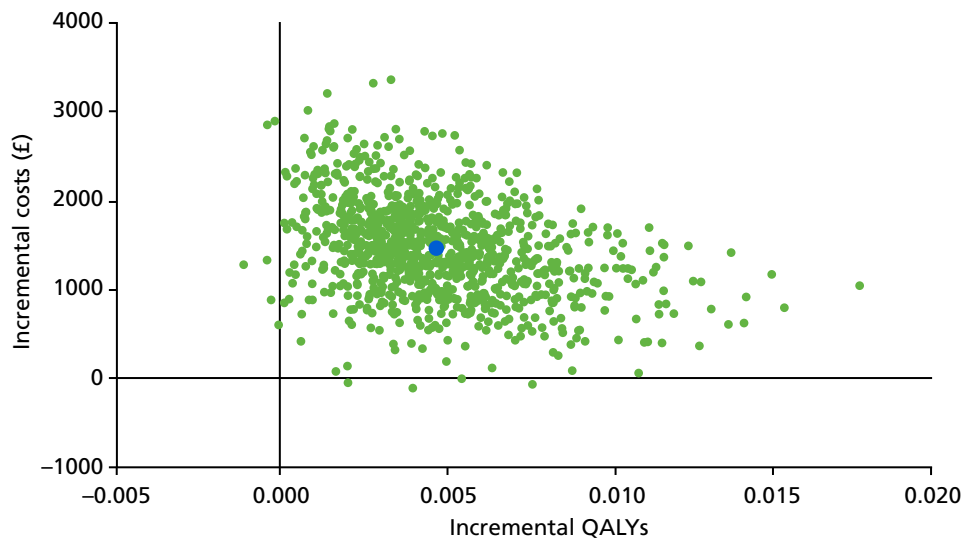


FIGURE 17 Incremental costs and QALY plots (model base case).

Time trade-off exercise

A TTO exercise was conducted to estimate the short-term impact of undergoing the treatments on health-related quality of life (HRQoL). This was to complement the results of completion of the EQ-5D-5L as part of trial follow-up. The EQ-5D-5L is a measure of HRQoL on the day of completion and, as such, it does not ask about the duration of any impacts on HRQoL. Thus, we wished to use a TTO exercise to assess the important but short-term changes in health that occurred at the time of a surgery, which would otherwise be missed in the EQ-5D-5L completion schedule. The TTO exercise gathers data on the impact of impaired health by asking participants to state preferences between quality and quantity of life in hypothetical scenarios. The TTO method is mainly used to elicit utility values for chronic health states that last for a number of years; however, the two surgical procedures in this study are likely to have a short impact over days or weeks postoperatively, before a return to normal health. In these circumstances, a conventional TTO exercise may become less responsive^{81,82} because the exercise offers an unrealistic choice, between an impaired health state for a fixed duration and a perfect health state for a shorter duration of time, both followed by death.⁸³ Attempts to remedy this problem have involved using an intermediate health state, rather than directly comparing the temporary health state with perfect health and death, and this method is referred to as the 'chained TTO'.⁸⁴ In this study, both the conventional and chained TTO exercise were used with participants who agreed to take part. The participants were randomly allocated to one of the two alternative methods of eliciting TTO valuations: the conventional and chained TTO.

Development of time trade-off materials

Prior to the TTO exercise being conducted among trial participants, extensive development and piloting of materials and processes were carried out. The TTO materials developed include a decision board, which was used as a visual aid for participants to compare health states, and written health state profiles (see *Appendix 7*), which described the likely side effects of the two procedures (categorised into mild, moderate and severe). These profiles were printed on A6-sized card for use with the decision board. An anchor health state was designed for the chained TTO, as an intermediate state that was worse than the six health profiles, but not as severe as death, and described a scenario containing severe pain with usual functioning impaired, but maintaining basic self-caring activities possible. A set of practice profiles was also designed based on a selection of EQ-5D-5L profiles to allow participants to become familiar with the process prior to valuing the health states relating to the study. The time horizon for the profiles to be evaluated was chosen as 14 days, and this was a balance between providing a clinically accurate prediction of the likely duration of side effects and providing participants with a clear scenario.

Three rounds of piloting were conducted with different groups of participants before finalising the materials and process: round 1 conducted with 17 male and female volunteers from Newcastle University; round 2 conducted with 15 male staff members at a participating (hospital) study site; and round 3 conducted with nine men eligible for the open trial. Piloting interviews consisted of mock TTO interviews, but also encouraged feedback on the process and materials. Feedback was collated and used iteratively to refine processes for subsequent pilots. Health-care professionals involved in the trial were consulted throughout the development process to ensure that the TTO materials were clinically accurate and understandable to a lay audience. A patient and public involvement representative was also consulted as part of the piloting process.

The TTO participants were recruited from those men who were eligible for the OPEN trial. At the point of consent to the main trial, participants were asked to indicate willingness to be contacted about a further interview study. Those men who expressed interest were posted an information pack regarding TTO, containing a response slip and post-paid envelope. On receipt of an affirmative response slip, a researcher contacted respondents to answer any further questions or arrange a time and place of the participant's choosing. Interviews were most frequently conducted in the participant's home and written consent was taken prior to commencing the interview.

Following the TTO interview, participants were asked to provide feedback on the interview process. Participants were asked to rate on a scale of 1 to 5 (with 1 being not difficult at all and 5 being very difficult) how difficult they found the TTO process and asked if they had any comments relating to the process. This was recorded by the researcher as free text. In addition, the interviewer recorded anything about the conduct and process of the interview that they felt to be important.

Data analysis

Stata was used to analyse data. Descriptive statistics were produced for demographic details of the sample and Tobit regressions of reported TTO values were performed, controlling for sociodemographic characteristics. The level of usual physical activity and place of residence (urban or rural) were included as variables in the analyses, as it was considered possible that these would have an impact on how participants valued health states in which their mobility was affected. An additional control variable was generated based on the consistency between utility values derived and how each participant ranked those profiles prior to the TTO exercise in order to indicate data quality. Predicted values of health state utility were estimated for each health state and compared using unpaired *t*-tests. Qualitative data collected were also analysed to understand the feasibility of conducting a TTO alongside a surgical RCT.

Results

Forty participants were recruited to take part in the TTO. Two participants had missing or invalid essential data and were excluded. Of the 38 participants included in the analysis, the sociodemographic details were as follows: mean age of the sample was 38 years; 84% were married; 41% had a household income > £36,400; just over half (55%) of the sample were employed and 29% were retired. The majority (71%) of participants described living in an urban area. Twenty-nine per cent of the sample reported high levels of physical activity, 47% reported medium levels and 24% reported low levels of activity.

The estimated utility values for the two types of surgery using the two TTO methods are presented in *Table 35*, together with significance of the difference in post-surgery utilities between the two surgeries. The majority of the urethroplasty health states had lower utility scores than the urethrotomy health states, this was significant for the severe scenario irrespective of the TTO method used. For both types of surgery, mean utility values decreased as health states became more severely impaired, which suggests face validity of the profiles.

The median difficulty for the TTO exercise reported by participants was 2 out of 5, which indicated that the TTO exercise was considered by most participants as reasonably easy to complete. Additional comments covered participants' opinions on the difficulty of the interview process, as well as elaborating on their individual decision-making process. Some described a desire to avoid particular symptoms, particularly pain

TABLE 35 Estimated utility values

TTO method	Health states by severity of side effects following surgery	Intervention, utility value (95% CI)		
		Urethrotomy	Urethroplasty	p-value
Conventional (n = 20)	Mild	0.81 (0.72 to 0.90)	0.79 (0.72 to 0.87)	0.61
	Moderate	0.58 (0.44 to 0.72)	0.54 (0.43 to 0.65)	0.48
	Severe	0.56 (0.45 to 0.68)	0.39 (0.26 to 0.51)	< 0.001
Chained (n = 18)	Mild	0.83 (0.74 to 0.92)	0.83 (0.73 to 0.93)	0.71
	Moderate	0.67 (0.56 to 0.77)	0.62 (0.54 to 0.69)	0.43
	Severe	0.44 (0.35 to 0.53)	0.29 (0.19 to 0.39)	0.03

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and anxiety. Some participants related previous life experience as informing their perception of the impact of certain symptoms; for example, one participant stated that having experienced frequent catheterisation, this was something he no longer worried about. In general, the interviewers felt that participants had understood the process reasonably well.

Discussion

Using a TTO nested in a clinical RCT allowed estimation of the short-term impact on HRQoL from side effects arising immediately following the procedures being compared.

Lower utility values were observed for urethroplasty-related health states, implying that there was a larger reduction in HRQoL immediately following the urethroplasty procedure, although the differences were seen to be statistically significant only for the severe impairment health states. Although this may be due to insufficient sample size, when taken in the context of the qualitative feedback regarding decision-making, this could be because participants were particularly averse to one or more of the symptoms described in the severe urethroplasty health state.

Only differences between utilities for each intervention were examined statistically, a more meaningful comparison would be to examine whether or not these differences were relevant from a clinical perspective. Further understanding of the short-term impact of the different treatments would offer valuable information from a policy-making perspective, as well as improving patient information on treatment choices. Combining these data with other information, such as incidence of side effects and recurrence rates, may help to support shared decision-making between patients and clinicians.

No attempt was formally made to incorporate the results of the exploratory analysis of the TTO exercise into the economic valuation. However, if the results were taken at face value and knowing something about the number of reoperations in both arms of the trial, then we might expect a more marked difference in QALYs between the two treatment groups, given that patients in the urethrotomy group are more likely to require repeated treatments than those patients in the urethroplasty group. Such marked difference is unlikely to come from the impact of the treatment itself if the findings were robust in terms of little difference found in utility between the two treatment strategies, except in the severe state which may account for only a small percentage of the patient population. Although qualitative comments were generally brief and did not constitute a valid or robust qualitative interview, they were useful to add to our understanding of people's experience of taking part in the interviews and highlight aspects which were deemed to be difficult and could be revised for future studies. The aim of this research was to ask people to compare two states of

health for varying lengths of time. People's decision-making process appeared to be influenced by multiple factors, including their own experience of health and illness, their current health and their family situation. These data are useful in developing future TTO exercises and, in particular, will help research teams to refine their information materials, such as introductory scripts.

Conclusion

The TTO exercise has proved to be a feasible method of collecting data on short-term changes in HRQoL within a clinical trial. Although the study finding is preliminary, it suggests that both urethroplasty and urethrotomy have a negative impact on HRQoL immediately following the procedures. The likelihood of men with recurrent urethral stricture requiring repeated treatments may indicate that this important but short-lived decrement to HRQoL immediately following the procedures should be incorporated into the calculation of QALYs associated with each intervention in the longer term. Future research should aim to elicit the utilities associated with this decrement with a large sample size.

Chapter 6 Discussion

Statement and interpretation of results

This RCT directly compared clinical effectiveness and cost-effectiveness of the options of open urethroplasty and endoscopic urethrotomy to manage recurrent bulbar urethral stricture in men. To achieve this, we measured outcomes important to patients, clinicians and funders or planners of health care. Men with recurrent stricture are most concerned about their poor and prolonged voiding which threatens urinary retention, a problem they find distressing and which negatively affects their lives.^{2,21} Men manage their symptoms by concealment and forbearance, acknowledging the benign nature of the underlying disease. When these management strategies become no longer tenable they seek medical help, principally from urologists. The advice they receive varies particularly depending on whether the urologist is a generalist or a specialist urethral surgeon.² Patients may also have established preferences based on their experience of previous interventions (predominantly urethrotomy) and their individual situation in terms of having resources to cope with the more prolonged recovery period and possible travel associated with urethroplasty.

The trial results show that they can be confident that either procedure will control their urinary symptoms and both require a short hospital stay and have a low risk of SAEs. They will then have to weigh up the contrasting aspects of the procedures confirmed by the trial results. The need for a longer period of catheterisation with urethroplasty was often highlighted as a negative by men, although recent quality improvement work suggests that this can be safely reduced to 8–10 days.⁸⁶ Wound and donor site discomfort are expected AEs of urethroplasty and when these were severe the TTO experiment, conducted in parallel with the OPEN trial, showed that a greater degree of short-term quality-of-life decrement occurred among men who underwent urethroplasty. This, together with the higher rate of, and shorter time to, recurrence associated with urethrotomy, will need to be considered in the light of preferences and values. It will be reassuring to men that both procedures were associated with greater satisfaction regarding sexual activity. Clinicians need to inform any prejudices they may hold regarding the two treatment options and present information in a balanced way, in light of the trial findings. In particular, older age, the number of previous urethrotomies and stricture severity do not appear to influence the estimate of treatment effect.

Outcomes for the procedures in the UK NHS seem equivalent across the OPEN trial sites and are similar to those outcomes in other European countries and the USA, suggesting that standards of care and surgical performance are consistent and reproducible. General urologists will need to ensure that there are efficient and workable pathways to allow men access to urethroplasty, irrespective of locality. Specialist urologists need to ensure that they have the capacity to offer a urethroplasty service and, through audit, monitor their outcome performance against the benchmark established by the OPEN trial results. All clinicians will need to ensure that men requiring further intervention for bulbar stricture have sufficient information based on evidence provided by the OPEN trial and other sources, and that the preferences and values of individual patients are elicited and taken into account during discussions around treatment decisions.

Providers of urology services can use the OPEN trial results to plan and cost the service provision required to offer men their preferred procedure. This may require the establishment of robust clinical pathways and ensuring that specialist urethroplasty services are sufficiently resourced in terms of theatre suite time and ongoing specialist surgeon availability.⁸⁷ This may also impact on training needs within the urology specialty. The greater initial cost for performance of urethroplasty seems to be partially offset over a longer time period by the lower need for reintervention.

The analyses suggest that urethroplasty is not cost-effective because it is likely to have a higher cost and does not result in a higher gain than urethrotomy. Reducing costs will improve the relative cost-effectiveness of urethroplasty. Further cost reduction for urethroplasty may be achievable by greater use of day-case surgery, which appears feasible,⁸⁸ and minimisation of follow-up.⁸⁹

The optimum outcome measure for routine clinical follow-up remains uncertain. In common with routine clinical experience, we found it difficult to motivate men to adhere to a follow-up schedule while they remained symptom free. In particular, attendance for measurement of maximum flow rate was poor and deteriorated over time. We considered whether or not a single question from the USS-PROM, such as self-rating of flow strength, aided by pictorial representation might be suitable.⁹⁰ During the trial this was sensitive to change and correlated well with improvement in maximum flow rate, but only about half of the participants answered the question after 2 years of follow-up. The primary result from the OPEN trial was reassuring to patients in that both urethroplasty and urethrotomy offered rapid symptom relief, sustained over 2 years, but there was no clear winner in terms of the 'best' procedure. The point estimate of symptom improvement showed a slight advantage for open urethroplasty, but this was less than the pre-stated minimum important difference on which we powered the study. Moreover, the CI included the possibilities of no difference and advantage for urethrotomy. Clinicians tend to favour objective outcome assessment, such as measurement of urinary flow rate and delineation of the stricture by visual inspection or radiographic imaging. Successful outcome of surgery is most often assessed by the rate of requirement for further intervention over a specified time period⁹¹ or improvement in maximum flow rate. Improvement of ≥ 10 ml/second in measured flow rate (Q_{max}) at 3 months and between 12 and 24 months was more likely in the urethroplasty group than in the urethrotomy group, although the number of participants with missing data was high, suggesting that this might not be a useful measure of outcome in routine care.

The important secondary outcome of need for reintervention showed a definite advantage for open urethroplasty, which had a 48% lower rate of recurrence over a minimum of 24 months and up to 4 years of observation, greater than the minimum important difference of 30% used in a secondary power calculation, and was statistically significant. A number of studies have investigated the usefulness of adjuncts that can be used at the time of, and following, urethrotomy to increase duration of benefit and decrease rate of recurrence, and hence overcome this main drawback of endoluminal treatment of stricture.

A number of participants undertook a period of intermittent self-dilatation with a plastic catheter following urethrotomy, which does have some evidence of effectiveness to support its use.¹⁸ The numbers were too small, however, to justify post hoc subgroup analysis in the OPEN trial. Other investigators have trialled a number of drugs injected into the strictures area at the time of urethrotomy, including steroids⁹² and mitomycin C,⁹³ but there is no robust evidence of benefit.⁹⁴ Another approach is to maintain luminal patency using an internal stent, but again there is no robust evidence of effectiveness.⁹⁵ Perhaps the most appropriate technology would be to combine an effective antifibrotic drug with a drug-eluting stent; developments for application in the field of urethral stricture are awaited.⁹⁶

Minor self-limiting adverse effects, particularly mouth pain from the graft donor site, were more common after urethroplasty, but severe complications were few for either procedure. Refinements to the urethroplasty technique to help minimise technical failure continue to be explored but the current results do appear stable and equivalent between different surgeons, countries and health-care systems.⁹⁷

From a health-care funder and planner perspective, the results suggest that both procedures should be available to men seeking relief of symptoms. We did not find that any particular subgroup of men defined by age or the number of previous interventions were more or less likely to benefit from either. Inclusion of these possible confounders and others did not modify the relative treatment effect. Higher procedure cost of urethroplasty is partially mitigated by the lower requirement for retreatment and the improvement in health state was similar for the two procedures at 2 years, although QALYs may be higher at 10 years for urethroplasty because of the lower requirement for retreatment. Nevertheless, for both the within-trial and model-based analyses, there was very little likelihood that urethroplasty would be considered cost-effective at values for a QALY that might be judged acceptable.

Our difficulties in recruitment did highlight the need for explicit and efficient care pathways to enable men to access urethroplasty, including change of provider if needed. Overall, the results of the OPEN trial provide the evidence required to enable well-informed shared decision-making discussions between patients and their urologists. The results will influence guideline formulation and planning of health-care provision.

Strengths and limitations

The OPEN trial was carried out in accordance with current best practice for pragmatic surgical trials. We used a remote internet-based randomisation system with the assignment algorithm written by an independent statistician to ensure concealment of allocation. This included stratification for the most important confounder: stricture severity defined by the time since previous intervention. We identified other possible confounders from our literature review. All likely confounders were well balanced across the two groups and their inclusion in the statistical model did not influence the primary result. 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 no obvious and feasible way to overcome this limitation. However, we think the repeated measure of outcome mitigates against this, given that likely demoralisation (or other) effects would dissipate over time from initial intervention. Although the primary outcome was subjective, we chose it because it was of most importance to men suffering recurrent stricture, as demonstrated by our qualitative study.³ We also included, as secondary outcomes, objective measures favoured by clinicians and a thorough health economic evaluation useful to funders and planners of health care. The randomised study design helps to minimise the risk of bias inherent in previous cohort studies. We anticipated that, in common with other pragmatic trials of surgical procedures being undertaken at the time of the OPEN trial, recruitment would be difficult.⁹⁸ To address this, we undertook a qualitative study as part of the feasibility phase. The study found wide support for the trial among men with recurrent stricture and urologists, which motivated us to persist with the trial. In addition, the qualitative study suggested two design modifications that were carried out: first, to establish general urology practices as research sites, with the aim of introducing the trial to men before they had formed strong preferences; and, second, to provide information resources to aid clinicians in balanced recruitment discussions. This was done by writing vignettes for use at site initiation visits and by producing a video showing how beliefs and preferences among possible participants could be challenged, to ensure a balanced discussion around possible trial participation. We also used emerging data as a more certain basis for a revised sample size calculation, which was checked and approved by external monitors of trial progress, and allowed a more realistic recruitment target to be set. The final trial results validated the assumptions made in the revised sample size calculation, with a SD for the primary outcome, scaled from 0 to 1, being 0.17 compared with the 0.21 that we assumed in the revised sample size calculation. These changes resulted in an increased recruitment rate over the final 12 months of the study, enabling attainment of the revised target sample size.

In common with previous clinical studies for this condition, attrition rates were relatively high and missing data points were frequent. For the primary complete-case ITT analysis we included 68% of those men randomised, a higher attrition rate (32%) than we anticipated (19%). The results of sensitivity analyses maintaining the groups as randomised and where multiple imputation for missing data was performed were able to include 90% of those randomised. In contrast a per-protocol analysis could include only 61% of those randomised. For all three analyses the proportion of included participants was lower in the urethroplasty group, owing to a lower questionnaire return rate, and, for the per-protocol analysis, a higher rate of crossover to the alternative intervention. This might be due to the longer interval between randomisation and intervention in the urethroplasty group. Despite these procedural difficulties, all three analyses showed consistent results for the primary outcome and the rate of reintervention. There are various degrees of missing EQ-5D-5L data across the different data collection points and, although this is inevitable for a surgical trial, it may affect the study results. Sensitivity analysis using multiple imputations, however, suggested that the study results were robust.

A further limitation of the study is the 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). The reasons for this imbalance are unknown, although the urethroplasty arm had longer waiting times between randomisation and intervention. Urethroplasty is usually available in specialty centres, whereas urethrotomy is more widely available. The imbalance between the two groups could also be due to the perceived intensity of the procedures. In any case, this could lead to biased estimates.

Generalisability

Baseline characteristics of the OPEN trial population were similar to recent published cohorts of men undergoing urethroplasty or urethrotomy. We found five recent studies validating translation of the USS-PROM from English into various languages.³¹⁻³⁵ The improvements found in voiding score were similar to the group of men allocated urethroplasty in the OPEN trial. The rate of recurrence following urethrotomy and the improvement in measured flow rate found in the urethrotomy group were also similar to the findings of recent published cohorts.^{15,99} A qualitative study from the USA found that men with recurrent stricture had similar concerns, particularly fear of retention, as documented in our qualitative study.²¹ It would therefore appear that the OPEN trial results are generalisable to the wider population of men suffering recurrence of bulbar urethra stricture across the world.

Future work

- Formulate methods to incorporate short-term disutility data into the main cost-effectiveness analysis.
- Survey pathways of care for men with urethral stricture across the UK NHS, including use of enhanced recovery after urethroplasty.
- Use other qualitative data and quantitative trial data to validate TTO findings.
- Establish a pragmatic and achievable follow-up schedule to allow national audit of outcomes following urethral surgery, with linkage to UK NHS Hospital Episode Statistics.

Chapter 7 Conclusions

The OPEN RCT provides unique high-level evidence of the relative benefits of open urethroplasty compared with endoscopic urethrotomy to manage recurrent bulbar urethral stricture in men. 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 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. This evidence will help inform discussions in the clinic and provision of impartial patient information. The current evidence on cost-effectiveness suggests that urethroplasty is highly unlikely to be considered cost-effective. However, this is mainly driven by the higher cost of urethroplasty compared with urethrotomy. Efforts to reduce the procedure cost for urethroplasty would substantially increase the likelihood that it could be cost-effective. Should that occur, then this would reinforce conclusions that the choice between urethrotomy and urethroplasty will remain preference sensitive, whereby men seeking treatment and clinicians advising them should come to a shared decision, guided by robust evidence provided by the OPEN trial and taking into account each individual's values and preferences. Health-care planners and funders should ensure equitable and ready access to the specialist care required for urethroplasty.

Recommendations for research

- Determine the most efficient pathway of care for men with urethral stricture, including enhanced recovery after urethroplasty.
- Identify factors driving choice of treatment in men with bulbar urethral stricture.
- Determine the most appropriate method of defining stricture recurrence.
- Experiment with adjunctive treatments that may lessen risk of recurrence after urethrotomy.
- A RCT to compare outcomes from non-transecting with transecting anastomotic urethroplasty.

Acknowledgements

We thank the patients and health-care professionals for their participation in qualitative interviews; Stewart Barclay, the patient and service user representative in the OPEN TMG; the TSC members, Roger Kockelburg (chairperson), John Matthews, Alan McNeil, Howard Kynaston and Neil Campling; DMC members, Gordon Murray (chairperson), Richard Martin and Thomas Pinkney. We also thank the following people who worked on the trial: Matthew Jackson, Research Fellow; Gladys McPherson, Data Manager; Lee Munro, Trial Manager; Rachel Stephenson, Trial Manager; Sue Tremble, Trial Manager; Robbie Brown, Trial Manager; Mark Deverill, Health Economist; Amy Collins, Project Secretary; Lavinia Miceli, Project Secretary; and Ann Payne, Project Secretary.

We thank Sarah Hill and David Mott, who contributed to the development and interviews of the TTO exercise; Joanne O'Connor and Beena David, who contributed to the interviews of the TTO exercise; and Peter Murphy and Wendy Robson for providing assistance when conducting TTO pilots in Freeman Hospital.

We thank all the volunteers and participants who took part in the TTO pilots and interviews, and the following sites and PIs for their support:

Trevor Dorkin, Freeman Hospital, Newcastle upon Tyne; Nick Watkin, St George's Hospital, London; Anthony Mundy, University College London Hospitals NHS Foundation Trust, London; Paul Anderson, Russells Hall Hospital, West Midlands; Suzie Venn, Queen Alexandra Hospital, Portsmouth; Ian Eardley, St James's University Hospital, Leeds; Mr David Dickerson, Weston General Hospital, Weston-super-Mare; Nikesh Thiruchelvam, Addenbrooke's Hospital, Cambridge; Richard Inman and Chris Chapple, Royal Hallamshire Hospital, Sheffield; Andrew Baird, Aintree University Hospital, Liverpool; Andrew Sinclair, Stepping Hill Hospital, Stockport; Rajeshwar Krishnanm, Kent and Canterbury Hospital, Canterbury; Rowland Rees, Southampton General Hospital, Southampton; James N'dow, Aberdeen Royal Infirmary, Aberdeen; Bruce Montgomery, Frimley Park Hospital, Surrey; Michael Swinn, East Surrey Hospital, Surrey; Alastair Henderson and John Donohue, Maidstone Hospital, Kent; Suzie Venn, St Richard's Hospital, Chichester; Robert Mason, Torbay Hospital, Torquay; Sanjeev Madaan, Darent Valley Hospital, Kent; Mustafa Hilmy, York Hospital, York; Vivienne Kirchin, Sunderland Royal Hospital, Sunderland; Kim Davenport, Cheltenham General Hospital, Cheltenham; John McGrath, Royal Devon Exeter, Hospital, Exeter; Tim Porter, Yeovil District Hospital, Yeovil; Ruaraidh MacDonagh and Amerdip Birring, Musgrove Park Hospital, Taunton; Ramachandran Ravi, Basildon University Hospital, Essex; Jawad Husain, Royal Albert Edward Infirmary, Wigan; Maj Shabbir, Guy's Hospital, London; Omer Baldo, Airedale General Hospital, West Yorkshire; Sadhanshu Chitale, Whittington Hospital, London; Mary Garthwaite, James Cook University Hospital, Middlesbrough; Shalom Srirangam, Royal Blackburn Hospital, Blackburn; Liaqat Chowoo, Bedford Hospital, Bedfordshire; Tina Rashid, Charing Cross Hospital, London; Rob Skyrme and Jon Featherstone, Princess of Wales Hospital, Bridgend; Ammar Alhasso, Western General Hospital, Edinburgh; and Oleg Tatarov, University Hospital of Wales, Cardiff.

We thank the following trusts for offering participant identification centre support:

Basingstoke and Northamptonshire NHS Foundation Trust; Royal Liverpool and Broadgreen University Hospitals NHS Trust; Chelsea and Westminster NHS Foundation Trust; and Wirral University Teaching Hospital NHS Foundation Trust.

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Robert Pickard (Professor of Urology) led the study and wrote the final report.

Beatriz Goulao (Research Fellow, Statistician) supervised by **Graeme MacLennan** (Professor of Medical Statistics and Director of CHaRT) performed the statistical analysis and co-wrote the final report.

Sonya Carnell (Senior Trial Manager, NCTU) and **Rebecca Forbes** (Trial Manager, NCTU) supported by **Stephanie Currer** (Trial Administrator, NCTU) and supervised by **Jennifer Wilkinson** (Senior Trial Manager, NCTU) managed the trial and co-wrote the final report.

Jing Shen (Senior Research Associate, Health Economist), supervised by **Luke Vale** (Professor of Health Economics), led the health economic evaluation and analysis, and co-wrote the final report.

John Norrie (Professor of Medical Statistics and Trial Methodology/Director of Edinburgh Clinical Trials Unit) contributed to the funding application and SAP. He commented on the final report and provided support to the statistical analysis team.

Matt Breckons (Research Associate, Qualitative Researcher), supervised by **Jing Shen**, carried out and wrote-up the TTO experiment.

Paul Whybrow (Research Associate, Qualitative Researcher), supervised by **Tim Rapley** (Professor, Medical Sociologist), carried out the qualitative research and co-wrote the final report.

Mark Forrest (Senior Information Technology Development Manager, CHaRT) managed and maintained the trial database.

Elaine McColl (Professor of Health Service Research) contributed to the funding application and protocol, and co-wrote the final report.

Daniela Andrich (Consultant Reconstructive Urological Surgeon), **Anthony Mundy** (Professor of Urology), **James N'Dow** (Professor of Urology) and **Stephen Payne** (Consultant Urological Surgeon) provided clinician support to the funding application, acted as PIs at key sites, and read and commented on the final report from a clinician perspective.

Stewart Barclay (Patient Representative) contributed a patient view to the trial, including the funding application, the protocol, input to the TMG and writing the final report.

Jonathan Cook (Associate Professor) was involved in the design of the study, interpretation and commented on the report. He also advised on sensitivity analyses around the primary result.

Nick Watkin (Professor of Urology) co-wrote the funding application, contributed clinical insight to the TMG and commented on the final report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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Appendix 1 Time trade-off protocol

To understand the short-term disutility of trade-offs that individuals may make in choosing between the two procedures of open urethroplasty and endoscopic urethrotomy, we will conduct a TTO exercise among a group of men eligible for trial participation and consented for this substudy, alongside the main trial.

Time trade-off theory

The TTO method is used to measure an individual's preference for particular health states. These preferences are measured in the form of utility values which, in the health context, are an assessment of how 'good' or 'bad' a health state is. Thus, different degrees of impairment can be weighted (or given a utility value) between 0 and 1, in which 0 is assumed to be equated to 'being dead' and 1 is equated with 'being in full/perfect health'.

Deriving utility values using the TTO method, health improvements are valued in terms of the amount of time an individual is prepared to spend in a worse health state in order to achieve a defined better health state. In the case of negative health consequences, disutility is measured in terms of the amount of time in perfect health an individual is prepared to sacrifice in order to avoid a defined worse health state.

Owing to the nature of the study, in which we are investigating short-term disutility, in addition to the conventional method of conducting TTO, we will also be using a chained method, and results from both methods will be compared. The conventional TTO method is commonly used to measure the utility of chronic health states in which participants typically remain in the impaired health state for the remainder of their lives. Temporary health states, however, only last for a defined period of time (e.g. days, weeks) before a return to normal health and, as a result, the conventional TTO method may become less feasible to use with temporary health states, as respondents may find it difficult to associate the severity of short-term impairment with death as a stated end point.^{81,82} In the chained method, an anchoring state is created to be used as a bridge between the temporary states and death.⁸⁴

Recruitment

The TTO will be conducted among the target patient population of men with recurrent bulbar urethral strictures. Patients will be identified by NHS clinical staff (principally consultant and trainee urologists) at participating centres as part of the trial. They will either be new referrals from primary care or men already under review in urology clinics. Following screening, eligible patients will be approached for their interest in participating (being randomised to a procedure) in the main trial. For both those men who consent to randomisation and those men who decline randomisation, they will also be asked for an expression of interest in participating in a 60-minute structured interview (TTO exercise), to explore their valuation of the health states with the immediate consequences of the two alternative procedures (*Table 36*).

Those men who express initial interest in participating in the TTO interview will be sent an invitation letter and the participant information sheet for this substudy. The patients will be asked to get in contact with the researchers if they wish to take part in the TTO study or require more information. If the patient fails to make contact after being sent the invitation letter and patient information sheet, we may try to make contact with them via telephone to gauge their continuing interest in the TTO study. Interviews will be arranged at a convenient time and place for the participants, and written consent will be sought before the start of the interviews.

TABLE 36 List of consequences for each procedure that are used to design the health profiles

Procedure	Common and well-understood consequences of treatment	Less common and unpleasant side effects	Rare events
Endoscopic urethrotomy	Mild urethral bleeding	Severe bleeding requiring reintervention	Extravasation of urine
	Local urinary tract infection		Persistent erectile dysfunction (> 12 months)
	Catheter discomfort	Systemic urinary infection (urosepsis) requiring parental antibiotics	
	Transient discomfort on passing urine after catheter removal	Transient (up to 12 months) erectile dysfunction	
Open urethroplasty	Mild mouth pain/discomfort if oral mucosal graft harvested	Severe mouth pain if oral mucosal graft harvested	Fistula formation
	Perineal wound pain	Scarring in mouth after oral mucosal harvest	Persistent erectile dysfunction (> 12 months)
	Catheter discomfort		
	Localised wound infection	Severe wound infection affecting deep layers	
	Local urinary tract infection	Systemic urinary infection (urosepsis) requiring parental antibiotics	
	Delayed healing requiring prolonged period of catheterisation	Transient (up to 12 months) erectile dysfunction	
	Transient discomfort on passing urine after catheter removal		
	Post-micturition dribble		

Health state profiles

Six health state profiles will be developed which describe the health consequences and discomforts immediately following the two procedures of open urethroplasty and endoscopic urethrotomy (three profiles for each procedure, representing 'best case', 'moderate case' and 'worse case' profiles for each procedure). The profiles are compiled based on information from health-care professionals on the likely consequences following each procedure, as well as findings from the qualitative interviews conducted in the pilot phase of the trial, in which patients provided a more personal and plausible account of their experience. The different health consequences and discomforts following each procedure can last for varying lengths of time, ranging from a few days to 4 weeks, and for consistency we chose 14 days as the length of the time used in the TTO study to value the health states.

In addition to the health state profiles for the effects of the procedures, there will also be a 'perfect health' profile and an anchoring state profile describing 'severe pain'. The anchor state profile will be used in the chained TTO^{81,82} in two stages: in the first stage it is evaluated as a temporary health state after which perfect health would resume, in the second stage it is evaluated as a short chronic state followed by death.

We will also use a set of practice profiles developed from the EQ-5D. These will be used to introduce the TTO method to participants at the beginning of the task, so that they become familiar with the procedure prior to completing the TTO exercise with the health states to be valued. For the chained TTO method we will use a practice profile before each of the two different stages, as the task differs slightly in each stage. Using practice profiles is common practice in TTO studies,¹⁰⁰ to reduce confusion with the task and thus increase the validity of the utilities derived.

An A3-size decision board will be used in the TTO exercises to help make the questions understandable to participants. The profiles will be printed on A5-size cards, coloured and laminated, using a different pastel colour for each health profile. During the TTO exercise, the health profiles will be placed on the decision board and the participant will be able to visually compare the length of time for each pair of health profiles being evaluated (detailed in *Interview schedule of time trade-off*).

Interview schedule of time trade-off

Two methods of TTO will be conducted: the conventional method and the chained method. There is an interview schedule designed for each method. Participants will be randomly allocated to one of the methods. The general approach is similar for each method; however, the chained TTO requires an additional step. In both methods, respondents will also be asked to rank the six health profiles to be valued from the best to the worst. Additionally, sociodemographic information will be collected at the interview to aid final analysis.

The conventional method

Respondents will be offered a choice between two alternative 'lives'. Life A, containing the less desirable health state (temporary health; h_i), is measured relative to life B, which contains the best health state (perfect health; 1). The respondents will be shown on the decision board one of the health state profiles describing the health consequences post treatment for the length of time (t) as life A and the perfect health profile as life B. The time in life A will be fixed at t (14 days), whereas there is a moving slider for the length of time (between 0 and t) spent in life B. Both lives are set at the maximum length t initially. Respondents will be asked to find a point on the board with the slider pointing at a time (x) for life B, at which they are indifferent to the length of time spent in life A (t) and life B (x). This is achieved by asking respondents a series of questions for each profile while moving the slider for life B. 'Assuming you are either in life A or life B for the specified number of days shown on the board, after which time you will die painlessly, which life would you prefer?' If the participant has a preference for life B, we will reduce the time (x) spent in life B, and if the respondent prefers life A, we will increase the time (x) spent in life B. The above question will be repeated until a point of indifference is reached, by confirming with the respondent that 'you consider spending t days in life A is equivalent to spending x days in life B', then we will take a note for the length of time the respondent settles on (x). We will do the same for all six health profiles to be valued in a random order.

For analysis, the value of each health state (h_i) is then calculated as:

$$h_i = x/t. \quad (1)$$

The chained method

This method requires two stages of comparison. In the first stage, we will ask the respondents to compare each health state profile (h_i) as life A with an anchor state (h_j) as life B. As with the conventional method, the number of days (t) in life A will be fixed at 14 days and the number of days (x) in life B will also be initially set at 14 days. Respondents will be asked a similar question to that in the conventional method, but instead of death following the length of time spent in the health states, they would return to full health: 'Assuming you are either in life A or life B for the specified number of days shown on the board, after which time you will return to full health, which life would you prefer?' If the participant has a preference for life B, we will increase the time (x) spent in life B; and if the respondent prefers life A, we will reduce the time (x) spent in life B. The above question will be repeated until a point of indifference is reached, by confirming with the respondent that 'you consider spending t days in life A is equivalent to spending x days in life B', then we will take a note for the length of time the respondent settles on (x). We will do the same for all six health profiles to be valued in a random order.

The second stage is then carried out to compare the anchor state profile with the perfect health profile. In this stage, participants will choose between the anchor state as life A for 14 (t) days and perfect health as life B for (y) days conducted using the conventional TTO approach. We choose to leave the value as 14 days to be consistent with the rest of the valuations, despite the length of life being relatively short for use in a conventional TTO method.

For analysis, the value of the anchor state (h_j) is calculated as:

$$h_j = y/t. \quad (2)$$

The utility of each health profile is then calculated as:

$$h_i = 1 - (1 - h_j) \times \left(\frac{x}{t}\right). \quad (3)$$

Appendix 2 Interview schedule: men who accepted randomisation

OPEN STUDY

QUALITATIVE SUB-STUDY

Draft Qualitative Interview Topic Guide – Accepted to take part in trial

The interview schedule is developmental. The questions will need to be tailored to the specific answers of each interviewee. As analysis proceeds and findings need to be further explored, question areas may be modified or new ones introduced. The interview schedule given here is therefore a general topic guide for the one-to-one qualitative interviews.

Introduction

Interviewee consent – discuss participant’s consent to be interviewed:

- Check participant is happy to go ahead with the interview
- Go through the consent form (emphasize confidentiality)
- Check participant is happy with audio recording of the interview
- Ask if there are any questions or concerns

Purpose of the study – You were approached about taking part in a trial about surgery for a urethral stricture. This interview is part of an additional study. We don’t know much about why people do or do not want to be involved in randomised controlled trials.

Aim of the interview – We are interested in hearing your opinions about a number of things such as your understanding of research, why you wanted to take part and how you have felt about the process so far.

Core Questions

Q1 Introduction to the trial

- How did you first hear about the trial?
 - Who first told you about it?
 - Had you meet them before?
 - What did you think about them?
 - What did they say?
 - What questions did you have?
 - What was your initial reaction?
 - What concerns did you have (if any)?

Q2 Recruitment information

- What did you think about the written information they gave you about the trial?
 - Is there any additional information you would have liked to have?
- Did you talk to anyone about taking part in the trial?
 - Partner? Family? Friends? Other Health Professionals?
 - What did you say to them?
 - What advice did they offer you?
- What concerns did you have (if any)?
 - What concerns did anyone else have (if any)?

Q3 Consent Meeting & Discussing Randomization Process

- What happened when you went to the follow-up meeting about taking part in the trial?
 - Did you go alone?
 - Who did you meet?
 - Had you meet them before?
 - What did you think about them?
 - What did they say?
- What questions did you ask?
 - What answers were you given?
- How was the randomization process explained to you?
 - How well do you feel you understood what the randomization process is?
 - Did you have any concerns about this?
 - What concerns did anyone else have (if any)?
- Did you feel that you had enough time to consider taking part in the trial?

Q4 Decision

- Why did you decide to take part in the trial?
 - What were/are your key concerns (if any)?
 - What were/are others key concerns (if any)?

Q5 Closing questions

- Have there been any aspects that you have found difficult so far?
- What could they do to improve your experience of taking part so far?
- What changes would you like to see made?
- What advice would you give to other people thinking about taking part in the trial?
- Is there anything else you would like to add?

Thank you for taking part in this interview

Appendix 3 Interview schedule: men who declined randomisation

OPEN STUDY

QUALITATIVE SUB-STUDY

Draft Qualitative Interview Topic Guide – Declined to take part in trial

The interview schedule is developmental. The questions will need to be tailored to the specific answers of each interviewee. As analysis proceeds and findings need to be further explored, question areas may be modified or new ones introduced. The interview schedule given here is therefore a general topic guide for the one-to-one qualitative interviews.

Introduction

Interviewee consent – discuss participant’s consent to be interviewed:

- Check participant is happy to go ahead with the interview
- Go through the consent form (emphasize confidentiality)
- Check participant is happy with audio recording of the interview
- Ask if there are any questions or concerns

Purpose of the study – You were approached about taking part in a trial about surgery for a urethral stricture. This interview is part of an additional study. We don’t know much about why people do or do not want to be involved in randomised controlled trials.

Aim of the interview – We don’t want to change your mind about not taking part in the trial but we are interested in hearing your opinions about a number of things such as your understanding of research, why you didn’t want to take part and how you have felt about the process so far.

Core Questions

Q1 Introduction to the trial

- How did you first hear about the trial?
 - Who first told you about it?
 - Had you meet them before?
 - What did you think about them?
 - What did they say?
 - What questions did you have?
 - What was your initial reaction?
 - What concerns did you have (if any)?

Q2 Recruitment information

- What did you think about the written information they gave you about the trial?
 - Is there any additional information you would have liked to have?
- Did you talk to anyone about taking part in the trial?
 - Partner? Family? Friends? Other Health Professionals?
 - What did you say to them?
 - What advice did they offer you?
- What concerns did you have (if any)?
 - What concerns did anyone else have (if any)?

Q3 Consent Meeting & Discussing Randomization Process

- What happened when you went to the follow-up meeting about taking part in the trial?
 - Did you go alone?
 - Who did you meet?
 - Had you meet them before?
 - What did you think about them?
 - What did they say?
- What questions did you ask?
 - What answers were you given?
- How was the randomization process explained to you?
 - How well do you feel you understood what the randomization process is?
 - Did you have any concerns about this?
 - What concerns did anyone else have (if any)?
- Did you feel that you had enough time to consider taking part in the trial?

Q4 Decision

- Why did you decline to take part in the trial?
 - What were/are your key concerns (if any)?
 - What were/are others key concerns (if any)?

Q5 Closing questions

- Have there been any aspects that you have found difficult so far?
- What could they do to improve your experience of taking part so far?
- What changes would you like to see made?
- What advice would you give to other people thinking about taking part in the trial?
- Is there anything else you would like to add?

Thank you for taking part in this interview

Appendix 4 Interview schedule: clinicians

OPEN STUDY

QUALITATIVE SUB-STUDY

Draft Qualitative Interview Topic Guide – Staff

The interview schedule is developmental. The questions will need to be tailored to the specific answers of each interviewee. As analysis proceeds and findings need to be further explored, question areas may be modified or new ones introduced. The interview schedule given here is therefore a general topic guide for the one-to-one qualitative interviews.

Introduction

Interviewee consent – discuss participant’s consent to be interviewed:

- Check participant is happy to go ahead with the interview
- Go through the consent form (emphasize confidentiality)
- Check participant is happy with audio recording of the interview
- Ask if there are any questions or concerns

Purpose of the study – You have been working on the OPEN trial about comparing open urethroplasty versus endoscopic urethrotomy. This interview is part of an additional study. We don’t know much about the role of staff in delivering randomised controlled trials.

Aim of the interview – We are interested in hearing your opinions about a number of things such as your practical experience of delivering the trial, how the trial has impacted on the work of the unit and your understanding of the impact on the patients involved.

Core Questions

Q1 Introduction to the trial

- How did you first hear about the trial?
 - What was your initial reaction?
 - What questions did you have?
 - What concerns did you have (if any)?

Q2 Usual practice

- Which treatments does your centre usually offer patients?
 - What factors do you feel most influence this?
 - Access to local expertise?
 - Local culture/custom and practice?
 - Evidence-base?
 - Local context/top-down directives
 - Cost considerations?
 - Has this changed over time?
- What are the factors you normally consider when recommending open urethroplasty to patients?
 - What are the key advantages and disadvantages for you?

- What are the factors you normally consider when recommending endoscopic urethrotomy to patients?
 - What are the key advantages and disadvantages for you?
- Has the trial impacted on your usual practice in any way?

Q3 Trial work

- How did the set-up of the trial go?
- How is recruitment going so far?
- How well do you feel patients are engaged and supported in the trial?
 - How effective do you feel the PIS are?
 - What are the key concerns they (or their family) raise?
 - How do you manage these?
 - What changes would you like to see to support patients' decision making more (if any)?
- How does this trial impact on your existing workload?
- How does it impact on the work of the unit as a whole?
 - Did you have enough support/time?
 - What changes would you like to support the staff more (if any)?
- Have you been involved in the delivery of other trials?
 - How does this one compare?

Q4 Closing questions

- Have there been any other aspects that you have found difficult or problematic so far?
- What can we do to improve how the trial is run?
- What changes would you like to see made?
- Is there anything else you would like to add?

Thank you for taking part in this interview

Appendix 5 Recruitment vignettes

Recruitment vignettes that are developed from real cases and illustrate patient eligibility and good recruitment practices

<p>Patient 1 Mr. RZ DoB: 14/01/1984</p> <p>RZ has been having serious difficulty urinating for the last five years, but has not previously presented his symptoms. Having seen an operation on 'embarrassing bodies', he decided to ask his GP for a referral. An x-ray reveals a very tight, long stricture. His flow is 4mls per second, leaving approximately 400ml in his bladder. RZ is keen to have the reconstructive surgery seen on television.</p> <p><i>The patient is not eligible because he has not previously been treated for urethral stricture. However, some clinicians feel that urethroplasty may be justified where the stricture is severe.</i></p>	<p>Patient 4 Mr. NB DoB: 07/01/1976</p> <p>NB has received numerous urethrotomies and practices daily ISD. He has previously been told about urethroplasty, but says that he is managing fine without a serious operation. He has been given a child-sized tube for ISD. The stricture is severe, making urethrogram very difficult. NB is otherwise healthy, of average weight and low blood pressure.</p> <p><i>The patient is eligible for the OPEN trial and should be invited to participate. Some clinician urge patients to consider urethroplasty when their symptoms are severe.</i></p>
<p>Patient 2 Mr. ML DoB: 07/09/1952</p> <p>ML first presented with stricture symptoms seven years ago. Since then he has received two urethrotomies. From his description, recurrence happened about a year and a half after each procedure. His flow rate is slow but still manageable. He does not see himself as having a problem that necessitates a 'serious' operation.</p> <p><i>LM eligible for OPEN trial and should be invited to participate. During consultations, clinician should explain why there is uncertainty between the procedures.</i></p>	<p>Patient 5 Mr. MT DoB: 03/05/1962</p> <p>MT has suffered with a stricture most of his adult life and has received numerous urethrotomies. His records show that he also had a urethroplasty operation in 2004. MT has a higher than average blood pressure and is overweight. His flow rate had become gradually slower and he is happy to try anything to get it sorted.</p> <p><i>Although the patient has had a previous urethroplasty, he is still eligible and should be invited to participate.</i></p>
<p>Patient 3 Mr. ST DoB: 23/04/1976</p> <p>ST has returned to clinic after his first urethrotomy operation four months ago. He says after an initial relief from his symptoms his flow rate quickly deteriorated. He feels frustrated and let down by the operation and wants to discuss a long-term solution.</p> <p><i>Although the patients felt they have made up their mind, they are eligible for the study and should be invited to participate. The recruiting consultant should explain why there is uncertainty between the available procedures.</i></p>	<p>Patient 6 Mr. NN DoB: 21/09/1983</p> <p>NN has returned to clinic after his stricture has returned three years after his initial urethrotomy. He wants to take part in the trial to help out people like him. However, he dislikes the idea of randomisation and says he would prefer to take part and choose his treatment.</p> <p><i>It is important that patients only take part if they are happy to be randomised. Recruiters should explain the process of randomisation and answer any concerns the patient has.</i></p>

Appendix 6 Consolidated Health Economic Evaluation Reporting Standards checklist

The CHEERS checklist: items to include when reporting economic evaluations of health interventions.

Section/item	Item number	Recommendation	Reported on page number/line number
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms, such as 'cost-effectiveness analysis', and describe the interventions compared	Not applicable. Economic evaluation was conducted as part of a clinical trial
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions	Page vii/lines 4–11 Page viii/lines 23–26 and 29–32
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study Present the study question and its relevance for health policy or practice decisions	Page 5/lines 6–22
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed, including why they were chosen	Page 7/lines 33–39 and page 9/lines 1–14
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	Page 7/lines 15–26
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	Page 57/lines 13–15
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	From page 2/line 11 to page 4/line 41
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	Page 57/lines 3–10
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Page 57/lines 13–15
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	From page 60/line 13 to page 61/line 28
Measurement of effectiveness	11a	Single study-based estimates: describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	From page 7/line 5 to page 22/line 7
	11b	Synthesis-based estimates: describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	Page 71/line 9 Page 71/lines 32–37

Section/item	Item number	Recommendation	Reported on page number/line number
Estimating resources and costs	13a	Single study-based economic evaluation: describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	Page 57/line 20 to page 60/line 12
	13b	Model-based economic evaluation: describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	Page 65/line 10 to page 66/line 5 Page 68/lines 1–5/see <i>Table 33</i>
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	Page 57/lines 24 and 25 and page 23/line 4
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	Page 65/lines 3–10 Page 66/see <i>Figure 15</i>
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model	Page 65/lines 3–13 Page 68/lines 1–18 and page 69/lines 1–4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	Page 67/lines 1 and 2 Page 57/lines 8 and 9 Page 60/lines 13–23 and page 61/lines 1–25
	Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended	Pages 67/see <i>Table 33</i>
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report ICERs	Page 62/lines 3–17/ see <i>Table 32</i> Page 68/lines 23–43/ see <i>Table 34</i>
Characterising uncertainty	20a	Single study-based economic evaluation: describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	Page 62/lines 8–17
	20b	Model-based economic evaluation: describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	Page 68/lines 26–43

Section/item	Item number	Recommendation	Reported on page number/line number
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	Not applicable
Discussion			
Study findings, limitations, generalisability and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	Page 75/lines 41–44 Page 76/lines 35–41 Page 77/lines 33–41
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support	Page xxv
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with the International Committee of Medical Journal Editors' recommendations	Pages iii

Appendix 7 Health state profiles

Health state profiles used in the study

Control intervention urethrotomy health state profiles

Urethrotomy: mild

- Discomfort in the penis and bladder from using a catheter for a few days.
- Brief discomfort on passing urine after the catheter is removed.
- A few drops of blood after you have finished passing urine.
- Mild urinary tract infection giving you mild fever-like symptoms.

Urethrotomy: moderate

- Discomfort in the penis and bladder from using a catheter for a few days.
- Discomfort on passing urine after the catheter is removed.
- Moderate urethral bleeding which requires you to keep the catheter in longer or have a telescopic examination under anaesthetic.
- Serious urinary tract infection which makes you feel ill and requires you to stay in hospital overnight for antibiotics from an intravenous drip.

Urethrotomy: severe

- Discomfort in the penis and bladder from using a catheter.
- Severe urethral bleeding which requires you to have a telescopic examination under anaesthetic.
- Serious urinary tract infection which makes you feel ill and requires you to stay in hospital overnight for antibiotics from an IV drip.
- Severe pain in the penis and bladder area, requiring you to take regular painkillers.
- Difficulty getting and maintaining a penile erection for sex.

Experimental intervention urethroplasty health state profiles

Urethroplasty: mild

- Discomfort in the penis and bladder from using a catheter.
- Mild mouth pain or discomfort when you eat or drink.
- Mild urinary tract infection giving you mild fever-like symptoms.
- Mild swelling and wound pain in the area between the testes and back passage.

Urethroplasty: moderate

- Discomfort in the penis and bladder from using a catheter.
- Moderate and constant mouth pain and scarring in the mouth needing regular painkillers.
- Serious urinary tract and wound infection which makes you feel ill and requires you to stay in hospital overnight for antibiotics from an intravenous drip.
- Moderate wound pain in the area between the testes and back passage needing regular painkillers.

Urethroplasty: severe

- Discomfort in the penis and bladder from using a catheter.
- Severe and constant mouth pain and scarring in the mouth needing regular painkillers.
- Serious urinary tract and wound infection which makes you feel ill and requires you to stay in hospital overnight for antibiotics from an intravenous drip.
- Severe wound pain in the area between the testes and back passage, needing regular painkillers.
- Leakage of urine from the area between the testes and back passage, requiring you to wear incontinence pads.
- Difficulty getting and maintaining a penile erection for sex.

EME
HS&DR
HTA
PGfAR
PHR

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*This report presents independent research funded by the National Institute for Health Research (NIHR).
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