Clarifying the management of men with recurrent urethral stricture: a pragmatic, randomised, multicentre superiority trial of **op**en urethroplasty versus **en**doscopic urethrotomy.

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1. TRIAL REGISTRATION

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Nick Watkin, Acting Chief Investigator

Signature ..... Date .....

Graeme MacLennan, Statistician

Signature ..... Date .....

Jennifer Wilkinson, Senior Trial Manager

3.2. Principal Investigator signature at individual study site

I confirm that I have read and understood protocol version 1.8 dated 3rd October 2016. I agree to comply with the study protocol, the principles of Good Clinical Practice, research governance, clinical trial regulations and appropriate reporting requirements.

Signature ..... Date .....

Print Name .....

Site ID .....

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5. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
BAUS	British Association of Urological Surgeons
CHaRT	Centre for Healthcare Randomised Trials, University of Aberdeen
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQoL 5 Dimension questionnaire (5-level version)
GCP	Good Clinical Practice for clinical trials
HRQoL	Health-Related Quality of Life
HSRU	Health Services Research Unit, University of Aberdeen
HTA	Health Technology Assessment Programme
ICIQ-Male SF	International Consultation on Incontinence Modular Questionnaire Male Short Form
IEEF	International Index of Erectile Function
IHS	Institute of Health and Society, Newcastle University
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NIHR CLRN	NIHR Comprehensive Local Research Network
NIHR CSP	NIHR Coordinated System for gaining national central NHS Permission
PI	Principal Investigator
PIC	Participant Identification Centre
PMG	Project Management Group
PROM	Patient-Reported Outcome Measure
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development Departments of NHS Trusts
SD	Standard Deviation
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UTI	Urinary Tract Infection

6. RESPONSIBILITIES

6.1. Sponsor

The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

The following functions falling under the responsibility of the sponsor will be delegated to the Chief Investigator (CI) Robert Pickard or the Acting Chief Investigator Nick Watkin:

- Ethics Committee opinion; including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial.
- Research and Development (R&D) approval; including application for global checks via the National Institute for Health Research Coordinated System for gaining national central NHS Permission (NIHR CSP).
- Good Clinical Practice (GCP) and trial conduct; including GCP arrangements, data monitoring, emergency and safety procedures.
- Administration of funding for the study.

6.2. Funder

This study has been funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, project reference 10-57-23.

6.3. Trial Management

The trial will be managed through the Newcastle Clinical Trials Unit (NCTU) with data management and statistical analysis being the responsibility of the Centre for Healthcare and Randomised Trials (CHaRT) in Aberdeen. The Trial Management Group (TMG) will be responsible for pursuing the trial according to the protocol. The TMG will include the co-applicants and senior trial staff. The Principal Investigators (PI) will be responsible for the day-to-day conduct of the study at their individual sites. The trial management team in Newcastle will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visits and routine monitoring visits. Quality control will be maintained through adherence to Standard Operating Procedures (SOP) within NCTU and CHaRT in Aberdeen, and within the research teams at each site. Quality control will also be maintained by adherence to protocol, the principles of GCP, research governance and clinical trial regulations. The TMG will meet at least twice per year and more frequently if required. Meetings of the NCTU trial management team will be convened by the Trial Manager on a regular basis, with meeting frequency dependent on study needs. The Data Manager at CHaRT will convene meetings of the data management team as needed. In addition, the Trial Manager in Newcastle and the Data Manager in Aberdeen will hold telephone conferences as required. The day-to-day management of the trial will be co-ordinated by the Trial Manager in Newcastle.

6.4. Principal Investigator

The PI will have overall responsibility for the conduct of the study at a particular trial site with the following responsibilities:

- Study conduct and the welfare of study participants.
- Familiarity with the study interventions.
- Screening and recruitment of subjects.
- Compliance with protocol, recording of protocol deviations and reporting of serious adverse events (SAE).
- Ensuring trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- Submission of the study for site-specific approval and for any additional local approvals required by the NHS organization responsible for the local trial site through the appropriate Research and Development (R&D) department.
- Accessing assistance from NIHR Comprehensive Local Research Network (CLRN)-funded staff.

- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, the Data Protection Act and any other relevant legislation and regulatory guidance.
- Ensuring that no participant is recruited into the study until all relevant local regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- Providing evidence of being suitably qualified to assume responsibility for the conduct of the trial. A current signed and dated curriculum vitae will be lodged in the Trial Master File and the Investigator Site File.
- Ensuring Site team members are qualified by education, training and experience to conduct the study; that their roles and responsibilities in the study are clearly identified on the site delegation log; and that their signed and dated current CVs are included in the Investigator Site File.
- Being available for Investigator meetings, monitoring visits and in the case of audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining an Investigator Site File, including copies of study approval, CVs of site staff, delegation log, screening logs, list of subjects and their signed informed consent forms.
- Documenting appropriate delegation of tasks to other study personnel e.g. Research Nurse, Co-Investigator(s), Trial Coordinators, Data Managers.
- Ensuring data collected is accurate, timely and complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 10 years following the end of the study, unless local arrangements stipulate a longer period.

7. PROTOCOL SUMMARY

Short title:	Open urethroplasty versus endoscopic urethrotomy
Protocol version:	1.8
Protocol date:	3rd October 2016
Chief Investigator:	Professor Robert Pickard
Acting Chief Investigator:	Nick Watkin
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR HTA programme
Study design:	Pragmatic, randomised, multi-centre superiority trial
Study interventions:	Experimental: open urethroplasty Control: endoscopic urethrotomy
Primary objectives:	1. Determine the intervention for recurrent bulbar urethral stricture that offers the most effective symptom control over 24 months. 2. Determine the relative cost-effectiveness of each intervention over 24 months.
Secondary objectives:	1. Determine the difference in objective outcome (urine flow rate). 2. Determine differences in recurrence and re-intervention rates. 3. To establish the safety profile of each procedure. 4. Determine the comparative quality of life (QoL) benefits, harms, costs and cost-effectiveness modelled over 10 years. 5. Determine the relative impact on symptom control and quality of life over the total study duration (median time since intervention). 6. To determine the relative rate of need for re-intervention over the total study duration (median time since intervention).
Primary outcome:	Area under curve (AUC) for serial repeated measurement of ICIQ-Male Short Form (ICIQ-Male SF) questionnaire over 24 months following randomisation.
Number of study sites:	Approximately 50
Study population:	210 men
Study duration:	63 months

8. BACKGROUND

Urethral stricture is a narrowing of the urethra caused by scarring after injury or infection. It is the commonest cause of difficulty passing urine in younger and middle aged men. The prevalence is approximately 200 per 100,000 men in their 20s rising to 900 per 100,000 men in their 70s. Urethral strictures affect about 62,000 men in the UK at any one time[1]. In the NHS in England this corresponds to 17,000 hospital admissions annually, 16,000 bed-days and 12,000 operations at a cost in excess of £10M[2]. The hallmarks of a urethral stricture are progressive voiding lower urinary tract symptoms and reduced maximum urinary flow rate (Q_{max} < 15 ml/s). The site and length of a stricture is characterised by endoscopic inspection and urethrographic imaging. The stricture is typically between one and five centimetres long and located in the section of urethra that runs between the legs in the perineum (bulbar urethra). Symptomatic men with a bulbar stricture need surgical treatment to widen the narrow section. The standard approach for newly diagnosed strictures is endoscopic urethrotomy. A rigid endoscope with cold steel blade attached to the end is passed into the urethra and the diseased segment is widened by incising it longitudinally through to healthy tissue. Cure rates for this first urethrotomy (defined as no recurrence within two years) are between 40 and 70%[3].

For men with a bulbar urethral stricture disease who recur after initial urethrotomy, the best way to tackle the recurrent stricture is uncertain. Repeat urethrotomy and urethroplasty are both reasonable options, and the choice between the two is the focus of this study. Repeat urethrotomy is more commonly performed for recurrent bulbar stricture because it is minimally invasive; does not require specialist surgical expertise, and has a short period of catheterisation and recovery. There is, however, a high rate of recurrence ranging from 50 to 100% (median 80%) at two years. Subsequent multiple recurrences can lead to a chronic stricture state requiring repeated urethrotomies, on average every two years during a man's lifetime[4]. While it is minimally invasive, endoscopic urethrotomy carries a significant risk of adverse effects; including protracted bleeding (6%) and urinary tract infection (UTI; 10%), leading to unplanned hospital admissions and unforeseen cost[5].

The alternative to endoscopic urethrotomy is reconstructive open urethroplasty. The urethra is approached through a skin incision in the perineum behind the scrotum and the narrow section is cut out (excised) or reconstructed. For strictures that are short and supple, simple excision and re-joining of the cut ends is performed (anastomotic urethroplasty). Most strictures however require a patch of graft material (patch urethroplasty) to rebuild the diseased area and permanently widen the lumen[6]. Urethroplasty was traditionally reserved for men with rapidly recurring strictures after multiple urethrotomies or complete obliteration of the urethral lumen, and was performed in a small number of specialist centres. Greater availability of trained urethroplasty surgeons; use of managed care pathways to reduce hospital stay, and adoption of oral mucosa as graft material has broadened its application. The main advantage of open urethroplasty is that it appears to offer a high rate of long term cure. A median success rate of 90% freedom from stricture recurrence at two years has been reported in two systematic reviews[6,7]. These success rates seem generalisable with similar outcomes reported in the United Kingdom and United States[8,9]. Major complications following urethroplasty for bulbar strictures are uncommon. Wound infection (5%) and post-micturition dribble (10%) are the most frequently occurring harms, together with temporary pain at the donor site in the mouth when an oral mucosal graft is harvested[6,10].

Despite promising superior long term success rates for urethroplasty, endoscopic urethrotomy remains the most frequently used treatment for recurrent bulbar strictures. Hospital episode statistics from NHS England show that 713 urethroplasties were carried out in 2010 compared with 15,000 endoscopic urethrotomies[2]. The reason for the restricted use of urethroplasty is attributable to a complex blend of clinician, patient and economic factors. In the United States clinician surveys indicate that about 70% of urologists would advise patients to proceed to repeat urethrotomy on initial stricture recurrence rather than consider urethroplasty[11]. Similarly, men undergoing urethroplasty in the UK have had a median of between three and five previous urethrotomies[12]. Data from the UK healthcare surveillance organization *Dr Foster,* suggests that 3,075 men in England had a urethrotomy for recurrent stricture in 2010. In both countries expert opinion has emphasised the underutilisation of urethroplasty surgery[13]. From the health economic perspective, a straightforward UK cost comparison proposed that a strategy of initial urethrotomy followed by urethroplasty at first recurrence was the most cost-effective management pathway[14]. In the United States, decision analytical modelling employing cost-minimisation and cost-effectiveness methodologies found that initial urethrotomy followed by urethroplasty on recurrence was the best strategy for men with bulbar urethral strictures[4,15]. The current lack of evidence regarding comparative effectiveness to inform decision-making has been confirmed by a recent Cochrane systematic review[16].

In the end, individual men have to make a trade off the between the invasiveness and effectiveness of each operation. In the NHS at the present time the decision-making process may be influenced by availability of local expertise and clinician guidance. In the OPEN trial, men with recurrent bulbar urethral strictures will be randomized to open urethroplasty or endoscopic urethrotomy. The aim is to determine which operation is most clinically-effective and which operation is most cost-effective.

9. OBJECTIVES

9.1. Summary of Research Objectives

The primary objective is to determine the relative clinical effectiveness and cost-effectiveness of open urethroplasty against the standard of endoscopic urethrotomy for the treatment of men with recurrent bulbar urethral stricture within the NHS. Outcomes will be collected until the end of study for each participant and analysed at trial termination according to intention to treat. Through existing collaboration with the British Association of Urological Surgeons (BAUS) audit database we will collect longer term outcome data from participants at five and ten years.

9.2. Hypothesis

The null hypothesis is that the clinical effectiveness and cost-effectiveness of open urethroplasty is not superior to endoscopic urethrotomy.

9.3. Feasibility and Acceptability Evaluation (Pilot Phase)

The first 10 months of this trial (45 site-months of active recruitment) will form a feasibility phase to ensure that recruitment to target is achievable. During this phase we will carry out qualitative research to explore possible barriers to recruitment and ensure that our trial processes and information are acceptable to patients and clinicians.

Specific objectives are:

- To establish whether the proposed rate of recruitment is feasible within the UK NHS.
- To identify barriers to recruitment and advise trial processes accordingly
- To determine which factors are important to men with bulbar urethral strictures in differentiating between treatments and agreeing to trial participation.
- To determine factors clinicians take into consideration when recommending specific treatments.
- To explore the short term disutility of trade-offs that men make when choosing between the two procedures.

9.4. Full trial phase

Provided recruitment to target is deemed feasible from the initial feasibility phase of the trial we will progress seamlessly to the full trial phase and increase the number of centres and accelerate the rate of recruitment.

Primary objectives are:

- To determine the relative impact on trajectory of symptom control and quality of life profile over 24 months.
- To determine the incremental cost per quality-adjusted life year (QALY) at 24 months.

Secondary objectives are:

- Clinical:
    - To determine the relative change in urinary flow rate at 24 months.
    - To determine the relative rate of recurrence and need for re-intervention up to 24 months.
    - To establish the safety profile of each procedure.
    - To determine the relative impact on symptom control and quality of life over the total study duration (median time since intervention).
    - To determine the relative rate of need for re-intervention over the total study duration (median time since intervention).

- Economic:
    - To calculate the incremental cost per QALY of the most effective treatment over 10 years.

10. STUDY DESIGN

10.1. Summary

This is a 50-centre, pragmatic patient randomised two-arm superiority trial comparing, in parallel groups, open urethroplasty (experimental) against endoscopic urethrotomy (control) for men with recurrent bulbar urethral stricture. The trial is set in a range of specialist and general NHS urology units. Patients and surgeons cannot be blinded to the allocated procedure. Central trial staff managing and analysing trial data will, as far as possible, be blinded to allocated group. We will perform a short term (within-trial) cost utility analysis, and a long term cost-utility analysis using a Markov model. During the initial feasibility phase thematic analysis of semi-structured interviews with participants and clinicians will explore factors that result in decisional conflict between the treatment options and which may affect willingness to be randomised. The time trade-off method will be used to estimate short-term disutility.

10.2. Criteria for Progression from Feasibility

The feasibility threshold for continuing the trial as planned will be completion of 45 site-months of active recruitment expected within 10 months of trial commencement following the progressive set up of the first 18 sites. During this period we expect to randomise approximately 45 participants. If we recruit 20 participants or less we will consider recruitment not feasible, and unless there are compelling mitigating circumstances we will terminate the project.

If we recruit 21 to 30 participants we will significantly revise the recruitment strategy, giving consideration to the addition of new sites or an extended period of active recruitment.

If we recruit 31 or more participants we will consider this to be within sampling variability of the stated target of 45 participants, and that only finessing of the recruitment strategy is indicated.

We plan for the majority (estimated at 30 site-months) of the 45 site-months to come from seven 'premier' feasibility sites set up over trial months five to six; the first two months of the six month recruitment phase of the feasibility study which is planned to run from trial calendar months five to 10. The purpose of the further 11 sites set up subsequently during the later feasibility period is to provide additional information from a more diverse set of centres. This will facilitate smooth expansion to the full study of 50 sites, avoiding a loss of momentum and assuming progression is warranted. If these thresholds are surpassed it will strongly indicate that recruitment of at least 210 participants can be achieved by trial month 38 after progressive set up of the remaining 20 sites.

10.3. Consort diagram

The anticipated trial flow for participants is illustrated in Figure 1.

10.4 Trial participants, Duration and Setting

We will recruit from the population of adult men seeking treatment within the NHS for recurrent bulbar urethral stricture. The setting is therefore NHS hospitals throughout the UK where this activity is carried out and within the community for follow up. The time delay between randomisation and performance of the allocated intervention will be minimised as far as possible within NHS constraints. We expect to randomise 210 participants over a 38 month period. For primary outcome purposes, follow up will continue for 24 months after randomisation. Recruitment started in February 2013 (trial month 4) and is set to end on 31st December 2015 (Trial month 38). For secondary outcome purposes, participant follow up will continue until 31st December 2017 (trial month 50). We will consent participants for extended follow up through their clinical records for a further eight years (ten years in total) and for life-long linkage to existing NHS databases (Hospital Episode Statistics). The total trial duration is 63 months.

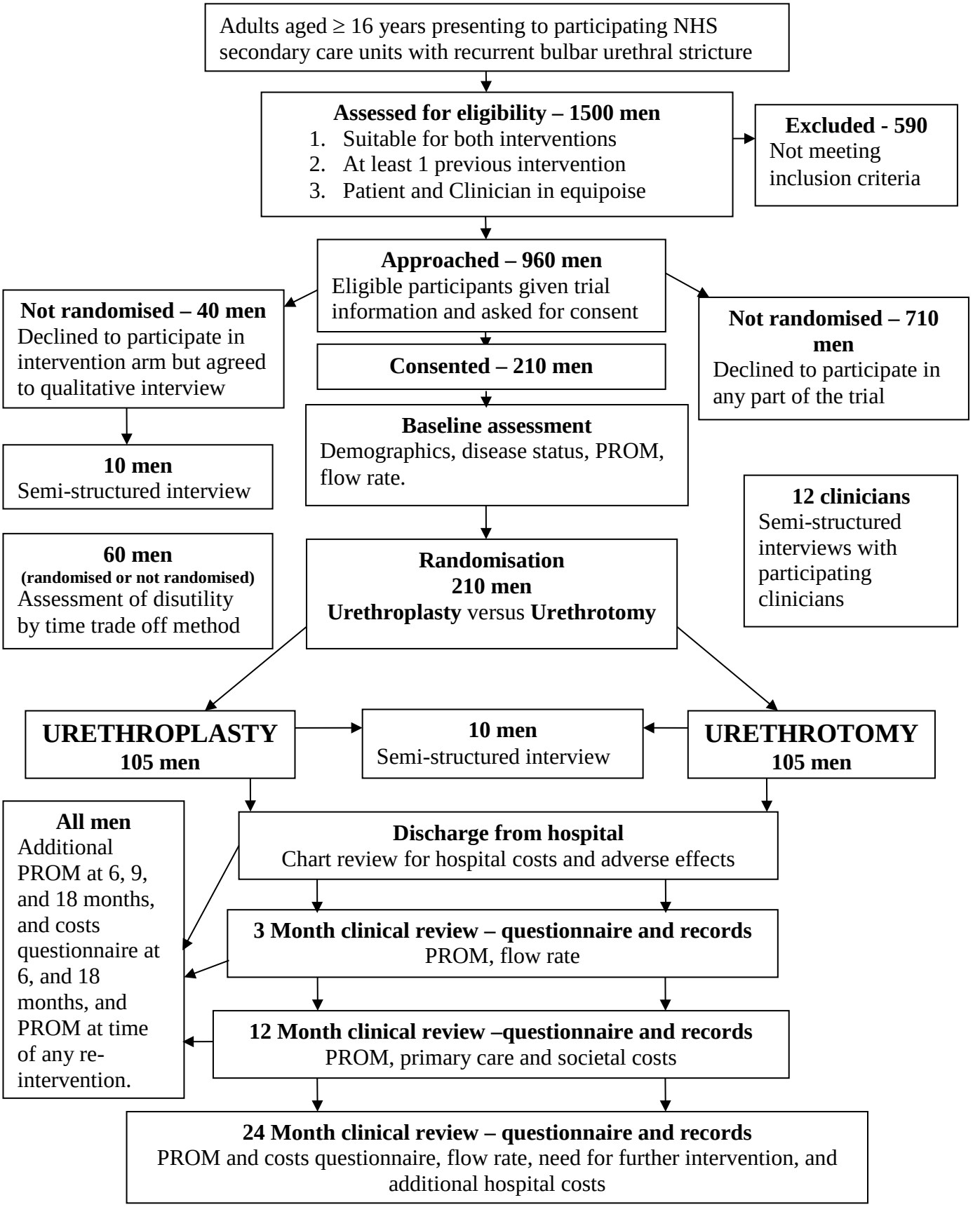
10.5. Primary effectiveness outcome measure

Difference in trajectory of **symptom control** measured by area under the curve (AUC) of the ICIQ-MaleSF symptom score[17] completed by participants during routine clinical visits or by postal or online questionnaire at baseline, immediately prior to surgery, 1 week after catheter removal, at 3, 6, 9, 12 months after intervention and at 18 and 24 months after randomisation and additionally prior to and subsequent to any surgical re-intervention. The ICIQ-MaleSF modular questionnaire has been validated in this patient group[18].

10.6. Secondary effectiveness outcome measures

1. Difference in **condition-specific quality of life** trajectory measured by the AUC for the single item ICIQ-MaleSF QoL score recorded by participant questionnaire completed during clinical visits or by post or online at baseline, immediately prior to surgery, 1 week after catheter removal, at 3, 6, 9 and 12 months after surgery, and at 18 and 24 months after randomisation and prior and subsequent to any surgical re-intervention. Further questionnaires will be completed at 24 months after initial surgery (if this time point occurs before the end of the study) and at the end of the study (December 2017).
2. Difference in **global sexual functioning** trajectory measured by the AUC for the single item IEEF male sexual QoL score recorded by participant questionnaire completed during clinical visits or by post or online at baseline, immediately prior to surgery, 1 week after catheter removal, at 3, 6, 9 and 12 months after surgery, and at 18 and 24 months after randomisation and prior and subsequent to any surgical re-intervention. Further questionnaires will be completed at 24 months after initial surgery (if this time point occurs before the end of the study) and at the end of the study (December 2017). Difference in **generic quality of life** trajectory measured by the AUC for the EQ-5D (5L version) total score based upon responses to 5 dimension items and using UK population valuations (0 death to 1 full health) and visual analogue scale score (0 worse possible health state – 100 best possible health state). Included in participant questionnaire administered during routine clinical visit or by postal or web-based participant questionnaire at baseline, immediately prior to surgery, 1 week after catheter removal at 3, 6, 9, and 12 months following surgery, 18 and 24 months after randomisation, and prior and subsequent to any surgical re-intervention. Further questionnaires will be completed at 24 months after initial surgery (if this time point occurs before the end of the study) and at the end of the study (December 2017).
3. Difference in rate of improvement of **urinary flow rate** measured as part of routine care at baseline, 3 and 24 months with an increase in $Q_{max} \geq 10$ ml/s from baseline taken to signify a successful outcome[19].
4. Difference in **rate of recurrence and need for further intervention** recorded from the clinical record for those 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 24 months after randomisation. Questionnaires regarding further intervention will be sent to participants at 24 months after their initial surgery if this falls before the end of the study and at the end of the study (December 2017). For participants in whom the clinical record documents stricture recurrence the relevant clinical information will be sent in anonymised form as a case vignette to an expert panel of five urology clinicians independent of the trial to determine whether or not there is a majority opinion that clinical recurrence of the stricture has been confirmed.

Figure 1: CONSORT diagram showing flow of participants through trial



PROM: Patient-reported outcome measure comprising ICIQ-MaleSF symptom score (primary outcome), condition-specific quality of life question (ICIQ-MaleSF QoL), global sexual function question (IEEF) and EQ-5D. 18 and 24 month time-points timed from date of randomisation; all other time-points timed from date of intervention.

10.7. Primary cost-effectiveness outcome measure

The primary cost-effectiveness outcome measure is cost-utility measured as **incremental cost per QALY at 24 months**; incorporating hospital costs based on resources absorbed to deliver trial interventions, inpatient care and follow up; and participant-level data on the trial interventions (e.g. operating time, grade of surgeon and protocol deviations) collected on the Case Report Form (CRF). Hospitalisation, secondary interventions provided in hospital, outpatient visits (number and specialty) will be obtained from clinical records and recorded on the CRF.

Hospital care costs will be determined from costs reported by participating centres and calculated according to NHS Trust reference cost schedules[20]. Adverse effects will be recorded on the CRF. We anticipate most adverse events will occur within three months of surgery. Study-specific estimates will be derived for the cost of the interventions and care of adverse events based on data on resource use recorded on the CRF. Use of primary care service (number and type of General Practitioner visits), secondary care service (hospital outpatient visits and inpatient stay following surgery) and other health care service (e.g. patients' out of pocket health expenses, use of private health care) will be collected from Part A of the Patient Costs Questionnaire completed at 6, and 12 months after initial surgery, and at 18 and 24 months after randomisation. Other related societal costs (e.g. time off work, time and travel costs on attending health services) will be obtained from part B of the Patient Costs Questionnaire completed at 6 months after initial surgery. Unit costs of health care services and medications will be based on published sources.

10.8. Secondary cost-effectiveness outcome measures

1. Difference in **mean costs** in secondary care, primary care and the NHS.
2. Longer term cost-utility reported as **incremental cost per QALY at 10 years**. Costs up to 24 months will be based on trial data and those beyond 24 months will be estimated from the literature for each trial intervention. Trial evidence of effectiveness at 24 months and that predicted by the literature over the subsequent eight years will be used.

10.9. Acceptability outcomes

1. What **factors are of most importance to men with bulbar urethral strictures** in differentiating between treatments and agreeing to trial participation? This will be explored through qualitative analysis of semi-structured interviews of up to 20 eligible participants (actual sample size informed by the point of data saturation) over the initial six months of recruitment, with subsequent adjustment of trial information as required.
2. What **factors do clinicians consider in recommending specific treatments**? Clinicians' interpretation of the meaning and quality of existing evidence will be explored through qualitative analysis of semi-structured interviews with 10 to 12 clinicians (actual sample size informed by the point of data saturation), purposively sampled to include specialist and general urologists over the initial six months with subsequent refinement of trial information.
3. What is the **short term disutility** of trade-offs that individuals may make in choosing between the two procedures? Patients' valuation of the decision between treatments will be examined using the time trade off method (detailed protocol can be found in Appendix 3) through structured interviews with 60 eligible participants (actual sample size informed by the point of data saturation) during the recruitment period.

10.9. Definition of end of study

The end of study is the last participant's final study contact, at the end of the total study duration (December 2017). We will also follow up participants through their clinical records for a further eight years (ten years in total) and for life-long linkage to existing NHS databases (Hospital Episode Statistics).

11. SUBJECT POPULATION

11.1. Participants

Participants will be adult men attending UK NHS services requiring treatment for recurrent bulbar urethral stricture.

11.2. Settings

Participant recruitment and the interventions being tested in the study will take place in specified UK NHS hospitals offering urology services. These will include general hospitals (secondary care) and regional specialist hospitals (tertiary care). There will be approximately 25 hospital-based 'main' sites carrying out urethroplasty surgery who will each establish at least one satellite site according to local referral arrangements and rate of recruitment (at least 50 sites in total). Furthermore, main sites will be asked to identify any smaller referring centres which may be suitable to become Participant Identification Centres (PICs).

The 25 main sites are: St George's Hospital, London*; Freeman Hospital, Newcastle upon Tyne*; Aberdeen Royal Infirmary*; Manchester Royal Infirmary*; University College Hospital, London*, Russells Hall Hospital, West Midlands*; Aintree Hospital, Liverpool*; Leicester Royal Infirmary; Western General Hospital, Edinburgh; Queen Alexandra Hospital, Portsmouth; Southern General Hospital, Glasgow; St. James' Hospital, Leeds; Addenbrooke's Hospital, Cambridge*; Weston General Hospital, Weston-super-Mare*; Stepping Hill Hospital, Stockport*; Royal Sussex Hospital, Brighton; Southampton General Hospital; Kent and Canterbury Hospital; St Richards Hospital, Chichester; Sunderland Royal Infirmary; Guy's Hospital, London; Charing Cross Hospital, London; Princess of Wales Hospital, Bridgend; Royal Hallamshire Hospital, Sheffield; and Salford Royal Hospital

Participant follow up will be by postal or online survey, sent to participants together with their outpatient review appointment at the hospital site where they were recruited, at approximately 3, 12 and 24 months. We have an outline agreement to participation from 25 other sites; Royal Devon and Exeter Hospital; Cumberland Infirmary, Carlisle; James Cook University Hospital, Middlesbrough; Southend University Hospital, Essex; West Middlesex Hospital, London; Whipps Cross University Hospital, London; Torbay Hospital; Cheltenham District Hospital; Frimley Park Hospital, Surrey; East Surrey Hospital, Redhill, Surrey; Maidstone Hospital, Kent; Chelsea and Westminster Hospital, London; Derriford Hospital, Plymouth; Darent Valley Hospital, Dartford; Royal Cornwall Hospital, Truro; Yeovil District Hospital; Musgrove Park Hospital, Taunton; Basildon and Thurrock University Hospitals, Essex; Wrightongton, Wigan and Leigh Hospitals; Royal Bournemouth Hospital; Airedale Hospital, West Yorkshire; Whittington Hospital, London; Royal Blackburn Hospital, East Lancashire; Southmead Hospital, Bristol; Arrowe Park Hospital, Wirral.

* premier feasibility sites with planned set up and recruiting by trial month six

11.3. Inclusion criteria

- Adult males aged 16 years or greater.
- Stricture located predominantly in the bulbar urethra.
- Undergone at least one previous intervention for bulbar urethral stricture.
- Clinician and patient agreement that intervention is required.
- Suitable for general or regional anaesthesia of up to three hours duration.
- Willingness to have two-week period of catheterisation.
- Provided written informed consent for participation in the study prior to any study-specific procedures.

11.4. Exclusion criteria

- Age less than 16 years.
- Stricture not involving the bulbar urethra.
- Perineal sepsis and/or fistula.
- No previous intervention for bulbar stricture.
- Not suitable for up to three hour period of anaesthesia, or inability to adhere to the trial protocol due to co-morbidity.
- Inability or unwillingness to provide informed consent to randomisation.

- Previous participation in this study.

12. SCREENING, RECRUITMENT AND CONSENT

12.1. Identification and Screening of Participants

Participants will be identified by NHS clinical staff (principally consultant and trainee urologists) at participating centres. They will either be new referrals from primary care or men already under review in urology clinics. The clinician will outline the OPEN trial and ask the patient if they are willing to discuss participation. If they respond affirmatively they will be referred to the local research team for eligibility assessment on the same day or at a mutually convenient time within two weeks.

A member of the local research team will complete a trial screening form using information from the prospective participant and from the clinical record to document fulfilment of the entry criteria. Eligibility criteria will be cross-checked with the clinical record. If the patient is eligible and in provisional agreement, a local research team member will meet with the patient either immediately in the clinic or within four weeks at a mutually convenient time and place. This initial meeting can take place by telephone. Eligible patients will either be identified at the main trial centres or at Participant Identification Centres (PIC) associated with each trial site. Those identified as being interested in participating at a PIC and who are willing to travel to the main trial site will be referred to the main trial site for further discussion regarding participation.

12.2. Recruitment Procedures

Eligible participants who express interest in participating in the OPEN trial will have the study explained to them by local research staff and will be given a patient information sheet to read. They will be informed that the local research team will contact them using their preferred means of contact within seven days to find out whether or not they would like to take part, or alternatively to provide further information. If they agree to take part they will be invited to meet with local research staff to give written consent to be randomised between open urethroplasty and endoscopic urethrotomy. The timing of randomisation will be according to patient and clinician wishes and local arrangements in terms of waiting times and operating theatre list planning. These factors will be balanced as far as possible to ensure that surgery takes place as soon after randomisation as is acceptable to participants and the treating NHS organisation. Standard local arrangements concerning pre-assessment, admission, consent for surgery, conduct of surgery and after care will continue unimpaired. Eligible participants who are not willing to consider randomisation will be asked for an expression of interest in participating in a semi-structured audio-recorded interview. Following discussion regarding consent for randomisation, participants will be asked for an expression of interest in participating in a 60 minute semi-structured audio-recorded interview to explore their feelings about the options for intervention for urethral stricture and randomisation in to this trial. Those who express interest in the qualitative interview element of the study (including both those who consent to randomisation and those who decline randomisation) and are selected to participate will be sent a Participant Information Sheet for this sub-study, and will be contacted by telephone by a member of the research team no longer than seven days later to discuss participation.

Urologists participating in trial recruitment will also be asked to give expression of interest in participating in a 45 minute semi-structured audio-recorded interview to explore their clinical decision making reading selection of options for treating men with recurrent bulbar stricture under their care.

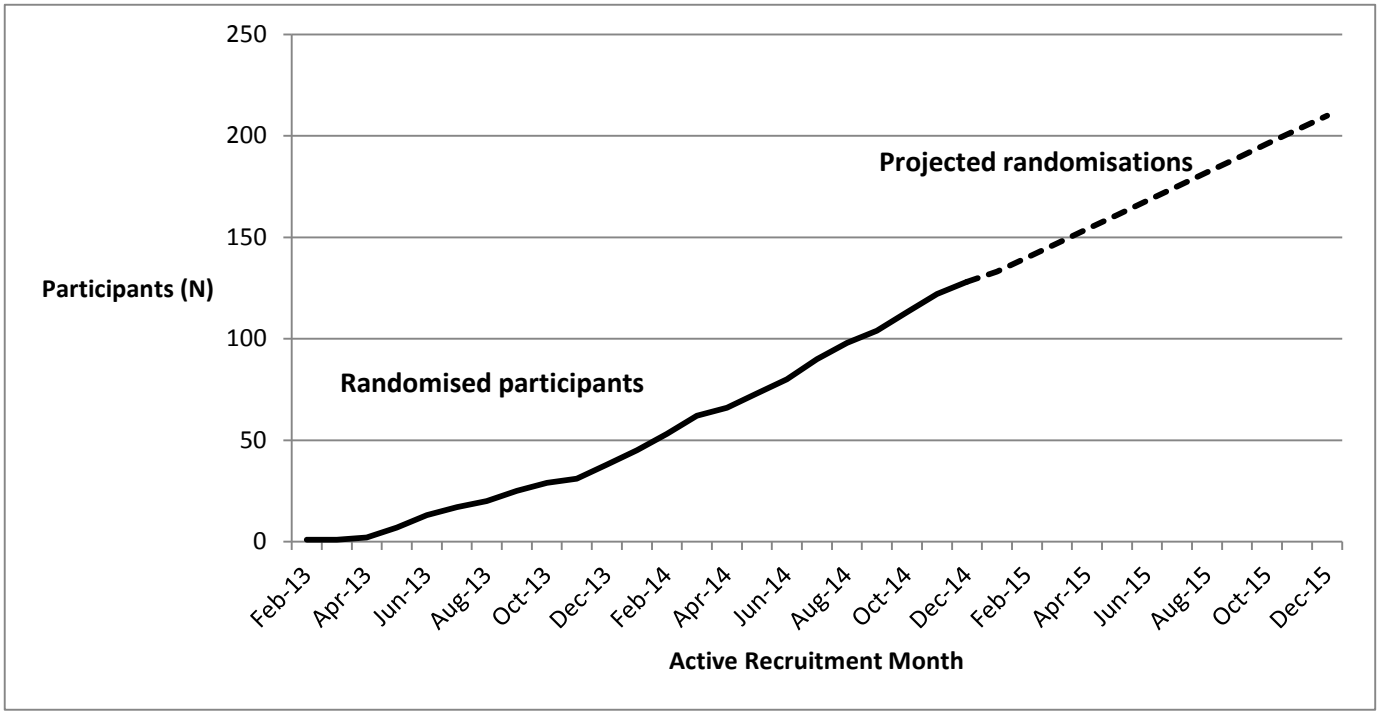
A screening log will be kept by local research staff to document details of subjects invited to participate in the study. Non-identifying patient details to allow assessment of selection bias such as age, number and type of previous procedures, recruitment site and length of stricture will be uploaded to a secure study website for analysis. For subjects who decline participation, this will document reasons for non-participation. The log will also ensure potential participants are approached only once. The projected recruitment timetable is shown in Figure 2.

12.3. Consent Procedures

Informed consent discussions will be untaken by appropriate staff at the main trial sites as detailed in the site delegation log. This will include medical staff and research nurses involved in the study who will give time for

participants to ask any questions they may have following review of the trial information pack. Following receipt of information about the study, participants will be given at least 48 hours and up to as much time as they need to decide whether or not they would like to participate. Those wishing to take part will provide written informed consent by signing and dating the study consent form, which will be witnessed and dated by a member of the research team with documented, delegated responsibility to do so. Written informed consent will always be obtained prior to randomisation and with additional clinical consent prior to study specific interventions. The original signed consent form will be retained in the Investigator Site File, with a copy filed in the clinical notes, a copy given to the participant and a copy faxed to the central trial office on +44 (0)191 5801105. The participant will specifically consent to their GP being informed of their participation in the study. The right to refuse to participate without giving reasons will be respected. During study set up we will consider requests for trial participant literature including the information sheet and consent form to be translated into other languages. Ability to complete the primary outcome questionnaires in English will be required for trial participation. If local NHS circumstances permit, sign interpreters will be arranged for all visits with patients who require them for deaf subjects wishing to take part in the study. Interpreters will be used where necessary to explain the consent form and information sheet, and great priority will be placed on finding the most direct means of communication. If local research staff are in any doubt with regards to the patient's understanding of crucial aspects of the trial or ability to complete the outcome measures in English, then consent for randomisation will not be sought.

Figure 2: Projected recruitment timetable



12.4 Participant expenses

Reasonable expenses incurred by participants as a result of for example extra hospital visits for study purposes outside of normal clinical care will be reimbursed, up to £25 per visit. We will offer consented and randomised participants a gift of £25 at the start of the study, £25 24 months after randomisation, and £25 after completing the end of study questionnaire (December 2017), in the form of shopping vouchers with written confirmation that this was a gift.

12.5. Subject Withdrawal

Patients will remain on the study unless they withdraw consent or in the unlikely event that the PI, CI or trial office feel it is no longer appropriate for the patient to continue. If a participant chooses to withdraw we will seek permission for the research team to continue to collect outcome data from their clinical records. Given that the trial involves a one-off intervention we will, within the consent and ethics framework, seek to complete trial follow up documentation as fully as possible in line with our pre-stated intention to treat primary analysis.

12.6. Study Interventions

This study has been planned as a pragmatic clinical trial. Apart from patient randomisation and collection of outcome data, it will adhere to standard care pathways at participating sites.

12.6.1. Endoscopic urethrotomy (control)

The control intervention of endoscopic urethrotomy typically takes 45 minutes or less under anaesthesia, with prophylactic antibiotic cover. With the patient's legs partially elevated in supporting stirrups the endoscope is passed along the lubricated penile urethra to locate the distal end of the stricture. A fine calibre wire guide is then passed through the stricture to the bladder. Using this guide the stricture is progressively divided longitudinally using the mounted scalpel in the dorsal '12 o'clock' orientation until the proximal end of the stricture is reached. For short flimsy strictures dilatation with the instrument may suffice without making a cut. The instrument is withdrawn and a 16Fr calibre silicon catheter inserted through the urethra to the bladder and left on free drainage[21]. The patient recovers on the ward and is discharged according to local practice (NHS median stay=one day) usually with the catheter in situ. He returns to hospital after an interval or remains as an in-patient according to local practice (typically 24-72 hours) for catheter removal and voiding check and then is followed up by out-patient review and urinary flow rate at 3, 12 and 24 months. According to the clinician's policy at individual recruiting sites a standardised self-dilation management programme following urethrotomy may be offered to participants.

12.6.2. Open urethroplasty (experimental)

Open urethroplasty involves the reconstruction of the urethra through an appropriately sited longitudinal skin incision made in the perineum beneath the scrotum between the legs. It requires a pre-operative X-ray urethrogram. The surgery takes two to three hours under anaesthesia with the patient's legs partially elevated in supports and prophylactic antibiotics given. The bulbar urethra is located through the skin incision and mobilised. The strictured segment is incised longitudinally with the cut extending into visibly healthy urethra proximally and distally. For the majority of cases where the stricture is relatively long and dense, a graft of oral mucosa is inserted to widen the strictured area of urethra (patch urethroplasty)[22]. The graft (typically 5 by 2 cm) is harvested according to a standard technique from the inner cheek with the donor site left open to heal spontaneously or closed with sutures according to surgeon practice[23]. The graft is prepared, positioned appropriately, sutured to the cut urethral edges, and stabilised on the deeper tissues within the perineal wound. This incorporates the graft mucosal surface into the lumen of the urethra. For short supple strictures simple excision of the scarred area and re-joining of the cut ends may be performed without a graft (anastomotic urethroplasty)[24]. A 16Fr silicon catheter is then passed to the bladder and left in situ on free drainage. The patient recovers on the ward before discharge home (NHS median stay=2 days). The patient returns after an interval according to local practice (typically 2 to 3 weeks) for an X-Ray urethrogram to check leak-free healing, and catheter removal. Follow up comprises out-patient review and urinary flow rate at 3, 12 and 24 months. Some surgeons prefer a urethrogram to be also performed at about 12 months to ensure that no recurrence has occurred.

12.7. Delivery of Interventions

The procedures will be delivered by existing surgeons with established expertise. A survey amongst members of the UK Urethral Surgeons Group and audit through BAUS has established that the PIs and their specialist colleagues in each of the 25 regional hubs have undergone appropriate training in open urethroplasty and carry out a sufficient number of procedures each year to maintain competency. Competency in endoscopic urethrotomy is a mandatory part of urology training in the UK and the proportion of urologists regularly performing the procedure as part of their day to day practice is likely to be close to 90%; similar to that found in a recent survey in The Netherlands[25]. Men randomised to urethroplasty will have their procedure performed by existing identified specialists at the recruitment hubs whilst those randomised to endoscopic urethrotomy may have their procedure performed by either a general or specialist urologist according to trial arrangements at the local site. The study will require that both interventions are delivered according to existing surgeon and site clinical practice reflecting current care in the NHS. Open urethroplasty will encompass both grafting and anastomotic techniques according to the surgeons' assessment of the individual patient's urethra at the time of surgery, and graft orientation will be according to surgeon preference. For participants allocated to endoscopic urethrotomy a post-operative programme of intermittent self-dilation will be offered if this is part of routine practice at individual sites. Urethroplasty technique and the use of self-dilation will be recorded on the participant case report form.

12.8. Switching trial Arms

Due to the pragmatic nature of this clinical trial there are likely to be occasions when participants who meet the criteria for randomisation don't go on to receive their allocated intervention. Examples of why this may occur include but are not limited to; a difference of clinical opinion between surgeons at the referral site and randomisation site, participant agreeing to randomisation but changing their mind before receiving their allocated intervention or clinical need to perform a different intervention due to prolonged waiting lists. Participants that do not receive their allocated intervention will continue to be followed-up to the pre-determined schedule of events outlined in this protocol and in line with our pre-stated intention to treat primary analysis. These participants will be included in the analysis subject to independent adjudication of their clinical symptoms.

12.9. Funding

The interventions will be funded by standing NHS contracting mechanisms. The NHS excess treatment costs have been approved by the Sponsor.

13. RANDOMISATION

13.1. Randomisation Process

Eligible and consenting participants will be randomised to one of the two intervention groups using the proven 24-hour telephone Interactive Voice Response randomisation application or via the web-based application, both hosted by CHaRT. The randomisation algorithm will use 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 will be incorporated into the randomisation algorithm. The PI at site, or individual with delegated authority, will access the telephone or web-based system. Patient screening identification, initials and recruiting site (the stratifying variable) will be entered into the voice-activated or web-based system, which will return the allocation status. Participants will be informed of their allocated treatment group following randomisation.

13.2. Contact Details for Randomisation

24-hour automated telephone randomisation service:	**0800 2802 307** *Each site will have a unique identifier that can be inputted using any telephone key pad*
Website with online messaging:	http://www.opentrial.co.uk/
Emergency contact numbers:	0191 208 7623 Monday – Friday 8 am – 4 pm 0191 233 6161 Ask switchboard operator to contact Robert Pickard, Consultant Urologist

14. BLINDING

Assignment to either urethroplasty or urethrotomy will not be blinded to either the participant or investigator or the local research staff (non-blinded study). However central trial staff responsible for data management, entry and analysis will be blinded to allocated intervention where possible.

15. DATA COLLECTION

For a tabulated schedule of events see Table 1. Items in italics are standard clinical care pathway events.

Timings in bold refer to duration of participant time required.

15.1. Screening: clinical records and face-to-face **20 minutes**

- Demographics
- Eligibility criteria
- Decision: eligible or not eligible?
- Trial Information provided

15.2. Baseline (before randomisation): face-to-face

- Consent for randomisation
- Baseline personal and disease details completed with research staff on the CRF
- Patient-reported outcome measure (PROM)* **5 minutes**
- *Urine flow rate (from clinical records if within 3 months of baseline)*
- *Urethrography (if performed as part of routine clinical care)*
- Decision with regards to questionnaire delivery and alerts
- Semi-structured interview with qualitative researcher from Newcastle University at time and place of mutual convenience **45 minutes (optional)**. Qualitative researcher to take consent.

15.3. Randomisation

Randomisation will be performed as close as possible to the date of admission for surgery, allowing for participant and institutional arrangements.

15.4. Pre-operative (after randomisation): face-to-face

- Local research staff to check baseline personal and disease details
- *Standard consent for surgery according to treating clinician or institution policy*
- PROM* **5 minutes**

15.5. Operative

- Description of intervention completed by site research staff on CRF from clinical records and treating clinician
    - Copy of operation note
    - Site and length (cm) of stricture
    - Duration of operation
    - Deviations from treatment plan with reasons
    - Operative complications

15.6. Post-operative

- Description of care (completed by site research staff on CRF)
    - Length of stay
    - Post-operative adverse events categorised by the Clavien-Dindo system[26]
    - Planned and unplanned readmissions within 30 days
    - Further procedures such as intermittent self-dilatation
    - Duration of catheterization
- PROM* (postal or online) one week after catheter removal **5 minutes**

15.7. Three months after surgery: face-to-face/remote (according to local clinical review policy)

- PROM* (postal or online) **5 minutes**
- *Urinary flow rate taken from clinical records provided within range of 2 - 6 months after intervention*
- Results of any repeat urethrography (open urethroplasty group) from the clinical record
- Resource use: a review of clinical records by site research staff with completion of CRF

15.8. Six months after surgery: face-to-face/remote (according to local clinical review policy)

- PROM* (postal or online) **5 minutes**
- Resource use: participant questionnaire face-to-face, by post or online **20 minutes**
    - Hospital visits
    - Use of primary care service
    - Medications
    - Time off work
    - Out of pocket expenses

15.9. Nine months after surgery: remote

- PROM* (postal or online) **5 minutes**

15.10. 12 months after surgery: remote

- PROM* (postal or online) **5 minutes**
- Results of any repeat urethrography (open urethroplasty group) from clinical record
- Resource use: review of clinical records by site research staff with completion of CRF and participant questionnaire (postal or online) **10 minutes**.

15.11. Eighteen months after randomisation: Remote

- PROM* (postal or online) **5 minutes**
- Resource use: participant questionnaire face-to-face, by post or online **10 minutes**

15.12. At time of further surgical intervention for urethral stricture during total study duration: Face to face/remote

- Prior to intervention
    - Patient-reported outcome measure (PROM)* (postal or online) **5 minutes**
- Within four weeks after intervention
    - PROM* (postal or online) **5 minutes**
    - Resource use: review of clinical records by site research staff with completion of CRF

15.13. 24 months after randomisation: face-to-face/remote **end of primary outcome collection**

- PROM* (postal or online) **5 minutes**
- Urinary flow rate taken from clinical records provided within range of 20 to 24 months after intervention
- *Additional urethrography results performed as part of standard care*
- Resource use: review of clinical records by site research staff with completion of CRF and participant questionnaire by post or online **10 minutes**.

15.15. 24 months after initial surgery (where this time point falls before 31 December 2017): remote

- PROM* (postal or online) **5 minutes**

- Further Intervention Questionnaire (postal or online) to determine whether re-interventions have occured. **5 minutes.** Where patients are unsure about any re-intervention information or are unable to complete the questionnaire, site research staff will be asked to review the clinical record.

15.16. End of study review (December 2017; **end of secondary outcome collection**): remote

- PROM* (postal or online) **5 minutes**
- Further Intervention Questionnaire (postal or online) to determine occurrence of re-intervention for stricture. **5 minutes.** Where patients are unsure about any re-intervention information or are unable to complete the questionnaire, site research staff will be asked to review the clinical record.

	Visit 1 Initial Screen	**Visit 2** Consent (C) Baseline(B) Randomisation (R)			**Visit 3** Intervention	**Visit 4** 3 month Clinical follow-up	**Postal 6 month follow-up**	**Postal 9, 12, 18 months and at re-intervention**	**Visit 5*** 24 month follow-up	**24 months after surgery**	**End of study (December 2017)**
		C	B	R	According to site processes (within 12 weeks of R)						
Eligibility checklist	X										
Trial discussed and PIS given	X										
Informed Consent		X									
PROM*			X		X(pre) X(post)	X	X	X X X X	X	X	X
Resource use questionnaire							X	X (12 and 18 months only)	X		
Further intervention questionnaire										X	X
Uroflowmetry			X			X			X		
Randomisation				X							
Process of care					X	X			X		
Adverse events					X	X			X	X	

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

Table 1: Schedule of study interventions and outcome data collection

15.14. Further Details

Data collected on paper CRF will be entered by local research staff identified in the delegation log onto a secure validated web-based clinical data management system supervised by the Health Services Research Unit at Aberdeen. Completed paper CRFs will be held securely at each site. Data transferred from site to the secure validated database by remote access will be secure and encrypted. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Under the trial participant consent identifiable data will be stored as a separate and limited access component of the trial database in Aberdeen to allow preparation and sending of follow up documentation. The quality and retention of study data will be the responsibility of the Health Services Research Unit at Aberdeen. All study data will be retained in accordance with the latest Directive on GCP and local policy.

Clinical data will be entered into the database remotely at each site by the local investigator or another member of the site research team with delegated responsibility for this activity, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial management office in Newcastle will be entered there. Trial management staff in the Newcastle trial office in collaboration with data management staff in the Aberdeen trial team will work closely with local site research teams to ensure that the data are as complete and accurate as possible. The Newcastle CTU will be responsible for chasing missing data. Extensive range and consistency checks will further enhance the quality of the data. Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Patient's details will be stored on a secure database under the guidelines of the 1988 Data Protection Act. Patients will be allocated an individual specific trial number to allow anonymised versions of the secure database to be available to the trial team and subsequently more widely under open data access arrangements. Encrypted identifiable data will be kept on the trial database within CHaRT. The web-based trial management system organises mail merging to ensure trial correspondence is sent to each participants using their preferred mode of delivery. Participants will be asked to give their preferred contact details for communication with trial staff. This will include access by qualitative researchers to contact details of participants who consent to the semi-structured interview. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired. The sponsor is responsible for ensuring that trial data is archived appropriately. Essential data will be retained for a period of at least 10 years following close of study in line with sponsor policy. Caldicott approval for use, transfer and storage of participant identifiable information will be obtained at each site.

16. STATISTICAL CONSIDERATIONS

16.1. Statistical analysis

The primary outcome, area under the curve (AUC) for the ICIQ-MaleSF symptom score, will be generated for each participant using the trapezoidal rule. Symptom score data for participants who have missed a scheduled time point will be estimated using a multiple imputation approach to make use of partial outcome data[27]. Sensitivity analyses will be conducted to assess the robustness of the treatment effect estimate to these approaches. The primary outcome measure will be analysed using linear regression with adjustment for the minimisation variables [site of recruitment and time since last procedure (<12 months or ≥12 months)]. Secondary outcomes will be analysed using generalised linear models with adjustment for minimisation and baseline variables as appropriate. Statistical significance will be at the 2-sided 5% level with corresponding confidence intervals derived. Subgroup analyses will explore 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 location, and length. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses. All analyses will initially be performed on an intention to treat basis, although we will consider additional analysis groups such as per-protocol. Further analysis will explore the impact of variations in treatment delivered; such as use of anastomotic urethroplasty, use of intermittent self-dilatation after urethrotomy, and delay between decision to treat and undergoing the intervention. The main statistical analyses will be based on all participants as randomised, irrespective of subsequent compliance with the treatment allocation. From the feasibility phase we will report estimates of recruitment rates and potential participant availability, together with appropriate confidence intervals. There are no planned interim outcome analyses; all analyses will occur following completion of trial follow up. Interim analyses will be performed if requested by the Data Monitoring and Ethics Committee (DMC).

16.2. Sample Size Calculation

We initially planned to recruit 500 participants to the study. This used the assumption that the standard deviation (SD) of the primary outcome measure (ICIQ-Male SF questionnaire scored 0 – 24) would be 0.3 Using this figure with 90% power (2-sided 5% significance level), 235 participants per group (470 in total) would have been required. This would equate to being able to detect at least a 0.1 difference in the AUC on the standardized 0-1 utility scale, assuming a SD of 0.33 or less. The SD of the ICIQ-MaleSF symptom AUC in a previous study was 0.15[18]. Given our lack of more precise information we initially conservatively allowed for a larger SD in recognition of the more representative population to be recruited to this trial and the shorter follow-up period in the previous study. Such a difference in symptom burden and associated quality of life has been observed in different clinical areas for health-related quality of life (HRQoL) measures[28]. In terms of treatment effect size, this is in the small to medium range as observed in other clinical studies[29]. To allow for the anticipated approximately 5% of participants for whom outcome data is completely missing, and therefore the AUC cannot be calculated, it was originally proposed to randomise 500 participants. The slower than expected recruitment rate has allowed us to use blinded trial outcome data to provide a more precise estimate of the SD. We have calculated the SD of the patient-reported symptom score (primary outcome measure) from 69 OPEN participants who have submitted at least one post-operative measure (220 measurements in total). The re-calculation gives a SD value of 0.165 which reduces to 0.15 when adjusted for baseline score and centre, considerably smaller than the assumed value of 0.33 which was used in our initial calculations. Using this SD in our sample size calculation would indicate a target population of 96 participants. However no 18 or 24 month data are currently available and variability would be expected to increase over time. Allowing for this and other factors increasing variability would suggest we should now assume a SD of 0.21 or less. This would require 170 randomised men with complete follow up inflated to 210 in total to allow for loss to follow-up. Based on findings from recruitment to the ProtecT trial which randomises between surgery and less invasive options for men with localised prostate cancer, we originally conservatively estimated a 55% agreement to participate rate amongst those eligible requiring 910 men to be approached[30]. We have reassessed this in the light of slower than anticipated recruitment rate from screening data from the trial now available to us showing a 22% agreement to participate rate. For the initial feasibility and acceptability study we estimate, based on previous experience in such methodology, that up to 10 men who agree, and up to 10 men who do not agree to be randomised and up to 12 purposively sampled specialist and general urologists will be required to achieve data saturation for thematic analysis. The trial is also secondarily powered to determine whether the use of urethroplasty will result in a 30% (from 50% to 20%) reduction in need for further intervention at two years compared to urethrotomy as a secondary outcome. To detect this difference using the binomial test of proportions with 90%

power at the 5% significance level would require 52 men to complete the study in each arm, giving a total of 104 men.

16.3. Health - Economic Analysis

For the within trial analysis the primary measure of effectiveness will be the QALY based on responses to the EQ-5D over a 24 month time horizon. Cumulative mean costs to patients and the NHS over the trial follow-up period for each intervention will be estimated from the collected patient and NHS resource use data and their unit cost. The difference between mean costs between the two arms will be combined with their relative effectiveness to produce an incremental cost per QALY gained at 24 months. Methods such as bootstrapping will be used to produce confidence intervals around difference in costs and effects. The same method will be used to produce cost-effectiveness acceptability curves. Sensitivity analysis will be used to explore other uncertainties such as alternative cost estimates. Open urethroplasty is expected to be both more effective and more costly than endoscopic urethrotomy, and its benefits may persist beyond 24 months. Therefore we will conduct a cost-utility analysis using a Markov model with 10-year time horizon to compare the costs, QALYs and incremental cost per QALYs of the interventions. The model structure will be based upon care pathways mapped out by the project team and using the literature. Guidelines for best practice for modelling will be followed[31]. Trial data will be a vital resource to populate the model, but additional data on care and events beyond 24 months will be based on structured literature review. Specific trial data will include effectiveness and costs of the interventions and on-going care for participants whose strictures recur. Utility scores will be calculated based on responses to the EQ-5D from participants whose strictures do not require re-intervention, and from those having adverse events. These will be cross validated with existing values[32]. We will also conduct extensive probabilistic sensitivity analyses by attaching appropriate distributions to the model input parameters. The results of these analyses will be presented as cost-effectiveness acceptability curves. Deterministic sensitivity analyses will be used to explore other forms of uncertainty such as varying the model's time horizon.

16.4. Acceptability Analysis

With prior informed consent, all interviews will be audio-recorded, transcribed and edited to ensure anonymity. Qualitative analysis of the transcripts will be conducted according to the standard procedures of rigorous thematic analysis using open and focused coding, constant comparison, deviant case analysis, memoing, and mapping. This will include collective analysis of a proportion of the data 'data clinics' where the research team share and exchange interpretations of emerging and key issues that arise from the transcripts. This analysis will particularly focus on ways to finesse the recruitment, both in terms of written information and verbal interaction between eligible participants, clinicians and local trial co-ordinators[20]. The time-trade off method will be used to explore valuations given to short-term health states that will otherwise not be captured by longer term quality of life instruments.

17. COMPLIANCE AND WITHDRAWAL

17.1. Assessment of Compliance

Outcome data will be collected remotely whenever feasible by participant completion of postal or secure web-based questionnaires. This will be supplemented by e-mail or text alerts to participants notifying them to complete questionnaires with additionally up to two reminders in these formats for non-responders. Local research staff will make use of planned routine clinical visits whether for primary surgery, ward re-attendance for catheter removal, follow-up out-patient attendance or re-intervention to check completion of trial documentation and collect clinical outcome information such as urine flow rate. We will contact, with permission and allowing for cost, the participant's general practice for missing resource use data. Non-attendance for study visits will prompt follow-up by telephone, text or e – mail according to participant preference.

17.2. Withdrawal of participants

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study intervention if it is judged to be in the patient's best interests. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable and therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. There are two withdrawal options:

1. Withdrawing completely (i.e. withdrawal from allocated treatment and provision of follow-up data)
2. Withdrawing partially (i.e. a request to move to alternative treatment arm) but continuing to provide follow-up data by attending clinic and/or completing questionnaires).

We will encourage participants that decide to withdraw to choose option 2 but if they wish to withdraw completely we will retain data collected up to the point of withdrawal. Participants will be asked if they would be happy for the reason for the decision to withdraw to be recorded.

18. DATA MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

18.1. Monitoring, Quality control/assurance

An independent Data Monitoring and Ethics Committee (DMC) will be set up to include one methodologist, one physician not connected to the trial, and one statistician (Chair). It will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMC, the statistical analysis programming team in Aberdeen and Graeme MacLennan, the trial statistician will have access to full study data prior to completion of the trial. The committee will meet at least 3 times, at the start, middle and completion of the study. At the first meeting, DMC will agree on its charter of operation, and discuss and advise on the inclusion of an interim analysis and possible adoption of a formal stopping rule for efficacy or safety.

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial. The TSC will consist of an independent Chair, two further independent clinicians, independent statistician, independent lay representative, and members of the TMG as required or requested by the chair. The committee will meet approximately every six months during recruitment, and annually thereafter for the duration of the trial.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by members of the TMG. The main areas of focus will include consent, serious adverse events and essential documents in study. Site monitoring will include:

- All original consent forms will be reviewed as part of the study file; the presence of a copy in the patient hospital notes will be confirmed for 10% participants
- All original consent forms will be compared against the study participant identification list
- All reported suspected unexpected adverse reactions (SUSAR) will be verified against treatment notes/medical records (source data verification)
- The presence of essential documents in the investigator site file and study files will be checked
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation will be reviewed prior to site authorization
- Statistical monitoring for outlier sites and unusual data patterns

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The study may be subject to inspection and audit by the Research and Development Directorate, The Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

18.2. Discontinuation Rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the DMC and/or TSC, Sponsor, regulatory authority or ethics committee concerned. The study will be terminated if recruitment to target is found not to be feasible in consultation with the funder. Following 45 site months of recruitment, initial rates of recruitment will be used to project total recruitment to ensure sufficient participants to power the trial. The criteria for recruitment feasibility are described in section 10.2. The TSC will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

19. ADVERSE EVENT MONITORING AND REPORTING

19.1. Definitions

Adverse event (AE): 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. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all interventions administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related adverse event: An AE resulting from administration of a study procedure. All AEs judged by either the reporting investigator or the sponsor as having "reasonable causal relationship" to a study procedure qualify as "related adverse events". The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 2. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e definitely, probably or possibly related) are considered to be related adverse events. If doubt about causality exists, the local investigator (PI) should inform the CI. In case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made it will be referred to the DMC for adjudication, and the main REC and other bodies will be informed.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:

- Results in death
- Is life-threatening (refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Table 2: Categorisation of causality of an observed adverse event

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the

patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
Expected adverse events: Most adverse events that are likely to occur in this study, whether they are serious or not, will be expected as recognised harms of the trial interventions. Expected AEs are summarised in Table 3.

19.2. Protocol Specifications for Adverse Event Reporting
For purposes of this protocol:

- All adverse events will be recorded at time of primary or re-intervention surgery, and at up to 24 months after surgery.
- Any serious adverse events will be recorded throughout the duration of the trial
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.
- Serious adverse events exclude stricture (symptom or urine flow) recurrence which is already documented and monitored within study.

19.3. Recording & Reporting Serious Adverse Events or Reactions
Research team staff at individual sites will complete the adverse events section of the relevant case report forms and input the details of the AEs into the database hosted by CHaRT via the secure study website. The CHaRT web-based system will automatically alert the Newcastle Trial Manager if any new AEs are added or any amendments are made to the data in existing ones. The trial management office in Newcastle in conjunction with the CI will have the responsibility for any decision making and forward reporting of AEs.

All adverse events should be recorded in the CRF. Suspected unexpected serious adverse events that are considered to be causally related, (SUSARs) should be separately reported on the specific OPEN Trial form. AEs that are serious but expected do not need to be reported on the SUSAR form. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CI or Trial Manager in the first instance.

Adverse Event (AEs): All adverse events during study participation will be reported on the study CRF and entered by local investigators into the trial web management system. The individual investigator at each site will be responsible for managing all adverse events according to local arrangements.

Serious Adverse Event (SAEs): All unexpected SAEs that are related or of uncertain causality during study participation shall be reported to the CI through completion of the study SAE form, which should be sent by secure FAX or secure email to the Newcastle Clinical Trials Unit within 24 hours of the site learning of its occurrence. The initial report will also be completed onto the electronic form which will automatically send e-mail notification to the Trial Manager and CI in Newcastle. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to trial participation should be assessed by the investigator at site, as should the expected or unexpected nature of the AE. The main REC will be notified by the Chief Investigator (on behalf of the Sponsor) of all SUSARs within 15 days of the CI becoming aware of the SUSAR (unless urgent safety measures are required, in which case initial notification by telephone will be made immediately the CI becomes aware of the AE, with notice in writing following within 3 days). SUSARs will be reported using the NRES Report of Serious Events Form, version 3, April 2007[33]. The CI will ensure that The Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SUSARs in accordance with local trust policy. Local

investigators should report any SUSARs as required by their local Research & Development Office.

Table 3: Expected and therefore not separately reported adverse events for study interventions and procedures

	Severity of adverse event		
	Common & well understood consequences of treatment	**Less common & unpleasant side effects**	**Rare events**
Endoscopic urethrotomy	Mild urethral bleeding Local urinary tract infection Catheter discomfort Transient discomfort on passing urine after catheter removal	Severe bleeding requiring re-intervention Systemic urinary infection (urosepsis) requiring parental antibiotics	Extravasation of urine Transient (up to 12 months) erectile dysfunction
Urethroplasty	Mild mouth pain/discomfort if oral mucosal graft harvested Perineal wound pain Catheter discomfort Localised wound infection Local urinary tract infection Delayed healing requiring prolonged period of catheterisation Transient discomfort on passing urine after catheter removal Post-micturition dribble	Severe mouth pain if oral mucosal graft harvested Scarring in mouth after oral mucosal harvest Severe wound infection affecting deep layers Systemic urinary infection (urosepsis) requiring parental antibiotics	Fistula formation Transient (up to 12 months) erectile dysfunction
Urethrography	Urethral pain on instillation of contrast Discomfort on catheter insertion Discomfort on voiding for antegrade study	Allergic reaction to contrast agent (no intervention required)	Anaphylactic reaction to instilled contrast agent
Intermittent self dilatation	Pain on catheter insertion Urinary tract infection	Systemic urinary infection (urosepsis) requiring parental antibiotics	

19.4. Contact details for reporting SUSARs

All adverse events and SUSARs will be inputted on the secure web-based trial support system via http://www.opentrial.co.uk. In case of difficulty the Trial Management Team can be contacted by telephone on 0191 208 3819. Finally the emergency contact number is 0191 233 6161 and ask the switchboard to contact Robert Pickard Consultant Urologist.

20. ETHICS & REGULATORY ISSUES

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Favourable ethical opinion from an appropriate REC and R&D approval will be sought prior to commencement of the study. Local approvals will be sought before recruitment may commence at each site. The Study Coordination Centre will require a written copy of local approval documentation before initiating each centre and accepting participants into the study. Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures.

21. CONFIDENTIALITY

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. With participants' consent, details required to send postal/web-based or e-mailed questionnaires and associated prompts will be provided to the trial data management centre in Aberdeen to enable remote follow up. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

22. INSURANCE AND FINANCE

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University and Aberdeen University Insurance schemes for those protocol authors who have their substantive contract of employment with the. This is a non-commercial study and there are no arrangements for non-negligent compensation. The NIHR HTA Programme is funding the study

23. STUDY REPORT AND PUBLICATIONS

The data will be the property of the Chief Investigator and Co-Investigators. Publication will be the responsibility of the Chief Investigator. It is planned to publish this study in peer reviewed articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web sites. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results. At a minimum this trial will have a results paper published in a peer-reviewed medical/scientific journal. If all grant-holders and research staff fulfil authorship rules, group authorship will be used under the collective title of 'The OPEN Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the OPEN Trial Group. For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the OPEN Trial Group'. To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the Trial Management and Trial Steering Committee. We will also send outputs to the funder prior to submission for publication.

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Appendix 1: Patient-reported outcome measure (PROM)

Please read and answer each question carefully.
Tick the box that describes your symptoms over the **PAST WEEK**

1 Is there a delay before you start to urinate?

Never	❑
Occasionally	❑
Sometimes	❑
Most of the time	❑
All of the time	❑

2 Would you say that the strength of your urinary stream is?

Normal	❑
Occasionally reduced	❑
Sometimes reduced	❑
Reduced most of the time	❑
Reduced all of the time	❑

3 Do you have to strain to continue urinating?

Never	❑
Occasionally	❑
Sometimes	❑
Most of the time	❑
All of the time	❑

4 Do you stop and start more than once while you urinate?

Never	❑
Occasionally	❑
Sometimes	❑
Most of the time	❑
All of the time	❑

5 How often do you feel your bladder has not emptied properly after you have urinated?

Never	❑
Occasionally	❑
Sometimes	❑
Most of the time	❑
All of the time	❑

6 How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

Never	❑
Occasionally	❑
Sometimes	❑
Most of the time	❑
All of the time	❑

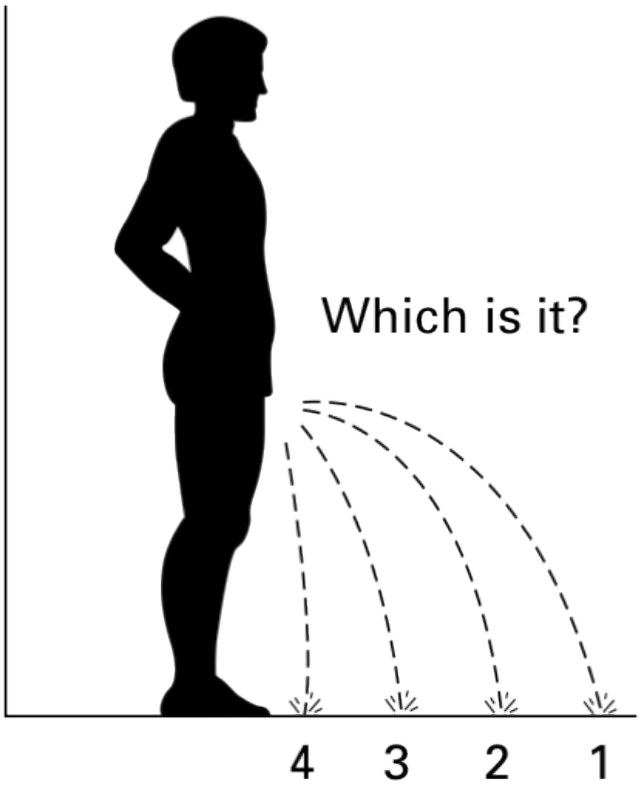
7 Overall, how much do your urinary symptoms interfere with your life?

Not at all	❑
A little	❑
Somewhat	❑
A lot	❑

8 Over the **PAST WEEK** how satisfied have you been with you overall sex life?

Very satisfied	❑
Moderately satisfied	❑
About equally satisfied and dissatisfied	❑
Moderately dissatisfied	❑
Very dissatisfied	❑

9 Please ring the number that corresponds with the strength of your urinary stream over the **PAST WEEK.**



(Peeling 1989)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES

e.g. work, study, housework, family or leisure activities

I have no problems with doing my usual activities ❑
I have slight problems with doing my usual activities ❑
I have moderate problems with doing my usual activities ❑
I have severe problems with doing my usual activities ❑
I am unable to perform my usual activities ❑

PAIN / DISCOMFORT

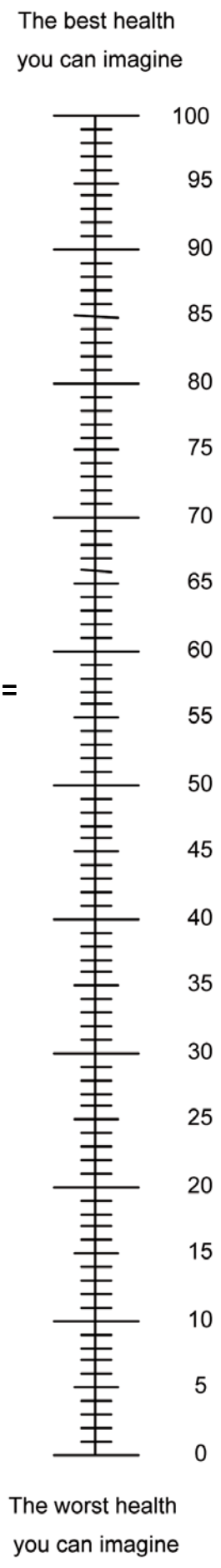
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY.**
- The scale on the right is numbered from **0** to **100.**
- **100** means the best health you can imagine.
- **0** means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY.**
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 2: Interview schedules

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 where 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 decide to take part in the trial?
    - What where/are your key concerns (if any)?
    - What where/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

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 where 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 decline to take part in the trial?
    - What where/are your key concerns (if any)?
    - What where/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

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 trail, 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 3:

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 time trade-off (TTO) exercise among a group of men eligible for trial participation consented for this sub-study alongside the main trial.

Time trade-off theory

The time trade-off (TTO) method is used to measure individual's preferences 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, where 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 define worse health state.

Due to the nature of the study where 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 where 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 (when asked to trade life – amount of time in prefect health being sacrificed) (Jansen et al., 2001; Locadia et al., 2004). In the chained method, an anchoring state is created to be used as a bridge between the temporary states and death (Torrance, 1986).

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 who consent to randomisation and those 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.

Those who express initial interest in participating in the TTO interview will be sent an invitation letter and the Participant Information Sheet for this sub study. 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 patients fails to make contact after being sent the invitation letter and Patient Information Sheet, we may try to make contact with them via phone to gauge their continuing interest in the TTO study**.** Interviews will be arranged at a convenient time and place for the participants, and consent will be sought before the start of the interviews.

Health state profiles

Six health state profiles are 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' profile 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 where 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 four weeks, and for consistency we choose to use fourteen days as the length of the time used 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 anchor state profile called "severe pain". The anchor state profile will be used in the chained TTO method (Jansen et al., 2001; Locadia et al., 2004) in two stages: in the first stage it is evaluated as a temporary health state after which full 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 (Brazier, 2007) to reduce confusion with the task and thus increase the validity of the utilities derived.

At the end of the task, each participant will be asked to value three additional profiles developed from the EQ-5D. Those extra profiles will be different from the initial practice profiles, but will be the same for every participant. The purpose of these extra profiles is to help with the comparison between utility values derived from the conventional and chained TTO methods as the EQ-5D profiles have a reference UK national tariff to compare against.

An A3-size decision board will be used in the TTO exercises to help make the questions understandable and approachable to participants. The profiles will be printed on a A5-size cards, coloured and laminated, using a different pastel colour for each health profile of the relevant procedure. When conducting the TTO exercise, the health profiles will be placed on the decision board, where the participant will be able to visually compare the length of time for each pair of health profiles being compared (detailed interview schedule below).

Interview schedule of TTO

Two methods of TTO - the conventional method and the chained method will be conducted. 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. Socio-demographic information will also 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* (fourteen days as mentioned above) 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 spend in life A (*t*) and life B (*x*). This is achieved by asking respondents a series of questions as below 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 before valuing the additional EQ-5D profiles.

For analysis, the value of each health state (h_i) is then calculated as: $h_i = x/t$

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. Same as the standard method, the number of days (*t*) in life A will be fixed at fourteen days and the number of days (*x*) in life B will also be initially set at fourteen days. Respondents will be asked a similar question to that in the conventional method, but instead of death following the length 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 before valuing the additional EQ-5D profiles.

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

For analysis, the value of the anchor state (h_j) is calculated as: $h_j = y/t$
The utility of each health profile is then calculated as: $h_i = 1 - \left(1 - h_j\right) * (\frac{x}{t})$

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

	Common & well understood consequences of treatment	**Less common & unpleasant side effects**	**Rare events**
Endoscopic urethrotomy	Mild urethral bleeding Local urinary tract infection Catheter discomfort Transient discomfort on passing urine after catheter removal	Severe bleeding requiring re-intervention Systemic urinary infection (urosepsis) requiring parental antibiotics	Extravasation of urine Persistent erectile dysfunction (more than 12 months)

		Transient (up to 12 months) erectile dysfunction	
Open urethroplasty	Mild mouth pain/discomfort if oral mucosal graft harvested Perineal wound pain Catheter discomfort Localised wound infection Local urinary tract infection Delayed healing requiring prolonged period of catheterisation Transient discomfort on passing urine after catheter removal Post-micturition dribble	Severe mouth pain if oral mucosal graft harvested Scarring in mouth after oral mucosal harvest Severe wound infection affecting deep layers Systemic urinary infection (urosepsis) requiring parental antibiotics Transient (up to 12 months) erectile dysfunction	Fistula formation Persistent erectile dysfunction (more than 12 months)

Appendix 4: Resource use questionnaire

Participant Costs Questionnaire

Part A

1a. Have you seen or contacted a GP in the last 6 months due to problems with passing urine?

YES
NO

If yes to Question 1a, please answer questions 1b-d; if no, please go to question 2a:

1b. How many appointments did you attend with a GP?

1c. How many times did a GP visit you at home?

1d. How many times did you have a telephone conversation with a GP?

2a. Have you seen a general practice nurse in the last 6 months due to problems with passing urine?

YES
NO

2b. If yes to Question 2a, how many times?

If no, please go to question 3a

3a. Have you had a hospital out-patient visit in the last 6 months due to problems of passing urine (**excluding** any study visit as part of this trial)?

YES
NO

3b. If yes to Question 3a, how many times?

If no, please go to question 4a

4a. Have you been admitted to hospital in the last 6 months due to problems with passing urine (**excluding** the initial surgery to remove catheter)?

YES
NO

4b. If yes to Question 4a, how many admissions did you have? If no, please go to question 5a

4c. For each admission, please indicate if it is a day-case or an overnight stay and for overnight stays please fill in the number of nights you stayed in hospital::

Admission 1: Day case ☐ Overnight stay ☐ number of nights_____

Admission 2: Day case ☐ Overnight stay ☐ number of nights_____

Admission 3: Day case ☐ Overnight stay ☐ number of nights_____

5a. Have you had prescription medicine in the last 6 months due to problems with passing urine (**excluding** medicine prescribed when you were discharged from hospital for initial surgery to remove catheter)?

YES
NO

5b. If yes to Question 5a, how many times for each of the following medications?

If no, please go to question 6a

Antibiotic, number of times_____
Pain killer, number of times_____
Tablet for bladder spasms, number of times_____
Other, please specify_____ number of times_____

6a. Have you purchased over the counter medicine in the last 6 months due to problems with passing urine?

YES
NO

6b. If yes to Question 6a, how much did you pay in total?

If no, please go to question 7a

7a. Have you paid for any other private health care during the last 6 months due to problems with passing urine?

YES
NO

7b. If yes to Question 7a, what type of care did you pay for?

7c. If yes to Question 7a, how much in total did it cost?

Thank you for completing this questionnaire, please return it using the envelope provided.

Participant Costs Questionnaire

Part B

Part 1 – Have you been admitted to hospital due to problems with passing urine in the last 6 months (excluding the initial surgery to remove catheter)

Yes

No

If in the last 6 months you were not admitted to hospital please go to Part 2

This is about your most recent admission to hospital due to problems with passing urine (excluding initial surgery to remove catheter)

1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

   Bus……..1
   Train……2
   Taxi……..3
   Private car……..4
   Hospital car……5
   Ambulance……6
   Other (please specify) _____7

2. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare. If you travelled by bus, train or taxi to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below.

   Cost of (one-way) fare (£) | | | – | | | Pence

3. Please put zero if you did not travel by private car at all. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below.

   Number of miles one-way | | | |

4. Please put zero if you did not pay a parking fee. If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below.

   Expenditure on parking fee (£) | | | – | | | Pence

5. When you were admitted to the hospital, how many days did you spend there? Please write the number of days in the box below.

Number of days | | |

6. What would you otherwise have been doing as your main activity if you had not had to be admitted to hospital? Please circle the number that best applies to you.

Paid work……1
Housework……..2
Childcare……..3
Caring for someone else……...4
Voluntary work……5
Leisure activities……6
Other (please specify) _____7

7. When you were admitted to hospital, did anyone come with you? Please circle the appropriate response.

Yes (continue with question 8)……1
No (go to Part 2) 2

8. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the hospital.

Paid work……1
Housework……..2
Childcare……..3
Caring for someone else……...4
Voluntary work……5
Leisure activities……6
Other (please specify)_____7

9. Did your main companion take time off from paid work (or business activity if self-employed)? Please circle the appropriate response.

Yes (continue with question 10)……1
No (go to Part 2) 2

10. Please put zero if your main companion did not take time off from paid work (or business activity if self-employed) to accompany you to the hospital. Please write the number of hours your companion took off from paid work (or business activity if self-employed) in the box below.

Number of hours | | |

11. Whilst you were in hospital, approximately how many times did your main companion come to visit you?

Number of times | | |

Part 2 - Your most recent outpatient visit due to problems with passing urine

If in the last 6 months you did not have an outpatients appointment please go to Part 3

1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

Bus……..1
Train……2
Taxi……..3
Private car……..4
Hospital car……5
Ambulance……6
Other (please specify) _____7

2. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare. If you travelled by bus, taxi or train to your outpatients appointment what was the total cost of the (one-way) journey? Please write the cost in the box below.

Cost of (one-way) fare (£) | | | – | | | pence

3. Please put zero if you did not travel by private car at all. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below.

Number of miles one-way | | | |

4. Please put zero if you did not pay a parking fee. If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below.

Expenditure on parking fee (£) | | | – | | | pence

5. When you visited outpatients, how long did it take to travel there? Please write the number of hours and minutes in the box below.

Number of hours ☐☐ – ☐☐ minutes

6. When you visited outpatients, how long did you spend there? Please write the number hours and minutes in the box below.

Number of hours ☐☐ – ☐☐ minutes

7. Please circle the number that best describes what you otherwise would have been doing as your main activity if you had not been visiting outpatients?

Paid work……1
Housework……2
Childcare……3
Caring for someone else……4
Voluntary work……5
Leisure activities……6
Other (please specify)_____7

8. When you visited outpatients did anyone come with you? Please circle the appropriate response.

Yes (continue with question 9)……..1
No (go to Part 3) 2

9. Please put zero if your main companion did not travel by bus or train at all. If your main companion travelled with you by bus or train approximately how much did they pay (one-way) in fares? Please write the approximate cost in the box below.

Cost of (one-way) fare (£) ☐☐ – ☐☐ pence

10. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to outpatients.

Paid work……1
Housework……2
Childcare……3
Caring for someone else……4
Voluntary work……5
Leisure activities……6
Other (please specify)_____7

Part 3 - Your most recent GP or practice nurse appointment due to problems with passing urine

If in the last 6 months you did not have a GP or practice nurse appointment, please return the questionnaire in the envelope provided. Thank you!

1. Please circle the number that best describes how you travelled to your most recent GP or practice nurse appointment. If you used more than one form of transport please indicate the way you travelled for the main (longest in terms of distance) part of your journey.

   Bus……..1
   Train……2
   Taxi……..3
   Private car……..4
   Bike……5
   Walk……6
   Other (please specify) _____7

2. Please put zero if you did not travel by bus or taxi or if you did not pay the fare. If you travelled by bus, taxi or train, what was the cost of the (one-way) fare? Please write the cost in the box below.

   Cost of (one-way) fare (£) | | | – | | | pence

3. Please put zero if you did not travel by private car at all. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below.

   Number of miles one-way | | | |

4. Please put zero if you did not pay for parking. If you travelled by private car and you or a companion had to pay a parking fee how much did this cost? Please write the cost in the box below.

   Expenditure on parking fee (£) | | | – | | | pence

5. When you visited the GP or practice nurse, how long did it take to travel there? Please write the number of minutes in the box below.

   Number of minutes | | | |

6. When you visited the GP or practice nurse, how long did you spend there? Please write the number minutes in the box below. Please include in your answer the time spent waiting and also the time spent with the doctors and nurses

Number of minutes | | | |

7. Please circle the number that best describes what you otherwise would have been doing as your main activity if you had not visited the GP or practice nurse.

Paid work……1
Housework……..2
Childcare……..3
Caring for someone else……...4
Voluntary work……..……5
Leisure activities……6
Other (please specify)_____7

8. When you visited the GP or practice nurse did anyone come with you? Please circle the appropriate response.

Yes (continue with question 9)……..1
No (Your questionnaire is complete).....2

9. Please put zero if your main companion did not travel by bus at all. If your main companion travelled with you by bus how much approximately did they pay (one-way) in fares (if anything)? Please write the cost in the box below.

Cost of (one-way) fare (£) | | | – | | | pence

10. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to see the GP or practice nurse.

Paid work……1
Housework……..2
Childcare……..3
Caring for someone else……...4
Voluntary work……..……5
Leisure activities……6
Other (please specify)_____7