

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



www.opentrial.co.uk

Supplementary Statistical Analysis Plan

ISRCTN: 56465715

Graeme MacLennan (Senior Statistician):

Signature: *Graeme MacLennan*

Date: *6/12/18*

Beatriz Goulao (Trial Statistician)

Signature: *BG*

Date: *6/12/18*

Robert Pickard (Chief Investigator):

Signature: *R Pickard*

Date: 31st January 2018

VERSION 1.1

January 2018

Contents

1. Rationale	3
2. Planned additional analyses.....	3
3. References.....	4

1. Rationale

The primary outcome analysis planned in the OPEN Trial Statistical Analysis Plan (final version published in August 2017) envisaged comparison of the area under the curve (AUC) of the participant-completed ICIQ symptom score plotted against time since randomisation. The score was measured at baseline prior to randomisation, at 1, 3, 6, 9 and 12 months after intervention and at 18 and 24 months after randomisation. Additional scores were obtained at the time of re-intervention, at 18 and 24 months post-surgery and at end of study (November 2017). All participants who had at least one early measure (baseline or prior to intervention), at least one mid-term measure (3-12 months post intervention) and at least one late term measure (18-24 months after randomisation) would be eligible for inclusion in the primary analysis. At November 2017 64/101 (63%) men allocated to intervention A and 78/103 (76%) men allocated to intervention B fulfilled the criteria for inclusion in the primary analysis. The statistical analysis plan required a sample size of 200 assuming a 15% attrition rate. Although, after an extended recruitment period, 220 participants were randomised the attrition rate (22+37/204) of 30% is twice that anticipated. We continue to strive as hard as possible to collect the missing patient-reported outcome measures but anticipate little further improvement at study closure on 23rd December 2017. This is likely to increase the uncertainty surrounding the primary result necessitating planning of additional sensitivity analyses using a larger sample with imputation of missing data. A further factor that may have an effect on the primary analysis is the variable delay between randomisation and undergoing the allocated intervention. This will require detailed examination to detect any influence on the primary result.

2. Planned additional analyses

We plan to carry out a range of sensitivity analysis to explore the robustness of treatment effect estimates to assumptions made. In addition to standard multiple imputation modelling:

- Missing not at random (MNAR): A pattern mixture modelling approach to explore departures from the missing at random (MAR) assumption. Imputation will be at the person level (i.e. the AUC) rather than at missing time points, using Stata package rctmiss (White 2011)
- Using available partial repeated measures data: We'll use methods outlined by Bell et al (2014) to impute data at missing time points and hence calculate AUCs with partial information, under MAR and MNAR assumptions.
- For the variation in delay between randomisation and intervention we will explore setting a threshold where delay in undergoing intervention precludes inclusion in the primary analysis; and we'll test how sensitive results are to varying that threshold.

- Given treatment crossover we'll explore per-protocol sensitivity analysis and using casual methods to estimate effects of the intervention actually received.

3. References

White IR, Kalaitzaki E, Thompson SG. Allowing for missing outcome data and incomplete uptake of randomised interventions, with application to an Internet-based alcohol trial. *Statistics in Medicine*. 2011;30(27):3192-3207.

Bell ML, King MT, Fairclough DL. Bias in area under the curve for longitudinal clinical trials with missing patient reported outcome data: Summary measures versus summary statistics. *SAGE Open* 2014; 4:2 <https://doi.org/10.1177/2158244014534858>