Prostate Surgery for Men with Lower Urinary Tract Symptoms: Do We Need Urodynamics to Find the Right Candidates? Exploratory Findings from the UPSTREAM Trial

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Abstract

Background: Identifying men whose lower urinary tract symptoms (LUTS) may benefit from surgery is challenging.

Objective: To identify routine diagnostic and urodynamic measures associated with treatment decision-making, and outcome, in exploratory analyses of the UPSTREAM trial.

Design, setting, and participants: A randomised controlled trial was conducted including 820 men, considering surgery for LUTS, across 26 hospitals in England (ISCTRN56164274).

Intervention: Men were randomised to a routine care (RC) diagnostic pathway (n = 393) or a pathway that included urodynamics (UDS) in addition to RC (n = 427).

Outcome measurements and statistical analysis: Men underwent uroflowmetry and completed symptom questionnaires, at baseline and 18 mo after randomisation. Regression models identified baseline clinical and symptom measures that predicted recommendation for surgery and/or surgical outcome (measured by the International Prostate Symptom Score [IPSS]). We explored the association between UDS and surgical outcome in subgroups defined by routine measures.

Results and limitations: The recommendation for surgery could be predicted successfully in the RC and UDS groups (area under the receiver operating characteristic curve 0.78), with maximum flow rate (Qmax) and age predictors in both groups. Surgery was more beneficial in those with higher symptom scores (eg, IPSS >16), age <74 yr, Qmax <9.8 ml/s, bladder outlet obstruction index >47.6, and bladder contractility index >123.0. In the UDS group, urodynamic measures were more strongly predictive of surgical outcome for those with Qmax >15, although patient-reported outcomes were also more predictive in this subgroup.

Conclusions: Treatment decisions were informed with UDS, when available, but without evidence of change in the decisions reached. Despite the small group sizes, exploratory analyses suggest that selective use of UDS could detect obstructive pathology, missed by routine measures, in certain subgroups.
Patient summary: Baseline clinical and symptom measurements were able to predict treatment decisions. The addition of urodynamic test results, while useful, did not generally lead to better surgical decisions and outcomes over routine tests alone.

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1. Introduction

Approximately 30% of men aged >65 yr suffer from troublesome lower urinary tract symptoms (LUTS), and this is expected to rise with an ageing population [1]. LUTS cover a variety of different symptoms, including voiding (eg, weak stream) and storage (eg, incontinence) [2], often associated with bladder outlet obstruction (BOO).

Surgery to remove BOO, such as transurethral resection of the prostate, carries risks of complications and potentially worsening of symptoms. Current national guidelines suggest offering surgery if LUTS are severe, and conservative treatments have been unsuccessful [3,4]. A recent qualitative evaluation, on treatment considerations in men with LUTS, indicated a preference for medical treatment to reduce the risk of undergoing surgery [5]. Treatment decision-making is made jointly by the clinician and the patient, based on the bothersomeness of LUTS and the diagnostic test results.

It is often argued that BOO should be diagnosed before proceeding with surgery [6], since men with weak bladder contractions, termed detrusor underactivity (DU), are less likely to benefit [7]. Tests used to assess LUTS include measuring maximum flow rate ($Q_{\text{max}}$) [8], where $Q_{\text{max}} <10$ ml/s suggests a high likelihood of BOO [9]. Urodynamics (UDS) can distinguish more accurately between BOO and DU [10,11]. It evaluates bladder outlet obstruction index (BOOI) and bladder contractility index (BCI), where values above 40 and 100, respectively, suggest that obstruction is present, rather than DU [12]. In theory, UDS could reduce the number of operations undertaken, by excluding men with pure DU. However, in practice, such a reduction did not arise [12].

The UPSTREAM multicentre trial randomly allocated 820 men, who were being considered for surgical management of LUTS, to UDS or no UDS in addition to the usual (routine) diagnostic pathway [13]. The aim of UPSTREAM was to investigate whether UDS would improve identification of cases suitable for surgical management, thereby avoiding surgery where it is unlikely to be beneficial. The main findings were published in 2020, and at 18 mo after randomisation, surgery rates were almost identical (38% vs 36%), with similar (noninferior) patient-reported outcome measures (PROMs) in the UDS arm to those in routine care (RC) [12]. Therefore, routine use of UDS for men with suspected BOO was not supported. However, the investigators highlighted the need to identify specific instances where UDS could provide useful additional information, supported by an accompanying editorial [14].

Here, we report exploratory analyses of the UPSTREAM trial data, which aim to investigate the following: (1) what information is being used to identify men suitable for surgical management, (2) what information is most predictive of surgical outcome, and (3) whether there are subgroups in which UDS improves the predictions, leading to better decisions and patient outcomes overall.

2. Patients and methods

2.1. Study design and participants

UPSTREAM recruited men, between October 2014 and December 2016, across 26 hospitals in England. The eligibility criteria were men aged $\geq 18$ yr, seeking treatment for bothersome LUTS, eligible for and considering surgery, and with no previous prostate surgery [13,15]. The sample size target of 776 was based on establishing whether a pathway including UDS led to IPSS values that were noninferior to the scores of a pathway without UDS (no more than 1 point higher) [16]. Using simple randomisation, 393 men were randomised to RC following usual diagnostic pathways and 427 were randomised to RC with additional UDS [15,16]. The outcomes of the trial have been published previously [12]. The intervention was not the surgery procedure itself; it was the inclusion of UDS in the treatment pathway, which could then act as an additional decision aid when determining which men should receive surgery.

In this pragmatic design, surgeons were not provided with treatment protocols.
curves were calculated for each baseline variable, as well as optimal cut points for anticipating the decision, with a value closer to 1 indicating better predictive performance. The optimal cut point was calculated using Liu’s [20] method, which optimises the product of sensitivity and specificity, therefore giving equal importance to identifying those recommended and not recommended for surgery. Where ties were found, Youden’s [21] method was used, which maximises the sum of sensitivity and specificity. The evidence for an association between the surgery decision and each baseline measure was quantified as a p value, calculated using logistic regression. Following the univariable analyses, a best fit multivariable logistic regression model was identified to see which variables could jointly predict the surgical decision; for further details, see the Supplementary material.

The association between the change in IPSS and baseline measures was investigated, separately for surgical and nonsurgical management. Evidence for a difference in association was quantified by adding an interaction term (baseline measure × surgical/nonsurgical management) to the linear regression model, then using a likelihood ratio test to calculate the interaction p value. Where baseline variables were skewed, analyses were also carried out on the log scale, to ensure that they produced similar findings. While continuous variables were used in the analysis, descriptives were presented as dichotomous variables, to aid in the interpretation. Thresholds for dichotomising these variables were defined, in advance of analysis, using current guidelines [22] or by trial team consensus (Supplementary Table 1). Best fit multivariable linear regression models were identified to see which variables could jointly predict the change in IPSS (see the Supplementary material). Adjusted R² values were then used to examine the proportion of the change in IPSS values that could be explained by the baseline variables. Men receiving surgery were then categorised into three categories of surgery success, based on the minimally clinically important difference [23]: “successful”, a decrease in IPSS of ≥3 points; “no improvement”, an increase/decrease of <3; or “unsuccessful”, an increase of ≥3 points. The optimal cut-off points for predicting successful surgery, compared with no improvement/unsuccessful surgery, were defined using Liu’s [20] method.

The ability of BOOI and BCI to identify men more likely to benefit from surgery, in those receiving UDS, was explored across different subgroups. DO diagnoses (yes/no) were compared, as well as Qmax in three groups identified in the guidelines [22]: <10, 10–15, and >15 ml/s. Linear regression models were used to identify whether there was an interaction between the subgroups and the BOOI/BCI measures, on the change in IPSS. Where found, an interaction would suggest that BOOI/BCI measures were better predictors in specific subgroups. As a comparator, in those receiving RC, the ability of the ICIQ voiding subscale to identify men more likely to benefit from surgery was explored across the subgroups of Qmax.

3. Results

The UPSTREAM trial consisted of 820 randomised men, with a mean age of 68 yr (standard deviation 9; Supplementary Fig. 2) [12]. Of these men, 381 underwent a diagnostic pathway that included UDS (28 from those allocated to RC), 428 underwent an RC pathway (68 from those allocated to UDS), and 11 withdrew. Of those receiving UDS, 52% (195/375) were recommended for surgery compared with 46% (183/400) who received RC. Of those recommended, 73% (275/378) went on to receive surgery; an additional 16 men underwent surgery although it had not been recommended for them. In total, 291 received surgery, with a median time from randomisation to surgery of 202 d (interquartile range 120–314 d). Over 78% of the men undergoing surgery received transurethral resection of the prostate, with no difference between the study arms allocated to UDS and no UDS [17]. Other treatments included holmium laser enucleation of the prostate, Urolift, and bladder neck incision. Conservative treatments (eg, fluid advice) and pharmaceutical interventions (eg, tamsulosin and finasteride) were similar between the two arms of the trial [17]. Men reporting mild symptoms at baseline (IPSS ≤7) were not included in the rest of the analysis (n = 47).

3.1. Factors predicting surgical decision-making

For those receiving UDS, a diagnosis of obstruction (BOOI ≥40) resulted in 71% (106/150) of men being given a surgery recommendation, compared with 12% (4/34) who were

Table 1 – Finding the optimum multivariate model to predict the decision, on whether or not to proceed with surgery, by treatment received (UDS/RC)

<table>
<thead>
<tr>
<th>Routine care (n = 311)</th>
<th>Model selection parameters</th>
<th>Urodynamics received (n = 220)</th>
<th>Model selection parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters included</td>
<td>OR</td>
<td>AUROC</td>
<td>AIC</td>
</tr>
<tr>
<td>Qmax</td>
<td>0.852</td>
<td>0.743</td>
<td>380.5</td>
</tr>
<tr>
<td>+Age</td>
<td>1.026</td>
<td>0.748</td>
<td>370.5</td>
</tr>
<tr>
<td>+ICIQ voiding</td>
<td>1.150</td>
<td>0.778</td>
<td>364.0</td>
</tr>
<tr>
<td>+IPSS total score</td>
<td>1.265</td>
<td>0.781</td>
<td>361.9</td>
</tr>
<tr>
<td>+Comorbidities</td>
<td>0.985</td>
<td>0.781</td>
<td>363.7</td>
</tr>
<tr>
<td>+IPSS total score</td>
<td>0.862</td>
<td>0.785</td>
<td>362.0</td>
</tr>
<tr>
<td>+ICIQ incontinence</td>
<td>1.030</td>
<td>0.783</td>
<td>362.9</td>
</tr>
<tr>
<td>+PVR</td>
<td>1.001</td>
<td>0.783</td>
<td>363.8</td>
</tr>
<tr>
<td>+VV</td>
<td>1.001</td>
<td>0.783</td>
<td>363.6</td>
</tr>
<tr>
<td>+BOOI</td>
<td>1.026</td>
<td>0.783</td>
<td>262.6</td>
</tr>
</tbody>
</table>

AIC = Akaike information criterion; AUROC = area under the receiver operating characteristic; BCI = bladder contractility index; BOOI = bladder outlet obstruction index; ICIQ = International Consultation on Incontinence Questionnaire; IPSS = International Prostate Symptom Score; OR = odds ratio; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; RC = routine care; UDS = urodynamics; VV = voided volume.

a Variables included, cumulatively, starting with the variable with the most evidence of an association with the surgical decision from a multivariate model.

b Where the variable increased the AIC, it was excluded from models, going forward (italics). The variables included in the optimum model, providing the lowest AIC, are in bold.

c Urodynamometric parameters were added to the optimum multivariate model to accurately assess the “additional value” from the measures.
**Table 2** – IPSS total scores at baseline and 18-mo assessments, for men undergoing surgery and men not undergoing surgery, presented for 12 subgroups (corresponding to Fig. 1)

<table>
<thead>
<tr>
<th>Variable Category</th>
<th>Surgery received</th>
<th>No surgery received</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery received</td>
<td>No surgery received</td>
<td>p value a</td>
</tr>
<tr>
<td></td>
<td>a, Baseline 18 mo</td>
<td>a, Baseline 18 mo</td>
<td></td>
</tr>
<tr>
<td>Age (yr) ≤65</td>
<td>69</td>
<td>139</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt;65</td>
<td>173</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Comorbidities ≥1</td>
<td>159</td>
<td>238</td>
<td>0.008</td>
</tr>
<tr>
<td>≤1</td>
<td>139</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>Qmax (ml/s) ≤10</td>
<td>108</td>
<td>230</td>
<td>0.040</td>
</tr>
<tr>
<td>&gt;10</td>
<td>133</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Postvoid residual (ml) ≤100</td>
<td>90</td>
<td>196</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;100</td>
<td>146</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Voided volume (ml) ≤200</td>
<td>111</td>
<td>143</td>
<td>0.042</td>
</tr>
<tr>
<td>&gt;200</td>
<td>128</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>IPSS score ≤20</td>
<td>88</td>
<td>205</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;20</td>
<td>154</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>IPSS QoL ≤4</td>
<td>51</td>
<td>140</td>
<td>0.012</td>
</tr>
<tr>
<td>&gt;4</td>
<td>191</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>ICIQ score ≤20</td>
<td>106</td>
<td>143</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;20</td>
<td>124</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>ICIQ incontinence ≤6</td>
<td>129</td>
<td>225</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;6</td>
<td>109</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>BOOI ≤40</td>
<td>17</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;40</td>
<td>90</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>BCI ≤100</td>
<td>15</td>
<td>58</td>
<td>0.16</td>
</tr>
<tr>
<td>&gt;100</td>
<td>100</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

BCI = bladder contractility index; BOOI = bladder outlet obstruction index; ICIQ = International Consultation on Incontinence Questionnaire; IPSS = International Prostate Symptom Score; QoL = quality of life.

a Number per group with both baseline and 18-mo IPSS scores available.

b p value from the likelihood ratio test, testing the null hypothesis of equal association between the baseline measure and change on the IPSS total score, comparing men undergoing surgery and those not undergoing surgery.

c Additional adjustment for age: p = 0.042.

Fig. 1 – Scatter plots, with line of best fit, showing the effect of baseline measures on the change in IPSS in those receiving surgery during the 18-mo follow-up (orange diamonds and line) and those who did not receive surgery during the 18-mo follow-up (blue circles and line). IC = International Consultation on Incontinence Questionnaire; IPSS = International Prostate Symptom Score; QoL = quality of life.
The mean overall change in IPSS, after 18 mo, was $-11.60$ (range $-34.12$) for those receiving surgery and $-2.59$ (range $-26.14$) for those not receiving surgery. Age, number of comorbidities, BOOI, Qmax, and urinary symptom PROMs modified the effect of surgery on change in IPSS values (Fig. 1 and Table 2). The ICIQ voiding subscale showed strong evidence of effect modification, with surgery being most effective in those with higher scores. Surgery also appeared to be most effective in younger men (lower end of 50–90 yr range), those with fewer or no comorbidities, those with higher BOO and BCI indices, and those with lower Qmax levels (Fig. 1A–E). Those with higher PROMs at baseline (ie, worse symptoms) saw the greatest symptomatic improvement from surgery (Fig. 1H–J and 1L). However, greater gains were also found for those not receiving surgery, suggesting that those with worse symptoms had most to gain, regardless of surgery. PVR, VV, and ICIQ incontinence subscale did not appear to moderate the effect of surgery on outcome (Fig. 1F, 1G, and 1K).

The optimum multivariate model, with an adjusted $R^2$ of 0.46, for predicting surgical outcome in those receiving surgery after RC ($n = 98$) consisted of IPSS, number of comorbidities, and Qmax (Table 3). The optimum multivariate model, with an adjusted $R^2$ of 0.31, for predicting surgical outcome in those receiving surgery after UDS ($n = 82$) consisted of IPSS, age, VV, and ICIQ incontinence subscale. The addition of BOOI improved the model, to give an adjusted $R^2$ of 0.37. A similar pattern was observed in those who received UDS, with data on all variables ($n = 220$) consisted of Qmax, PVR, ICIQ total score, and age. The addition of BOOI, from the UDS results, raised the AUROC to 0.78. The addition of BCI did not improve the prediction.

### 3.2. Factors predicting surgery outcomes, with and without UDS

As $Q_{\text{max}}$ was the strongest predictor of the surgical decision, the impact of BOOI and BCI on change in IPSS was compared unobstructed (Supplementary Table 2). The recommendations for surgery appeared to be dependent on various baseline measures (Supplementary Table 3). The cut points suggested that the surgeons were applying current guidelines (see the Supplementary material).

The optimum multivariate model, with an AUROC of 0.78, for predicting a surgical decision in men receiving RC with data on all variables ($n = 311$) consisted of $Q_{\text{max}}$, age, ICIQ voiding subscale, and IPSS QoL (Table 1). The optimum model, with an AUROC of 0.69, for men receiving UDS with data on all variables ($n = 220$) consisted of $Q_{\text{max}}$, PVR, ICIQ total score, and age. The addition of BOOI, from the UDS results, raised the AUROC to 0.78. The addition of BCI did not improve the prediction.

### 3.3. Value of UDS in patient subgroups

As $Q_{\text{max}}$ was the strongest predictor of the surgical decision, the impact of BOOI and BCI on change in IPSS was compared

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across three subgroups of $Q_{\text{max}}$. Although based on a small number ($n = 16$), the line of best fit for those with $Q_{\text{max}} > 15$ suggested that UDS was a better predictor of surgical outcome in this group (Fig. 2D–I and Supplementary Table 5). The ICIQ voiding subscale was also a better predictor of surgical outcome in higher $Q_{\text{max}}$ groups, in the RC group (Fig. 2A–C and Supplementary Table 5). The presence of DO appeared to substantially weaken the relationship between the UDS indices and the change in IPSS (Fig. 3 and Supplementary Table 6). Where DO was absent, BOOI and BCI were better predictors of outcome, with higher levels resulting in more successful surgery.

4. Discussion

These exploratory analyses of the UPSTREAM trial have shown that, in a pragmatic trial setting, surgical decision-making reflects current guidelines [22], utilising both clinical and patient-reported measures. While indices derived from UDS were influential in the decision, standard measures alone predicted them to the same extent, suggesting that an informed decision can be made with or without UDS.

This analysis has also highlighted measurements that were predictive of surgical success (decrease in IPSS). Suggested cut-offs for predicting success from surgery, which could be explored in future research, include ICIQ voiding subscale score > 8, IPSS > 16, ICIQ score > 18, $Q_{\text{max}} < 9.8 \text{ml/s}$, IPSS QoL > 4, and age < 74 yr. Those outside of these ranges were at a greater risk of poor outcomes after surgery. The incontinence subscale, specifically, was not associated with outcome, regardless of whether or not surgery was received. Age anticipated the decision for surgery, which was more likely in older men; yet, younger men benefited the most out of those receiving surgery (50–90 yr range).

While previous research in UDS has shown how it can alter clinical decisions, there is very little research on how the results from UDS affect symptom outcome [24]. Appropriate use of UDS in suitable situations is key, and these findings suggest that UDS may provide useful additional information when $Q_{\text{max}}$ is $\geq 10 \text{ml/s}$, especially when $Q_{\text{max}}$ is $> 15 \text{ml/s}$, where BOOI and BCI predicted the change in IPSS most successfully. In other words, the data suggested that UDS may identify cases of obstructive pathology not apparent from uroflowmetry. Interestingly, in those men following the RC pathway, ICIQ voiding subscales were also

Fig. 2 – Scatter plots, with line of best fit, showing the effect of ICIQ voiding score/BOOI/BCI on the change in IPSS in those receiving surgery during the 18-mo follow-up (orange diamonds and line) and those who did not receive surgery during the 18-mo follow-up (blue circles and line), including those receiving (A–C) routine care (RC) and (D–I) urodynamics (UDS), broken down into three subgroups: $Q_{\text{max}} < 10$, $Q_{\text{max}} 10–15$, and $Q_{\text{max}} > 15$. BCI = bladder contractility index; BOOI = bladder outlet obstruction index; ICIQ = International Consultation on Incontinence Questionnaire; IPSS = International Prostate Symptom Score; $Q_{\text{max}}$ = maximum flow rate; RC = routine care; UDS = urodynamics.
better predictors of a change in IPSS for $Q_{\text{max}} > 15 \, \text{ml/s}$, suggesting that closer scrutiny of all measurements in this subgroup could aid the surgical decision. Where DO was present, levels of BOOI and BCI were obsolete in identifying those who benefit from surgery. The opposite was true where DO was not observed, providing an additional subgroup where UDS may aid the surgical decision. However, this subgroup would benefit only if DO could be diagnosed in isolation from UDS. High prevalence of DO in people with urgency urinary incontinence or high scores on the urgency severity scale suggests that this may be possible [25].

These analyses add extra clarity to the findings of the UPSTREAM trial, although, as they are exploratory, they should be treated as signposts for future investigations rather than definitive in themselves. The findings highlight the areas of future interest: firstly, UDS seems unnecessary in those with $Q_{\text{max}} < 10 \, \text{ml/s}$, and secondly, voiding symptoms and quality-of-life score are important in finding those most suitable for surgery. Thus, outcome of surgery was generally good for men confirmed to have voiding symptoms, but not storage symptoms, which were badly affecting quality of life. For men with high overall symptom scores, it is potentially prudent to establish the contribution of voiding symptoms to the impairment of quality of life. Where $Q_{\text{max}}$ was $\geq 10 \, \text{ml/s}$, UDS may have a role in establishing whether BOO is present and hence whether surgery will realistically improve symptoms. The threshold at which this applies is not certain, since the analysis used $Q_{\text{max}}$ groupings given in the EAU guidelines; establishing a more specific threshold merits further research [22].

The diagnostic and treatment pathways in the UPSTREAM trial reflect current NHS practice in England. A wide range of PROMs were collected in a standardised manner, with low rates of missing data. However, treatment delays affected the UDS arm (median 216 vs 177 d to undergo surgery) [17], leading to less comparable groups in terms of treatment receipt. Timing of questionnaires was based on randomisation, rather than treatment start, leading to symptom variations at 18 mo after randomisation. UPSTREAM phase II is currently underway, which will investigate the PROMs at 5 yr after randomisation.

5. Conclusions

This exploratory analysis shows that, while urodynamic results are utilised when making a surgery recommenda-

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Fig. 3 – Scatter plots, with line of best fit, showing the effect of BOOI/BCI on the change in IPSS in those receiving surgery during the 18-mo follow-up (orange diamonds and line) and those who did not receive surgery during the 18-mo follow-up (blue circles and line), including those receiving UDS, further broken down into two subgroups: those with detrusor overactivity (DO) and those without. BCI = bladder contractility index; BOOI = bladder outlet obstruction index; IPSS = International Prostate Symptom Score; UDS = urodynamics.
tion for LUTS, other less invasive measures can support the decision adequately. This was also true for predicting surgical outcome, where age, number of comorbidities, $Q_{\text{max}}$, and PROMs predicted symptom improvement. While selective use of UDS may be helpful in those with $Q_{\text{max}} > 10$ mL/s or those without DO, these findings support the recent conclusions from the UPSTREAM trial that routine use of UDS is unjustified.

**Author contributions:** Marcus J. Drake had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Drake, Young.

**Acquisition of data:** Drake, Young, Lewis.

**Analysis and interpretation of data:** Drake, Young, Metcalfe, Lane.

**Drafting of the manuscript:** Drake, Young, Metcalfe, Lane, Lewis.

**Critical revision of the manuscript for important intellectual content:** Abrams, Blair, Ito, Chapple.

**Statistical analysis:** Young, Metcalfe.

**Obtaining funding:** Drake.

**Administrative, technical, or material support:** Lewis.

**Supervision:** Drake, Metcalfe, Lane.

**Other:** None.

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**Appendix A. Supplementary data**

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