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# Primary trabeculectomy versus primary glaucoma eye drops for newly diagnosed advanced glaucoma: TAGS RCT

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# Abstract

## Primary trabeculectomy versus primary glaucoma eye drops for newly diagnosed advanced glaucoma: TAGS RCT

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**Background:** Patients diagnosed with advanced primary open-angle glaucoma are at a high risk of lifetime blindness. Uncertainty exists about whether primary medical management (glaucoma eye drops) or primary surgical treatment (augmented trabeculectomy) provide the best and safest patient outcomes.

**Objectives:** To compare primary medical management with primary surgical treatment (augmented trabeculectomy) in patients with primary open-angle glaucoma presenting with advanced disease in terms of health-related quality of life, clinical effectiveness, safety and cost-effectiveness.

**Design:** This was a two-arm, parallel, multicentre, pragmatic randomised controlled trial.

**Setting:** Secondary care eye services.

**Participants:** Adult patients presenting with advanced primary open-angle glaucoma in at least one eye, as defined by the Hodapp–Parrish–Anderson classification of severe glaucoma.

**Intervention:** Primary medical treatment – escalating medical management with glaucoma eye drops. Primary trabeculectomy treatment – trabeculectomy augmented with mitomycin C.

**Main outcome measures:** The primary outcome was health-related quality of life measured with the Visual Function Questionnaire-25 at 2 years post randomisation. Secondary outcomes were mean intraocular pressure; EQ-5D-5L; Health Utilities Index 3; Glaucoma Utility Index; cost and cost-effectiveness; generic, vision-specific and disease-specific health-related quality of life; clinical effectiveness; and safety.

**Results:** A total of 453 participants were recruited. The mean age of the participants was 67 years (standard deviation 12 years) in the trabeculectomy arm and 68 years (standard deviation 12 years) in the medical management arm. Over 65% of participants were male and more than 80% were white. At 24 months, the mean difference in Visual Function Questionnaire-25 score was 1.06 (95% confidence interval -1.32 to 3.43;  $p = 0.383$ ). There was no evidence of a difference between arms in the EQ-5D-5L score, the Health Utilities Index or the Glaucoma Utility Index. At 24 months, the mean intraocular pressure was 12.40 mmHg in the trabeculectomy arm and 15.07 mmHg in the medical management arm (mean difference -2.75 mmHg, 95% confidence interval -3.84 to -1.66 mmHg;  $p < 0.001$ ). Fewer types of glaucoma eye drops were required in the trabeculectomy arm. LogMAR visual acuity was slightly better in the medical management arm (mean difference 0.07, 95% confidence interval 0.02 to 0.11;  $p = 0.006$ ) than in the trabeculectomy arm. There was no evidence of difference in safety between the two arms. A discrete choice experiment updated the utility values for the Glaucoma Utility Index. The within-trial economic analysis found a small increase in the mean EQ-5D-5L score (0.04) and that trabeculectomy has a higher probability of being cost-effective than medical management. The incremental cost of trabeculectomy per quality-adjusted life-year was £45,456. Therefore, at 2 years, surgery is unlikely to be considered cost-effective at a threshold of £20,000 per quality-adjusted life-year. When extrapolated over a patient's lifetime in a model-based analysis, trabeculectomy, compared with medical treatment, was associated with higher costs (average £2687), a larger number of quality-adjusted life-years (average 0.28) and higher incremental cost per quality-adjusted life-year gained (average £9679). The likelihood of trabeculectomy being cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life year gained was 73%.

**Conclusions:** Our results suggested that there was no difference between treatment arms in health-related quality of life, as measured with the Visual Function Questionnaire-25 at 24 months. Intraocular pressure was better controlled in the trabeculectomy arm, and this may reduce visual field progression. Modelling over the patient's lifetime suggests that trabeculectomy may be cost-effective over the range of values of society's willingness to pay for a quality-adjusted life-year.

**Future work:** Further follow-up of participants will allow us to estimate the long-term differences of disease progression, patient experience and cost-effectiveness.

**Trial registration:** Current Controlled Trials ISRCTN56878850.

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# Contents

List of tables	xiii
List of figures	xvii
List of boxes	xix
List of supplementary material	xxi
List of abbreviations	xxiii
Plain English summary	xxv
Scientific summary	xxvii
<b>Chapter 1 Introduction</b>	<b>1</b>
Background	1
Advanced glaucoma at presentation: a risk factor for blindness	1
Current treatment options	2
Rationale for this study	2
Patient and public involvement	3
Aims of the trial	4
<i>Primary objective</i>	4
<i>Secondary objectives</i>	4
<b>Chapter 2 Methods</b>	<b>5</b>
Study design	5
Setting	5
<i>Clinical centres</i>	5
<i>Population</i>	5
Participants	5
Consent to participate	6
Health technologies compared	6
<i>Primary medical management: escalating medical therapy</i>	6
<i>Primary trabeculectomy: standard trabeculectomy augmented with mitomycin C</i>	7
<i>Compliance with study treatment</i>	7
<i>Accountability of the study treatment</i>	7
<i>Concomitant medication</i>	7
Treatment allocation	7
Study outcome measures and schedule of assessment	8
<i>Primary outcomes</i>	8
<i>Secondary outcomes</i>	9
Masking	11
<i>Methods to protect against sources of bias</i>	11
Statistical analysis	11
<i>Ground rules for statistical analysis</i>	11
<i>Sample size</i>	11

## CONTENTS

<i>Primary/secondary outcome analysis</i>	12
<i>Subgroup analyses</i>	12
<i>Criteria for the termination of the trial</i>	13
Economic evaluation	13
Research ethics and regulatory approvals	13
Changes to the protocol	13
Management of the trial	13
Study oversight committees	13
<i>Study Management Group</i>	13
<i>Project Management Group</i>	13
<i>Trial Steering Committee</i>	14
<i>Data Monitoring Committee</i>	14
<b>Chapter 3 Participant baseline characteristics</b>	<b>15</b>
Trial recruitment	15
Participant flow	16
Baseline characteristics	17
Treatment received	20
<b>Chapter 4 Trial results</b>	<b>23</b>
Primary outcome	23
<i>Subgroup analysis</i>	25
Secondary outcomes	27
EQ-5D-5L	27
<i>Health Utility Index version 3</i>	29
<i>Glaucoma Utility Index</i>	29
<i>Patient perception: glaucoma getting worse</i>	29
<i>Intraocular pressure</i>	29
<i>LogMAR visual acuity</i>	30
<i>Visual fields mean deviation</i>	30
<i>Need for cataract surgery</i>	30
<i>Visual standards for driving (pass/no defects)</i>	30
<i>Registered as sight impaired at 24 months</i>	30
Safety	31
<i>Antiglaucoma medication</i>	36
<i>Other trabeculectomy interventions</i>	39
<i>Non-index eye</i>	39
<b>Chapter 5 Discrete choice experiment</b>	<b>43</b>
Introduction	43
Methods	43
<i>Stage 1: identification of attributes and levels</i>	44
<i>Stage 2: creating an efficient design</i>	44
<i>Stage 3: data collection</i>	44
<i>Stage 4: data analysis and interpretation</i>	46
Preference-based weights	46
Sensitivity analysis	46
Results	46
<i>Participant characteristics</i>	47
Discrete choice experiment results	47
<i>Regression model results</i>	47
<i>Preference-based weights</i>	48
<i>Sensitivity analyses</i>	50

<b>Chapter 6 Economic evaluation</b>	<b>51</b>
Within-trial economic evaluation	51
<i>Introduction</i>	51
Methods	51
<i>Data collection</i>	51
Derivation of costs	52
<i>Inpatient costs</i>	52
<i>Outpatient costs</i>	52
<i>Medication costs</i>	53
<i>Primary care costs</i>	53
<i>Costs to participants and their main caregiver</i>	53
Estimation of effects	54
<i>Estimation of quality-adjusted life-years for the cost-utility analysis</i>	54
Analysis of costs and benefits	55
Costs	55
<i>Quality-adjusted life-years</i>	55
<i>Missing data</i>	55
Sensitivity analysis	55
<i>Stochastic sensitivity analysis</i>	55
<i>Deterministic sensitivity analysis</i>	55
Results	56
<i>Response rates</i>	56
<i>Total resource use</i>	56
Economic evaluation	58
<i>Cost-utility analysis using the EQ-5D-5L</i>	58
<i>Sensitivity analysis</i>	60
Model-based economic evaluation analysis	60
<i>Background and rationale</i>	60
<i>Objective</i>	61
<i>Methods</i>	61
<i>Model overview</i>	61
<i>Model structure</i>	61
<i>Treatment pathway</i>	63
<i>Model assumptions</i>	64
<i>Model parameters</i>	64
<i>Utilities specified in the model</i>	65
<i>Model validation</i>	65
<i>Base-case analysis</i>	67
<i>Evaluation of uncertainty</i>	67
Results	68
<i>Progression from one health state to another</i>	68
<i>Incremental costs, quality-adjusted life-years and cost-effectiveness</i>	68
<i>Sensitivity analysis</i>	72
<i>Impact of missing data</i>	72
Discussion	73
<b>Chapter 7 Discussion</b>	<b>77</b>
Summary of findings	77
Primary outcome	77
<i>Quality of life</i>	77
Secondary outcomes	78
<i>Quality of life</i>	78

## CONTENTS

Clinical effectiveness	79
<i>Intraocular pressure</i>	79
<i>Glaucoma drop usage</i>	80
<i>Visual acuity</i>	81
<i>Safety</i>	82
<i>Treatments received</i>	83
<i>Economic evaluation</i>	83
<i>Discrete choice experiment</i>	84
<i>Cost-effectiveness</i>	85
<i>Strengths and limitations</i>	85
<i>Further research planned</i>	87
<b>Chapter 8 Conclusions</b>	<b>89</b>
Implications for health care	89
Recommendations for research	89
<b>Acknowledgements</b>	<b>91</b>
<b>References</b>	<b>97</b>
<b>Appendix 1</b> Trial flow diagram	<b>109</b>
<b>Appendix 2</b> Participant characteristics	<b>111</b>
<b>Appendix 3</b> Clinical results	<b>113</b>
<b>Appendix 4</b> Discrete choice experiment	<b>127</b>
<b>Appendix 5</b> Health economic results	<b>129</b>
<b>Appendix 6</b> Analysis of pre-trabeculectomy questionnaire utility scores	<b>139</b>
<b>Appendix 7</b> Model parameters	<b>141</b>
<b>Appendix 8</b> Protocol changes	<b>157</b>

# List of tables

<b>TABLE 1</b> Timing of outcome measurements	<b>8</b>
<b>TABLE 2</b> Recruitment by centre	<b>15</b>
<b>TABLE 3</b> Baseline characteristics	<b>17</b>
<b>TABLE 4</b> Trabeculectomy procedure: index eye	<b>20</b>
<b>TABLE 5</b> The number of VFQ-25 questionnaires, full VFQ-25 scores and subscale scores by treatment arm	<b>23</b>
<b>TABLE 6</b> Secondary outcomes	<b>27</b>
<b>TABLE 7</b> Safety events, as allocated, ocular events for index eye	<b>31</b>
<b>TABLE 8</b> Safety events, as treated, ocular events for index eye	<b>34</b>
<b>TABLE 9</b> Antiglaucoma medication in index eye, by treatment allocated	<b>37</b>
<b>TABLE 10</b> Antiglaucoma medication in index eye, by treatment received	<b>38</b>
<b>TABLE 11</b> Other trabeculectomy interventions	<b>39</b>
<b>TABLE 12</b> Baseline characteristics of responders and non-responders	<b>47</b>
<b>TABLE 13</b> Summary of conditional logit regression exploring preferences for DCE attribute levels ( $n = 308$ )	<b>48</b>
<b>TABLE 14</b> Preference-based weights	<b>49</b>
<b>TABLE 15</b> Rates of completion of data collection instruments in each arm at each time point	<b>56</b>
<b>TABLE 16</b> Breakdown of resource costs across 2 years	<b>57</b>
<b>TABLE 17</b> Total unadjusted costs in each arm during the first and second 12 months of trial follow-up	<b>57</b>
<b>TABLE 18</b> Utility values and QALYs for each utility measure by treatment arm along with differences in QALYs at 24 months (unadjusted analysis)	<b>58</b>
<b>TABLE 19</b> Complete and multiple imputation EQ-5D-5L results	<b>59</b>
<b>TABLE 20</b> Initial and transition probabilities of stages in the model	<b>66</b>
<b>TABLE 21</b> Incremental cost-effectiveness measures (model-based analysis)	<b>71</b>
<b>TABLE 22</b> Sensitivity analyses of main parameters in the model	<b>73</b>

## LIST OF TABLES

<b>TABLE 23</b>	Description of excluded patients	<b>111</b>
<b>TABLE 24</b>	Baseline characteristics of the non-index eye	<b>112</b>
<b>TABLE 25</b>	Hodapp–Parrish–Anderson classification of glaucoma severity	<b>112</b>
<b>TABLE 26</b>	Details of trabeculectomy procedure	<b>113</b>
<b>TABLE 27</b>	Trabeculectomy procedure for non-index eye	<b>115</b>
<b>TABLE 28</b>	Per-protocol analysis for VFQ-25	<b>117</b>
<b>TABLE 29</b>	Complier-average causal effect analysis for VFQ-25	<b>119</b>
<b>TABLE 30</b>	Sensitivity analysis incorporating data from the non-index eye for participants with bilateral disease	<b>119</b>
<b>TABLE 31</b>	Visual fields mean deviation (dB) sensitivity analysis	<b>120</b>
<b>TABLE 32</b>	Eligible to be registered visual impairment at baseline	<b>120</b>
<b>TABLE 33</b>	Safety events: as treated for non-index eye	<b>120</b>
<b>TABLE 34</b>	Safety events: as allocated for non-index eye	<b>122</b>
<b>TABLE 35</b>	Intraocular pressure, logMAR VA and VFMD for non-index eye	<b>123</b>
<b>TABLE 36</b>	Antiglaucoma medication in non-index eye	<b>124</b>
<b>TABLE 37</b>	The number of different bottles of medication: index eye as allocated	<b>125</b>
<b>TABLE 38</b>	The number of different bottles of medication: as treated	<b>126</b>
<b>TABLE 39</b>	Baseline characteristics by DCE block	<b>127</b>
<b>TABLE 40</b>	Unit costs for hospital appointments	<b>129</b>
<b>TABLE 41</b>	Unit costs for glaucoma procedures	<b>129</b>
<b>TABLE 42</b>	Unit costs for glaucoma medications	<b>130</b>
<b>TABLE 43</b>	Unit costs for community appointments	<b>132</b>
<b>TABLE 44</b>	Complete and multiple imputation HUI-3 cost–utility analysis results	<b>133</b>
<b>TABLE 45</b>	Complete and multiple imputation GUI cost–utility results	<b>135</b>
<b>TABLE 46</b>	EQ-5D-5L data with patient time and travel costs included cost–utility results	<b>137</b>
<b>TABLE 47</b>	Summary of the mean utility scores for the pre-trabeculectomy questionnaire in the trabeculectomy arm	<b>139</b>



<b>TABLE 48</b> Option 1: combinations of three conditions of index eye (S3, S4 and S5) with eight conditions of non-index eye (S0, border, SB, S1, S2, S3, S4 and S5)	<b>142</b>
<b>TABLE 49</b> Option 2: combinations of three conditions of index eye (S3, S4 and S5) with four conditions of non-index eye (non-severe, S3, S4 and S5)	<b>142</b>
<b>TABLE 50</b> Option 3: combinations of three conditions of index eye (S3, S4 and S5) with two conditions of non-index eye (non-severe and severe)	<b>143</b>
<b>TABLE 51</b> Option 4: combinations of one condition of index eye (severe) with four conditions of non-index eye (non-severe, S3, S4 and S5)	<b>143</b>
<b>TABLE 52</b> Option 5: combinations of one condition of index eye (severe) with two conditions of non-index eye (non-severe, severe)	<b>143</b>
<b>TABLE 53</b> Transition to the same and/or higher stages during first year in trabeculectomy arm ( <i>n</i> )	<b>144</b>
<b>TABLE 54</b> Transition to the same and/or higher stages during first year in trabeculectomy arm (%)	<b>145</b>
<b>TABLE 55</b> Transition to the same and/or higher stages during first year in medical management arm ( <i>n</i> )	<b>146</b>
<b>TABLE 56</b> Transition to the same and/or higher stages during first year in medical management arm (%)	<b>147</b>
<b>TABLE 57</b> Transition to the same and/or higher stages during second year in trabeculectomy arm ( <i>n</i> )	<b>148</b>
<b>TABLE 58</b> Transition to the same and/or higher stages during second year in trabeculectomy arm (%)	<b>149</b>
<b>TABLE 59</b> Transition to the same and/or higher stages during second year in medical management arm ( <i>n</i> )	<b>150</b>
<b>TABLE 60</b> Transition to the same and/or higher stages during second year in medical management arm (%)	<b>151</b>



# List of figures

<b>FIGURE 1</b> Recruitment over time	16
<b>FIGURE 2</b> The CONSORT flow diagram presenting participant flow in the trial	16
<b>FIGURE 3</b> Mean (SD) VFQ-25 by arm over time	25
<b>FIGURE 4</b> Subgroups for trabeculectomy vs. medical management: (a) 4 months, (b) 12 months and (c) 24 months	26
<b>FIGURE 5</b> Mean (SD) IOP by arm over time	30
<b>FIGURE 6</b> Example of a choice-set question	45
<b>FIGURE 7</b> Cost-effectiveness curves for the trabeculectomy arm and the medical management arm using the results from the EQ-5D-5L and multiply imputed data	60
<b>FIGURE 8</b> Cost-effectiveness plane for the trabeculectomy arm vs. the medical management arm: adjusted bootstrapped replications for CUA for EQ-5D-5L results	60
<b>FIGURE 9</b> Model structure	63
<b>FIGURE 10</b> Markov tracings of disease states over time for (a) the trabeculectomy arm; and (b) the medical management arm	69
<b>FIGURE 11</b> Cost-effectiveness analysis in the base-case analysis	72
<b>FIGURE 12</b> Tornado diagram for the main parameters (EQ-5D-5L measure)	74
<b>FIGURE 13</b> Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment in the base-case analysis	74
<b>FIGURE 14</b> Model-based CEAC for the base-case analysis (lifetime horizon; EQ-5D-5L measure)	75
<b>FIGURE 15</b> Cost-effectiveness curves for the trabeculectomy and medical management arms using the results from the imputed HUI-3 sample	134
<b>FIGURE 16</b> Cost-effectiveness plane for the trabeculectomy and medical management arms using the results from the imputed HUI-3 sample	134
<b>FIGURE 17</b> Cost-effectiveness curves for the trabeculectomy and medical management arms using the results from the imputed GUI sample	136
<b>FIGURE 18</b> Cost-effectiveness plane for the trabeculectomy and medical management arms using the results from the imputed GUI sample	136
<b>FIGURE 19</b> Cost-effectiveness curves for the trabeculectomy and medical management arms using the results from the EQ-5D-5L using the time and travel data	138

## LIST OF FIGURES

<b>FIGURE 20</b> Cost-effectiveness plane for adjusted bootstrapped replications for cost-utility analysis for EQ-5D-5L results with time and travel costs	<b>138</b>
<b>FIGURE 21</b> Cost-effectiveness analysis for a lifetime horizon (30 years): HUI-3 measure	<b>152</b>
<b>FIGURE 22</b> Cost-effectiveness analysis for a lifetime horizon (30 years): GUI measure	<b>152</b>
<b>FIGURE 23</b> Tornado diagram for the main parameters (HUI-3 measure)	<b>153</b>
<b>FIGURE 24</b> Tornado diagram for the main parameters (GUI measure)	<b>153</b>
<b>FIGURE 25</b> Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment (HUI-3 measure)	<b>154</b>
<b>FIGURE 26</b> Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment (GUI measure)	<b>154</b>
<b>FIGURE 27</b> Model-based cost-effectiveness acceptability curve for a lifetime horizon (30 years): HUI-3 measure	<b>155</b>
<b>FIGURE 28</b> Model-based cost-effectiveness acceptability curve for a lifetime horizon (30 years): GUI measure	<b>155</b>

# List of boxes

**BOX 1** Stages of the disease used within the economic model

**62**



# List of supplementary material

**Report Supplementary Material 1** Patient Paperwork, Case Report Forms and Participant Questionnaires

**Report Supplementary Material 2** Statistical Analysis Plan

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/hta25720>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.





## List of abbreviations

AE	adverse event	logMAR	logarithm of the mean angle of resolution
AGIS	Advanced Glaucoma Intervention Study	MD	mean difference
CACE	complier-average causal effect	NICE	National Institute for Health and Care Excellence
CARF	Central Angiographic Resource Facility	NMB	net monetary benefit
CEAC	cost-effectiveness acceptability curve	OAG	open-angle glaucoma
CHaRT	Centre for Healthcare Randomised Trials	PI	principal investigator
CI	confidence interval	PMG	Project Management Group
CIGTS	Collaborative Initial Glaucoma Treatment Study	PPI	public and patient involvement
CRF	case report form	PSA	probabilistic sensitivity analysis
CUA	cost-utility analysis	PSS	Personal Social Services
DCE	discrete choice experiment	QALY	quality-adjusted life-year
DMC	Data Monitoring Committee	QoL	quality of life
DVLA	Driver and Vehicle Licencing Agency	RCT	randomised controlled trial
ETDRS	Early Treatment Diabetic Retinopathy Study	REC	Research Ethics Committee
GP	general practitioner	RR	relative risk
GPI	glaucoma profile instrument	SAE	serious adverse event
GSS2	Enhanced Glaucoma Staging System	SD	standard deviation
GUI	Glaucoma Utility Index	SITA	Swedish Interactive Threshold Algorithm
HPA	Hodapp-Parrish-Anderson	SMG	Study Management Group
HRQoL	health-related quality of life	SUREG	seemingly unrelated regression
HUI-3	Health Utility Index version 3	TAGS	Treatment of Advanced Glaucoma Study
ICER	incremental cost-effectiveness ratio	TSC	Trial Steering Committee
IGA	International Glaucoma Association	UK-DUETS	UK Database of Uncertainties about the Effects of Treatments
IOP	intraocular pressure	VA	visual acuity
IQR	interquartile range	VF	visual field
		VFMD	visual field mean deviation
		VFQ-25	Visual Function Questionnaire-25



## Plain English summary

**G**laucoma is an eye condition in which the intraocular pressure is too high, causing damage to the optic nerve and loss of vision. Patients with severe vision loss at diagnosis are the most at risk of blindness in their lifetime.

Lowering pressure in the eye is the only way to prevent further vision loss. Two treatments to lower pressure are commonly used: using eye drops or having an operation known as a trabeculectomy. In England, Wales and Northern Ireland, the National Institute for Health and Care Excellence recommends surgery as the first treatment. However, we do not know which treatment is best for preventing vision loss or which is safest, has the best patient experience or provides the best value for money for the NHS. Therefore, surgery is not usually carried out in the first instance and patients start with eye drops instead.

This study compared whether starting treatment with eye drops affected the quality of life of patients with advanced glaucoma more or less than starting treatment with trabeculectomy. We also investigated if initial treatment with surgery and initial treatment with eye drops were equally good at controlling pressure and were equally safe, and how much each treatment cost the NHS. Every patient had an equal chance of starting treatment with surgery or eye drops and they participated in the study for 2 years.

We found that quality of life was similar regardless of treatment. Those starting with surgery had lower pressure and needed far fewer types of eye drops than those starting with eye drops. Thirty-nine patients in the eye drop arm required surgery to control their glaucoma. Initial treatment with eye drops was cheaper over 2 years' follow-up.

Our study suggests that, over a 2-year period, having surgery in the first instance lowers intraocular pressure more than eye drops and is equally as safe as eye drops. Although eye drops are a cheaper treatment option for the NHS, if the effects of surgery on intraocular pressure are lasting, then the increased cost may be justified.



# Scientific summary

## Background

Glaucoma is a pressure-related optic neuropathy that results in progressive visual field deterioration. Glaucoma affects  $\approx 2\%$  of the UK population aged  $> 40$  years. Glaucoma is the second most common cause of registration as being visually impaired in the UK. In England, there are more than 1 million glaucoma-related visits to the NHS per year. The management of glaucoma patients constitutes a major part of ophthalmologists' workload. The number of people with glaucoma is predicted to increase substantially as the population ages.

Sight loss from glaucoma is preventable. However, people are unaware of the onset of glaucoma because it is typically asymptomatic in the early stages and, as a consequence, in the UK 10–39% of people with glaucoma present with advanced disease in at least one eye. Presentation with advanced visual field loss is the major risk factor for lifetime blindness in people with glaucoma.

Reducing intraocular pressure is currently the only effective treatment for glaucoma. Better control of intraocular pressure from diagnosis reduces the risk of progression to blindness. The primary treatment options in the UK for advanced glaucoma are mainly medical or surgical interventions.

The National Institute for Health and Care Excellence guidelines suggest that patients presenting with advanced disease are offered augmented trabeculectomy as a primary intervention and are offered medical management only if surgery is declined.

Currently, most ophthalmologists treat patients medically with an escalating eye drop regime and are reluctant to carry out primary surgery because of concerns regarding surgical adverse events and an inadequate evidence base to support primary surgery.

By using eye drops as a first-line treatment instead of surgery and by operating only on patients in whom eye drop therapy fails, NHS resources in the short term might be saved. However, the long-term effects on visual outcome and cost are uncertain. Modern glaucoma eye drops lower intraocular pressure significantly better and have fewer side effects than those previously used; therefore, this may reduce the need for surgery.

Avoiding surgery could improve patient health and quality of life. A head-to-head trial of these two primary treatments is, therefore, required.

## Objectives

The overarching objectives of this trial are to investigate if eye drop treatment in patients presenting with advanced glaucoma leads to better health-related quality of life than first-line surgery and to determine whether or not this is associated with reduced costs, better clinical outcomes and better safety, and if this is cost-effective.

### Primary objective

The primary objective of this trial was to compare primary medical management with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced primary open-angle glaucoma (Hodapp–Parrish–Anderson Classification severe) in terms of patient-reported health status using the National Eye Institute's Visual Function Questionnaire-25.

### *Secondary objectives*

- To compare generic and vision- and glaucoma-specific patient-reported health and patient experiences in the short and medium term.
- To compare the incremental cost per quality-adjusted life-year gained at 2 years of the more effective treatment based on responses to the EQ-5D-5L, the Health Utilities Index and the Glaucoma Utility Index.
- To compare clinical outcomes [i.e. visual field mean deviation changes, logMAR (logarithm of the mean angle of resolution) visual acuity changes, intraocular pressure, Esterman visual field for driving vision and registered visual impairment].
- To compare the need for additional cataract surgery.
- To compare safety by comparing adverse events from both surgical and medical interventions.
- To employ a discrete choice experiment among participants with advanced glaucoma to generate a revised scoring system for the Glaucoma Utility Index that is more sensitive and specific for those with advanced disease.
- To compare lifetime costs and benefits through an economic model.

## **Methods**

### *Design*

We designed a pragmatic, multicentre, randomised controlled trial to compare primary medical management with primary augmented trabeculectomy (standard care). Participants were unmasked to their treatment allocation. Participants were randomised to medical management or primary augmented trabeculectomy (1 : 1 allocation, minimised by centre and bilateral disease). Participants were followed for 2 years and received ongoing care and monitoring in accordance with standard clinical care. Further management decisions were made by the consulting clinician in collaboration with their patient.

### *Setting*

In total, 27 NHS secondary care glaucoma departments, each with at least one fellowship-trained glaucoma specialist, took part in the trial.

### *Participants*

Adult patients with primary open-angle glaucoma (including normal tension, pigment dispersion and pseudoexfoliation glaucoma) presenting with advanced glaucoma in one or both eyes defined as severe according to the Hodapp–Parrish–Anderson classification of visual field loss were eligible to participate in the trial.

### *Intervention*

#### **Primary medical management: escalating medical therapy**

Participants randomised to medical management could be prescribed a variety of licensed glaucoma medications (eye drops). These eye drops were used in accordance with National Institute for Health and Care Excellence guidelines. Escalating medical management was defined as follows: study participants may be started on one or more medications at their initial visit depending upon the judgement of the treating clinician. When monotherapy is initiated this should be with a prostaglandin analogue. Subsequent addition of medications was based on clinician judgement/preference. When drops failed to control IOP adequately oral carbonic anhydrase inhibitors may be used.

## Primary augmented trabeculectomy: standard trabeculectomy augmented with mitomycin C

Standard trabeculectomy was defined as the creation of a 'guarded fistula' by making a small hole in the eye, covered by a flap of partial thickness sclera, that allows aqueous humour to egress from the eye into the subconjunctival space. The operation could be performed under either local or general anaesthetic.

The dose of mitomycin C in terms of exposure time and concentration was left to the discretion of the operating surgeon and decided on a case-by-case basis.

## Main outcome measures

### Primary outcome measure

The primary outcome measure was the score on the vision-specific health profile (Visual Function Questionnaire-25) at 24 months.

### Secondary outcome measures

The secondary outcome measures fell into three categories:

1. patient-reported health status – Health Utility Index version 3, EQ-5D-5L, Glaucoma Utility Index, Visual Function Questionnaire-25 and patient experience
2. clinical outcomes – visual field mean deviation, intraocular pressure, logMAR, visual acuity, need for cataract surgery, visual standards for driving, registered visual impairment and safety at 24 months
3. economic outcomes – incremental costs, quality-adjusted life-years, incremental cost per quality-adjusted life-year gained (based on responses to the EQ-5D-5L, Health Utility Index version 3 and updated Glaucoma Utility Index values).

### Discrete choice experiment

A discrete choice experiment using the attributes and levels of the Glaucoma Profile Instrument was used to revise the Glaucoma Utility Index scoring system in a population with advanced glaucoma. Trial participants were randomised to one of four blocks, each with 15 choice-set questions. The discrete choice experiment was administered as a postal questionnaire at 27 months post randomisation. Logistic regression methods were used to analyse participants' responses for each choice-set question and quantify the relative importance of each attribute level. The results of the regression analysis were then converted into preference-based weights for the Glaucoma Utility Index.

### Economic evaluation

A within-trial analysis was carried out to compare the costs and benefits of medical and surgical management. Resource use was measured using the study case report forms and bespoke questionnaires. Costs were derived from published sources and from study-specific estimates. Missing data were accounted for using multiple imputation. A seemingly unrelated regression was used to assess for the difference between the costs and the EQ-5D-5L, results between treatment arms. Stochastic and deterministic sensitivity analyses were carried out. In addition, a Markov model was used to compare lifetime costs and quality-adjusted life-years between the two treatment arms. The model described disease progression and how treatments may alter that progression. Data for the model came from the Treatment of Advanced Glaucoma Study (TAGS), supplemented with data from the literature. Results were presented as mean costs, mean quality-adjusted life-years and the incremental cost per quality-adjusted life-year gained. The uncertainty surrounding the model findings was assessed using probabilistic sensitivity analysis and deterministic sensitivity analysis.

## Results

Between 3 June 2014 and 21 May 2017, we screened 962 potentially eligible patients, of whom 509 were excluded: 233 patients were ineligible and 276 patients declined to participate. We, therefore, recruited 453 participants, of whom 227 were randomised to the trabeculectomy arm and 226 to the medical management arm.

The mean age of the participants was 67 years (standard deviation 12 years) in the trabeculectomy arm and 68 years (standard deviation 12 years) in the medical management arm. More than 65% of participants were male and more than 80% were white. The proportion of patients with bilateral disease was 19.4% in the trabeculectomy arm and 19.5% in the medical management arm. More than 90% of patients had primary open-angle glaucoma and just over 30% had a family history of glaucoma.

At baseline, the mean Visual Function Questionnaire-25 score was 87.1 (standard deviation 13.6) in the trabeculectomy arm and 87.1 (standard deviation 13.4) in the medical management arm; the mean visual field mean deviation (dB) was -14.91 (standard deviation 6.36) and -15.26 (standard deviation 6.34), respectively; and the logMAR visual acuity was 0.15 (standard deviation 0.25) and 0.17 (standard deviation 0.26), respectively. The intraocular pressure was 19.4 mmHg (standard deviation 6.2 mmHg) in the trabeculectomy arm and 19.0 mmHg (standard deviation 5.7 mmHg) in the medical management arm. In total, 27 participants were classified as having sight impairment or severe sight impairment. Other health-related quality-of-life outcomes were balanced between arms.

Twenty-six participants (11.1%) in the trabeculectomy arm did not have surgery. In the medical management arm, 39 participants (17.3%) required trabeculectomy for glaucoma control before the 24-month follow-up.

At 24 months, the difference in the mean Visual Function Questionnaire-25 score between the arms was 1.06 (95% confidence interval -1.32 to 3.43;  $p = 0.383$ ).

The mean difference between arms in EQ-5D-5L score at 24 months was 0.016 (95% confidence interval -0.021 to 0.053;  $p = 0.405$ ). Similarly, the mean difference in Health Utility Index version 3 at 24 months was 0.036 (95% confidence interval -0.006 to 0.078;  $p = 0.094$ ) and the mean difference in Glaucoma Utility Index was 0.011 (95% confidence interval -0.017 to 0.039;  $p = 0.434$ ).

In both arms, participants' perception that their glaucoma was getting worse diminished during the course of the study. At 24 months, there was no evidence of a difference between the treatment arms (relative risk 0.70, 95% confidence interval 0.46 to 1.07;  $p = 0.099$ ).

The mean intraocular pressure at 24 months was 12.40 mmHg in the trabeculectomy arm and 15.07 mmHg in the medical management arm (mean difference -2.75 mmHg, 95% confidence interval -3.84 mmHg to -1.66 mmHg;  $p < 0.001$ ). Fewer types of glaucoma eye drops were required in the trabeculectomy arm than in the medical management arm to achieve this lower intraocular pressure. The logMAR visual acuity at 24 months was slightly better in the medical management arm than in the trabeculectomy arm (mean difference 0.07, 95% confidence interval 0.02 to 0.11;  $p = 0.006$ ). In the case of visual field mean deviation, there was no evidence of a difference between arms at 24 months (mean difference 0.18, 95% confidence interval -0.58 to 0.94;  $p = 0.645$ ).

At 24 months, there was no evidence of a difference between arms in the requirement for cataract surgery (relative risk 0.98, 95% confidence interval 0.50 to 1.95;  $p = 0.963$ ). There was also no evidence of a difference between arms in the number of participants meeting visual standards for driving or registering as sight impaired at 24 months.



The number of participants who had a safety event during the 24-month follow-up was 88 (38.8%) in the trabeculectomy arm and 100 (44.2%) in the medical management arm (relative risk 0.88, 95% confidence interval 0.66 to 1.17;  $p = 0.366$ ). The number of participants who had a serious adverse event was 12 out of 226 (5.3%) for those who received trabeculectomy and 8 out of 226 (3.5%) for those who received medical management.

The logMAR visual acuity declined by  $> 10$  letters in three participants, who were all in the trabeculectomy arm: in two cases because of glaucoma progression and in one case because of a central serous retinopathy. Two participants, one in each arm, developed endophthalmitis.

### **Discrete choice experiment**

Nearly 97% ( $n = 438$ ) of participants who were randomised in the main trial were randomly allocated to a discrete choice experiment block. Of these participants, 70% ( $n = 308$ ) returned the discrete choice experiment questionnaire at least partially completed. Participants reported having a strong preference for improvements in central and near vision, mobility and activities of daily living. Utility values were estimated for all attribute levels and a revised value set for the Glaucoma Utility Index was created and incorporated into the economic evaluation.

### **Economic evaluation**

The within-trial analysis found an increase in average quality-adjusted life-years gained (0.04) and average cost (£2013) in the trabeculectomy arm, giving an incremental cost per quality-adjusted life-year of £45,456. The stochastic sensitivity analysis revealed that the probability of medication being cost-effective is 100% at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year, 88% at the £30,000 threshold and 44% at the £50,000 threshold.

The model-based analysis found that, compared with medical management, trabeculectomy was associated with an average additional cost of £2687, an average additional gain of 0.28 quality-adjusted life-years and an incremental cost per quality-adjusted life-year of £9679 over a patient's lifetime. The likelihood of trabeculectomy being considered cost-effective over a range of society's willingness to pay for a quality-adjusted life-year of £0–20,000 was 73%. The results appeared to be robust over all sensitivity analyses considered.

## **Conclusions**

We found no evidence of a difference in health-related quality of life at 24 months between patients treated with medical management and those treated with surgery. Furthermore, the precision of the confidence intervals shows that any meaningful difference favouring either treatment is incompatible with the data in the Treatment of Advanced Glaucoma Study. Intraocular pressure was better controlled in the trabeculectomy arm, which may have longer-term implications for further visual field progression. It is unlikely that trabeculectomy would be cost-effective over the trial follow-up duration at the range of threshold values for willingness to pay for a quality-adjusted life-year that we considered. However, over a patient's lifetime, the benefits of trabeculectomy, in terms of health-related quality of life, would continue to accrue and the initial costs of surgery would be offset by a reduction in ongoing medication costs. The consequence of these impacts is that, over a patient's lifetime, trabeculectomy is likely to be considered cost-effective over the range of values of society's willingness to pay for a quality-adjusted life-year that we considered.

### **Implications for health care**

The significant additional reduction in intraocular pressure achieved in patients in the trabeculectomy arm decreases the risk of further lifetime visual field loss and vision-related disability. The lack of significant adverse events associated with trabeculectomy will reassure both clinicians and patients of

its safety as a primary intervention, but a judgement is needed by the health service as to whether or not any long-term gains would be worth the extra cost of trabeculectomy.

### **Recommendations for research**

For participants in the Treatment of Advanced Glaucoma Study, longitudinal research into the clinical effectiveness, safety, patient experience and cost of eye drops and trabeculectomy as first-line treatments will determine which treatment offers better lifetime outcomes, specifically:

- the exploration of mechanisms to prevent people presenting with advanced glaucoma
- the development of improved patient-reported outcome measures for measuring glaucoma
- ways to improve clinical trial methodology to reduce the length of time required to undertake a trial for chronic disease
- further research into suitable outcome measures to measure quality of life for glaucoma
- further estimation work to explore the negative preferences reported in the discrete choice experiment
- further research into cross-walking the Visual Function Questionnaire-25 instrument to the EQ-5D-5L to allow comparison between the two measures and to potentially reduce the data collection burden of future trials.

### **Trial registration**

This trial is registered as ISRCTN56878850.

### **Funding**

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 72. See the NIHR Journals Library website for further project information.

# Chapter 1 Introduction

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## Background

Glaucoma is a pressure-related optic neuropathy that results in progressive visual field (VF) deterioration. The World Health Organization estimates that, in 2010, 4.5 million people were blind because of glaucoma,<sup>2</sup> which accounts for 12.3% of global blindness. Glaucoma is estimated to affect around 2% of the UK population aged > 40 years, and this percentage increases with age,<sup>3-7</sup> with as many as 10% of those in their 80s affected. Glaucoma is the second most common cause of registration as being visually impaired in the UK, accounting for 8.4–11.6% of registrations in those aged > 65 years.<sup>8,9</sup> However, this is likely to be an underestimate.<sup>10</sup>

In England, there are over 1 million glaucoma-related visits to the NHS per year. The management of glaucoma patients constitutes a major part of ophthalmologists' workload, accounting for 23% of all follow-up attendances to the UK hospital eye service<sup>11</sup> and 13% of all new referrals.<sup>12</sup> The number of patients with glaucoma is predicted to increase substantially as the result of an ageing population.<sup>13</sup> There is currently no effective screening strategy in the UK for the early identification of all patients with glaucoma.<sup>14</sup>

Sight loss from glaucoma is preventable; the Public Health Outcomes Framework for England 2013–16<sup>15</sup> has made reducing the number of people living with preventable sight loss a priority. However, people are unaware of the onset of glaucoma because it is typically asymptomatic in the early stages and, as a consequence, between 10% and 39% of patients with glaucoma in the UK present with advanced disease in at least one eye.<sup>16-20</sup> In the most recent study, more than one-third of patients presenting to secondary care had severe disease in at least one eye.<sup>18</sup> Those most at risk include the socially disadvantaged with no family history of glaucoma, those with high intraocular pressure (IOP) and those who do not attend an optometrist regularly.<sup>18,20-22</sup>

## Advanced glaucoma at presentation: a risk factor for blindness

Presentation with advanced VF loss increases the risk of further progression and blindness.<sup>23-28</sup> Odberg *et al.*<sup>23</sup> noted in a cohort of patients with advanced glaucoma that 70% of the affected eyes had progressed after a mean of 7.6 years despite treatment. Grant and Burke<sup>25</sup> found that eyes with a VF defect at the beginning of treatment were more likely to progress to blindness than eyes in which treatment was started when there was no VF loss. Wilson *et al.*<sup>26</sup> found that initial VF loss was the strongest determinant of the rate of further VF loss. The rate of deterioration was 11.7 times faster in eyes with more advanced VF loss at presentation. Mikelberg *et al.*<sup>24</sup> found that, when scotoma mass was small (i.e. early glaucoma), the rate of VF loss was slow, but, when scotoma mass was large (i.e. severe glaucoma), rapid linear progression of VF loss occurred. Oliver *et al.*<sup>29</sup> found that unilateral blindness owing to glaucoma more than doubled the risk of bilateral blindness.

## Current treatment options

Reducing IOP is currently the only effective treatment for glaucoma.<sup>30-33</sup> Better control of IOP at an early stage reduces the risk of progression to blindness. The Advanced Glaucoma Intervention Study (AGIS) demonstrated that the extent of lowering of IOP was related to the progression of VF loss over an 8-year period, showing that progression was least when IOP was maintained below 18 mmHg at all follow-up visits.<sup>34</sup>

The primary treatment options in the UK for advanced glaucoma are mainly medical or surgical interventions. Currently, most ophthalmologists treat patients medically, starting with topical drop monotherapy followed by escalating the number of drop therapies until the maximum tolerated combination therapy is achieved.<sup>35</sup> All frequently used eye drops (i.e. prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists and anticholinergic miotics) are now available in generic form and, therefore, cost less. In patients whose glaucoma continues to progress despite eye drop treatment or in whom the target IOP is not achieved, clinicians may opt for surgical intervention, most frequently trabeculectomy.<sup>30-33,36</sup> Patients have indicated that they are not concerned about the treatment that they receive as long as it is effective in the prevention of further visual loss.<sup>37</sup>

Recently published National Institute for Health and Care Excellence (NICE) guidelines suggest that patients presenting with advanced disease should be offered augmented trabeculectomy as a primary intervention and should be offered medical management only if surgery is declined, but point out that the evidence to support this recommendation is of poor quality.<sup>38</sup> By using eye drops as a first-line treatment instead of surgery and by operating on patients only in whom drop therapy fails, NHS resources could be saved in the short term; however, the long-term effects on visual outcome are uncertain. Modern glaucoma eye drops lower IOP significantly more and have fewer side effects than those previously used, which may or may not reduce the need for surgery. Social resources may be saved by avoiding the need to support those becoming blind. A survey of consultant ophthalmologists indicated that most do not follow NICE guidance and prefer medical management because of the poor evidence base and concern regarding surgery complications.<sup>35</sup>

Compared with surgery, primary eye drop treatment would save upfront surgery costs and may save other NHS costs in the short term, such as intensive follow-up, and reduce the number of patients requiring cataract surgery to restore visual function. Avoiding surgery could improve patient health and quality of life (QoL) in the short term; however, in the long term, insufficient IOP control may produce more VF loss and poorer health outcomes. A head-to-head trial of these two primary treatments is, therefore, required.

## Rationale for this study

There is uncertainty about how best to manage patients diagnosed with advanced glaucoma. Such individuals have a high risk of blindness, and effective treatment is required to minimise the chances of disease progression. Currently, NICE guidelines recommend initial surgery but acknowledge the lack of evidence to support this recommendation. Surgery may be more effective in the long term but is associated with potential adverse events (AEs) and increased costs at the time of surgery. Current medical therapies (e.g. eye drops) may be able to control the disease in a proportion of patients with advanced glaucoma. Within the Treatment of Advanced Glaucoma Study (TAGS), we considered whether or not primary medical management is clinically effective and cost-effective for the management of newly diagnosed advanced glaucoma compared with the NICE-recommended treatment of augmented trabeculectomy (glaucoma surgery).

A recent Cochrane systematic review<sup>30</sup> comparing primary medical management with surgical treatment for open-angle glaucoma (OAG) identified four relevant studies.<sup>31,39-41</sup> Despite methodological weaknesses and non-standard treatments, the review authors concluded that in severe OAG evidence

suggested, that medication was associated with more progressive VF loss and less IOP lowering than surgery. The authors also reported that 'risk of treatment failure was greater with medication than trabeculectomy [odds ratio (OR) 3.90, 95% confidence interval (CI) 1.60 to 9.53; hazard ratio (HR) 7.27, 95% CI 2.23 to 25.71]'.<sup>30</sup> Three of these four trials are now obsolete because new types of medical management have since been introduced, and the most recent study did not include patients with advanced disease.

The authors<sup>30</sup> concluded that surgery lowers IOP more than medication; however, none of these trials specifically addressed the management of those presenting with advanced glaucoma or used modern glaucoma medications that are more effective at lowering IOP and have fewer side effects than previous generations of eye drops. The authors recommended that further randomised controlled trials (RCTs) comparing current medical managements with modern glaucoma surgery be carried out in people with advanced OAG.<sup>30</sup>

This uncertainty has subsequently been added to the UK Database of Uncertainties about the Effects of Treatments (UK-DUETS) as an important question requiring further investigation: <https://jla.nihr.ac.uk/news-and-publications/downloads/2007-2008-DUETS-Development-Report.pdf> (accessed in 2014).

No previous RCT has explored the best treatment options for patients presenting with advanced glaucoma. The AGIS, for example, did not compare primary medical and surgical interventions and did not explore primary treatment options, as all patients had failed on maximum medical management prior to entry.<sup>42</sup> In addition, it included patients with mild glaucoma. The USA-based Collaborative Initial Glaucoma Treatment Study (CIGTS), although comparing the outcomes of primary medical with primary surgical treatment in newly diagnosed patients with glaucoma, enrolled patients presenting with mild disease (CIGTS score of  $4.6 \pm 4.2$ ).<sup>31</sup> A recent update from the CIGTS suggests that, in a subgroup of patients presenting with more advanced disease [mean difference (MD)  $< -10$  dB], VF progression was slower in those in whom the primary intervention was surgical.<sup>43</sup>

We aimed to reduce the uncertainty identified by the Cochrane review,<sup>30</sup> UK-DUETS and NICE<sup>38</sup> by undertaking a pragmatic RCT of current best medical care in the NHS (a stepped approach of medications) compared with primary surgery. In addition, we aimed to address the concerns of the Public Health Outcomes Framework for England 2013–16<sup>45</sup> by identifying the best treatment approach to minimise preventable sight loss in this group of vulnerable patients.

## Patient and public involvement

The research topic was identified in a review of primary medical management compared with primary surgical treatment in glaucoma and was subsequently adopted by UK-DUETS. Patients fulfilling the eligibility criteria for the proposed trial agreed to participate in a focus group discussion to identify concerns that they had about the value of such a trial and their participation. Several themes were identified: patients were concerned about the real need for such a trial, that if they participated in a trial they may be going against the judgement of their clinician and that they may be randomised to the wrong group.<sup>44</sup> Discussion of these points in the focus group setting reassured patients both that the trial itself was important and necessary and that, currently, clinicians do not possess the evidence required to recommend one treatment above the other. Several of the patients who contributed to the focus group discussions agreed to form a patient group to develop patient-related material for the trial, particularly in relation to the consenting process, and one was a member of the Trial Steering Committee (TSC). In addition, a patient representative organisation the International Glaucoma Association (IGA) endorsed this study and its chairperson sat on the TSC (until retirement in 2018, when he continued to participate as a lay representative but not representing the IGA).

A patient representative was an active member of the Project Management Group (PMG) and, as part of this role, contributed to the development of trial materials and processes. He participated in the focus group discussions and, therefore, had insight into the experience and concerns of other glaucoma sufferers. In addition to this representative, several other patients with glaucoma who participated in the focus group discussions agreed to form a patient representative group that advised the study team on the development of patient-related study material. This was primarily aimed at the development of the patient information leaflet to provide patients with all of the information that they required to make a decision when asked to participate in the study, specifically regarding concerns about surgery.

### **Aims of the trial**

#### ***Primary objective***

The primary objective of this trial was to compare primary medical management with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced glaucoma [Hodapp–Parrish–Anderson (HPA) Classification severe] in terms of patient-reported health status using the National Eye Institute’s Visual Function Questionnaire-25 (VFQ-25).<sup>45–54</sup>

#### ***Secondary objectives***

- To compare generic and vision- and glaucoma-specific patient-reported health and experiences in the short and medium term.
- To compare the costs and benefits [quality-adjusted life-years (QALYs) gained] of surgery and medication at 2 years based on responses to the (1) EQ-5D-5L, (2) the Health Utilities Index version 3 (HUI-3) and (3) the Glaucoma Utility Index (GUI).<sup>55</sup>
- To compare clinical outcomes (VFMD changes, logMAR visual acuity changes, IOP, Esterman VF for driving vision, registered visual impairment).
- To compare the need for additional cataract surgery.
- To compare safety by comparing AEs arising from both surgical and medical interventions.
- To employ an existing discrete choice experiment (DCE) among participants with advanced glaucoma to generate a revised scoring system for the GUI that is more sensitive and specific for those with advanced disease.
- To compare long-term costs and benefits through a modelling evaluation.

## Chapter 2 Methods

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### Study design

The TAGS is a pragmatic,<sup>57</sup> two-arm, parallel-arm multicentre RCT comparing primary medical management with primary augmented trabeculectomy (standard care) (see *Appendix 1*). Participants were randomised to medical management or augmented trabeculectomy (1 : 1 allocation, minimised by centre and bilateral disease).

The perspective of this study was that of the NHS and the patient, with the economic perspective also reflecting Personal Social Services (PSS) and a wider perspective including patients and their families. The framework of the study was an integrated clinical and economic evaluation of the patient outcomes, costs and cost-effectiveness of the two alternative established methods of management of patients presenting with advanced glaucoma. Both treatment strategies currently have been evaluated to assess efficacy and safety.<sup>58–63</sup> The study protocol was published in 2017.<sup>1</sup>

### Setting

#### *Clinical centres*

Twenty-seven secondary care centres with at least one consultant who subspecialises in glaucoma recruited patients for the study.

#### *Population*

Adults with advanced (severe) glaucoma in at least one eye defined as severe according to the HPA grading<sup>64</sup> for VF loss severity were invited to participate in the study.

### Participants

Disease was classified as advanced if it met the criteria for 'severe' VF loss according to the HPA classification of glaucoma severity<sup>64</sup> (the presence of any of the following):

1. VFMD < -12.00 dB
2. > 50% of points depressed below the 5% level on the pattern deviation probability plot
3. > 20 points depressed below the 1% level on the pattern deviation probability plot
4. one point in the central 5° has a sensitivity of 0 dB
5. points within 5° of fixation under 15 dB sensitivity in both upper and lower hemifields.

## Consent to participate

Potential participants who were likely to be eligible for the RCT were identified at their initial consultation for glaucoma by a member of the clinical assessment team. In centres in which it was possible to vet clinic referrals prior to the patient's attendance at clinic, potentially eligible subjects were identified from their referral letters. At the initial consultation, the consultant, research nurse or another delegated individual introduced the study and, if potential interest was expressed, provided further details of the study by means of the patient information leaflet. The contact details of all interested patients were passed on to the recruitment centre's study research team if they were not part of the initial consultation. If the patient agreed in principle to the study, then arrangements were made for assessment and consent to be taken. This may have been at a separate appointment or at the initial visit if the patient consented to participate at that visit. Arrangements were individualised for each centre. Eligible patients were asked for their signed informed consent before being randomised. Both the patient information leaflet and the consent form referred to the possibility of long-term follow-up.

We included people who:

- had severe glaucomatous VF loss (HPA classification)<sup>64</sup> in one or both eyes at presentation
- had OAG, including pigment dispersion glaucoma, pseudoexfoliative glaucoma and normal tension glaucoma
- were willing to participate in a trial
- were able to provide informed consent
- were aged  $\geq 18$  years
- agreed, if female and of childbearing potential, to ensure that they used effective contraception during the study and for 3 months thereafter (a negative urine pregnancy test for females of childbearing potential was required prior to randomisation).

We excluded people who:

- were unable to undergo incisional surgery owing to an inability to lie flat or unsuitable for anaesthetic
- had a high risk of trabeculectomy failure, such as previous conjunctival surgery or complicated cataract surgery
- had secondary glaucomas and primary angle-closure glaucoma
- were pregnant, nursing or planning a pregnancy, or were of childbearing potential not using a reliable method of contraception (a woman was considered to be of childbearing potential unless she was without a uterus or was post-menopausal and had been amenorrhoeic for at least 12 consecutive months).

## Health technologies compared

The intervention was either primary medical management or augmented trabeculectomy. Both interventions are established and well-documented approaches to the management of glaucoma.<sup>65</sup> Following randomisation, care for both treatment arms followed NICE guideline recommendations.<sup>65</sup>

### *Primary medical management: escalating medical therapy*

Participants randomised to medical management could be prescribed a variety of licensed glaucoma medications (eye drops). These eye drops were used in accordance with NICE guidelines.<sup>65</sup> Escalating medical management was defined as follows: study participants may be started on one or more medications at their initial visit depending upon the judgement of the treating clinician. When monotherapy is initiated this should be with a prostaglandin analogue as directed by NICE guidelines. Subsequent addition of medications was based on clinician judgement/preference. When drops failed to control IOP adequately oral carbonic anhydrase inhibitors may be used.



### **Primary trabeculectomy: standard trabeculectomy augmented with mitomycin C**

Standard trabeculectomy was defined as the creation of a 'guarded fistula' by making a small hole in the eye that is covered by a flap of partial-thickness sclera, which allows aqueous humour to egress from the eye into the subconjunctival space. The operation could be performed under either local or general anaesthetic. The dose of mitomycin C in terms of exposure time and concentration was left to the discretion of the operating surgeon and decided on a case-by-case basis.

The protocol specified that all surgery be undertaken within 3 months of randomisation by a consultant who subspecialises in glaucoma or a glaucoma fellow who has performed at least 30 trabeculectomies. Where both eyes were eligible for the study, the eye with better VFMD was allocated as the index eye. An amendment to the protocol allowed the decision about which eye would undergo trabeculectomy first to be made locally when subjects were allocated to the trabeculectomy arm.<sup>1</sup>

To ensure that recognised standard trabeculectomy procedures<sup>66,67</sup> were being followed by all participating glaucoma surgeons, all potential surgeons completed a questionnaire about their surgical technique that was reviewed and signed off by the chief investigator. No feedback was given because all surgeons were essentially conducting the same operation.

### **Compliance with study treatment**

We designed TAGS as a pragmatic trial and compliance with study treatment was monitored as it would be in routine clinical practice – by asking the patient if they are using their eye drops. There is currently no practical and effective method for monitoring compliance in patients taking glaucoma medications.<sup>68</sup> The degree of compliance feeds into the outcome measurements, as poor compliance for medications is likely to lead to further disease progression. There was no requirement for participants to return any unused eye drops.

### **Accountability of the study treatment**

The local clinical team used a standard hospital prescription form or asked patients' general practitioners (GPs) to prescribe the medications required in line with standard practice for that team, pragmatically reflecting standard NHS practice.

### **Concomitant medication**

Medications as required for normal clinical care were prescribed for the participants irrespective of their randomised allocation. Throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

## **Treatment allocation**

All participants who agreed to enter the study were logged with the central trial office and given a unique study number. Randomisation utilised the existing proven remote automated computer randomisation application at the central trial office in the Centre for Healthcare Randomised Trials (CHaRT) (a fully registered UK Clinical Research Network clinical trials unit) in the Health Services Research Unit (HSRU), University of Aberdeen. This randomisation application was available as a telephone-based interactive voice response system and as an internet-based service.

Randomisation was computer allocated, minimised by centre and bilateral disease status. The unit of randomisation was the participant (not the eye). Participants with both eyes affected by advanced glaucoma and eligible were expected to undergo the same treatment in both eyes following randomisation. For those participants with both eyes eligible, an index eye was selected for evaluating clinical outcomes. The eye with better MD value (less severe VF damage) was nominated as the index eye.

For those randomised to the trabeculectomy arm with both eyes eligible, a period of 2–3 months would normally be allowed between operations (but this was at the discretion of the treating clinician). Prior to surgery, IOP was controlled using temporary medical management.

## Study outcome measures and schedule of assessment

The TAGS outcomes and schedule of measurement are detailed in *Table 1*.

### Primary outcomes

The primary outcome was a vision-specific patient-reported outcome QoL measurement, the vision-specific health profile (VFQ-25), which was evaluated at 24 months. The VFQ-25 is a validated questionnaire that has been widely used to evaluate visual outcomes in glaucoma.<sup>47,69-71</sup> In addition to eliciting information about general health and vision, it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision.

TABLE 1 Timing of outcome measurements

Outcomes	Time point							
	Baseline	Post randomisation (months)						
		1	3	4	6	12	18	24
<b>Patient outcomes</b>								
VFQ-25	✓			✓		✓		✓
EQ-5D-5L	✓	✓	✓		✓	✓	✓	✓
HUI-3 <sup>a</sup>	✓	✓	✓		✓	✓	✓	✓
GUI <sup>a</sup>	✓	✓	✓		✓	✓	✓	✓
Patient experience questions	✓	✓	✓		✓	✓	✓	✓
<b>Clinical outcomes</b>								
Medical history	✓							
VFMD	✓			✓		✓		✓
Esterman VF	✓							✓
LogMAR VA	✓			✓		✓		✓
IOP	✓			✓		✓		✓
Standard clinical examination	✓					✓		✓
<b>Health economics<sup>b,c</sup></b>								
Health-care utilisation				✓		✓		✓
Participant cost				✓		✓		✓
Participant time and travel <sup>d</sup>							✓	

LogMAR, logarithm of the mean angle of resolution; VFMD, visual field mean deviation.  
a Additional questionnaire undertaken immediately prior to trabeculectomy surgery.  
b Discrete choice experiment at 27 months.  
c EQ-5D-5L, HUI-3 and GUI responses were used to estimate health state utility values for use in the economic evaluation (see *Chapter 6*).  
d Time and travel questionnaire sent after 30 months.

## Secondary outcomes

### Patient centred

Patient-centred data were mainly collected through patient-completed questionnaires. The VFQ-25 was completed at baseline and 4, 12 and 24 months post randomisation. The EQ-5D-5L, HUI-3 and GUI responses were converted into health state utility values. These questionnaires were completed at baseline and at 1, 3, 6, 12, 18 and 24 months post randomisation and immediately prior to trabeculectomy.

### Clinical

#### Visual field mean deviation

Visual field mean deviation (VFMD), a global measure of the VF, represents the amount of vision loss occurring because of glaucoma during the study period. It is a routinely measured parameter in standard care of glaucoma patients and it is the primary clinical measure on which management decisions for glaucoma are made, in accordance with NICE guidelines.<sup>65</sup> VF damage is the major measure of the functional impact of glaucoma with direct relevance to QoL measures.<sup>69,72-74</sup> The Humphrey Visual Fields test [24-2 Swedish Interactive Threshold Algorithm (SITA standard)] was performed in all participants. All VF tests were performed by VF technicians or nurses trained to carry out VF tests. VF tests eligible for analysis had to achieve predefined reliability criteria (false positives < 15%). If the VF tests were not reliable, they were repeated at the clinicians' discretion in accordance with local clinical practice. Two baseline VF tests (24-2 SITA standard) were performed prior to randomisation to confirm eligibility. If the second VF test did not fulfil the criteria for 'severe defect' by the HPA criteria, a third VF test was undertaken prior to randomisation and the result of this was deemed to define whether or not the patient was eligible. These were performed at the same baseline clinic evaluation or at a separate evaluation, but had to be completed prior to randomisation. At 24 months, two reliable 24-2 SITA standard VF tests were performed and used to establish the VF outcome VFMD. In addition, a reliable Esterman VF test was performed and was used to assess driving eligibility. An independent VF reading centre assessed all the VF tests. The reading centre was masked to the treatment received by the study participant.

#### Intraocular pressure

Intraocular pressure was measured by Goldman tonometry at baseline and at 4, 12 and 24 months. The unit of IOP measurement is mmHg. The measurement was undertaken by two observers, and the first observer interacted directly with the patient. Without looking at the measurement dial, the investigator applied the Goldman tonometer to the eye and reached the end point for the measurement value of IOP. The second observer then recorded the values from the measurement dial. This process was repeated and both measures were recorded. If the difference between the first and the second measurements was > 3 mmHg, a third measurement was undertaken.

#### Visual acuity

Best-corrected log-median angle of resolution (logMAR) visual acuity (VA) was measured at baseline and at 4, 12 and 24 months post randomisation.

#### Ability to drive

The retention of the ability to drive is one of the most important issues to patients with glaucoma who drive.<sup>37</sup> All patients diagnosed with glaucoma are obliged to inform the Driver and Vehicle Licensing Agency (DVLA) of their diagnosis. Visual standards for driving are assessed on the basis of VF and VA levels. This assessment is arranged at regular intervals by the DVLA. To evaluate visual standard for driving, all participants had an Esterman VF test performed (on the Humphrey VF Analyser) at baseline and at the final visit at 24 months. Registration as visually impaired was based on VA and VF criteria. The consultant ophthalmologists were responsible for registering patients as visually disabled on the basis of these criteria. If a participant has been registered as visually impaired or severely visually impaired, this was recorded along with the date of registration in the study case report form (CRF) at 24 months.

The complications of surgery, the need for cataract surgery and therapy changes were captured from the participants' case records. All clinical outcomes were recorded on a trial-specific CRF.

Clinical data were collected and entered onto the TAGS secure web database at the participating sites.

### **Economic**

The objective of the economic analysis was to determine the relative cost-effectiveness of augmented trabeculectomy compared with medical management (usual care) over the trial follow-up period and extrapolated over the participant's lifetime. Economic outcomes were:

- incremental costs to the NHS, PSS and participants
- incremental QALYs (based on responses to the EQ-5D-5L, HUI-3 and glaucoma utility index).

In addition, an existing DCE questionnaire with an updated design was administered to trial participants to estimate the value that individuals with advanced glaucoma place on different health states associated with glaucoma and to obtain utility scores for these health states in a population with advanced glaucoma.<sup>55</sup> These data were used to score the GUI responses and were incorporated into the economic evaluation reported in *Chapter 6*.

Details of the DCE are reported in *Chapter 5*, and the economic evaluation is reported in *Chapter 6*.

### **Safety reporting**

We defined AEs as those events that occurred after randomisation and within the 24-month follow-up period of the trial. To be considered as an AE, an event had to be categorised as related to participation in the trial or related to glaucoma. Thus, we excluded a continuous and persistent disease or symptom, present before the trial, which failed to progress and signs or symptoms of the disease being studied (except where they deteriorated sufficiently to be considered serious).

We identified potentially expected AEs linked to medical management and trabeculectomy (with mitomycin C) as:

- Medical management – redness, stinging, itching, transient blurred vision, eye watering, ocular discomfort, allergy, eyelash growth, change in skin colour around eye, change in iris colour, shortness of breath, unpleasant taste in mouth, dry mouth, fatigue, kidney stones, skin rash, cataract formation and retinal detachment. In some cases, some of these symptoms may have been because of preservatives in the eye drops and, if this was the case, preservative-free eye drops were used.
- Trabeculectomy with mitomycin C – discomfort, blurred vision, corneal epithelial defect, conjunctival button hole, flap dehiscence, IOP too low, transient choroidal effusion, suprachoroidal haemorrhage, hyphaema, early bleb leak, shallow anterior chamber (grades 1–3), iris incarceration, persistent uveitis, transient or permanent ptosis, macular oedema, malignant glaucoma, corneal decompensation, cataract formation and retinal detachment, late bleb leak, bleb infection, bleb-related endophthalmitis, permanent severe loss of vision at time of surgery (< 1/500), bleeding in the eye, broad complex tachycardia while under general anaesthetic and post-operative dizziness.

In addition, a VA AE was defined as any of the following:

- irreversible loss of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters of logMAR VA
- loss of two or more stages of categorical VA measurement (count fingers, hand motion, light perception, no light perception)
- any loss to no light perception.

These definitions were based on knowledge of AEs associated with augmented trabeculectomy and the relevant product information documented in the summary of product characteristics for eye drops.

The latest online version of the appropriate summary of product characteristics was considered in the assessment of an AE.

We adhered to the standard definition of serious adverse events (SAEs) as those leading to death, hospitalisation (or prolongation of existing hospitalisation), persistent or significant disability or incapacity, congenital anomaly or birth defect, as well as an event that was considered life-threatening or otherwise considered medically significant.

Pregnancy was not considered an AE or SAE; however, we put in place processes (see the trial protocol for details<sup>1</sup>) to collect pregnancy information for participants who became pregnant while participating in the study (defined as while taking or within 3 months of ceasing to take study medications).

## Masking

Given that TAGS investigated medical versus surgical management, neither the participants nor the local clinical team could be masked to the randomised treatment allocation. The only masked aspect was the evaluation of VFs at the end of the study, which was undertaken by an independent reading centre masked to the allocation: Central Angiographic Resource Facility (CARF), Queen's University Belfast.

### *Methods to protect against sources of bias*

The allocation to treatment arms was concealed by using a central randomisation service that could be accessed only by clinical trials unit programming staff.

The evaluation of VFs collected during the study period was by CARF masked to the participant intervention. IOP was measured by two observers: one taking the reading and the other reading the IOP value to minimise the risk of measurement bias.

The expected attrition rate was low based on a previous glaucoma treatment RCT,<sup>75</sup> but we allowed for a potential attrition rate of 13.5% over 24 months to accommodate this.

External validity was maximised by recruiting from multiple centres and participants were treated by multiple clinicians.

## Statistical analysis

### *Ground rules for statistical analysis*

The trial analysis followed a statistical analysis plan (see *Report Supplementary Material 2*), which was agreed in advance by the TSC. The main analyses were based on the intention-to-treat (i.e. analyse as randomised) principle and took place after the 24-month follow-up. Baseline and follow-up data were summarised using appropriate statistics and graphical summaries. Statistical significance was at the two-sided 5% level with corresponding CIs derived. All analyses were carried out using Stata<sup>®</sup> version 16 software (StataCorp LP, College Station, TX, USA).

### *Sample size*

The primary patient-reported outcome was the health status measured by the VFQ-25 assessment at 24 months. A study with 190 participants in each arm would have 90% power at a two-sided 5% significance level to detect a difference in means of 0.33 of a standard deviation (SD), which translates to 6 points on the VFQ-25 assuming a common SD of 18 points observed in previous work that has a clinically relevant effect size in patients with advanced glaucoma.<sup>76,77</sup> Seven points is a likely minimally important difference based on our pilot work on VFQ-25 scores in patients with glaucoma,<sup>77</sup> but there is uncertainty, and so we opted for a more conservative 6-point difference, which is supported by the

literature for another chronic eye disease, macular degeneration.<sup>78</sup> Assuming a drop-out rate of 13.5% as a result of declining further follow-up and death, we had to randomise a total of 440 participants to detect this difference.

For the secondary clinical outcome (VFMD), TAGS had 90% power at 5% significance to detect a 1.3 dB difference in VFMD. This is derived from a subgroup of patients with advanced glaucoma and is a clinically significant difference in the context of advanced glaucoma and predictive further visual disability.<sup>30,43</sup>

Centres that had a throughput of at least 20 eligible patients annually were approached to participate in the trial. This enabled the development of a recruitment projection based on 20 sites recruiting approximately 9–11 patients per year, with a staggered start of recruiting sites, and allowed 440 participants to be recruited over 3 years (assuming a reduced rate during the first month of each site set-up and 50% reduction during the holiday months of August and December).

### **Primary/secondary outcome analysis**

The primary outcome, VFQ-25 assessed at 24 months, was analysed using a heteroscedastic partially nested repeated-measures mixed-effects linear model correcting for baseline score and bilateral disease, and time as a fixed effect.<sup>79</sup> The repeated measures were VFQ-25 assessed at 4, 12 and 24 months. Treatment effects were estimated from time-by-treatment interactions at each time point; the primary time of interest was 24 months. This approach uses participant data from all of the time points and incorporates a random effect for centre and surgeon using restricted maximum likelihood. We used this approach to account for the potential lack of independence of outcome data for patients treated by the same surgeon. This is known as clustering or the surgeon effect, and occurs in the trabeculectomy arm only (hence the 'nested' approach) in TAGS. We also adjusted for heteroscedastic errors because the residuals compared with the fitted values showed evidence that the variance of errors were different between treatment arms. We did not carry out any sensitivity analysis for missing data because < 10% of VFQ-25 data were missing. Given the pragmatic nature of TAGS, there was the potential for participants to cross over from one intervention to the other. To estimate the treatment effect in the subgroup of participants who complied with allocated treatment, we used complier-average causal effect (CACE) methods using instrumental variable regression<sup>80</sup> and a per-protocol analysis.

For the secondary outcomes, EQ-5D-5L, HUI-3, GUI, IOP and logMAR VA, VFs were analysed following the same method as the primary outcome. The utility values for the GUI were derived from the results of the DCE (which are presented in *Chapter 5*). For the IOP, logMAR VA and VF tests, a sensitivity analysis was performed using data from all eligible eyes by also including a random effect at the participant level to reflect the lack of independence of eyes within participants. In addition, for the VFs a further two sensitivity analyses were performed: the first included only the VF tests performed in accordance with SITA standard and the second removed participants who had only one VF test or in whom the false positive standard was > 15%. The post hoc Dunnett's multiplicity *p*-values were presented for IOP and logMAR VA. Patient experience (glaucoma getting worse) was analysed using a repeated-measures mixed-effects Poisson model adjusting for bilateral disease and including a random effect for surgeon and treatment. The need for cataract surgery, visual standards for driving and safety outcomes were analysed using the same modelling approach. Given that the number of events for patients registered as sight impaired was small, we used Fisher's exact test. Data missing at baseline were reported as such, and for the primary/secondary outcomes continuous data were imputed using the centre-specific mean of that variable.

### **Subgroup analyses**

Planned subgroup analyses explored the potential treatment effect moderation of sex, age (< 65 years vs. ≥ 65 years), one or both eyes affected with advanced glaucoma, Index of Multiple Deprivation (quintile) and extent of VF loss at baseline (< -20 dB, ≥ -20 dB) on the primary outcome. The subgroup-by-treatment interaction was assessed by including interaction terms in the models outlined above.

We used a stricter level of statistical significance (two-sided 1% significance level) and 99% CIs to reflect the exploratory nature of these analyses. A post hoc subgroup analysis of IOP at diagnosis (< 21 mmHg vs. ≥ 21 mmHg) was also explored following the same analysis method as the planned subgroup analysis.

### **Criteria for the termination of the trial**

Owing to the staggered nature of recruitment and, therefore, the measurement of the primary outcome at 24 months, we did not anticipate that the trial would be terminated early for benefit. We proposed one main effectiveness analysis at the end of the trial. During the trial, safety and other data were monitored by reports prepared for the Data Monitoring Committee (DMC). The DMC decided to meet every 6 months until June 2018.

## **Economic evaluation**

In this study both a 'within-trial' and a model-based economic evaluation were conducted. These are described in detail in *Chapter 6*.

## **Research ethics and regulatory approvals**

TAGS received favourable ethics opinion from the East Midlands – Derby Research Ethics Committee (REC) on 12 December 2013 (REC reference number 13/EM/0395).

## **Changes to the protocol**

The main changes to the protocol (see *Appendix 8*) since original ethics approval include the addition of further follow-up assessments (at 3, 4 and 5 years) and a genetics substudy. All amendments were reviewed by the sponsor and the independent TSC on behalf of the funder before being submitted to, and then approved by, the REC. The results of these studies are not reported in this monograph.

## **Management of the trial**

The trial management team, based within CHaRT, University of Aberdeen, provided day-to-day support for the recruiting centres and was led by a local principal investigator (PI). The PIs, in most cases supported by research nurses, trial co-ordinators or dedicated staff, were responsible for all aspects of local organisation, including the recruitment of participants, delivery of the interventions and notification of any problems or unexpected developments during the study period.

## **Study oversight committees**

### **Study Management Group**

The Study Management Group (SMG) was responsible for the day-to-day management of the trial. This group consisted of the chief investigator, trial manager, senior trial manager, data co-ordinator, statistician and a sponsor representative. Members of the SMG are listed in the *Acknowledgements*.

### **Project Management Group**

The Project Management Group (PMG) was responsible for overseeing the management of the trial. This group consisted of the SMG plus grant applicants, a public and patient involvement (PPI) representative and a senior programmer. Members of the PMG are listed in the *Acknowledgements*.

### ***Trial Steering Committee***

The Trial Steering Committee (TSC) was responsible for monitoring and supervising the progress of TAGS. The committee met seven times between April 2014 and December 2019 at agreed intervals. The TSC consisted of independent experts, a PPI member, the chief investigator and key members of the PMG. Members of the TSC are listed in the *Acknowledgements*.

### ***Data Monitoring Committee***

The DMC was independent of the trial and was responsible for monitoring safety and data integrity. The committee met eight times between April 2014 and August 2018, approximately every 6 months at intervals agreed by the committee. The trial statistician provided the data and analyses requested by the DMC prior to each meeting. The committee consisted of three independent experts. Members of the DMC are listed in the *Acknowledgements*.



## Chapter 3 Participant baseline characteristics

### Trial recruitment

Between 3 June 2014 and 21 May 2017, we recruited 453 participants from 27 centres (Table 2): 227 were randomised to the trabeculectomy arm and 226 to the medical management arm. The trajectory of recruitment from all centres is shown in Figure 1.

TABLE 2 Recruitment by centre

Centre	All (N = 453), n (%)	Treatment arm, n (%)	
		Trabeculectomy (N = 227)	Medical management (N = 226)
Queen Alexandra Hospital, Portsmouth	52 (11.5)	26 (11.5)	26 (11.5)
Queen's Medical Centre, Nottingham	46 (10.2)	24 (10.6)	22 (9.7)
Guy's and St Thomas', London	36 (7.9)	18 (7.9)	18 (8.0)
Moorfields Eye Hospital, London	26 (5.7)	12 (5.3)	14 (6.2)
Bristol Eye Hospital, Bristol	26 (5.7)	14 (6.2)	12 (5.3)
Norfolk and Norwich University Hospital, Norwich	24 (5.3)	12 (5.3)	12 (5.3)
Manchester Royal Eye Hospital, Manchester	21 (4.6)	10 (4.4)	11 (4.9)
York Hospital, York	19 (4.2)	9 (4.0)	10 (4.4)
Princess Alexandra Eye Hospital, Edinburgh	17 (3.8)	8 (3.5)	9 (4.0)
Hinchingbrooke Hospital, Huntingdon	17 (3.8)	9 (4.0)	8 (3.5)
Western Eye Hospital, Imperial, London	16 (3.5)	9 (4.0)	7 (3.1)
Sunderland Eye Infirmary, Sunderland	16 (3.5)	8 (3.5)	8 (3.5)
Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast	15 (3.3)	7 (3.1)	8 (3.5)
Maidstone Hospital, Maidstone	14 (3.1)	7 (3.1)	7 (3.1)
Royal Derby Hospital, Derby	13 (2.9)	6 (2.6)	7 (3.1)
Warrington Hospital, Warrington	13 (2.9)	6 (2.6)	7 (3.1)
James Paget Hospital, Great Yarmouth	13 (2.9)	7 (3.1)	6 (2.7)
Birmingham and Midland Eye Centre, Birmingham	12 (2.6)	7 (3.1)	5 (2.2)
Birmingham Heartlands Hospital, Birmingham	12 (2.6)	6 (2.6)	6 (2.7)
University Hospital Coventry, Coventry	10 (2.2)	6 (2.6)	4 (1.8)
Queen Margaret Hospital, Dunfermline	9 (2.0)	4 (1.8)	5 (2.2)
Cheltenham General Hospital, Cheltenham	8 (1.8)	4 (1.8)	4 (1.8)
Harrogate District Hospital, Harrogate	6 (1.3)	3 (1.3)	3 (1.3)
Ninewells Hospital, Dundee	4 (0.9)	2 (0.9)	2 (0.9)
Royal Hallamshire Hospital, Sheffield	3 (0.7)	1 (0.4)	2 (0.9)
Hairmyres Hospital, Lanarkshire	3 (0.7)	1 (0.4)	2 (0.9)
Gartnavel General Hospital, Glasgow	2 (0.4)	1 (0.4)	1 (0.4)

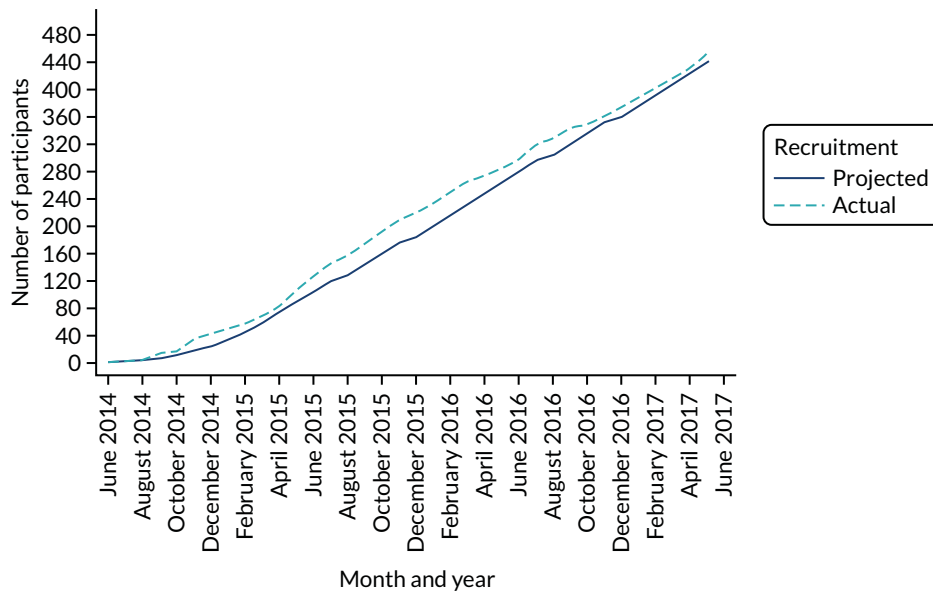


FIGURE 1 Recruitment over time.

### Participant flow

Figure 2 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram for TAGS. A total of 962 potentially eligible patients were screened, of whom 509 were excluded: 233 because they were ineligible and 276 because they declined to participate. The main reasons for ineligibility were that VFs did not meet the inclusion criteria (24%) and that patients could not be randomised within 3 months of diagnosis (22.7%). Those who declined either did not give a reason (27.9%) or did not want surgery (19.6%). Further details on reasons why patients were excluded can be found in *Appendix 2, Table 23*.

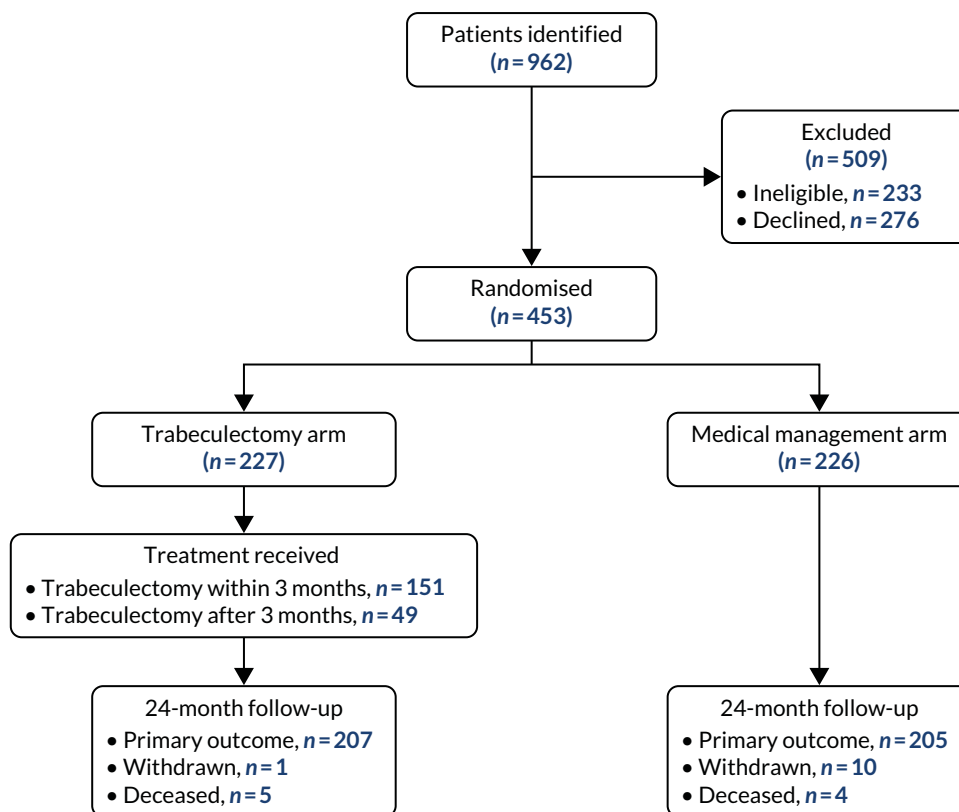


FIGURE 2 The CONSORT flow diagram presenting participant flow in the trial.

All of the participants attended a baseline clinical assessment, but one participant in the trabeculectomy arm and two participants in the medical management arm did not provide baseline VFQ-25 (primary outcome). A total of 11 participants declined further questionnaires and clinical follow-up (not including treatment clinics) from the study, and nine deaths were reported, none of which was caused by a study intervention. In the trabeculectomy arm, 201 (88.5%) participants underwent trabeculectomy in their index eye: trabeculectomy was performed within 3 months of randomisation in 151 (66.5%) participants and after 3 months in 49 (21.2%) participants. For one participant, the timing of trabeculectomy was unknown (see *Figure 2*). There were 16 (7.0%) participants who declined trabeculectomy, two (0.9%) died before they could receive a trabeculectomy and eight (3.5%) did not receive trabeculectomy in their index eye. Further details about the treatment received are described later in this chapter. At the 24-month follow-up, 207 (91.2%) participants in the trabeculectomy arm and 205 (90.7%) participants in the medical management arm provided primary outcome data.

## Baseline characteristics

The baseline characteristics are shown in *Table 3* and the treatment arms were well balanced. The mean age of the participants was 67 years in the trabeculectomy arm and 68 years in the medical management arm. Over 65% of participants were male and over 80% were white. In total, the percentage of participants who had bilateral disease was 19.4% in the trabeculectomy arm and 19.5% in the medical management arm, and over 90% in both arms had primary OAG. The mean VFQ-25 was 87.1 in both arms and the mean VFMD (dB) was -14.9 and -15.3 in the trabeculectomy arm and the medical management arm, respectively. The baseline characteristics for the non-index eye and the HPA classification of glaucoma severity are shown in *Appendix 2, Tables 24 and 25*, respectively.

TABLE 3 Baseline characteristics

Characteristic	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Age (years), n; mean (SD)	227; 67 (12.2)	226; 68 (12.4)
Sex, n (%)		
Male	156 (68.7)	147 (65.0)
Female	71 (31.3)	79 (35.0)
Ethnicity, n (%)		
White	182 (80.2)	191 (84.5)
Afro-Caribbean	32 (14.1)	27 (11.9)
Asian – India/Pakistan/Bangladesh	8 (3.5)	4 (1.8)
Asian – Oriental	2 (0.9)	0 (0)
Mixed	0 (0)	1 (0.4)
Other	3 (1.3)	2 (0.9)
Missing	0 (0)	1 (0.4)
Advanced glaucoma in both eyes, n (%)		
Yes	44 (19.4)	44 (19.5)
No	183 (80.6)	182 (80.5)

continued

PARTICIPANT BASELINE CHARACTERISTICS

TABLE 3 Baseline characteristics (continued)

Characteristic	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Glaucoma in both eyes, n (%)		
Yes	178 (78.4)	169 (74.8)
No	49 (21.6)	57 (25.2)
Eligible to be registered as sight impaired, n (%)		
No	214 (94.3)	212 (93.8)
Sight impaired	10 (4.4)	12 (5.3)
Severely sight impaired	3 (1.3)	2 (0.9)
Glaucoma diagnosis, n (%)		
Primary OAG (including NTG)	219 (96.5)	220 (97.3)
Pigment dispersion syndrome	5 (2.2)	4 (1.8)
Pseudoexfoliation syndrome	3 (1.3)	2 (0.9)
Lens status, n (%)		
Phakic	212 (93.4)	209 (92.5)
Pseudophakic	15 (6.6)	17 (7.5)
Central corneal thickness (µm), n; mean (SD)	226; 539.4 (35.7)	223; 541.4 (35.7)
Glaucoma eye drops, n (%)		
Prostaglandin analogue	186 (81.9)	182 (80.5)
Beta-blocker	52 (22.9)	52 (23.0)
Carbonic anhydrase inhibitor	45 (19.8)	33 (14.6)
α-agonist	7 (3.1)	4 (1.8)
Diamox <sup>a</sup>	6 (2.6)	2 (0.9)
Family history of glaucoma, n (%)		
Yes	63 (27.8)	79 (35.0)
No	152 (67.0)	131 (58.0)
Missing	12 (5.3)	16 (7.1)
Number of times visited the optician in the last 10 years, n; median (IQR)	214; 5 (2-6)	209; 5 (3-8)
Index of Multiple Deprivation, n (%)		
First quintile (most deprived)	54 (23.8)	52 (23.0)
Second quintile	30 (13.2)	37 (16.4)
Third quintile	45 (19.8)	43 (19.0)
Fourth quintile	50 (22.0)	43 (19.0)
Fifth quintile (least deprived)	47 (20.7)	49 (21.7)
Missing	1 (0.4)	2 (0.9)
Ocular comorbidity, n (%)		
Yes	50 (22.0)	50 (22.1)
No	177 (78.0)	176 (77.9)

TABLE 3 Baseline characteristics (continued)

Characteristic	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Ocular comorbidity details, <sup>b</sup> n (%)		
AMD	6 (12.0)	4 (8.0)
Cataract	42 (84.0)	42 (84.0)
Vascular occlusion	2 (4.0)	1 (2.0)
Diabetic retinopathy	1 (2.0)	1 (2.0)
Other	9 (18.0)	6 (12.0)
VFQ-25, n; mean (SD)	226; 87.1 (13.6)	224; 87.1 (13.4)
VFQ-25 subscales, n; mean (SD)		
Near activities	225; 84.2 (18.5)	224; 84.4 (16.9)
Distance activities	226; 88.5 (16.1)	224; 89.7 (14.4)
Dependency	226; 94.0 (17.3)	222; 94.9 (15.7)
Driving	171; 85.9 (26.7)	158; 84.8 (26.2)
General health	225; 63.6 (23.4)	223; 60.9 (22.6)
Role difficulties	226; 87.1 (19.8)	222; 87.4 (20.8)
Mental health	226; 81.1 (21.2)	224; 81.8 (19.9)
General vision	223; 74.9 (14.5)	223; 72.8 (14.2)
Social function	225; 95.2 (11.9)	224; 94.9 (12.1)
Colour vision	223; 96.9 (10.9)	222; 96.6 (11.1)
Peripheral vision	224; 86.6 (20.8)	224; 87.2 (20.2)
Ocular pain	225; 84.7 (19.0)	224; 83.9 (17.2)
VFMD (dB), n; mean (SD)	227; -14.91 (6.36)	226; -15.26 (6.34)
LogMAR VA, n; mean (SD)	227; 0.15 (0.25)	223; 0.17 (0.26)
Intraocular pressure (mmHg), n; mean (SD)		
Diagnosis	226; 26.9 (9.1)	223; 25.9 (8.4)
Baseline	222; 19.4 (6.2)	221; 19.0 (5.7)
EQ-5D-5L, n; mean (SD)	222; 0.844 (0.185)	222; 0.837 (0.176)
HUI-3, n; mean (SD)	214; 0.814 (0.202)	214; 0.809 (0.208)
GUI, n; mean (SD)	219; 0.884 (0.131)	222; 0.863 (0.130)
Participant experience (glaucoma getting worse), n (%)		
Yes	95 (41.9)	76 (33.6)
No	113 (49.8)	133 (58.8)
Missing	19 (8.4)	17 (7.5)
Visual standards for driving, n (%)		
Pass	187 (82.4)	196 (86.7)
Fail	27 (11.9)	21 (9.3)
Missing	13 (5.7)	9 (4.0)

AMD, age-related macular degeneration; IQR, interquartile range; NTG, normal tension glaucoma.

a Taken orally.

b Participants can have more than one.

## Treatment received

In the trabeculectomy arm, 201 (88.5%) participants received surgery in their index eye. Of the remaining 26 participants, four had surgery in their non-index-eye only, 16 declined surgery, two died prior to having surgery and four had yet to receive surgery. Thirty-four (15.0%) participants underwent trabeculectomy in their non-index eye, of whom four did not undergo trabeculectomy in their index eye (see *Appendix 3, Table 27*). In the medical management arm, 39 (17.3%) participants underwent trabeculectomy (*Table 4*). The median time to trabeculectomy was 8.9 weeks in the trabeculectomy arm. Among the 27 participants in the medical management arm for whom the date of surgery was known, the median time to surgery was 47.7 weeks post randomisation, and in 15 cases was more than 12 months post randomisation. At the time of surgery, the mean number of eye drop agents that the patient had received pre-operatively was 1.4 (SD 1.1) in the trabeculectomy arm and 1.9 (SD 1.1) in the medical management arm (see *Table 4* for the classes of eye drops prescribed.) At the time of surgery, the mean pre-operative IOP was 19.3 mmHg in the trabeculectomy arm and 21.1 mmHg in the medical management arm. *Appendix 3, Table 26*, gives further details of the trabeculectomy procedure. *Appendix 3, Table 27*, shows the results for the non-index eye.

TABLE 4 Trabeculectomy procedure: index eye

Trabeculectomy details	Treatment arm	
	Trabeculectomy	Medical management
Received surgery in their index eye, n/N (%)	201/227 (88.5)	39/226 (17.3)
Time to trabeculectomy (weeks), n; median (IQR)	200; 8.9 (5.3–11.9)	39; 47.4 (23.0–63.1)
Reasons for trabeculectomy, <sup>a</sup> n (%)		
Uncontrolled IOP		23 (60.5)
VF progression		6 (15.8)
Drop intolerance		4 (10.5)
Missing		11 (28.9)
Trabeculectomy clinical report form provided (n)	199	27
Number of different types of eye drops received pre-operatively, mean (SD)	1.4 (1.1)	1.9 (1.1)
Type of pre-operative eye drop, n (%)		
Carbonic anhydrase inhibitor	57 (28.6)	14 (51.9)
Prostaglandin analogue	148 (74.4)	21 (77.8)
Beta-blocker	56 (28.1)	12 (44.4)
$\alpha$ -agonist	9 (4.5)	4 (14.8)
Parasympathomimetic	3 (1.5)	0 (0)
Diamox, n (%)		
Yes	3 (1.5)	1 (3.7)
No	192 (96.5)	26 (96.3)
Missing	4 (2.0)	0 (0)
Pre-operative IOP (mmHg), n; mean (SD)	179; 19.3 (6.0)	26; 21.1 (4.0)

IQR, interquartile range.  
<sup>a</sup> More than one reason is possible.

At the 24-month follow-up, 9 out of 181 (5.0%) participants in the trabeculectomy arm had been added to a waiting list to have a trabeculectomy in their non-index eye. In their medical management arm, 14 out of 204 (6.9%) participants had been added to a waiting list to have a trabeculectomy, in 11 of whom trabeculectomy was planned for the index eye.





## Chapter 4 Trial results

### Primary outcome

The mean VFQ-25 score in the trabeculectomy arm and the medical management arm at baseline was 87.1 (Table 5). Figure 3 shows the mean (SD) VFQ-25 score over time. At 24 months, the difference between arms was 1.06 (95% CI -1.32 to 3.43;  $p = 0.383$ ). The results were similar at all other time points (see Table 5). The VFQ-25 subscales are presented in Table 5. The per-protocol analysis (see Appendix 3, Table 28) showed similar results across all time points; at 24 months, the adjusted MD was 0.95 (95% CI -1.54 to 3.45;  $p = 0.454$ ). The per-protocol analysis for VFQ-25 subscales is also presented in Appendix 3, Table 28. The CACE results for VFQ-25 score were also similar at 24 months (MD 1.52, 95% CI -1.27 to 4.30;  $p = 0.286$ ) (see Appendix 3, Table 29).

TABLE 5 The number of VFQ-25 questionnaires, full VFQ-25 scores and subscale scores by treatment arm

Measure	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>VFQ-25</b>					
Baseline	226; 87.1 (13.6)	224; 87.1 (13.4)			
4 months	212; 85.1 (14.9)	216; 86.5 (13.6)	-1.24	-3.58 to 1.11	0.301
12 months	214; 85.4 (14.3)	209; 86.3 (13.1)	-0.64	-3.00 to 1.72	0.595
24 months	207; 85.4 (13.8)	205; 84.5 (16.3)	1.06	-1.32 to 3.43	0.383
<b>VFQ-25 subscales</b>					
<i>Near activities</i>					
Baseline	225; 84.2 (18.5)	224; 84.4 (16.9)			
4 months	211; 83.9 (18.0)	214; 84.9 (17.1)	-0.56	-4.12 to 3.01	
12 months	214; 84.1 (18.6)	209; 84.7 (18.4)	-0.06	-3.63 to 3.52	
24 months	205; 82.8 (18.4)	204; 82.3 (19.9)	1.11	-2.50 to 4.73	
<i>Distance activities</i>					
Baseline	226; 88.5 (16.1)	224; 89.7 (14.4)			
4 months	211; 87.8 (16.8)	216; 89.0 (15.4)	0.10	-2.92 to 3.13	
12 months	214; 88.2 (16.3)	209; 88.6 (15.7)	0.94	-2.10 to 3.99	
24 months	207; 88.0 (15.9)	204; 86.2 (18.9)	2.89	-0.18 to 5.96	
<i>Dependency</i>					
Baseline	226; 94.0 (17.3)	222; 94.9 (15.7)			
4 months	211; 91.2 (20.2)	216; 93.4 (17.5)	-1.67	-4.97 to 1.62	
12 months	213; 92.1 (19.6)	209; 94.3 (14.5)	-1.40	-4.71 to 1.90	
24 months	206; 93.6 (15.6)	203; 92.7 (17.7)	2.00	-1.34 to 5.35	

continued

TABLE 5 The number of VFQ-25 questionnaires, full VFQ-25 scores and subscale scores by treatment arm (continued)

Measure	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<i>Driving</i>					
Baseline	171; 85.9 (26.7)	158; 84.8 (26.2)			
4 months	151; 82.1 (30.6)	155; 83.0 (27.4)	-0.10	-7.00 to 6.80	
12 months	152; 81.3 (28.9)	149; 79.9 (29.8)	0.63	-6.33 to 7.59	
24 months	143; 81.1 (29.3)	138; 79.9 (28.7)	1.88	-5.18 to 8.94	
<i>General health</i>					
Baseline	225; 63.6 (23.4)	223; 60.9 (22.6)			
4 months	211; 66.0 (23.4)	215; 64.8 (20.9)	-0.07	-4.68 to 4.54	
12 months <sup>a</sup>	214; 66.1 (23.8)	208; 60.5 (22.4)	4.86	0.23 to 9.49	
24 months	206; 63.3 (25.5)	205; 59.9 (23.5)	2.44	-2.22 to 7.09	
<i>Role difficulties</i>					
Baseline	226; 87.1 (19.8)	222; 87.4 (20.8)			
4 months <sup>a</sup>	212; 82.5 (24.5)	216; 86.3 (21.7)	-4.60	-8.70 to -0.50	
12 months	213; 83.2 (23.2)	209; 84.8 (21.1)	-2.07	-6.19 to 2.06	
24 months	207; 83.0 (22.7)	203; 83.4 (23.4)	-0.80	-4.97 to 3.37	
<i>Mental health</i>					
Baseline	226; 81.1 (21.2)	224; 81.8 (19.9)			
4 months	212; 79.5 (23.3)	216; 83.5 (19.6)	-3.76	-7.55 to 0.02	
12 months	214; 79.6 (22.4)	209; 83.2 (19.7)	-3.26	-7.06 to 0.54	
24 months	207; 80.8 (20.7)	205; 81.4 (21.6)	-0.55	-4.38 to 3.28	
<i>General vision</i>					
Baseline	223; 74.9 (14.5)	223; 72.8 (14.2)			
4 months <sup>a</sup>	211; 71.7 (14.4)	215; 74.0 (12.5)	-3.17	-6.03 to -0.32	
12 months	213; 73.1 (14.6)	208; 73.8 (13.9)	-1.70	-4.57 to 1.17	
24 months	206; 73.3 (13.4)	203; 72.2 (14.6)	-0.03	-2.92 to 2.87	
<i>Social function</i>					
Baseline	225; 95.2 (11.9)	224; 94.9 (12.1)			
4 months	211; 95.1 (12.0)	216; 94.6 (11.9)	0.33	-2.29 to 2.95	
12 months	214; 94.3 (13.5)	208; 94.5 (11.8)	-0.34	-2.98 to 2.29	
24 months	206; 95.0 (12.2)	205; 93.2 (16.1)	1.47	-1.18 to 4.13	
<i>Colour vision</i>					
Baseline	223; 96.9 (10.9)	222; 96.6 (11.1)			
4 months	209; 97.4 (8.8)	214; 96.8 (10.2)	0.44	-1.40 to 2.28	
12 months	212; 96.1 (11.1)	205; 97.4 (8.7)	-1.37	-3.22 to 0.49	
24 months	206; 95.6 (13.9)	204; 95.0 (15.2)	0.70	-1.17 to 2.57	

TABLE 5 The number of VFQ-25 questionnaires, full VFQ-25 scores and subscale scores by treatment arm (continued)

Measure	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<i>Peripheral vision</i>					
Baseline	224; 86.6 (20.8)	224; 87.2 (20.2)			
4 months	210; 85.4 (21.1)	214; 85.6 (20.4)	-0.43	-4.59 to 3.74	
12 months	214; 86.4 (20.8)	207; 85.6 (20.2)	0.87	-3.31 to 5.06	
24 months	205; 85.1 (19.6)	204; 83.8 (22.4)	0.86	-3.35 to 5.08	
<i>Ocular pain</i>					
Baseline	225; 84.7 (19.0)	224; 83.9 (17.2)			
4 months	212; 81.3 (19.2)	216; 80.5 (18.9)	0.22	-2.96 to 3.40	
12 months	214; 81.6 (20.0)	209; 81.9 (16.3)	-0.61	-3.80 to 2.59	
24 months	207; 81.6 (19.7)	205; 80.5 (18.7)	0.98	-2.25 to 4.21	

a Statistical significance at the 5% level.

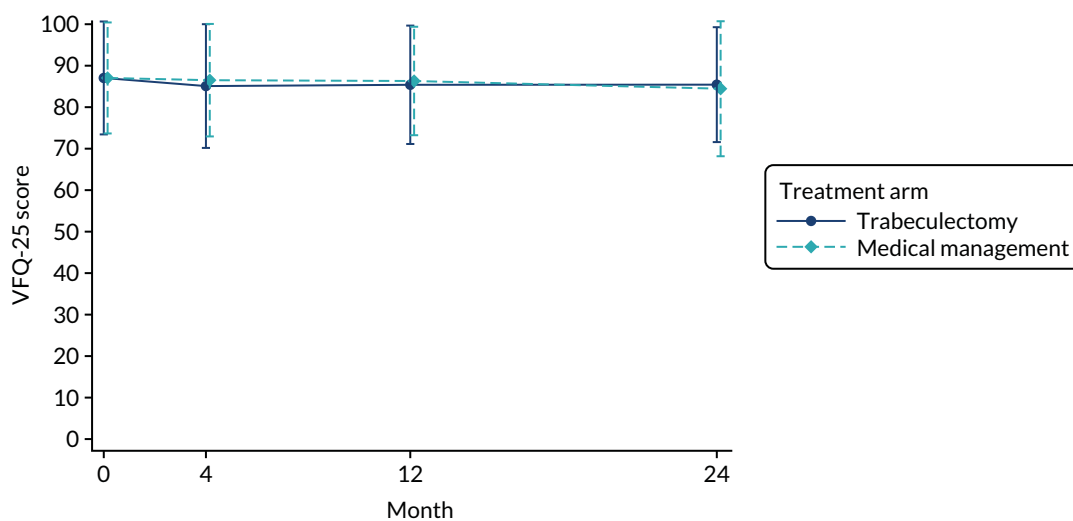


FIGURE 3 Mean (SD) VFQ-25 by arm over time.

### Subgroup analysis

Figures 4a–c show the prespecified subgroup analyses at 4, 12 and 24 months for VFQ-25 score, sex, age (< 65 vs. ≥ 65 years), VFs (< -20 dB vs. ≥ -20 dB), advanced glaucoma in both eyes, Index Multiple Deprivation quintile (most deprived to least deprived) and IOP at diagnosis (< 21 mmHg vs. ≥ 21 mmHg). There was no evidence of any treatment effect heterogeneity at 4 or 12 months. At 24 months, a potential moderating effect of age is emerging; however, there is considerable uncertainty around the estimate of the interaction effect.

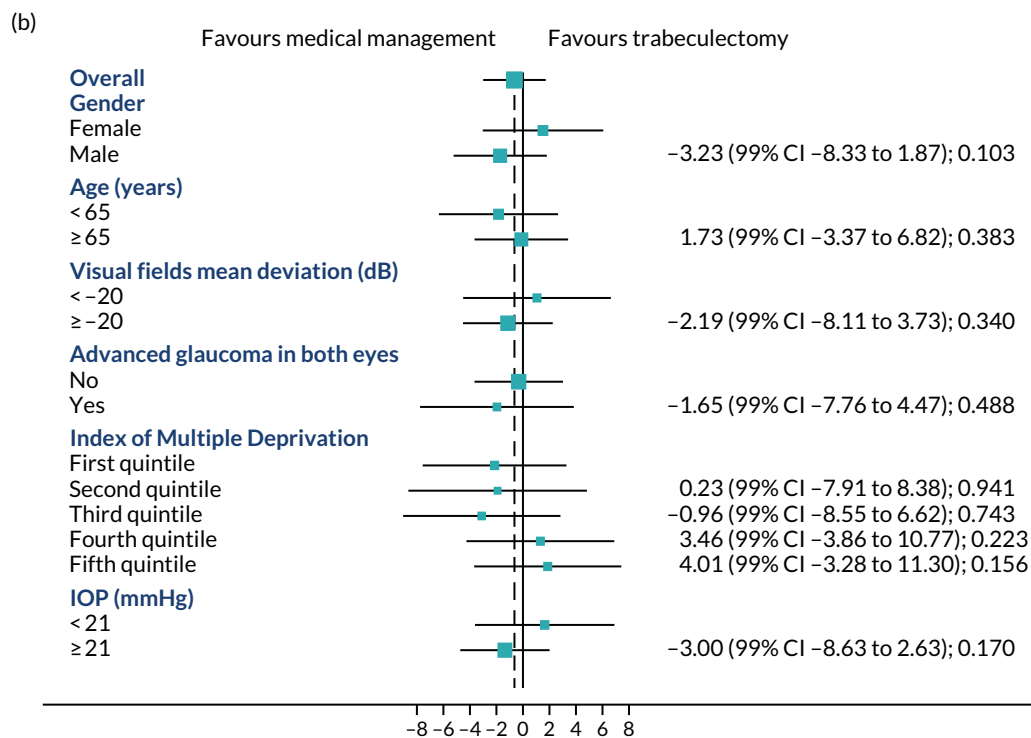
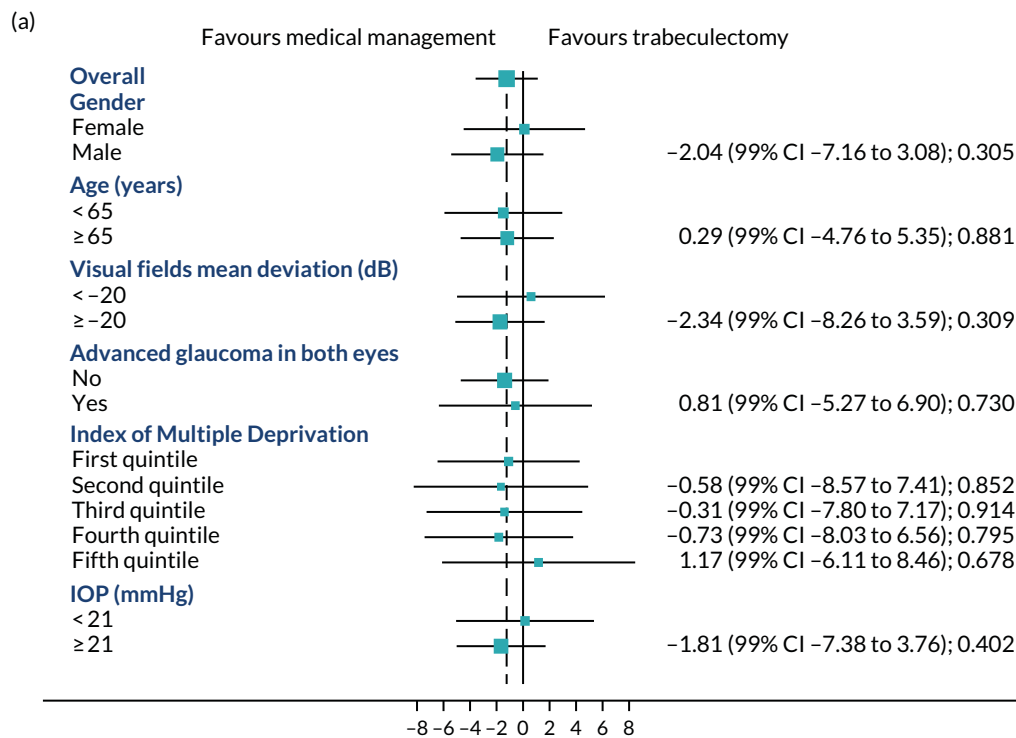


FIGURE 4 Subgroups for trabeculectomy vs. medical management: (a) 4 months, (b) 12 months and (c) 24 months. First quintile, most deprived; fifth quintile, least deprived. Boxes indicate mean differences. Solid black line indicates 99% CI. Solid vertical line indicates no effect. Dashed vertical line indicates overall effect. (continued)

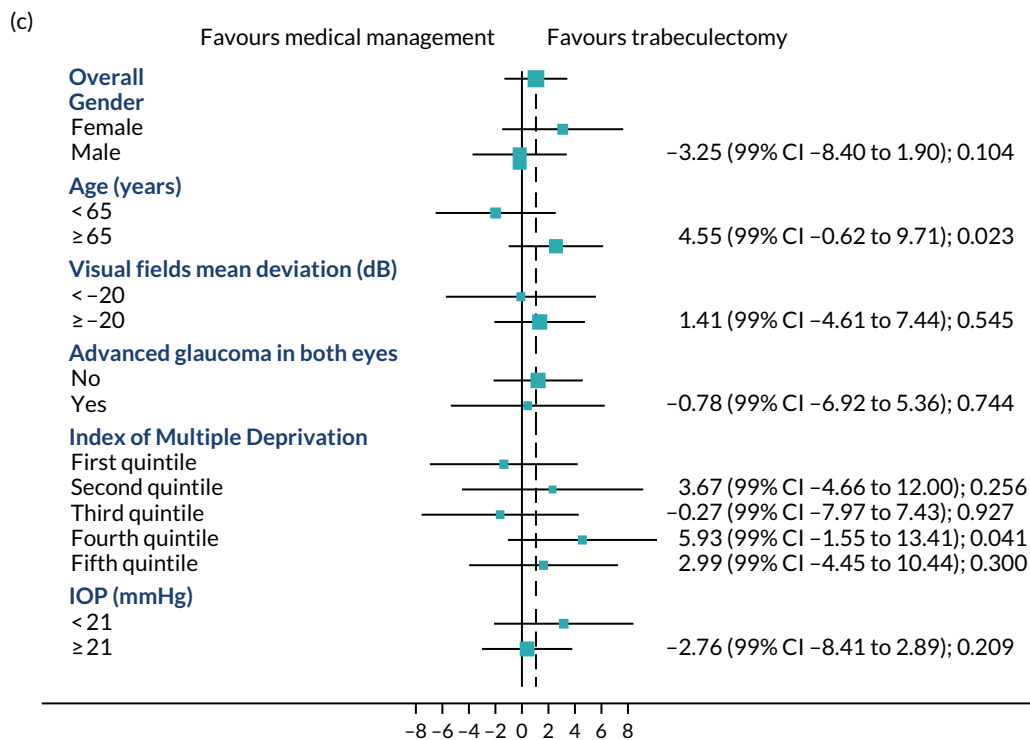


FIGURE 4 Subgroups for trabeculectomy vs. medical management: (a) 4 months, (b) 12 months and (c) 24 months. First quintile, most deprived; fifth quintile, least deprived. Boxes indicate mean differences. Solid black line indicates 99% CI. Solid vertical line indicates no effect. Dashed vertical line indicates overall effect.

## Secondary outcomes

### EQ-5D-5L

The mean baseline EQ-5D-5L score was 0.844 in the trabeculectomy arm and 0.837 in the medical management arm. At the follow-up time points, there was no evidence of a difference in the mean EQ-5D-5L score, and at 24 months the MD was 0.016 (95% CI -0.021 to 0.053;  $p = 0.405$ ) (Table 6).

TABLE 6 Secondary outcomes

Measure	Treatment arm		Estimate <sup>a</sup>	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
EQ-5D-5L, n; mean (SD)					
Baseline	222; 0.844 (0.185)	222; 0.837 (0.176)			
1 month	194; 0.838 (0.185)	203; 0.808 (0.203)	0.025	-0.012 to 0.062	0.189
3 months	186; 0.836 (0.167)	179; 0.814 (0.195)	0.015	-0.024 to 0.053	0.455
6 months	186; 0.850 (0.184)	195; 0.822 (0.204)	0.016	-0.021 to 0.054	0.391
12 months	211; 0.837 (0.177)	209; 0.823 (0.164)	0.014	-0.022 to 0.051	0.442
18 months	181; 0.828 (0.185)	184; 0.791 (0.219)	0.023	-0.016 to 0.061	0.244
24 months	206; 0.810 (0.179)	203; 0.796 (0.191)	0.016	-0.021 to 0.053	0.405

continued

TABLE 6 Secondary outcomes (continued)

Measure	Treatment arm		Estimate <sup>a</sup>	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>HUI-3, n; mean (SD)</b>					
Baseline	214; 0.814 (0.202)	214; 0.809 (0.208)			
1 month	184; 0.791 (0.232)	193; 0.786 (0.230)	-0.000	-0.043 to 0.043	1.000
3 months	180; 0.796 (0.223)	179; 0.779 (0.222)	0.007	-0.036 to 0.051	0.741
6 months	180; 0.805 (0.216)	182; 0.782 (0.224)	0.020	-0.024 to 0.063	0.376
12 months	204; 0.829 (0.193)	196; 0.798 (0.199)	0.024	-0.018 to 0.066	0.262
18 months	169; 0.802 (0.212)	174; 0.749 (0.258)	0.022	-0.022 to 0.066	0.324
24 months	198; 0.786 (0.227)	193; 0.751 (0.246)	0.036	-0.006 to 0.078	0.094
<b>GUI, n; mean (SD)</b>					
Baseline	219; 0.884 (0.131)	222; 0.863 (0.130)			
1 month	194; 0.862 (0.138)	205; 0.853 (0.156)	-0.000	-0.028 to 0.028	0.984
3 months	187; 0.849 (0.130)	190; 0.844 (0.156)	-0.008	-0.036 to 0.021	0.589
6 months	186; 0.839 (0.159)	191; 0.853 (0.135)	-0.024	-0.052 to 0.005	0.105
12 months	209; 0.857 (0.139)	204; 0.860 (0.143)	-0.012	-0.039 to 0.016	0.403
18 months	181; 0.851 (0.144)	184; 0.832 (0.157)	0.003	-0.026 to 0.032	0.832
24 months	205; 0.849 (0.152)	202; 0.830 (0.184)	0.011	-0.017 to 0.039	0.434
<b>Patient experience (glaucoma getting worse), n/N (%)</b>					
Baseline	95/208 (45.7)	76/209 (36.4)			
1 month	60/188 (31.9)	50/201 (24.9)	1.19	0.79 to 1.80	0.392
3 months	37/182 (20.3)	40/185 (21.6)	0.88	0.55 to 1.41	0.591
6 months	30/182 (16.5)	40/189 (21.2)	0.74	0.45 to 1.21	0.229
12 months	38/207 (18.4)	57/199 (28.6)	0.59	0.38 to 0.91	0.018
18 months	40/180 (22.2)	38/181 (21.0)	0.99	0.62 to 1.59	0.979
24 months	44/196 (22.4)	57/194 (29.4)	0.70	0.46 to 1.07	0.099
<b>IOP (mmHg), n; mean (SD)</b>					
Baseline	222; 19.40 (6.15)	221; 19.05 (5.73)			
4 months	217; 12.39 (5.73)	220; 16.40 (4.12)	-4.11	-5.18 to -3.05	< 0.001
12 months	215; 11.90 (4.48)	209; 16.12 (4.54)	-4.25	-5.33 to -3.18	< 0.001
24 months	206; 12.40 (4.71)	202; 15.07 (4.80)	-2.75	-3.84 to -1.66	< 0.001
<b>LogMAR VA, n; mean (SD)</b>					
Baseline	227; 0.15 (0.25)	223; 0.17 (0.26)			
4 months	210; 0.25 (0.31)	217; 0.16 (0.24)	0.10	0.05 to 0.14	< 0.001
12 months	212; 0.18 (0.23)	209; 0.16 (0.26)	0.03	-0.02 to 0.08	0.198
24 months	199; 0.21 (0.28)	201; 0.16 (0.26)	0.07	0.02 to 0.11	0.006
<b>VFMD (dB)</b>					
Baseline, n; mean (SD)	227; -14.91 (6.36)	226; -15.26 (6.34)			
4 months, n; mean (SD)	211; -14.35 (6.78)	217; -14.84 (6.52)	-0.05	-0.79 to 0.70	0.897
12 months, n; mean (SD)	214; -14.76 (6.92)	209; -14.95 (6.53)	0.03	-0.72 to 0.78	0.939
24 months, n; mean (SD)	202; -15.15 (6.63)	200; -15.42 (6.39)	0.18	-0.58 to 0.94	0.645

TABLE 6 Secondary outcomes (continued)

Measure	Treatment arm		Estimate <sup>a</sup>	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>Need for cataract surgery</b>					
Yes, n/N (%)	28/222 (12.6)	27/221 (12.2)	0.98	0.50 to 1.95	0.963
<b>Visual standards for driving (pass/no defects), n/N (%)</b>					
Baseline	187/214 (87.4)	196/217 (90.3)			
24 months	167/187 (89.3)	168/188 (89.4)	1.01	0.81 to 1.25	0.951
<b>Registered as sight impaired at 24 months, n/N (%)</b>					
No	182/186 (97.8)	184/184 (100.0)			0.123
Sight impaired	4/186 (2.2)	0/184 (0)			
<b>Eligible to be registered at 24 months, n/N (%)</b>					
No	188/199 (94.5)	187/196 (95.4)			
Sight impaired	8/199 (4.0)	7/196 (3.6)			
Severe sight impaired	3/199 (1.5)	2/196 (1.0)			

<sup>a</sup> Adjusted MD for continuous variables and adjusted risk ratios for dichotomous variables.

### Health Utility Index version 3

The mean baseline HUI-3 score was 0.814 in the trabeculectomy arm and 0.809 in the medical management arm, with no evidence of a difference at the follow-up time points. At 24 months, the mean score was 0.786 in the trabeculectomy arm and 0.751 in the medical management arm, with a MD of 0.036 (95% CI -0.006 to 0.078;  $p = 0.094$ ) (see Table 6).

### Glaucoma Utility Index

The baseline mean GUI score was 0.884 in the trabeculectomy arm and 0.863 in the medical management arm. These mean scores decreased in both arms over the course of the study, but there was no evidence of a difference at any time point. At 24 months, the mean score was 0.849 in the trabeculectomy arm and 0.830 in the medical management arm, with a mean difference of 0.011 (95% CI -0.017 to 0.039;  $p = 0.434$ ) (see Table 6).

### Patient perception: glaucoma getting worse

At baseline, 95 out of 208 (45.7%) participants in the trabeculectomy arm and 76 out of 209 (36.4%) participants in the medical management arm perceived that their glaucoma was getting worse. At the later follow-up time points, this proportion decreased in both study arms. At 12 months, 38 out of 207 (18.4%) participants in the trabeculectomy arm and 57 out of 199 (27.3%) participants in the medical management arm perceived that their glaucoma was getting worse [relative risk (RR) 0.59, 95% CI 0.38 to 0.91;  $p = 0.018$ ]. At 24 months, the RR was 0.70 (95% CI 0.46 to 1.07;  $p = 0.099$ ) (see Table 6).

### Intraocular pressure

At baseline, the mean IOP was 19.40 mmHg in the trabeculectomy arm and 19.05 mmHg in the medical management arm. At later time points, the mean IOP decreased, with lower IOP in the trabeculectomy arm at all follow-up time points. Figure 5 shows the mean and SD over time. At 24 months, the mean IOP was 12.40 mmHg in the trabeculectomy arm and 15.07 mmHg in the medical management arm (mean difference -2.75, 95% CI -3.84 to -1.66;  $p < 0.001$ ) (see Table 6). The Dunnett's multiplicity  $p$ -value was also  $< 0.001$  for all time points. The sensitivity analysis incorporating data from the non-index eye for participants with bilateral disease (see Appendix 3, Table 30) showed similar results.

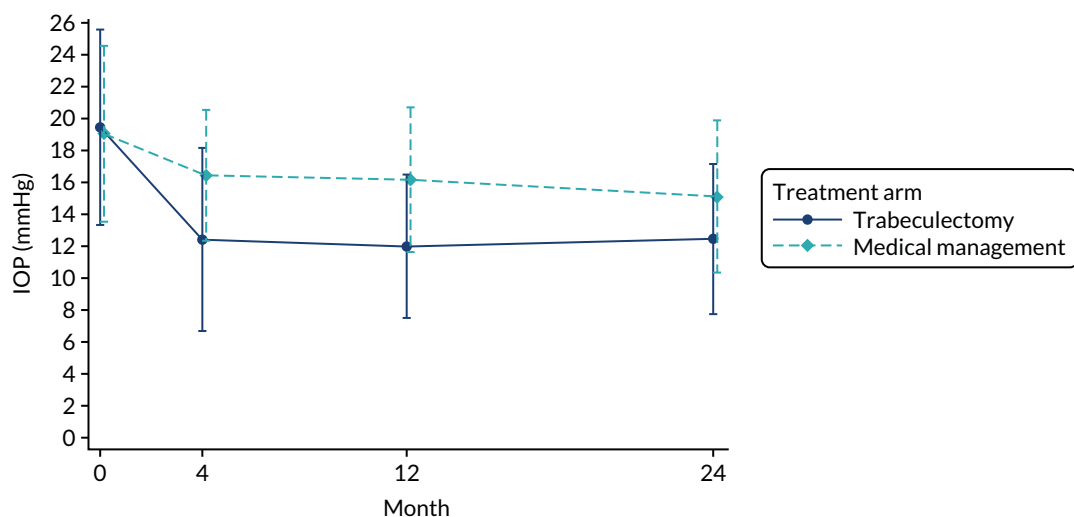


FIGURE 5 Mean (SD) IOP by arm over time. The SD values are at the end point of the vertical lines.

### LogMAR visual acuity

At 4 and 24 months, there was evidence of a difference in logMAR VA in favour of medical management (MD at 24 months 0.07, 95% CI 0.02 to 0.11;  $p = 0.006$ ) (see Table 6). The Dunnett's multiplicity  $p$ -value was 0.002 for 4 months, 0.483 for 12 months and 0.061 for 24 months. The sensitivity analysis incorporating data from the non-index eye for participants with bilateral disease showed similar results (see Appendix 3, Table 30).

### Visual fields mean deviation

At 24 months, the mean VFMD was  $-15.15$  in the trabeculectomy arm and  $-15.42$  in the medical management arm, with no evidence of a difference between arms [mean difference 0.18, 95% CI  $-0.58$  to  $0.94$ ;  $p = 0.645$ ] (see Table 6). Two sensitivity analyses were carried out. The first included only SITA standard VF (excluding SITA fast) and the second removed participants who had only one VF or for whom the false positive standard was  $> 15\%$  required for reliability. Overall, the results were similar (see Appendix 3, Table 31). The sensitivity analysis incorporating data from the non-index eye for participants with bilateral disease showed similar results (see Appendix 3, Table 30).

### Need for cataract surgery

Over the course of the trial, 28 out of 222 participants (12.6%) in the trabeculectomy arm and 27 out of 221 participants (12.2%) in the medical management arm needed cataract surgery, with no evidence of a difference between arms (RR 0.98, 95% CI 0.50 to 1.95;  $p = 0.963$ ) at 24 months (see Table 6).

### Visual standards for driving (pass/no defects)

At 24 months, 167 out of 187 participants (89.3%) in the trabeculectomy arm and 168 out of 188 participants (89.4%) in the medical management arm passed the visual driving standards, with no evidence of a difference between arms (RR 1.01, 95% CI 0.81 to 1.25;  $p = 0.951$ ) (see Table 6).

### Registered as sight impaired at 24 months

At 24 months, 4 out of 186 participants (2.2%) in the trabeculectomy arm and 0 out of 184 participants (0%) in the medical management arm were registered as sight impaired, with the difference between the arms having a  $p$ -value of 0.123 (see Table 6). In addition, we also recorded whether or not participants were eligible to be registered (see Table 6 and Appendix 3, Table 32, for baseline data). At baseline, 10 participants (94.3%) in the trabeculectomy arm were sight impaired and three participants (1.3%) were severely sight impaired. In the medical management arm, 12 participants (5.3%) were sight impaired at baseline and two participants (0.9%) were severely sight impaired. At 24 months, the results were similar.



## Safety

A safety event is defined as either a SAE or an AE.

### By allocation

The number of participants who experienced a safety event during the 24-month follow-up was 88 (38.8%) in the trabeculectomy arm and 100 (44.2%) in the medical management arm (RR 0.88, 95% CI 0.66 to 1.17;  $p = 0.366$ ). The number of participants who experienced a SAE was 12 out of 226 (5.3%) participants in the trabeculectomy arm and 8 out of 226 (3.5%) participants in the medical management arm. One participant in the trabeculectomy arm had two SAEs. *Table 7* provides further details of the safety events throughout the follow-up period. *Appendix 3, Table 34*, shows details for the non-index eye.

TABLE 7 Safety events, as allocated, ocular events for index eye

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of participants with a safety event, n (%)	88 (38.8), adjusted risk ratio 0.88	100 (44.2), 95% CI 0.66 to 1.17; $p = 0.366$
<b>SAE</b>		
Number of participants, n/N (%)	12/226 (5.3)	8/226 (3.5)
Number of events (n)	13	8
<b>Details (n)</b>		
Death	5	4
Life-threatening	–	1
Hospitalisation	3	4
Significant disability	2	–
Important condition	3	1
Expected event	3	2
<b>Classification (n)</b>		
General medical (death)	2	4
Unclassified (death)	3	–
General medical	2	3
Related to glaucoma surgery	3	1
General ophthalmology	1	–
Non-glaucoma vision loss	1	–
Glaucoma progression despite treatment	1	–
<b>4 months</b>		
Number of participants, n/N (%)	49/217 (22.6)	45/220 (20.5)
Number of events (n)	63	54
<b>Details (n)</b>		
Shallow anterior chamber	3	–
Early bleb leak	10	–
Corneal epithelial defect	2	–

continued

TABLE 7 Safety events, as allocated, ocular events for index eye (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Conjunctival buttonhole	2	-
Hyphaema	4	-
Choroidal effusion	6	-
Suprachoroidal haemorrhage	1	-
Hypotony requiring intervention	6	-
Late bleb leak	1	-
Ptosis	2	-
Drop related	9	39
Ocular surface related	9	11
Potential AE related to surgery	1	-
Non-specific	6	3
Glaucoma progression	1	1
<b>12 months</b>		
Number of participants, n/N (%)	35/216 (16.2)	43/211 (20.4)
Number of events (n)	43	48
Details (n)		
Irreversible loss of $\geq 10$ ETDRS letters <sup>a</sup>	1	-
Shallow anterior chamber	3	-
Early bleb leak	1	2
Persistent uveitis	1	-
Conjunctival button hole	1	-
Choroidal effusion	2	-
Suprachoroidal haemorrhage	1	-
Hypotony requiring intervention	3	1
Late bleb leak	1	-
Blebitis	1	-
Ptosis	3	-
Non-specific unrelated uveitis	1	-
Drop related	4	29
Ocular surface related	12	11
Potential AE	2	-
Non-specific	5	4
Cataract	1	1
<b>24 months</b>		
Number of participants, n/N (%)	30/211 (14.2)	41/208 (19.7)
Number of events (n)	33	53
Details (n)		

TABLE 7 Safety events, as allocated, ocular events for index eye (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Irreversible loss of $\geq 10$ ETDRS letters <sup>a</sup>	2	–
Shallow anterior chamber	1	2
Early bleb leak	1	1
Corneal epithelial defect	1	–
Macular oedema	–	1
Choroidal effusion	1	2
Hypotony requiring intervention	2	2
Late bleb leak	2	–
Blebitis	1	–
Endophthalmitis <sup>a</sup> – endogenous	1	–
Endophthalmitis <sup>a</sup> – bleb related	–	1
Ptosis	–	1
Drop related	5	15
Ocular surface related	8	15
Potential AE related to surgery	–	1
Non-specific	8	10
Glaucoma progression	–	1
Cataract	–	1

<sup>a</sup> Also recorded as a SAE.

Three participants who received trabeculectomy had irreversible loss of  $\geq 10$  ETDRS letters:

Case 1 – at baseline the patient's IOP was 62 mmHg (VFMD = –24.78 dB, logMAR = 70 letters). The patient underwent trabeculectomy and was followed up routinely afterwards. At 24 months, the logMAR VA had fallen to 16 owing to glaucoma progression. The patient had lost 54 letters of vision.

Case 2 – at baseline the patient's IOP was 26 mmHg (VFMD = –21.5 dB, logMAR = 82 letters). The patient underwent trabeculectomy and was followed up routinely afterwards. At 24 months, the logMAR VA had fallen to 69 owing to glaucoma progression. The patient had lost 13 letters of vision.

Case 3 – at baseline the patient's IOP was 24 mmHg (VFMD = –24.08 dB, logMAR = 80 letters). The patient underwent trabeculectomy and as followed up routinely afterwards. At 12 months, VA recorded at hand movements with IOP 12 mmHg. The participant died before the 24-month visit. The PI reported vision loss owing to central serous retinopathy unresponsive to treatment.

One participant developed a bleb-related endophthalmitis:

Case 1 – the patient was allocated to the medical management arm but underwent trabeculectomy for uncontrolled IOP. The patient developed a bleb-related endophthalmitis. A vitreous fluid sample obtained by vitreous tap grew *Staphylococcus aureus*. The patient was given intravitreal antibiotics and made a full recovery. At 24 months VFMD was –3.75 dB, VA was 78 and IOP was 13 mmHg, and the patient did not require eye drops.

One patient also developed an endogenous endophthalmitis unrelated to their glaucoma surgery:

Case 2 – the patient was allocated to the trabeculectomy arm and underwent left eye trabeculectomy in 2016. The patient then developed endophthalmitis in the absence of either a bleb leak or blebitis 21 months later. The patient was admitted, underwent a vitreous tap and was treated with intravitreal antibiotics. A diagnosis of endogenous endophthalmitis was made. The patient was diabetic, and a foot ulcer was believed to be the source of the infection. The patient made a full recovery with no visual loss. At 24 months, VFMD was -14.0, VA was 75 and IOP was 20 mmHg, and the patient required two types of eye drop.

### By treatment received

During the 24-month follow-up period, 101 out of 240 participants (42.1%) who received trabeculectomy and 87 out of 213 participants (40.8%) who received medical management had a safety event (RR 1.03, 95% CI 0.77 to 1.37;  $p = 0.850$ ).

The number of participants who had a SAE was 12 out of 239 (5.0%) in the trabeculectomy arm and 8 out of 213 (3.8%) in the medical management arm. One participant in the trabeculectomy arm had two SAEs.

At 4 months, the number of participants who had experienced an AE was 55 out of 234 (23.5%) in the trabeculectomy arm and 39 out of 203 (19.2%) in the medical management arm. At 12 months, the number of participants who had experienced an AE was 38 out of 233 participants (16.3%) who received trabeculectomy and 40 out of 194 participants (20.6%) who received medical management. At 24 months, the number of participants who had experienced an AE was 38 out of 228 participants (16.7%) who received trabeculectomy and 33 out of 191 participants (17.3%) who received medical management. *Table 8* provides further details of the safety events throughout the follow-up. *Appendix 3, Table 33*, shows details for the non-index eye.

TABLE 8 Safety events, as treated, ocular events for index eye

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of patients receiving treatment (n)	240	213
Number of participants with a safety event, n (%)	101 (42.1) adjusted RR 1.03	87 (40.8), 95% CI 0.77 to 1.37; $p = 0.850$
<b>SAE</b>		
Number of participants, n/N (%)	12/239 (5.0)	8/213 (3.8)
Number of events (n)	13	8
Details (n)		
Death	4	5
Life-threatening	-	1
Hospitalisation	4	3
Significant disability	2	-
Important condition	3	1
Expected event	4	1
Classification (n)		
General medical (death)	3	3
Unclassified (death)	1	2
General medical	2	3

TABLE 8 Safety events, as treated, ocular events for index eye (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Related to glaucoma surgery	4	–
General ophthalmology	1	–
Non-glaucoma vision loss	1	–
Glaucoma progression despite treatment	1	–
<b>4 months</b>		
Number of participants, n/N (%)	55/234 (23.5)	39/203 (19.2)
Number of events (n)	71	46
Details (n)		
Shallow anterior chamber	3	–
Early bleb leak	10	–
Corneal epithelial defect	2	–
Conjunctival button hole	2	–
Hyphaema	4	–
Choroidal effusion	6	–
Suprachoroidal haemorrhage	1	–
Hypotony requiring intervention	6	–
Late bleb leak	1	–
Ptosis	2	–
Drop related	23	25
Ocular surface related	3	18
Potential AE	1	–
Non-specific	6	3
Glaucoma progression	1	1
<b>12 months</b>		
Number of participants, n/N (%)	38/233 (16.3)	40/194 (20.6)
Number of events (n)	48	43
Details (n)		
Irreversible loss of $\geq 10$ ETDRS letters <sup>a</sup>	1	–
Shallow anterior chamber	3	–
Early bleb leak	3	–
Persistent uveitis	1	–
Conjunctival buttonhole	1	–
Choroidal effusion	2	–
Suprachoroidal haemorrhage	1	–
Hypotony requiring intervention	4	–
Late bleb leak	1	–
Blebitis	1	–

continued

TABLE 8 Safety events, as treated, ocular events for index eye (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Ptosis	3	-
Non-specific unrelated uveitis	-	1
Drop related	5	28
Ocular surface related	14	9
Potential AE related to surgery	2	-
Non-specific	4	5
Cataract	1	1
<b>24 months</b>		
Number of participants, n/N (%)	38/228 (16.7)	33/191 (17.3)
Number of events (n)	47	39
Details (n)		
Irreversible loss of $\geq 10$ ETDRS letters <sup>a</sup>	2	-
Shallow anterior chamber	3	-
Early bleb leak	2	-
Corneal epithelial defect	1	-
Macular oedema	1	-
Choroidal effusion	3	-
Hypotony requiring intervention	4	-
Late bleb leak	2	-
Blebitis	1	-
Endophthalmitis: <sup>a</sup> endogenous	1	-
Endophthalmitis: <sup>a</sup> bleb related	1	-
Ptosis	1	-
Drop related	3	17
Ocular surface related	13	10
Potential AE related to surgery	1	0
Non-specific	8	10
Glaucoma progression	-	1
Cataract	-	1
a Also recorded as a SAE.		

### Antiglaucoma medication

Table 9 shows the prescribed antiglaucoma medication agents as allocated. The mean number of glaucoma eye drop agents at 4 months was 0.43 (SD 0.79) in the trabeculectomy arm and 1.77 (SD 0.92) in the medical management arm. At 12 months, the mean was 0.34 (SD 0.79) and 1.78 (SD 1.01) and at 24 months the mean was 0.47 (SD 0.92) and 1.64 (SD 1.15) for the trabeculectomy and medical management arm, respectively. The majority of participants used prostaglandin analogue and beta-blocker.

TABLE 9 Antiglaucoma medication in index eye, by treatment allocated

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>4 months</b>		
Number of participants, <i>n</i>	217	220
Number of glaucoma eye drops, mean (SD)	0.43 (0.79)	1.77 (0.92)
Number of participants receiving eye drops, <i>n</i> (%)	61 (28.1)	210 (95.5)
Glaucoma eye drop type, <i>n</i> (%)		
Prostaglandin analogue	57 (26.3)	205 (93.2)
Beta-blocker	22 (10.1)	91 (41.4)
Carbonic anhydrase inhibitor	13 (6.0)	75 (34.1)
$\alpha$ -agonist	1 (0.5)	18 (8.2)
Pilocarpine	1 (0.5)	0 (0)
Diamox	2 (0.9)	1 (0.5)
<b>12 months</b>		
Number of participants, <i>n</i>	216	211
Number of glaucoma eye drops, mean (SD)	0.34 (0.79)	1.78 (1.01)
Number of participants receiving eye drops, <i>n</i> (%)	41 (19.0)	188 (89.1)
Glaucoma eye drop type, <i>n</i> (%)		
Prostaglandin analogue	38 (17.6)	182 (86.3)
Beta-blocker	22 (10.2)	98 (46.4)
Carbonic anhydrase inhibitor	14 (6.5)	76 (36.0)
$\alpha$ -agonist	0 (0)	19 (9.0)
Pilocarpine	0 (0)	1 (0.5)
Diamox	2 (0.9)	0 (0)
<b>24 months</b>		
Number of participants, <i>n</i>	211	208
Number of glaucoma eye drops, mean (SD)	0.47 (0.92)	1.64 (1.15)
Number of participants receiving eye drops, <i>n</i> (%)	53 (25.1)	163 (78.4)
Glaucoma eye drop type, <i>n</i> (%)		
Prostaglandin analogue	43 (20.4)	154 (74.0)
Beta-blocker	30 (14.2)	91 (43.8)
Carbonic anhydrase inhibitor	22 (10.4)	76 (36.5)
$\alpha$ -agonist	4 (1.9)	18 (8.7)
Pilocarpine	0 (0)	2 (1.0)
Diamox	1 (0.5)	1 (0.5)

SD, standard deviation.

Table 10 shows the antiglaucoma medication agents prescribed by as treated. At 24 months, the mean number of antiglaucoma eye drops was 0.29 (SD 0.72) for those who received trabeculectomy and 1.96 (SD 0.98) for those who received medical management.

TABLE 10 Antiglaucoma medication in index eye, by treatment received

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of patients receiving treatment (n)	240	213
<b>4 months</b>		
Number of participants, n	234	203
Number of glaucoma eye drops, n; mean (SD)	234; 0.55 (0.95)	203; 1.74 (0.85)
Number of participants receiving eye drops, n (%)	71 (30.3)	200 (98.5)
Glaucoma eye drop type, n (%)		
Prostaglandin analogue	65 (27.8)	197 (97.0)
Beta-blocker	32 (13.7)	81 (39.9)
Carbonic anhydrase inhibitor	29 (12.4)	59 (29.1)
$\alpha$ -agonist	2 (0.9)	17 (8.4)
Pilocarpine	1 (0.4)	0 (0)
Diamox	1 (0.4)	2 (1.0)
<b>12 months</b>		
Number of participants, n	233	194
Number of glaucoma eye drops, n; mean (SD)	233; 0.38 (0.89)	194; 1.87 (0.88)
Number of participants receiving eye drops, n (%)	41 (17.6)	188 (96.9)
Glaucoma eye drop type, n (%)		
Prostaglandin analogue	35 (15.0)	185 (95.4)
Beta-blocker	24 (10.3)	96 (49.5)
Carbonic anhydrase inhibitor	26 (11.2)	64 (33.0)
$\alpha$ -agonist	3 (1.3)	16 (8.2)
Pilocarpine	0 (0)	1 (0.5)
Diamox	1 (0.4)	1 (0.5)
<b>24 months</b>		
Number of participants, n	228	191
Number of glaucoma eye drops, n; mean (SD)	228; 0.29 (0.72)	191; 1.96 (0.98)
Number of participants receiving eye drops, n (%)	37 (16.2)	179 (93.7)
Glaucoma eye drop type, n (%)		
Prostaglandin analogue	27 (11.8)	170 (89.0)
Beta-blocker	18 (7.9)	103 (53.9)
Carbonic anhydrase inhibitor	18 (7.9)	80 (41.9)
$\alpha$ -agonist	2 (0.9)	20 (10.5)
Pilocarpine	0 (0)	2 (1.0)
Diamox	1 (0.4)	1 (0.5)
SD, standard deviation.		



Appendix 3, Table 36, shows the antiglaucoma medication prescribed for the non-index eye.

Appendix 3, Tables 37 and 38, show the number of different bottles of medication as allocated and as treated, respectively.

### Other trabeculectomy interventions

Table 11 shows details of other trabeculectomy interventions for those who received a trabeculectomy and were followed up. The total number of participants who received any intervention was 123 out of 200 (61.5%) in the trabeculectomy arm and 26 out of 39 (66.7%) in the medical management arm. The median time to the first intervention was 8 [interquartile range (IQR) 6–27] days in the trabeculectomy arm and 11 (IQR 7–19) days in the medical management arm, with the majority of participants receiving a massage or releasable release.

### Non-index eye

A post hoc analysis looked at IOP (mmHg), logMAR and VFMD for the non-index eye (see Appendix 3, Table 35).

TABLE 11 Other trabeculectomy interventions

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of patients who received trabeculectomy and were followed up (n)	200	39
<b>Any intervention</b>		
Number of participants who received intervention, n (%)	123 (61.5)	26 (66.7)
Number of interventions received, n (%)		
0	77 (38.5)	13 (33.3)
1	29 (14.5)	9 (23.1)
2	23 (11.5)	4 (10.3)
≥ 3	71 (35.5)	13 (33.3)
Time to first intervention (days)		
Mean (SD); (min., max.)	27 (50); (1, 322)	19 (28); (1, 112)
Median (IQR)	8 (6–27)	11 (7–19)
<b>Bleb massage</b>		
Number of participants who received intervention, n (%)	70 (35.0)	12 (30.8)
Number of interventions received, n (%)		
0	130 (65.0)	27 (69.2)
1	32 (16.0)	8 (20.5)
2	17 (8.5)	2 (5.1)
≥ 3	21 (10.5)	2 (5.1)
Time to first intervention (days)		
Mean (SD); (min., max.)	10 (15); (1, 82)	11 (9); (1, 29)
Median (IQR)	7 (1–8)	8 (7–19)

continued

TABLE 11 Other trabeculectomy interventions (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>Suture adjustment</b>		
Number of participants who received intervention, n (%)	5 (2.5)	1 (2.6)
Number of interventions received, n (%)		
0	195 (97.5)	38 (97.4)
1	3 (1.5)	1 (2.6)
2	2 (1.0)	
Time to first intervention (days)		
Mean (SD); (min., max.)	64 (117); (4, 274)	
Median (IQR)	15 (13–16)	
<b>Suture lysis release</b>		
Number of participants who received intervention, n (%)	10 (5.0)	2 (5.1)
Number of interventions received, n (%)		
0	190 (95.0)	37 (94.9)
1	7 (3.5)	2 (5.1)
2	1 (0.5)	
≥ 3	2 (1.0)	
Time to first intervention (days)		
Mean (SD); (min., max.)	28 (14); (15, 50)	21 (-); (21, 21)
Median (IQR)	24 (15–37)	21 (21–21)
<b>Releasable suture release</b>		
Number of participants who received intervention, n (%)	63 (31.5)	15 (38.5)
Number of interventions received, n (%)		
0	137 (68.5)	24 (61.5)
1	28 (14.0)	10 (25.6)
2	27 (13.5)	5 (12.8)
≥ 3	8 (4.0)	
Time to first intervention (days)		
Mean (SD); (min., max.)	22 (20); (1, 106)	17 (12); (1, 36)
Median (IQR)	15 (8–31)	15 (8–25)
<b>Unknown suture release</b>		
Number of participants who received intervention, n (%)	3 (1.5)	
Number of interventions received, n (%)		
0	197 (98.5)	39 (100.0)
1	1 (0.5)	
2	0	0 (-)
≥ 3	2 (1.0)	

TABLE 11 Other trabeculectomy interventions (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Time to first intervention (days)		
Mean (SD); (min., max.)	12 (8); (8, 21)	
Median (IQR)	8 (8-21)	
<b>5-FU injection</b>		
Number of participants who received intervention, n (%)	26 (13.0)	8 (20.5)
Number of interventions received, n (%)		
0	174 (87.0)	31 (79.5)
1	15 (7.5)	7 (17.9)
2	7 (3.5)	1 (2.6)
≥ 3	4 (2.0)	
Time to first intervention (days)		
Mean (SD); (min., max.)	60 (86); (1, 391)	62 (62); (21, 171)
Median (IQR)	29 (15-53)	36 (26-56)
<b>Steroid injection</b>		
Number of participants who received intervention, n (%)	19 (9.5)	5 (12.8)
Number of interventions received, n (%)		
0	181 (90.5)	34 (87.2)
1	12 (6.0)	2 (5.1)
2	5 (2.5)	1 (2.6)
≥ 3	2 (1.0)	2 (5.1)
Time to first intervention (days)		
Mean (SD); (min., max.)	25 (15); (7, 60)	19 (-); (19, 19)
Median (IQR)	19 (15-34)	19 (19-19)
<b>Needling plus 5-FU injection</b>		
Number of participants who received intervention, n (%)	31 (15.5)	8 (20.5)
Number of interventions received, n (%)		
0	169 (84.5)	31 (79.5)
1	18 (9.0)	7 (17.9)
2	9 (4.5)	
≥ 3	4 (2.0)	1 (2.6)
Time to first intervention (days)		
Mean (SD); (min., max.)	70 (75); (15, 322)	70 (60); (7, 150)
Median (IQR)	40 (30-67)	71 (17-105)

continued

TABLE 11 Other trabeculectomy interventions (continued)

Measure	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>Bleb resuturing</b>		
Number of participants who received intervention, n (%)	5 (2.5)	1 (2.6)
Number of interventions received, n (%)		
0	195 (97.5)	38 (97.4)
1	5 (2.5)	1 (2.6)
Time to first intervention (days)		
Mean (SD); (min., max.)	93 (75); (30, 188)	
Median (IQR)	78 (33–154)	
<b>Anterior chamber reformation</b>		
Number of participants who received intervention, n (%)	5 (2.5)	1 (2.6)
Number of interventions received, n (%)		
0	195 (97.5)	38 (97.4)
1	5 (2.5)	1 (2.6)
Time to first intervention (days)		
Mean (SD); (min., max.)	33 (32); (3, 71)	
Median (IQR)	22 (6–63)	
<b>Bleb revision</b>		
Number of participants who received intervention, n (%)	7 (3.5)	2 (5.1)
Number of interventions received, n (%)		
0	193 (96.5)	37 (94.9)
1	7 (3.5)	2 (5.1)
Time to first intervention (days)		
Mean (SD); (min., max.)	93 (54); (28, 156)	112 (-); (112, 112)
Median (IQR)	95 (53–134)	112 (112–112)
<b>Other interventions</b>		
Number of participants who received intervention, n (%)	25 (12.5)	2 (5.1)
Number of interventions received, n (%)		
0	175 (87.5)	37 (94.9)
1	25 (12.5)	2 (5.1)
Time to first intervention (days)		
Mean (SD); (min., max.)	95 (104); (17, 331)	33 (15); (22, 43)
Median (IQR)	43 (28–126)	33 (22–43)

5-FU, 5 fluorouracil; IQR, interquartile range; max., maximum; min., minimum; SD, standard deviation.

# Chapter 5 Discrete choice experiment

## Introduction

A DCE was undertaken to estimate the value that individuals with advanced glaucoma place on different health states associated with glaucoma (the approach is outlined in *Methods*) and to update the GUI QoL weights estimated by Burr *et al.*<sup>55</sup> The GUI QoL weights needed to be updated for this population because the preferences of those with advanced glaucoma were under-represented in the Burr *et al.*<sup>55</sup> study, with only 15% of the sample self-reporting severe glaucoma. Given that the severity of disease was not standardised, this could result in variations between participants, including some over-reporting their severity, thus diluting the preferences of those with advanced glaucoma. Furthermore, Burr *et al.*<sup>55</sup> found that individuals' preferences changed depending on the severity of disease reported, hence the need to re-estimate the GUI utility weights based on the preferences of those with advanced glaucoma.

A selection of attributes (symptoms) and attribute levels (severity of symptoms), which can be found in the Glaucoma Profile Instrument (GPI), informed the health state profiles. The GPI is a disease-specific QoL measure that was used to develop health state profiles for glaucoma.<sup>55</sup> These health state profiles were used in the DCE valuation study to estimate QoL weights that could be used to estimate QALYs in the economic evaluation reported in *Chapter 6*.

The aim of the DCE was to identify the relative importance of each attribute and attribute level of the GPI based on the preferences of individuals with advanced glaucoma by asking participants to choose between two health state profiles. It was expected that the values for each health state profile presented to participants would vary depending on the attribute levels presented. Similar to Burr *et al.*,<sup>55</sup> the results of the model estimation were to be used to estimate preference-based weights for the GPI health state profiles in a population with advanced glaucoma.<sup>55</sup> These QoL weights were then incorporated into the economic evaluation to evaluate the cost-effectiveness of the surgical management of glaucoma compared with medical management (see *Chapter 6*).

## Methods

Discrete choice experiments have been used to elicit values in different areas of economics, including transport and environmental, with increasing focus on these methods in health to elicit individuals' preferences for products, services and health states.<sup>55,81-83</sup> A DCE is a type of conjoint analysis and is based on random utility theory.<sup>84</sup> In a DCE, individuals are asked to choose the best (or worst) alternative between at least two alternatives that have the same attributes but differing levels. Respondents are expected to act rationally when evaluating the alternatives and to choose the alternative that maximises their expected utility (i.e. satisfaction).<sup>85</sup> Logistic regression techniques are used to identify the relative importance of attributes and attribute levels on an individual's utility function.

There are four stages involved in undertaking a DCE:

- stage 1 – identification of attributes and levels
- stage 2 – creating an efficient design
- stage 3 – data collection
- stage 4 – data analysis and interpretation.

### **Stage 1: identification of attributes and levels**

The attributes and levels used in the DCE were informed by the GPI developed by Burr *et al.*<sup>55</sup> The work of Burr *et al.*<sup>55</sup> involved using a DCE to estimate the preference weights for the glaucoma utility index (GUI).<sup>55</sup> Briefly, Burr *et al.*<sup>55</sup> considered a wide range of potentially relevant attributes and levels that could be used to define a range of glaucoma health state profiles. These were identified using established glaucoma QoL instruments and expert opinion. These attributes and levels were refined using qualitative research methods (focus groups) with individuals with glaucoma. The attributes identified as important to individuals with glaucoma were central and near vision, lighting and glare, mobility, activities of daily living, eye discomfort, and other effects of glaucoma and its treatment. Each of these six attributes had the same four levels: no difficulty, some difficulty, a lot of difficulty or severe difficulty.<sup>55</sup> These six attributes with their corresponding levels were used to inform the health state profiles valued in the DCE.

### **Stage 2: creating an efficient design**

The combinations of all attributes ( $n = 6$ ) and levels ( $n = 4$ ) from the GPI generates 4096 possible health state profiles (4<sup>7</sup>). In the DCE, participants were asked their preference between two of these health state profiles (a choice-set question); however, asking participants to choose between all possible combinations of these health state profiles would be too onerous and not feasible. As with all DCEs, an experimental design was used so that the number of choice-set questions being valued was manageable and the main effects and higher-order interactions could still be estimated in the logistic regression.<sup>86</sup> The experimental design used by Burr *et al.*<sup>55</sup> was not used in the DCE conducted as part of TAGS because the design methodology has developed since that work was conducted.<sup>55</sup> For the current study, the experimental design followed best practice guidelines and a D-efficient design was used to identify the most efficient combination of choice-set questions.<sup>86,87</sup> The D-efficient design was produced using Ngene design software (ChoiceMetrics Pty Ltd, Sydney, NSW, Australia) and the design chosen was the best design that minimised the standard errors.<sup>86</sup>

The design was split into four blocks to maximise variance in the data, and each participant was randomly allocated to one block and presented with 15 choice-set questions. Only participants who had not withdrawn from TAGS follow-up or who had not died during the study were included in the block randomisation. *Figure 6* is an illustrative example of a choice-set question that participants were asked to answer.

### **Questionnaire design**

A paper-based questionnaire was developed for each of the blocks and included the following sections (see *Report Supplementary Material 1*):

- An introduction and explanation of the choice-set questions, with an illustrative example.
- Fifteen choice-set questions, from which the participant had to choose the health state profile that they considered to be worse.
- An 'about you' section that included information on level of education and annual household income, which was not collected as part of the main study.
- A comments box where participants were asked to provide any comments they had on the questionnaire and an approximation of how long it took them to complete the questionnaire. This section was included to gauge how difficult participants found completing the choice-set questions.

### **Stage 3: data collection**

The paper-based questionnaire and guide to completing the DCE were sent to participants, who were randomly allocated to one of the four blocks at 27 months post randomisation, 3 months after their final study visit. The randomisation was adjusted to ensure that equal numbers of respondents were randomised to each block at the end. A freepost envelope was provided for participants to return the completed questionnaire. After 3 weeks, a reminder was sent to participants who had not returned the questionnaire.

<b>Question 1 Which situation is worse for you?</b>	
<b><u>SITUATION A</u></b>	<b>SITUATION B</b>
<p><b>No difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Central and near vision</li> <li>• Local eye discomfort</li> </ul> <p><b>Some difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Activities of daily living</li> <li>• The effects of glaucoma and its treatment</li> </ul> <p><b>Severe difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Mobility</li> <li>• Lighting and glare</li> </ul>	<p><b>Some difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Lighting and glare</li> <li>• Mobility</li> </ul> <p><b>Quite a lot of difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Activities of daily living</li> <li>• Local eye discomfort</li> </ul> <p><b>Severe difficulty with:</b></p> <ul style="list-style-type: none"> <li>• Central and near vision</li> <li>• The effects of glaucoma and its treatment</li> </ul>
<b>(Tick one box only)</b>	
<b>Situation A</b> <input type="checkbox"/>	<b>Situation B</b> <input type="checkbox"/>

FIGURE 6 Example of a choice-set question.

#### Stage 4: data analysis and interpretation

The data were analysed in Stata® version 15 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used to describe the demographic characteristics of the full sample, responders and non-responders to identify any potential differences between responders and non-responders. Descriptive statistics were also used to identify any potential differences in demographic and socioeconomic characteristics (i.e. income and education) between participants in each of the four blocks.

The DCE was analysed under a random utility framework. Logistic regression techniques, specifically a conditional regression logistic model, were used to analyse participants' stated preference for each choice-set question and quantify the relative importance of each attribute and attribute level.<sup>84</sup> A base category (i.e. severe difficulty) was selected for each attribute and against which the other levels of that attribute were compared; hence, 18 explanatory variables (six attributes × three levels) were included in the model. It was hypothesised that each attribute level would be positive compared with the severe difficulty level and that the coefficients would increase with improvements in difficulty. Given that all six attributes had the same levels, comparisons could be made across the attributes and the attribute levels could be ranked in order of preference.

### Preference-based weights

As previously mentioned, the GPI represents 4096 possible health state profiles. Each health state profile could be classified by the levels for each attribute (1 = no difficulty, 2 = some difficulty, 3 = quite a lot of difficulty and 4 = severe difficulty), similarly to the EQ-5D-5L classification system.<sup>88</sup> The QoL weights were based on the QoL scale of 1 (perfect health) and 0 (severe difficulty in all of the attributes). The results of the logistic regression model were converted into preference-based weights on the assumption that the health state profile 111111 (having no difficulty with any of the attributes) was equivalent to perfect health score of 1. The coefficients associated with the other attribute levels were then anchored on this value to ensure that the ratio of preference for the different attribute levels was maintained in the QoL weights. It was also assumed that the health state profile 000000 (having severe difficulty with all of the attributes) was scored as zero.

### Sensitivity analysis

A sensitivity analysis adopting the methods outlined by Burr *et al.*<sup>55</sup> was undertaken when there was no evidence of a statistically significant difference in attribute levels.<sup>55</sup> The levels of an attribute that were not statistically significant according to the Wald test were combined to determine whether or not the strength of preference for that attribute improved with the increased explanatory power.<sup>55</sup>

A complete-case analysis that included participants who completed all 15 of their choice-set questions was also undertaken, as it could be argued that they had a better understanding of the task than those who only partially completed their choice-set questions.

## Results

Of the 453 participants randomised into the TAGS study, 438 were assigned a random block for the DCE study ( $n = 15$  withdrew/died). A total of 308 questionnaires (70%) were returned with the 15 choice-set questions at least partially completed. Of the 130 remaining questionnaires (30%), eight were returned with partial information provided for the demographic questions and/or with comments on why they did not complete the choice-set questions. The remaining 122 questionnaires were not returned.



### Participant characteristics

Table 12 presents a summary of the demographic characteristics of the participants in the overall sample, and Appendix 4, Table 39, presents a summary of the sociodemographics of those who responded to the questionnaire and the difference in characteristics between blocks. Participants who responded to the DCE questionnaire had a mean age of 68 years. The majority of these participants were white (91%) and male (67%), and almost half (45%) had attended college or university. Each of the income brackets was equally represented across the four blocks, with nearly half of the participants who responded to the DCE questionnaire (48%) reporting an income of  $\geq$  £20,000. The proportion of non-responders was similar across the four blocks.

### Discrete choice experiment results

Of the 308 DCE questionnaires returned and used in the analysis, 283 (92%) were fully completed with all 15 choice-set questions answered. A total of 295 participants (96%) reported how long it took them to complete the DCE questionnaire, with 286 participants providing a time in minutes or hours that could be quantified. On average, it took participants 24 minutes to complete the DCE questionnaire. A descriptive summary of the number of choice-set questions completed and the time taken to complete the questionnaire is provided in Appendix 4, Table 39.

### Regression model results

The Walt test determined that the explanatory variables were not equal to zero and should, therefore, be included in the model ( $p < 0.01$ ). The results of the conditional logit model for the full sample are presented in Table 13. The levels for four of the attributes (i.e. central and near vision, lighting and glare, mobility, and activities of daily living) and the level 'no difficulty' for the attribute 'eye discomfort' were positive compared with the base level (i.e. severe difficulty), as expected. These results suggest

TABLE 12 Baseline characteristics of responders and non-responders

Characteristic	Complete sample (N = 438)	DCE questionnaire returned (N = 308)	DCE questionnaire not returned (N = 130)
Age (years), mean (SD)	66.83 (12)	68.42 (11)	63.08 (14)
Male, n (%)	293 (67)	205 (67)	88 (68)
Ethnicity, n (%)			
White	361 (82)	280 (91)	80 (62)
Asian – Oriental	2 (< 1)	1 (< 1)	1 (< 1)
Afro-Caribbean	57 (13)	19 (6)	38 (30)
Asian (India/Pakistan/Bangladesh)	12 (3)	5 (2)	7 (5)
Mixed heritage	1 (< 1)	1 (< 1)	
Black British	2 (< 1)		2 (2)
Colombian	1 (< 1)		1 (< 1)
Nigerian	1 (< 1)	1 (< 1)	
Block allocation, n (%)			
1	107 (24)	77 (25)	30 (23)
2	118 (27)	74 (24)	44 (34)
3	107 (24)	75 (24)	32 (25)
4	106 (24)	82 (27)	24 (18)

TABLE 13 Summary of conditional logit regression exploring preferences for DCE attribute levels (n = 308)

Attribute	Level	Coefficient	SE	p-value
Central and near vision	No difficulty	0.552	0.072	0.000
	Some difficulty	0.326	0.082	0.000
	Quite a lot of difficulty	0.191	0.082	0.019
Lighting and glare	No difficulty	0.131	0.079	0.098
	Some difficulty	0.021	0.075	0.782
	Quite a lot of difficulty	0.007	0.085	0.931
Mobility	No difficulty	0.408	0.083	0.000
	Some difficulty	0.290	0.079	0.000
	Quite a lot of difficulty	0.135	0.082	0.097
Activities of daily living	No difficulty	0.352	0.076	0.000
	Some difficulty	0.415	0.071	0.000
	Quite a lot of difficulty	0.188	0.074	0.011
Eye discomfort	No difficulty	0.105	0.087	0.228
	Some difficulty	-0.118	0.088	0.180
	Quite a lot of difficulty	-0.026	0.083	0.756
Other effects of glaucoma and its treatment	No difficulty	-0.004	0.079	0.961
	Some difficulty	-0.029	0.082	0.717
	Quite a lot of difficulty	-0.096	0.080	0.231
Alternatives	Alternative A	0.070	0.031	0.22

The base category for the attributes central and near vision, lighting and glare, mobility, activities of daily living, eye discomfort, and other effects of glaucoma and its treatment was severe difficulty. The base category for alternative A was alternative B.

that participants have a preference for health state profiles that report lower levels of difficulty in these attributes. At a 95% confidence level, only three of the attributes [i.e. central and near vision (all levels), mobility (excluding the level quite a lot of difficulty) and activities of daily living (all levels)] were statistically significant, suggesting that participants had a stronger preference for improvements in these attributes than in the other attributes.

Counterintuitively, two of the levels for the attribute 'eye discomfort' and three levels for the attribute 'other effects of glaucoma and its treatment' had negative coefficients on average, suggesting that there was a negative preference (disutility) associated with improvements in these attributes compared with the base level (severe difficulty). However, there was no evidence that the preference for these attribute levels differed to the base level ( $p$ -values were 0.180 and 0.756, respectively).

Given that all of the attributes had the same levels, comparisons could be made across the attributes to identify the order of preference for the attributes and attribute levels. Improvements in 'central and near vision', 'activities of daily living' and 'mobility' yielded the most utility for participants. The attribute level with the greatest utility gain was 'no difficulty' with 'central and near vision'.

### Preference-based weights

Similarly to Burr *et al.*,<sup>55</sup> preference-based weights were estimated for each of the attribute levels so that the health state profiles generated by the GPI could be assigned a QoL weight that could be used

to estimate QALYs.<sup>55</sup> These health-related quality-of-life (HRQoL) weights, based on responses to the GPI administered at baseline and at 1, 3, 6, 12, 18 and 24 months post randomisation, were used in a sensitivity analysis in the economic evaluation (further details are shown in *Appendix 5, Table 45*).

It was assumed that attribute levels that were negative and not statistically significant had a value of zero, indicating that there was no utility to be gained from having reduced difficulty in these attributes. This assumption was made because these results did not adhere to theoretical validity (i.e. there was a negative preference associated with an improvement in the attribute level compared with severe difficulty) and there was no evidence that this value was different from zero, based on the significance levels estimated from our model. *Table 14* summaries the HRQoL weights for each attribute level and provides an illustrative example of how to estimate a value that can be used to estimate QALYs for a health profile based on the HRQoL weights.

TABLE 14 Preference-based weights

Attribute	Level	HRQoL weight
Central and near vision	No difficulty	0.356
	Some difficulty	0.211
	Quite a lot of difficulty	0.124
	Severe difficulty	0
Lighting and glare	No difficulty	0.085
	Some difficulty	0.013
	Quite a lot of difficulty	0.005
	Severe difficulty	0
Mobility	No difficulty	0.264
	Some difficulty	0.188
	Quite a lot of difficulty	0.087
	Severe difficulty	0
Activities of daily living	No difficulty	0.227
	Some difficulty	0.268
	Quite a lot of difficulty	0.121
	Severe difficulty	0
Eye discomfort	No difficulty	0.068
	Some difficulty	0
	Quite a lot of difficulty	0
	Severe difficulty	0
Other effects of glaucoma and its treatment	No difficulty	0
	Some difficulty	0
	Quite a lot of difficulty	0
	Severe difficulty	0

TABLE 14 Preference-based weights (continued)

Profile	Health state description	QoL weight
111111	No difficulty with central and near vision, lighting and glare, mobility, activities of daily living, eye discomfort, and other effects of glaucoma and its treatment	1 (0.356 + 0.085 + 0.264 + 0.227 + 0.068 + 0)
122321	No difficulty with central and near vision and other effects of glaucoma and its treatment	0.678
	Some difficulty with lighting and glare, mobility, and eye discomfort	(0.356 + 0.013 + 0.188 + 0.121 + 0 + 0)
	Quite a lot of difficulty with activities of daily living	
333223	Some difficulty with activities of daily living and eye discomfort	0.484
	Quite a lot of difficulty with central and near vision, lighting and glare, mobility, and other effects of glaucoma and its treatment	(0.124 + 0.005 + 0.087 + 0.268 + 0 + 0)

### Sensitivity analyses

A sensitivity analysis adopting the methods outlined by Burr *et al.*,<sup>55</sup> combining the levels of attribute levels that were not statistically significant, was undertaken. In this analysis, the levels of 'lighting and glare', 'eye discomfort' and 'other effects of glaucoma and its treatment' were each combined into one variable and compared with the base level for that attribute, 'severe difficulty'. In this analysis, the statistical significance of these attribute levels did not improve. However, the level 'quite a lot of problems' for the attribute 'mobility' did reach statistical significance at the 5% level. There was still a negative preference for the attribute 'other effects of glaucoma and its treatment' despite the combination of the three levels.

The model was re-estimated on a subset of the data, including only participants who completed all 15 choice-set questions ( $n = 283$ ). This analysis produced similar results to the base-case analysis in terms of the importance of the attributes and levels and the statistical significance of attributes and levels did not change in the complete-case analysis.

## Chapter 6 Economic evaluation

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The economic evaluation component of the study comprised both a within trial economic evaluation and a model-based economic evaluation to extrapolate beyond the end of the 2 years of the trial follow-up period.

### Within-trial economic evaluation

#### Introduction

An economic evaluation is defined as a comparative analysis in terms of both costs (resource use) and consequences (outcomes and effects).<sup>89</sup> For this trial, the economic evaluation was to be carried out in two parts. The first part was a 'within-trial' economic evaluation that was conducted as part of the RCT to compare the costs and benefits of both medical and surgical pathways of glaucoma management. This within-trial analysis assessed the costs and benefits at the end of the 24-month trial period based on the trial data. The second part of the economic evaluation (discussed later in this chapter) is a model-based economic evaluation, which uses existing literature and the trial results to extrapolate the results beyond the end point of the trial.

There is evidence that, for advanced presentations of glaucoma, keeping IOP lower than 17.5 mmHg and stable has a beneficial effect on visual outcome.<sup>34,90</sup> However, the relative effectiveness and cost-effectiveness of medical and surgical pathways of glaucoma management are unclear. *Chapter 4* describes the relative effectiveness of treatments. This section reports the methods and results of the within-trial economic evaluation (the model-based economic evaluation that extrapolated beyond the results of the trial is reported in the second part of this chapter).

The primary measures of effectiveness used in the economic evaluation are based on responses to the EQ-5D-5L, HUI-3 and GUI. The analysis was carried out from a health-care (NHS) perspective and from a patient perspective. NHS costs include the costs borne by the health service over the course of the trial and PSS costs (i.e. costs for local social services). Patient costs were estimated as well, and these included time and travel costs borne by the patient and those assisting participants to attend appointments in addition to any private health-care costs.

### Methods

#### Data collection

#### Health service use costs

Data on the use of secondary care health care that each patient had accessed were collected using the CRFs completed at baseline and at 4, 12 and 24 months. Primary care costs were collected using a resource utilisation questionnaire completed at 4, 12 and 24 months. This questionnaire included visits to the ophthalmology outpatient clinic, outpatient procedures and glaucoma medications that the participants have taken. Unit costs for each item were derived from published sources including the *NHS Reference Costs 2017/18*<sup>91</sup> and *Unit Costs of Health and Social Care 2018*.<sup>92</sup> The cost for medications were taken from the *British National Formulary 2018*.<sup>93</sup>

### Personal Social Services and patient costs

The 4-, 12- and 24-month patient questionnaires also measure the support services that the participant has accessed. This may include low-vision support services, support provided by the Royal National Institute for the Blind (RNIB) or travel assistance, such as bus passes or rail cards. Published costs were used to estimate the cost of these services.

Costs falling on the participants and any companions who accompanied the participants were estimated using the responses to the time and travel questionnaire, which was administered at 18 months, and information on use of health services. Travel costs were derived by asking participants to identify how they travelled to the appointments. If public transport or taxis were used, the fare would represent the individual's travel costs. If the patient drove to the appointment, the participants were asked to estimate the journey in miles and a cost for each mile was taken from the TAG data book May 2018.<sup>94</sup> The questionnaires also included questions about the length of time that travelling to and attending one of these appointments would take. The cost of the time to attend the appointments for both the participant and any accompanying caregiver was also calculated based various activity rates published by the Office for National Statistics.<sup>95</sup> Any out-of-pocket private health-care costs were also included when calculating patient time and travel costs.

## Derivation of costs

### Inpatient costs

Participants in the trial were randomised into the trabeculectomy or medical management arm of the trial. If the participants were in the trabeculectomy arm, the baseline CRF asked details about the trabeculectomy procedure. This includes the time spent in the operating theatre, the equipment used and the staff present. Two kinds of admissions were associated with the trabeculectomy procedures in this trial: a day-case admission and an overnight inpatient admission. Costs for both kinds of procedure are available in the *NHS Reference Costs 2017/18*<sup>91</sup> and are attributed to each participant who completed the surgical CRF. If the admission type was not stated, the day-case rate was assumed, as this was the most common admission for the procedure according to the *NHS Reference Costs 2017/18*.<sup>91</sup>

Those who were allocated to the medical management arm of the trial were not allocated an inpatient cost at baseline, but both treatment arms were asked about any inpatient stays or procedures on each subsequent CRF form. The patient was asked about any inpatient stays associated with a list of procedures and, if appropriate, provided admission and discharge dates so that the duration of any inpatient stay could be calculated. Both the cost of the hospital and the cost of the procedure were taken from *NHS Reference Costs 2017/18*.<sup>91</sup> Further details of unit costs for hospital appointments are provided in *Appendix 5, Table 40*.

### Outpatient costs

Secondary care outpatient costs were elicited from the CRF data collected from the 4-month visit onwards. This included both visits to the outpatient ophthalmology clinic and any necessary ophthalmological outpatient procedures. The CRF asked about outpatient-specific procedures including:

- massage
- adjustment/suture lysis/releasable release
- 5-FU injection
- steroid injection
- needling and 5-FU injections
- bleb resuturing
- anterior chamber reformation
- bleb revision
- phacoemulsification and intraocular lens.

There was also an option to include a different procedure to any of the ones named above. The number of ophthalmology outpatient appointments and the dates of attendance were collected on each CRF form. The procedures were costed using the NHS *National Reference Costs 2017/18*.<sup>96</sup> Further details of unit costs for procedures are provided in *Appendix 5, Table 41*.

### Medication costs

Medications were also captured in the CRFs. Details on the use of the following glaucoma medications were collected:

- prostaglandin analogues
- beta-blockers
- carbonic anhydrase inhibitor
- pilocarpine
- $\alpha$ -agonists
- other.

In the trabeculectomy arm of the trial, the use of pre-operative eye drops was recorded on the CRFs and costed. Medication costs were taken from the 2018 *British National Formulary*.<sup>93</sup> Drug start dates and stop dates were reported on the CRFs. If a participant started a drug before the 2-year trial period and was still taking the medication at the end of the trial, it was assumed, for costing purposes, that they were taking the drug for the entire trial period. If, however, the participant started or stopped the medication during the course of the trial, the length of time that the participant was on the drug was calculated in months and then the cost of the drug was calculated using this duration. Further details of unit costs for medications are provided in *Appendix 5, Table 42*.

### Primary care costs

Patients in the trial were asked to complete a participant questionnaire at baseline and at 1, 3, 4, 6 and 12 months. As part of the 4- and 12-month questionnaire, participants were also asked about the health-care resources that they utilised over the trial period, for example:

- GP appointments in practice
- GP appointments at home
- GP telephone appointments
- community optometry appointments
- district nurse appointments
- practice nurse appointments.

Costs for these appointments were taken from the *Unit Costs of Health and Social Care 2018*.<sup>97</sup>

The number of appointments for each of the types above was multiplied by the unit costs for each appointment. Further details of unit costs for primary care are provided in *Appendix 5, Table 43*.

### Costs to participants and their main caregiver

This study measured the travel costs that were incurred by participants when they travelled to appointments. This was measured using a dedicated time and travel questionnaire that the participant completed during the course of the study. It was originally planned to administer the questionnaire at 18 months, but, because of a change to the protocol, the questionnaire was administered at 30 months. The questionnaire asked participants to provide the average cost of a typical journey to:

- outpatient appointment
- GP appointment
- community optometrist appointments
- inpatient hospital stays.

If the journey was undertaken using public transport, the fare was used to represent travel costs. If a journey was undertaken by private car, a fuel rate of £0.45 per mile was applied based on the business and self-employed expense rate per mile.<sup>98</sup> Finally, if hospital transport was used, travel costs were estimated from the *Unit Costs of Health and Social Care 2018*.<sup>97</sup>

The costs of the time commitments of the participants and their companions were also measured in this evaluation; this was also measured in the time and travel questionnaire. Participants were asked to choose which best described how they would spend their time if they were not attending appointments to manage their glaucoma. The participant chose from one of the following:

- paid work
- homemaking
- child care
- caring for a friend/relative
- retired
- full-time education
- unemployed
- voluntary work
- leisure activities
- other (please specify).

Paid work, child care, caring for a relative or friend and voluntary work were valued at £13.88 per hour, which is the average hourly wage according to the Office for National Statistics.<sup>95</sup> Housework and leisure activities were valued at £10.10 per hour. The time spent in unemployment, retirement or full-time education was valued at £6.04 per hour. Finally, private out-of-pockets expenses reported by participants were included in the patient time and travel costs.

### Estimation of effects

#### *Estimation of quality-adjusted life-years for the cost-utility analysis*

Given that the within-trial economic evaluation is a cost-utility analysis (CUA), outcomes were measured in QALYs. QALYs were estimated from three sources: the EQ-5D-5L,<sup>99</sup> HUI-3 (because the HUI-3 does not have a UK value set, the existing Canadian value set was used<sup>100</sup>) and GUI.<sup>14</sup> The utility values for the EQ-5D-5L were mapped to an existing value set for the validated data set of results for the EQ-5D-3L.<sup>101</sup> During the course of the study, a UK value set for the EQ-5D-5L was produced,<sup>102</sup> but, given that this is currently not validated, the cross-walked values from the EQ-5D-3L data set were used in the base case and the EQ-5D-5L values were examined in a sensitivity analysis. The EQ-5D-5L instrument was administered at seven time points during the trial: baseline and 1, 3, 6, 12, 18 and 24 months. The complete-case analysis included all participants who had completed the EQ-5D-5L at all seven time points. Those who had completed the EQ-5D-5L at five of the seven time points were included (as long as one of those points was baseline) with imputed data. Some participants completed an additional EQ-5D-5L before their trabeculectomy. These values are summarised in *Appendix 6, Table 47*.

The QALYs gained was also calculated using the scores that were derived from the responses from the HUI-3 complete cases were considered to be those who had all seven time points and values were imputed for those who had four time points or more. The utility values for the GUI were derived from the results of the DCE (which are presented in *Chapter 5*).



## Analysis of costs and benefits

### Costs

A total NHS cost per participant was calculated using data from the trial. A seemingly unrelated regression (SUREG) was used to identify any difference between the trabeculectomy and the medical management arm of the trial while controlling for any modifying factors, such as the participant's age and their baseline utility score. In a further analysis, the SUREG was repeated with the inclusion of patient time and travel costs.

### Quality-adjusted life-years

As with the costs, a total QALYs gained per participant was calculated using trial data. A SUREG was used to calculate the differences between the costs and to control for modifying factors, such as baseline utility score and treatment arm.

### Missing data

Cost data were reported as missing either if the sections of the CRF reporting medications taken and procedures undertaken were completely blank (no values, positive or negative, were given in either section) or if the total costs on the CRF were reported as zero and the answer to the question 'Has participant completed the TAGS Participant Questionnaire?' was 'no', as this indicates incomplete data.

With respect to the estimation of QALYs, those who had completed four of the seven data collection surveys were included for analysis. First, to account for the missing data points, it was assumed that the previous utility remained stable. This meant that the weighted average of the two utility scores around the missing values was used to calculate the missing data. Second, multiple imputation was used to estimate missing utility values for QALY scores. No patterns were observed in the missing data, so the data were imputed randomly.<sup>103</sup>

## Sensitivity analysis

### Stochastic sensitivity analysis

To assess the robustness of the study sampling, non-parametric bootstrapping was carried out. Bootstrapping is a statistical procedure that resamples a single data set to create many simulated samples to assess statistical precision. This can model the difference in net benefit if the sampling process could be repeated many times. In this example, 1000 iterations of the bootstrapping procedure were performed. This simulation process created a sample of bootstrapped means for costs and QALYs, with distributions for each. The means and other parametric statistics were then calculated for the bootstrap distribution. Bootstrapped estimates of the difference in costs and QALYs between the experimental and the control arm were used to populate the cost-effectiveness plane (the horizontal axis represents the difference in QALYs between two interventions and the vertical axis represents the corresponding difference in costs).

A cost-effectiveness acceptability curve (CEAC) quantifying the probability that an intervention is cost-effective [based on the decision-maker's maximum willingness to pay over a range of values (e.g. £0–100,000 per QALY)] was derived from the results of the non-parametric bootstrapping.

### Deterministic sensitivity analysis

Deterministic sensitivity analysis was carried out to assess the variability of different parameters on the outcomes of the economic evaluation. The QALYs were recalculated using the utility values generated from both the HUI-3 and the GUI QoL tools to see if this changed the results. Patient time and travel costs were included to assess how these contacts have an impact on potential conclusions.

## Results

### Response rates

The response rates for the data collection instruments used in the economic evaluation are described in *Table 15*. Data completion in this trial was generally very high.

### Total resource use

The total costs for the different areas of resource use are summarised in *Table 16*. The largest cost drivers for total costs were ophthalmology outpatient appointments, prostaglandin analogue medications and, principally, the trabeculectomy procedure itself. The total costs are summarised in *Table 17* and there was evidence of a higher cost in the first year for the trabeculectomy arm, which is largely because of the costs of the trabeculectomy procedure in the first year. In the second year, there was no evidence of a difference in the cost between the arms.

The results of the analysis of QALYs gained using different QALY measures are summarised in *Table 18*. Based on the EQ-5D-5L, the QALY gain at 24 months was slightly higher in the trabeculectomy arm than in the medical management arm based on the unadjusted means. Neither the HUI-3 nor the GUI provided any evidence of a difference between arms in QALYs gained.

TABLE 15 Rates of completion of data collection instruments in each arm at each time point

Time point	Treatment arm, % (n)	
	Trabeculectomy	Medical management
<b>Case report form</b>		
4 months	99 (226)	99 (223)
12 months	99 (226)	100 (226)
24 months	96 (217)	97 (219)
<b>EQ-5D-5L</b>		
Baseline	98 (222)	98 (222)
1 month	85 (194)	90 (203)
3 months	82 (186)	79 (179)
6 months	82 (186)	86 (195)
12 months	93 (211)	92 (209)
18 months	80 (181)	81 (184)
24 months	91 (206)	90 (203)
<b>Resource use questionnaire</b>		
4-months	93 (210)	96 (216)
12 months	94 (213)	92 (208)
24 months	92 (208)	90 (204)
<b>Time and travel questionnaire</b>		
30 months	68 (154)	65 (148)

TABLE 16 Breakdown of resource costs across 2 years

Resource	Total cost per treatment arm (£)					
	Trabeculectomy			Medical management		
	Mean	Median	SD	Mean	Median	SD
GP surgery consultations	26	0	103	13	0	34
GP home consultations	3	0	20	2	0	18
GP telephone consultations	22	0	63	32	0	97
Practice nurse consultations	26	0	49	45	0	128
District nurse consultations	10	0	81	8	0	33
Optometrist consultations	29	21	38	21	21	25
Ophthalmology consultations	1313	1129	615	593	407	524
Other consultations	41	0	246	69	0	311
Nights in hospital	28	0	166	10	0	78
Releasable release	101	0	160	17	0	59
Ocular massage	97	0	192	5	0	30
Trabeculectomy	1821	1639	850	394	0	800
5-Fluorouracil injection	30	0	95	8	0	37
Steroid injection	18	0	59	6	0	44
Needling plus 5-fluorouracil injection	37	0	99	10	0	54
Bleb resuturing	20	0	160	7	0	94
Anterior chamber reformation	3	0	20	1	0	9
Bleb revision	45	0	242	7	0	94
Phacoemulsification	63	0	309	81	0	374
Prostaglandin analogues	181	178	141	286	320	120
Carbonic anhydrase inhibitor	7	0	15	18	0	25
Beta-blockers	9	0	16	19	10	22
$\alpha$ -agonists	5	0	19	15	0	50
Pilocarpine	0	0	5	1	0	21
Combinations	4	0	22	1	0	10
Diamox	1	0	10	1	0	18
Others	0	0	4	0	0	0

TABLE 17 Total unadjusted costs in each arm during the first and second 12 months of trial follow-up

Total cost	Treatment arm (£)						Mean difference (p-value)
	Trabeculectomy			Medical management			
	Mean	Median	SD	Mean	Median	SD	
Total cost to the NHS over 24 months	3826	3509	1648	1685	1057	1401	2141 (< 0.01)
Total cost to the NHS between baseline and 12 months	3157	2995	1299	1067	523	1299	2090 (< 0.01)
Total cost to the NHS between 12 and 24 months	669	353	977	618	410	632	51 (0.53)

TABLE 18 Utility values and QALYs for each utility measure by treatment arm along with differences in QALYs at 24 months (unadjusted analysis)

Treatment	Treatment arm				Mean difference ( <i>p</i> -value)
	Trabeculectomy		Medical management		
	Mean	SD	Mean	SD	
<b>Effectiveness</b>					
<b>EQ-5D-5L</b>					
Baseline ( <i>n</i> = 444)	0.84	0.18	0.84	0.18	
1 month ( <i>n</i> = 397)	0.84	0.18	0.81	0.20	
3 months ( <i>n</i> = 365)	0.84	0.17	0.81	0.20	
6 months ( <i>n</i> = 381)	0.85	0.18	0.82	0.20	
12 months ( <i>n</i> = 420)	0.84	0.18	0.82	0.16	
18 months ( <i>n</i> = 365)	0.83	0.19	0.79	0.22	
24 months ( <i>n</i> = 409)	0.81	0.18	0.80	0.19	
Complete QALYs over 24 months using EQ-5D-5L ( <i>n</i> = 290)	1.65	0.24	1.59	0.28	0.06 (0.04)
<b>HUI-3</b>					
Baseline ( <i>n</i> = 428)	0.81	0.20	0.80	0.20	
1 month ( <i>n</i> = 377)	0.79	0.23	0.79	0.23	
3 months ( <i>n</i> = 359)	0.80	0.22	0.78	0.22	
6 months ( <i>n</i> = 362)	0.81	0.22	0.78	0.22	
12 months ( <i>n</i> = 400)	0.83	0.19	0.80	0.20	
18 months ( <i>n</i> = 343)	0.80	0.21	0.75	0.26	
24 months ( <i>n</i> = 391)	0.79	0.23	0.75	0.25	
Complete QALYs over 24 months using HUI-3 ( <i>n</i> = 240)	1.61	0.30	1.54	0.36	0.07 (0.09)
<b>GUI</b>					
Baseline ( <i>n</i> = 441)	0.88	0.13	0.86	0.13	
1 month ( <i>n</i> = 399)	0.86	0.14	0.85	0.16	
3 months ( <i>n</i> = 377)	0.85	0.13	0.84	0.16	
6 months ( <i>n</i> = 377)	0.84	0.16	0.85	0.14	
12 months ( <i>n</i> = 413)	0.86	0.14	0.86	0.14	
18 months ( <i>n</i> = 365)	0.85	0.14	0.83	0.16	
24 months ( <i>n</i> = 407)	0.85	0.15	0.83	0.18	
Complete QALYs over 24 months using GUI ( <i>n</i> = 293)	1.67	0.20	1.64	0.24	0.03 (0.25)

## Economic evaluation

### Cost-utility analysis using the EQ-5D-5L

The results of the cost-utility analysis are presented in Table 19 and Figures 7 and 8. The results of the SUREG, reported in Table 19, show a small incremental QALY gain for surgery compared with medical management, but this small gain does not appear to be offset by the higher costs of surgery. The effectiveness plane demonstrates that the difference in costs and QALYs for surgery compared with medical management is almost entirely in the quadrant that represents greater effect at greater cost (see Figure 8). The CEAC in Figure 7 shows that surgery is unlikely to be considered cost-effective over the range of values that society may be willing to pay for a QALY.

TABLE 19 Complete and multiple imputation EQ-5D-5L results

EQ-5D-5L data	Treatment arm	Unadjusted cost (£)	Adjusted incremental cost (£)	Unadjusted QALY	Adjusted incremental QALY	ICER ( $\Delta$ cost/ $\Delta$ QALY) (£)	Probability cost-effective at threshold (%)			
							£0	£20,000	£30,000	£50,000
Complete-case data (n = 290)	Trabeculectomy	3686	2089	1.65	0.03	64,303	0	0	6	35
	Medical management	1605		1.59			100	100	94	65
Multiple imputation data (n = 403)	Trabeculectomy	3622	2013	1.61	0.04	45,456	0	0	12	56
	Medical management	1605		1.56			100	100	88	44

ICER, incremental cost-effectiveness ratio.

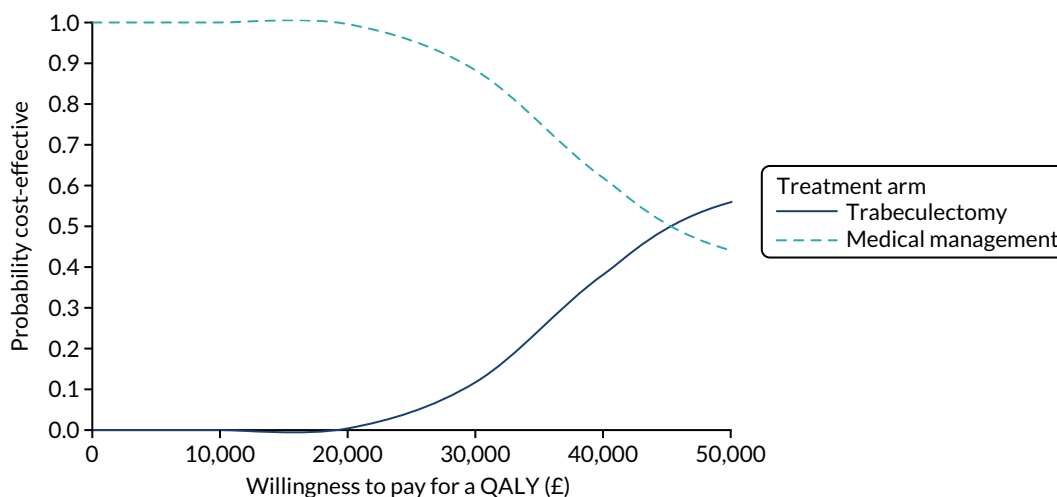


FIGURE 7 Cost-effectiveness curves for the trabeculectomy arm and the medical management arm using the results from the EQ-5D-5L and multiply imputed data.

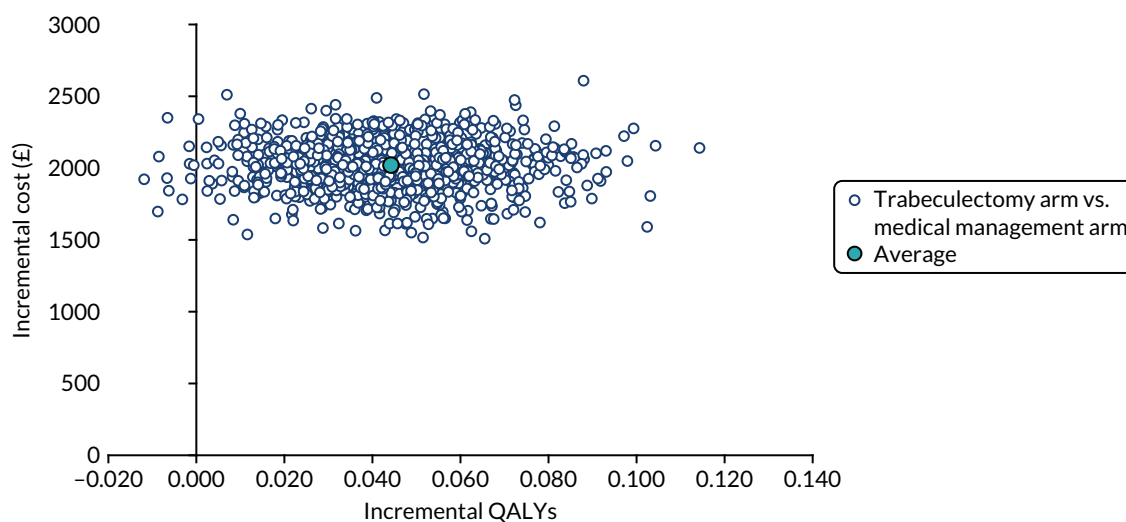


FIGURE 8 Cost-effectiveness plane for the trabeculectomy arm vs. the medical management arm: adjusted bootstrapped replications for CUA for EQ-5D-5L results.

**Sensitivity analysis**

Appendix 5, Tables 44 and 45, and Figures 15–18 display the results of the sensitivity analysis when the HUI-3 and GUI QoL instruments are used in place of the EQ-5D-5L. Although the incremental cost-effectiveness ratios (ICERs) for the HUI-3 are smaller than that for the EQ-5D-5L, the probability of the trabeculectomy intervention being cost-effective is still very small, so the conclusions remain unchanged. A similar result was also seen for the GUI.

The inclusion of the participants' time and travel costs in Appendix 5, Table 46, and Figures 19 and 20, demonstrate an increased difference in costs between arms and further supports the conclusion that medical management is likely to be considered more cost-effective than surgery over a 24-month period.

**Model-based economic evaluation analysis**

**Background and rationale**

Although the within-trial analysis is useful for informing decisions about cost-effectiveness in the short to medium term, it provides limited evidence to inform decisions about the cost-effectiveness of interventions in the longer term.<sup>104</sup> This is a very important limitation owing to the chronic nature

of glaucoma,<sup>105</sup> which can progress over time,<sup>106</sup> and because the effects of treatment on costs and outcomes may persist into the future, with patients often living for many years after their glaucoma diagnosis. Therefore, a further analysis of the longer-term effects based on a Markov model<sup>107,108</sup> was undertaken to extrapolate results of the trial beyond the 2-year follow-up and over the expected lifetime of patients. The results of this model can be used to inform decisions about the longer-term cost-effectiveness of trabeculectomy and medical management for people with newly diagnosed advanced glaucoma. In simple words, we tried to anticipate (extrapolate) the long-term impact of medication compared with surgery based on trial data and other related data from the literature. The logic of the modelling for this research is that the surgical procedure is expensive and, therefore, surgery is associated with higher initial costs than medical management. A longer-term time horizon would allow more time for any additional benefits of surgery to offset these initial higher costs. Essentially, a short time horizon could act as a bias against surgery.

### Objective

The purpose of this model-based economic evaluation is to compare primary medical treatment with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced glaucoma (HPA classification severe<sup>64</sup>) in terms of costs and QALYs.

### Methods

This section describes the methodology underpinning the model-based economic evaluation results. Detail is provided on the estimations of parameters used within the model and on how these values are used within the model to inform how patients move through the model. This section also describes how the model was validated to ensure that it estimates the costs of real-world glaucoma care service in the UK. Furthermore, the section describes the sensitivity analyses performed. These were carried out to analyse how uncertainty in the model's parameters affect the final outcomes.

### Model overview

A Markov model was constructed to model both treatments (trabeculectomy and primary medication)<sup>1</sup> and disease progression that reflects the timing and allowed modelling of the logical and temporal sequence of events following the initial treatment strategies. The primary source of data for the model was the trial data set, supplemented with data from the literature where necessary. The uncertainty surrounding the model findings was assessed using probabilistic sensitivity analysis (PSA) and deterministic analysis.<sup>107</sup> The model was developed using TreeAge Pro 2019 (Williamstown, MA, USA).

To design the structure of the model and to classify the stages of glaucoma, we used the Enhanced Glaucoma Staging System (GSS2).<sup>109</sup> An external independent reading centre (CARF) reviewed and categorised TAGS visual fields into stages of VF loss based on the GSS2 system of grading. The consequences considered were the costs (of treatment and of subsequent management of patients with severe glaucoma) to the NHS and the effects on quality of life (QALYs). QALYs were estimated by assigning utility weights based on data on health state utility values derived from responses to the EQ-5D-5L (and GUI or HUI).<sup>1</sup> Combining these data with information on the probabilities of events occurring over time enabled cost, patient outcomes and QALYs to be estimated for a hypothetical cohort of patients undergoing each treatment strategy.

### Model structure

The Markov model was developed using in-house experience of previous evaluations of glaucoma treatment,<sup>110-113</sup> as well as the literature and advice from clinical colleagues. The model is used to simulate patient pathways from initial treatment until the end of life using data from the TAGS trial along with the best available UK relevant data to define transition probabilities for the model. All other model parameter estimates beyond 2 years were informed by the data from TAGS, other existing data sources (routine databases and the literature) and expert opinion.

Typically, Markov models have states (Markov states) in which individuals stay for a period of time. Each state reflects the subject's level of well-being at that time. In each Markov state, the model will assign a cost and utility weight to each individual depending on the different interventions received by that individual while in that state and/or how long the individual remains a member (time spent) of that state.<sup>107,114</sup> The model is run for a length of time (e.g. 25 years), known as the 'model time horizon'. This time horizon is broken down into equal parts, denoted as Markov cycles (e.g. 1-year intervals).

The cycle must be a period relevant to the condition considered (e.g. 6 months, 1 year). At the end of each cycle, individuals can remain in the state in which they started the cycle or move to a different state. Movement is dependent on the transition probability, which is defined as the probability of moving from one state to another.<sup>115</sup> Such models can be useful in capturing the costs and benefits of treating chronic medical conditions, such as glaucoma, over time.<sup>116</sup> In addition, all Markov models have at least one absorbing state, typically death, which all individuals will eventually enter if the model is given a sufficiently long time horizon. The sum of the cost in each year and the product of the utilities in each year were summed over the time horizon of the simulated patient cohort to compute total cost and quality-adjusted life-years (QALYs) for that cohort.<sup>115</sup>

Within the model, and mirroring the trial inclusion and exclusion criteria, on entry into the model patients could have disease in one or both eyes. Again mirroring the trial inclusion criteria, one eye is defined as the index eye in terms of initial treatment and, in terms of disease severity, has advanced glaucoma, as this was also an inclusion criterion for the trial. Based on the (modified) disease classification (GSS2), we defined the stages for the economic model shown in *Box 1*. Other possible options for model structure are provided in *Appendix 7, Tables 48–52*.

#### BOX 1 Stages of the disease used within the economic model

Stage 1: index eye, severe (S3); non-index eye, non-severe (S0 + border + SB + S1 + S2).

Stage 2: index eye, severe (S4); non-index eye, non-severe (S0 + border + SB + S1 + S2).

Stage 3: index eye, severe (S5); non-index eye, non-severe (S0 + border + SB + S1 + S2).

Stage 4: index eye, severe (S3); non-index eye, severe (S3).

Stage 5: index eye, severe (S4); non-index eye, severe (S3).

Stage 6: index eye, severe (S5); non-index eye, severe (S3).

Stage 7: index eye, severe (S3); non-index eye, severe (S4).

Stage 8: index eye, severe (S4); non-index eye, severe (S4).

Stage 9: index eye, severe (S5); non-index eye, severe (S4).

Stage 10: index eye, severe (S3); non-index eye, severe (S5).

Stage 11: index eye, severe (S4); non-index eye, severe (S5).

Stage 12: index eye, severe (S5); non-index eye, severe (S5).



We adopted this model structure because it allows us to model both eyes independently and estimate the chance of unilateral and bilateral progression more precisely than modelling a single eye, even with a cohort Markov model. This is especially important in the case of eye disease because HRQoL and, therefore, QALYs are thought to be determined by the quality of vision in the better eye.<sup>117</sup> The model allows progression of the disease in both eyes over time. For the purposes of modelling, the time step over which progression could occur is 1 year because glaucoma is generally only slowly progressive.<sup>116</sup>

Within the model, the mean age and sex distribution of the modelled cohort matches that of the trial participants at baseline. For those with binocular disease, the risk of visual loss in each eye is modelled independently. The model structure is presented in *Figure 9*.

### Treatment pathway

A patient starts with one of the two randomised treatments (trabeculectomy or medical management). The medical treatment strategy was chosen as the comparator and trabeculectomy as the intervention in this trial. A patient is categorised in different stages of glaucoma (based on the GSS2 classification system; see *Box 1*) for both the trabeculectomy arm and the medical management arm. The initial and transition probabilities of patients in each stage are based on trial data. Disease progression may occur during the trial and some patients move to more severe levels of glaucoma. Disease progression in the model is determined by a set of transition probabilities, each of which is defined in the sections below. Patients may also experience some complications that may affect related cost/utility in both arms. Therefore, complication-related cost/utility has been included in the model as well.

In the model, a patient may progress through a number of different states, each represented by increasing severity of disease (*Figure 9*). The Markov model used in this study (see *Figure 9*) considers increasing severity of glaucoma for each eye separately, as has been undertaken by others.<sup>118</sup> The level of the patient's disease on entry into the model determines the Markov model state at which the patient starts.

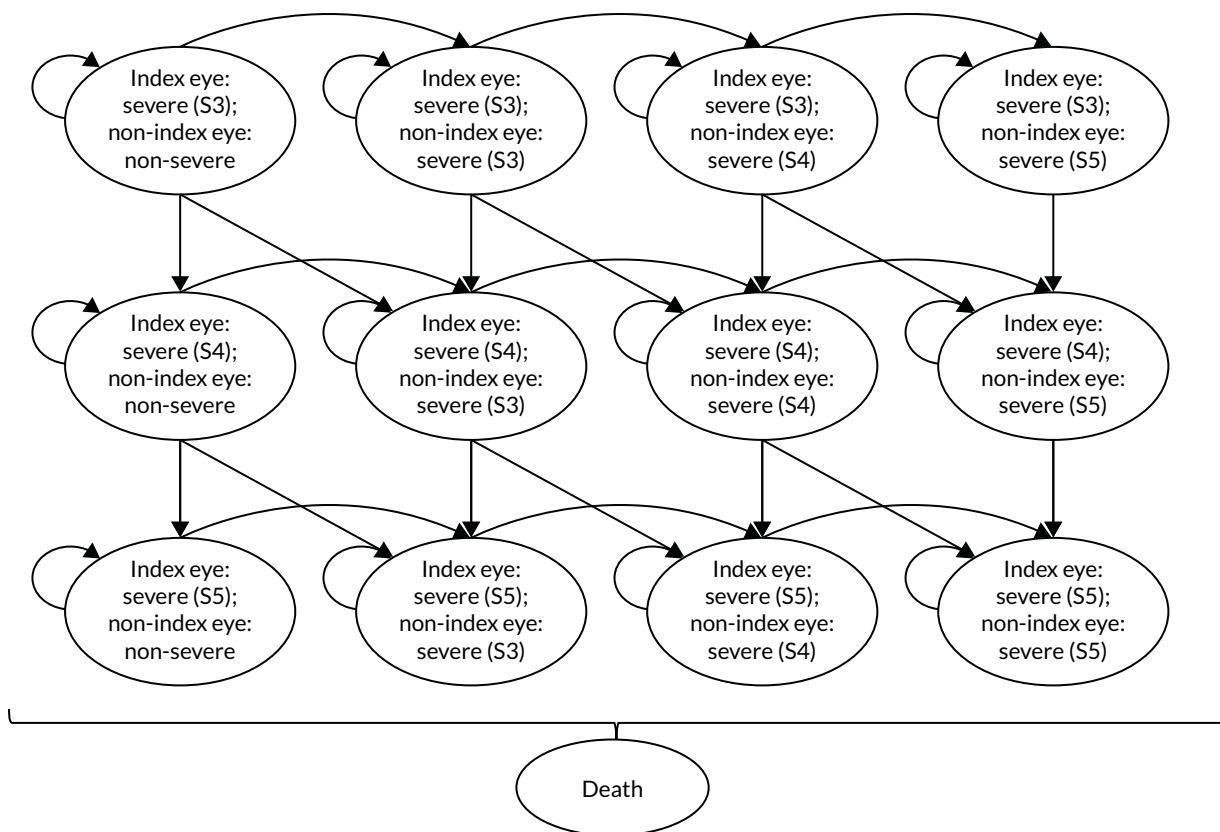


FIGURE 9 Model structure.

The progress of patients through the model reflects disease progression, but it is possible that patients can stay in a state and not progress further. However, they cannot move back to a less severe state because glaucoma is an irreversible disease.<sup>117</sup>

During each model cycle, a portion of the cohort progresses based on the probabilities of progression derived from the analysis of the trial and other relevant data. In addition, it is assumed that patients move sequentially between states and cannot skip states because of the relatively slow evolution of glaucoma.<sup>106</sup> Finally, death from all causes is included in the model as an absorbing state (a state that someone can enter but cannot leave). Transition probabilities to this state are assumed to be independent of severity and treatment history and are derived from age-/sex-specific UK life tables.<sup>119</sup> Patients who are blind (in one or both eyes) are taken to have a higher risk of death than the general population and, hence, standardised mortality ratios were used to adjust the risk of death for those who are blind in one or both eyes.<sup>120</sup> Surgical mortality was not included in the model. All of the programming for the model was implemented in TreeAge Pro 2019.

### Model assumptions

- The model-based economic evaluation analysis took the perspective of the NHS and Personal Social Services (PSS).
- For extrapolation, the cost and utility values (by clinical severity state and treatment allocation) beyond 24 months (beyond the duration of trial follow-up) in the model were assumed to be the same as those incurred in the second year.
- Independent variables (e.g. progression state, have trabeculectomy treatment) and constant value of year 1 were assumed as a proxy to estimate the cost and utility for the second year.
- All model input parameters are defined as statistical distributions in the model, allowing probabilistic sensitivity analysis to be conducted.<sup>107</sup>
- Ranges and distributional assumptions for input parameters were based on the trial data. We assigned gamma distributions for costs and beta distributions for utility data.<sup>121</sup> We have described these in more detail in *Model parameters*.
- All future costs and QALYs were discounted at 3.5% per annum, the UK recommended rate, as the duration of follow-up (time horizon) was > 1 year.<sup>122</sup>

### Model parameters

#### Costs specified within the model

Costs were assigned to each state in the model, reflecting the costs for each 12-month period. All costs are presented in Great British pounds for the year 2018. Costs were assumed to vary according to glaucoma severity and initial treatment in both (trabeculectomy/medical management) groups. Regression techniques were applied to the data on total costs per participant obtained from the trial to identify whether or not there is a difference between those randomised to the trabeculectomy arm and those randomised to the medical management arm, for potentially modifying factors (e.g. progression rate). The objective of this is to make the model more dynamic and sensitive to main drivers of the cost over patient lifetimes. An ordinary least squares regression technique was applied:

$$F(\text{NHS costs}) = \beta_0 + \beta_1 P + \beta_2 T + \hat{\epsilon} \quad (1)$$

In *Equation 1*, we assumed that the cost in that the second year of the model is a function of treatment ( $T$ ), progression state of the disease ( $P$ ) and a constant value from year 1. A dummy variable for the trial intervention arm estimates the difference in costs between the arms, controlling for all other factors in the model. Estimated beta values describe the direction and magnitude of the relationship between each variable and the dependent variable (cost). For example, if the dummy variable is specified as trabeculectomy arm = 1 and medical management arm = 0, and the beta estimate of the cost coefficient

is 500. This indicates that the trabeculectomy arm (coded as 1 in the dummy variable) is £500 more costly, on average, than the medical treatment arm controlling for all other factors. If the coefficient was -500, then trabeculectomy would, on average, be £500 cheaper than medical management. We also used Cholesky decomposition and assigned multinormal distributions to these parameters to enable the model for sensitivity analysis.<sup>121</sup>

### Utilities specified in the model

Utilities associated with each health state were attached to the modelled severity states, allowing cumulative model-based QALYs to be estimated in both (trabeculectomy/medical management) arms. We assigned a zero utility weight for death. The mean QALYs for each intervention were calculated by multiplying the amount of time that patients spent in each health state by the associated health state utility values. The estimated utility used in the model was based on data retrieved from the trial using instruments such as EQ-5D-5L;<sup>123</sup> data from the trial were also available for the HUI-3<sup>124</sup> and the GUI,<sup>55</sup> and these data have been used in the sensitivity analysis.

As with costs, regression techniques were carried out to derive the drivers of the difference in QALYs for a 12-month period between the arms of the trial (trabeculectomy vs. medical management) after controlling for the key predictors of QALYs. The purpose of this regression was to determine the consequences of a glaucoma state (based on GSS2 measure) and its effect on a participant's overall QALYs:

$$f(\text{QALY}) = \beta_0 + \beta_1 P + \beta_2 T + \hat{\epsilon} \quad (2)$$

The variables considered were:

- dependent variable – QALYs (total QALY score across the two arms of the trial controlling for the independent factors)
- independent variables – progression rate ( $P$ ) and trabeculectomy ( $T$ ).

Here, the dummy variable for the treatment arms estimates the difference in QALYs between the trabeculectomy and the medical management arms, controlling for all other factors in the model. For example, if the dummy is specified as trabeculectomy arm = 1 and medical management arm = 0 and the beta value of the coefficient is 0.50, this indicates that the trabeculectomy (coded as 1 in the dummy) provided 0.50 more QALYs over 12 months than current practice, on average, after controlling for all other factors. If the coefficient was -0.50, the QALY gain resulting from the intervention would, on average, be -0.50 lower than that achieved by medical management. As with costs, we also used Cholesky decomposition and assigned multinormal distributions to these parameters to enable the model for sensitivity analysis.<sup>121</sup>

### Progression and transition probabilities

The model structure allows a cohort of patients with advanced glaucoma to enter into the model and for disease to progress over time to eventual death. During each model cycle, a portion of the cohort progresses in severity (from no glaucoma to early, early to moderate and moderate to severe) based on the probabilities of progression derived from the analysis of the trial data.

Table 20 presents a summary of the initial and transition probabilities of progression that are used in the model. More details of initial and transition probabilities are provided in Appendix 7, Tables 53–60.

### Model validation

The model was validated by checking the model structure, calculations and data inputs for technical correctness.<sup>115</sup> The structure was reviewed by clinical experts from our TAGS team to establish that it was appropriate for the disease and its treatment. The robustness of the model to change input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude. To establish its external consistency, the

TABLE 20 Initial and transition probabilities of stages in the model

Trabeculectomy arm					Medical management arm				
Stage	Initial	Transition			Stage	Initial	Transition		
		To	Year 1	Year 2			To	Year 1	Year 2
Stage 1	0.14	Stage 1	0.63	0.84	Stage 1	0.13	Stage 1	0.68	0.79
		Stage 2	0.30	0.16			Stage 2	0.29	0.11
		Stage 4	0.07	0.00			Stage 4	0.00	0.11
		Stage 5	0.00	0.00			Stage 5	0.04	0.00
Stage 2	0.35	Stage 2	0.86	0.92	Stage 2	0.34	Stage 2	0.80	0.95
		Stage 3	0.11	0.03			Stage 3	0.04	0.05
		Stage 5	0.01	0.05			Stage 5	0.12	0.00
		Stage 6	0.03	0.00			Stage 6	0.04	0.00
Stage 3	0.18	Stage 3	0.82	0.93	Stage 3	0.21	Stage 3	0.98	0.98
		Stage 6	0.18	0.08			Stage 6	0.02	0.02
Stage 4	0.01	Stage 4	1.00	0.75	Stage 4	0.01	Stage 4	0.33	1.00
		Stage 5	0.00	0.00			Stage 5	0.33	0.00
		Stage 7	0.00	0.00			Stage 7	0.00	0.00
		Stage 8	0.00	0.25			Stage 8	0.33	0.00
Stage 5	0.07	Stage 5	0.53	0.90	Stage 5	0.06	Stage 5	0.69	0.79
		Stage 6	0.13	0.10			Stage 6	0.08	0.05
		Stage 8	0.20	0.00			Stage 8	0.23	0.16
		Stage 9	0.13	0.00			Stage 9	0.00	0.00
Stage 6	0.05	Stage 6	0.91	0.84	Stage 6	0.05	Stage 6	0.80	0.85
		Stage 9	0.09	0.16			Stage 9	0.20	0.15
Stage 7	0.02	Stage 7	1.00	1.00	Stage 7	0.02	Stage 7	0.60	0.67
		Stage 8	0.00	0.00			Stage 8	0.40	0.33
		Stage 10	0.00	0.00			Stage 10	0.00	0.00
		Stage 11	0.00	0.00			Stage 11	0.00	0.00
Stage 8	0.05	Stage 8	0.70	0.70	Stage 8	0.03	Stage 8	0.83	0.92
		Stage 9	0.00	0.10			Stage 9	0.00	0.08
		Stage 11	0.10	0.20			Stage 11	0.17	0.00
		Stage 12	0.20	0.00			Stage 12	0.00	0.00
Stage 9	0.02	Stage 9	1.00	0.75	Stage 9	0.02	Stage 9	0.75	1.00
		Stage 12	0.00	0.25			Stage 12	0.25	0.00
Stage 10	0	Stage 10	0.00	0.00	Stage 10	0.04	Stage 10	0.88	1.00
		Stage 11	0.00	0.00			Stage 11	0.12	0.00
Stage 11	0.05	Stage 11	0.73	0.89	Stage 11	0.03	Stage 11	0.83	0.71
		Stage 12	0.27	0.11			Stage 12	0.17	0.29
Stage 12	0.06	Stage 12	1	1	Stage 12	0.06	Stage 12	1	1

model results were compared with outcomes reported in other trials and other economic evaluations. Moreover, we assigned the same time horizon of 24 months of for the trial-based economic evaluation (reported in the first half of this chapter) to the model-based analysis (2 years) and compared the model-based with the within trial-based incremental cost-effectiveness analysis to check the accuracy of the model compared with the within trial analysis.

### Base-case analysis

The base-case analysis considered a cohort of 67 year olds (65% were male) as the start of the model. Each person had severe glaucoma in at least one eye. The costs and outcomes were modelled over their estimated lifetimes (i.e. a lifetime horizon adopted). As described above, the analysis adopted a UK NHS and PSS perspective, the cycle length was set at 1 year and a discount rate of 3.5% for costs and benefits was used.<sup>122</sup>

The results of the model are presented in ICERs. The ICER is a ratio of the difference in costs divided by the difference in the effectiveness between two alternative strategies. These data can be interpreted as how much society would have to pay for an extra unit of effectiveness.<sup>108</sup> Central to the assessment of cost-effectiveness is the value that society would put on gaining an additional QALY. NICE states that 'Below a most plausible ICER of £20,000 per QALY, judgements about the acceptability of a technology as an efficient use of NHS resources are based primarily on the cost-effectiveness estimate'<sup>122</sup> (© NICE 2018 *Guide to the Methods of Technology Appraisal 2013*. Available from [www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781](http://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781). All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication). Between £20,000 per QALY and £30,000 per QALY, judgements about the acceptability of the technology should take into account factors such as the degree of uncertainty surrounding the calculation of ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, and, where appropriate, the wider societal costs and benefits. Above an ICER of £30,000 per QALY, the case for supporting the technology on these factors has to be increasingly strong. In the absence of a more definitive statement, this report focuses on a willingness-to-pay threshold of £30,000 for a QALY.

To further this aim, we have also adopted the net monetary benefit (NMB) statistic. NMB represents the value of an intervention in monetary terms when a willingness-to-pay threshold for a unit of benefit (e.g. QALY) is known.<sup>125</sup> A net benefit in terms of NHS costs and benefits, expressed in commensurate units, was calculated for each participant in the model according to *Equation 3*:

$$(\text{NMB})_i = \text{WTP} \times \text{QALY}_{S_i} - \text{cost}_i, \quad (3)$$

where  $i$  = individual and WTP = maximum WTP threshold for a QALY.

### Evaluation of uncertainty

Both probabilistic and deterministic sensitivity analysis were used to explore parameters and other forms of uncertainty surrounding model-based estimates of cost-effectiveness.<sup>115</sup> The deterministic sensitivity analyses were conducted to investigate the impact of varying key assumptions and/or parameter values used in the base-case analysis. A deterministic sensitivity analysis with the results presented in the form of tornado diagrams was also conducted. For the deterministic sensitivity analysis, we explored the impact of the results of changes in costs of medical management in year 1 (Cost\_Year1\_MD). For this analysis, the costs of medical management in year 1 were varied between £1500 and £1700. We likewise varied the cost of trabeculectomy in year 1 (Cost\_Year1\_TB). The cost of this was varied between £2000 and £4000. The cost of year 2 (Cost\_Year2) was also varied in the range £700–10,000. Similar deterministic sensitivity analyses were conducted for utilities. For the utility of year 1 for medical management (Util\_Year1\_MD) and the utility of year 1 for trabeculectomy (Util\_Year1\_TB), utility values were varied between 0 and 1. Other deterministic sensitivity analyses included changing the time horizon for the analysis from 0 to

30 years; changing the age at which severe glaucoma started (start age) by varying the age on entry into the model from 30 to 80 years; and changing the percentage of males and females (sex ratio), with the percentage of females varying between 40% and 60%.

Alternative scenarios have been explored using PSA. PSA is a technique used in economic modelling that allows the modeller to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs.<sup>125</sup> For the PSA, all parameter values, including costs and utilities, were defined as statistical distributions using parameters, such as a mean and SD, for a normal distribution, for example. Ranges and distributional assumptions for input parameters were based on the trial data. In a PSA, a set of input parameter values is drawn by random sampling from each distribution, and the model is 'run' to provide the results as probability of being cost-effective for different thresholds. This is repeated many times (typically 1000 to 10,000), resulting in a distribution of outputs that can be graphed on the cost-effectiveness plane and analysed. Different distributions are generally appropriate for different types of variable.<sup>125</sup> We assigned gamma distributions for costs and beta distributions for utility data.<sup>121</sup> We also calculated correlations between the coefficients of cost and utility for the variables included logistic regression analyses using Cholesky decomposition and assigned multinormal distributions to these parameters in the model to account uncertainty in the estimated transition probabilities.

A key output of a PSA is the proportion of results that fall favourably (i.e. considered cost-effective) in relation to a given cost-effectiveness threshold. This may be represented using a plot of costs and QALYs and a CEAC. The CEAC is a graph summarising the impact of uncertainty on the results of an economic evaluation, estimating the NMB for each strategy for each iteration of the Monte Carlo simulation so that a CEAC can be generated. The uncertainty surrounding the cost-effectiveness of the treatment is represented on a CEAC according to the probability that the intervention will be cost-effectiveness at a particular willingness-to-pay threshold.

## Results

This section reports the proportion of patients in the cohort models by the level of severity of glaucoma in both eyes over time. It also reports the model-based cost-effectiveness results for primary medical treatment with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced glaucoma in terms of costs and QALYs. Results in terms of costs and QALYs are presented for each arm, with costs and benefits discounted at 3.5% per annum.<sup>122</sup>

### *Progression from one health state to another*

In the analysis, all patients start with severe glaucoma in at least one eye (see *Figure 9*). Patients were assumed to progress from less severe disease states to more severe disease states. Once patients were in a more severe state, they could either remain in that state or continue to progress to the next, more severe, disease state.

For each cohort of patients with advanced glaucoma, we determined disease progression from lower stages of glaucoma to higher stages based on the TAGS trial data. We used the GSS2 progression rates to capture the progression for both the trabeculectomy arm and the medication treatment arm who progressed from less severe to more severe disease states. We generated plots of progression through disease states on a year-by-year basis for both arms for a 30-year time horizon (*Figure 10*).

### *Incremental costs, quality-adjusted life-years and cost-effectiveness*

*Table 21* shows the QALYs (for EQ-5D-5L, HUI-3 and GUI, presented separately), total cost, incremental cost per QALY and NMB for three time horizons (and utility measures). In the base-case analysis (lifetime horizon and EQ-5D-5L-based QALYs), trabeculectomy had an additional cost of £2687, an additional 0.28 QALYs and an incremental cost per QALY gained of £9679 compared with primary medical treatment. Furthermore, the results of the PSA show that, should society be willing to pay £20,000 per QALY, the likelihood of trabeculectomy being cost-effective compared with medical treatment would be 73%.

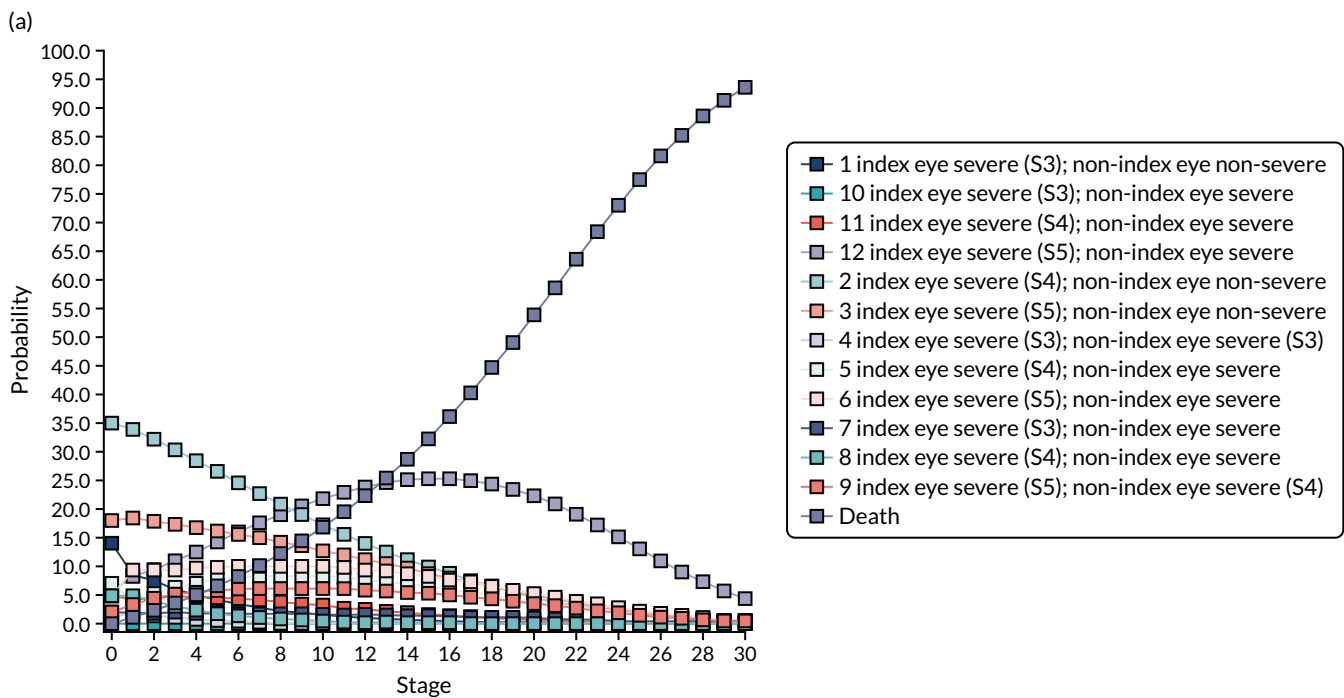


FIGURE 10 Markov tracings of disease states over time for (a) the trabeculectomy arm; and (b) the medical management arm. (continued)

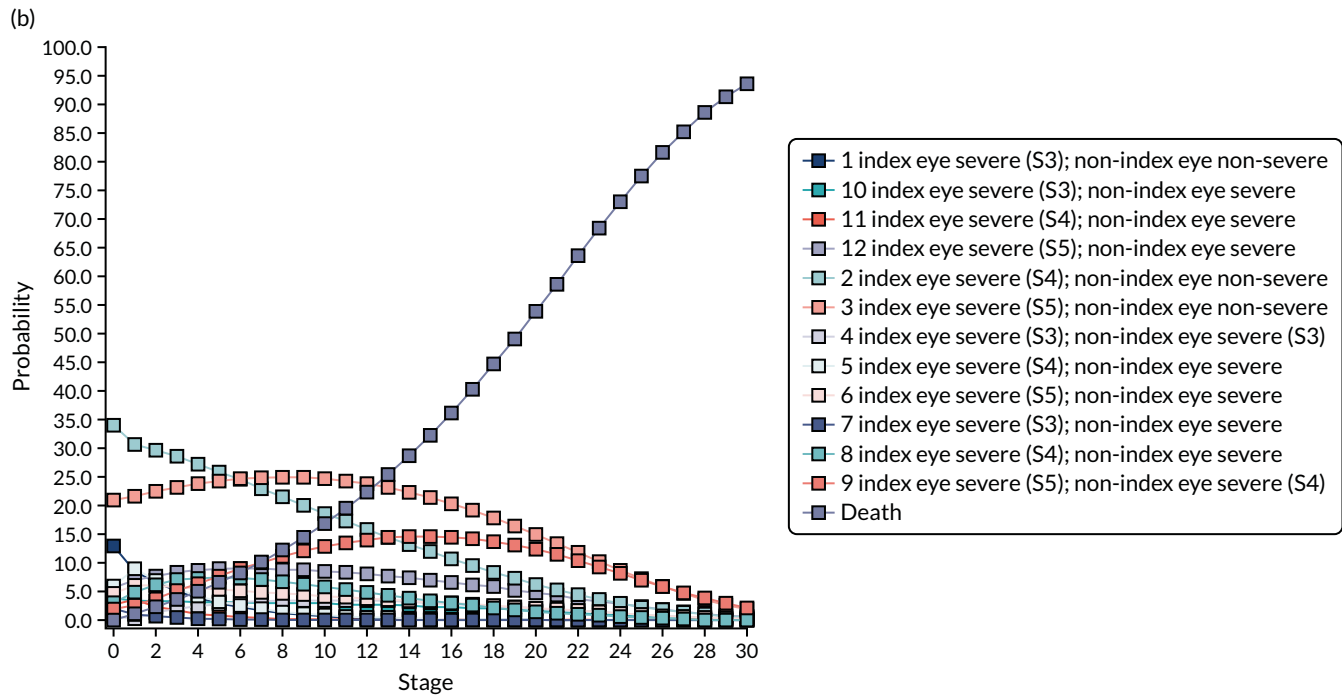


FIGURE 10 Markov tracings of disease states over time for (a) the trabeculectomy arm; and (b) the medical management arm.



TABLE 21 Incremental cost-effectiveness measures (model-based analysis)

Time horizon	Treatment arm	Cost (£)	ΔCost (£)	QALY	ΔQALY	ICER (ΔCost/ ΔQALY) (£)	NMB	Probability cost-effective at Rc			
								0	£10,000	£20,000	£50,000
<b>EQ-5D-5L-based QALYs</b>											
2-year time horizon	Trabeculectomy	3436	2106	1.23	0.04	47,663	21,108	0.10	0.26	0.39	0.05
	Medical management	1330		1.18			22,330	0.90	0.74	0.61	0.50
10-year time horizon	Trabeculectomy	5421	2362	3.72	0.17	13,911	69,024	0.08	0.40	0.59	0.73
	Medical management	3059		3.55			67,990	0.92	0.60	0.41	0.27
Lifetime horizon	Trabeculectomy	7273	2687	5.92	0.28	9679	111,052	0.08	0.50	0.73	0.85
	Medical management	4586		5.64			108,187	0.92	0.50	0.27	0.15
<b>HUI-3-based QALYs</b>											
2-year time horizon	Trabeculectomy	3436	2106	1.17	0.05	39,724	19,978	0.09	0.29	0.40	0.52
	Medical management	1330		1.12			21,024	0.91	0.71	0.60	0.48
10-year time horizon	Trabeculectomy	5421	2362	3.58	0.22	10,506	66,115	0.10	0.50	0.65	0.75
	Medical management	3059		3.35			63,980	0.90	0.50	0.35	0.25
Lifetime horizon	Trabeculectomy	7273	2687	5.70	0.38	7016	106,779	0.06	0.62	0.81	0.88
	Medical management	4586		5.32			101,806	0.94	0.38	0.19	0.12
<b>GUI-based QALYs</b>											
2-year time horizon	Trabeculectomy	3436	2106	1.24	0.01	147,247	21,302	0.09	0.18	0.28	0.41
	Medical management	1330		1.23			23,122	0.91	0.82	0.72	0.59
10-year time horizon	Trabeculectomy	5421	2362	3.73	0.1	24,179	69,269	0.08	0.26	0.44	0.60
	Medical management	3059		3.64			69,677	0.92	0.74	0.56	0.40
Lifetime horizon	Trabeculectomy	7273	2687	5.92	0.16	16,805	111,165	0.06	0.32	0.55	0.74
	Medical management	4586		5.76			110,655	0.94	0.68	0.45	0.26
Rc, ceiling ratio of willingness to pay per QALY gained.											

The model-based estimates of mean costs and QALYs at 2 years indicate that trabeculectomy for the treatment of glaucoma is expected to cost an additional £2106, on average, and to provide an average QALY gain of 0.04 compared with medical management. The corresponding incremental cost per QALY for surgery compared with medical management would be £47,663 (see *Table 21*). At a 10-year time horizon, the corresponding figures are £2362 and 0.17 QALYs (ICER £13,911). When running the model over 10 years, the results of the PSA show that, should society be willing to pay £20,000 per QALY, the likelihood of trabeculectomy being cost-effective compared with medical treatment would be 59% (see *Table 21*). *Table 21* also reports the incremental cost, incremental QALY and incremental cost per QALY when QALYs are based on HUI-3 or GUI utility values. *Figure 11* presents a plot of costs and QALYs in the base-case analysis. Similar results for the analyses using HUI-3- and GUI-based QALYs are presented in *Appendix 7, Figures 21 and 22*.

### Sensitivity analysis

#### One-way deterministic sensitivity analysis

Deterministic sensitivity analysis shows that the model-based findings are generally robust to the changes examined. Main model inputs were varied in the sensitivity analyses to determine whether or not they may affect the ICER of trabeculectomy versus medical management (*Table 22*). The results of these sensitivity analyses are depicted in the form of a tornado diagram (*Figure 12*). The tornado diagram helped to identify main inputs that could be altered to make trabeculectomy more or less cost-effective relative to medical management. Similar analyses are shown in *Appendix 7, Figures 23 and 24*, for the HUI-3 and GUI, respectively.

#### Impact of missing data

The base-case analysis made use of the EQ-5D-5L measure and lifetime horizon duration. Running multiple imputation shows a slight difference in the incremental cost value (£2707 vs. £2687) and no difference in the incremental QALYs value (0.28) compared with the base-case analysis. The input parameters of the model were based on a data set where multiple imputations (MI) were performed for missing data. These data were used to parameterise uncertainty surrounding the joint incremental costs and effects. This is presented graphically as confidence ellipses on the incremental cost-effectiveness plane (*Figure 13*). Moreover, the model-based CEACs based on the lifetime horizon are presented in *Figure 14*. The related results of all other scenario analyses (HUI-3 and GUI QALYs measures) are presented in *Appendix 7*; for the incremental cost-effectiveness plane these are shown in *Figures 25 and 26*, respectively. The CEACs are shown in *Appendix 7, Figures 27 and 28*, for the GUI and HUI-3, respectively.

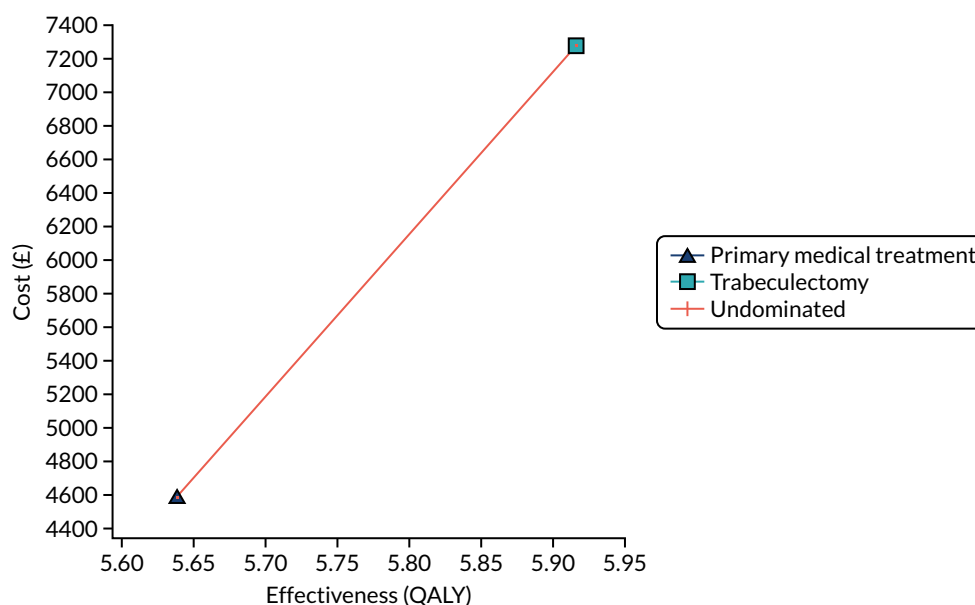


FIGURE 11 Cost-effectiveness analysis in the base-case analysis.

TABLE 22 Sensitivity analyses of main parameters in the model

Parameter	Value	ICER (£ per QALY)		
		EQ-5D-5L	HUI-3	GUI
Cost of year 1 (trabeculectomy) (£)	2000	5594	4055	9713
	3000	9196	6666	15,967
	4000	12,798	9277	22,222
Cost of year 1 (medical management) (£)	700	10,986	7963	19,076
	1100	9546	6919	16,574
	1500	8105	5875	14,072
Utility of year 1 (trabeculectomy)	0.2	Dominated	Dominated	Dominated
	0.6	70,594	14,483	Dominated
	1	6134	4589	8625
Utility of year 1 (medical management)	0.2	3012	2819	3331
	0.6	5461	4856	6606
	1	29,197	17,528	395,757
Cost of year 2 (£)	700	7726	5600	13,415
	1100	7878	5711	13,679
	1500	8031	5821	13,944
Utility of year 2	0.2	52,124	50,146	96,391
	0.5	34,466	33,590	49,497
	1	20,546	20,231	25,087
Time horizon (years)	2	47,663	39,724	147,247
	10	13,910	10,506	24,179
	30	9679	7016	16,805
Age at (severe) glaucoma (years)	30	7924	5614	13,914
	42	8037	5703	14,099
	55	8406	5997	14,701
	67	9776	7093	16,972
	80	14,438	10,769	25,930

## Discussion

The focus of the present model-based analysis was to perform a comparison of the cost-effectiveness of trabeculectomy and medication for treatment in patients with severe glaucoma. This analysis was completed alongside the trial-based economic evaluation and was based on TAGS data, but sought to extrapolate findings over the expected lifetime of patients treated with either trabeculectomy or medical therapy.

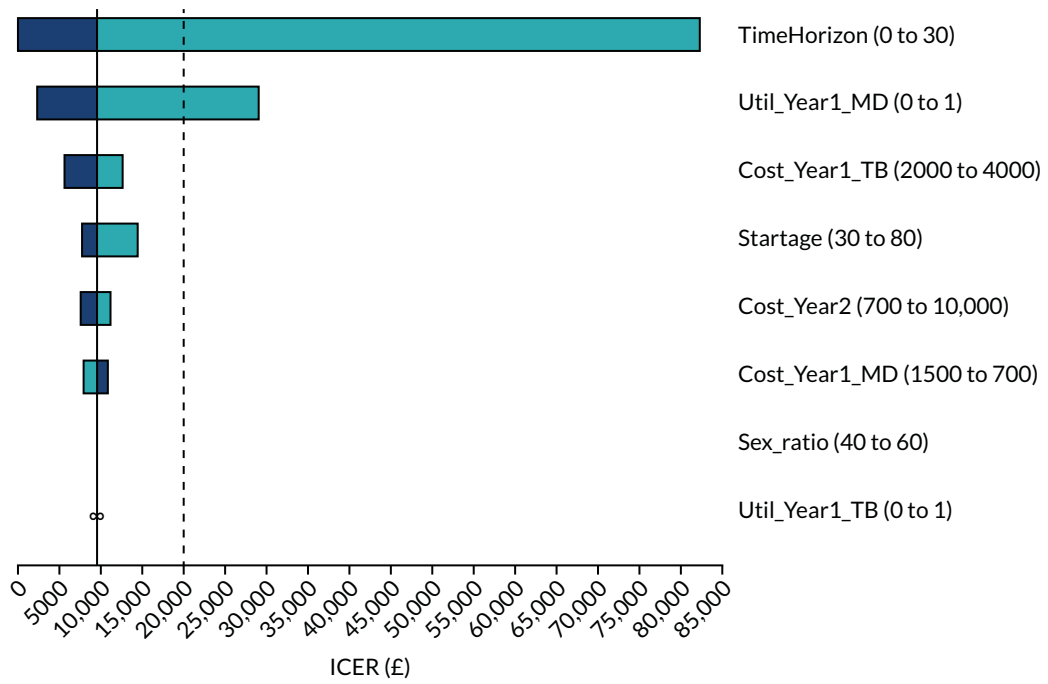


FIGURE 12 Tornado diagram for the main parameters (EQ-5D-5L measure). EV, expected value; WTP, willingness to pay.

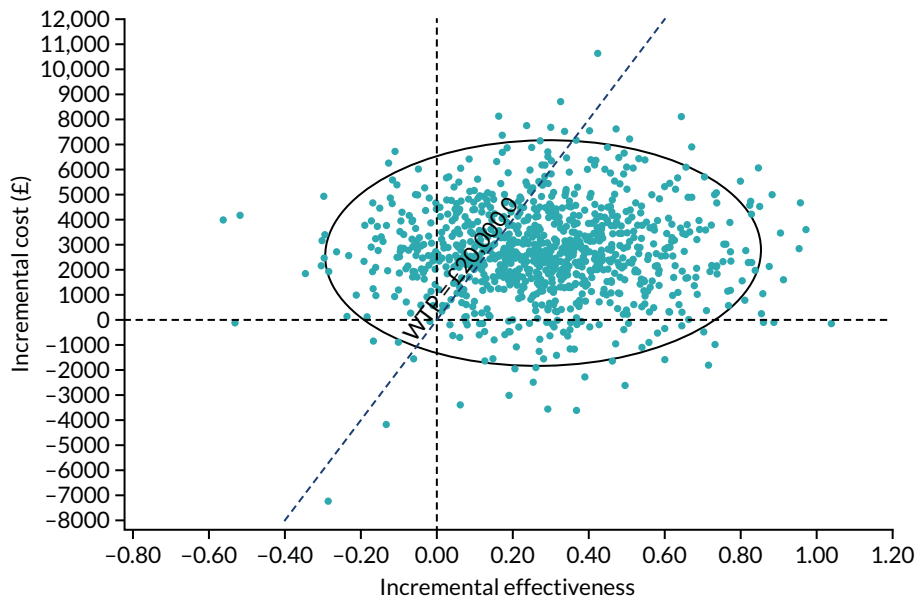


FIGURE 13 Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment in the base-case analysis. WTP, willingness to pay.

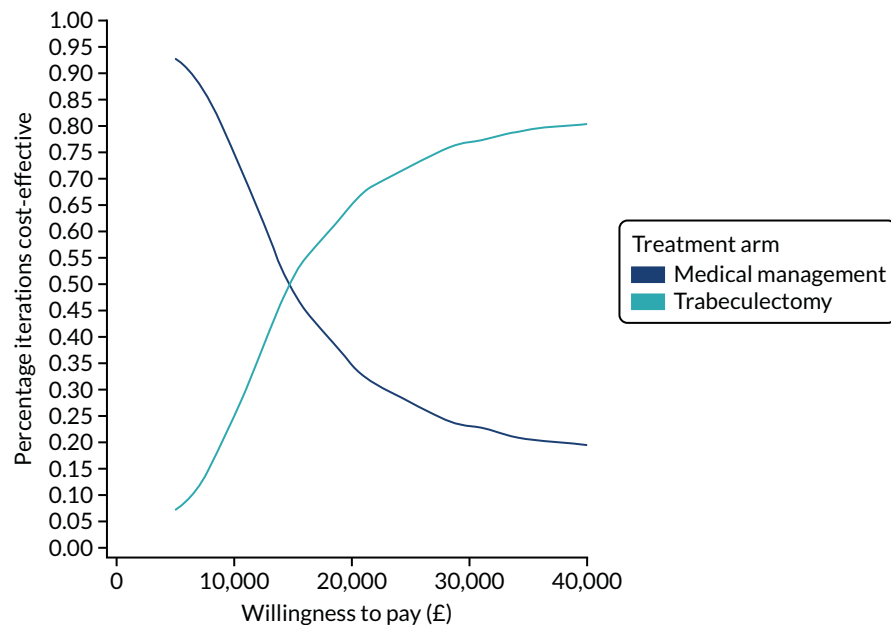


FIGURE 14 Model-based CEAC for the base-case analysis (lifetime horizon; EQ-5D-5L measure).



# Chapter 7 Discussion

## Summary of findings

This multicentre RCT compared initial treatment of advanced primary OAG with either augmented trabeculectomy or medical management. Patient HRQoL, clinical effectiveness and cost-effectiveness were investigated in 453 participants from 27 NHS ophthalmology departments in the UK. The duration of the trial was 24 months. The study provided no evidence of a difference in the primary outcome of vision HRQoL as measured by the VFQ-25, and a meaningful difference favouring either arm is not compatible with the data from the trial given the precision of the CIs. There was a sustained reduction in IOP in both arms, with a reduction of 21% in the medical management arm and 38% in the trabeculectomy arm compared with IOP at baseline, with a much smaller requirement for antiglaucoma eye drops in the trabeculectomy arm. The DCE questionnaire was completed by 70% of participants at 27 months post randomisation. Participants had a strong preference for reduced difficulty with central and near vision, mobility, and activities of daily living. Revised reference-based weights were estimated for the GUI based on the logistic regression results and these utility values were incorporated into the economic evaluation to estimate QALYs. In the within-trial analysis, the small increase in quality of life generated by surgery was not offset by the additional upfront costs and, therefore, trabeculectomy is unlikely to be cost-effective within the 24-month time horizon of the trial. When the results from the decision model were considered, trabeculectomy was associated with an additional cost of £2687, an additional 0.28 QALYs and an incremental cost per QALY of £9679 compared with primary medical treatment, and the likelihood of a trabeculectomy being considered cost-effective over a £0 to £20,000 range of society's willingness to pay for a QALY was 73%. Over shorter time horizons, the incremental cost per QALY of surgery compared with medical therapy increased (£47,663 over a 24-month time horizon). The results appeared robust over the other sensitivity analyses considered.

## Primary outcome

### Quality of life

The outcome of management of glaucoma that is most important to patients is their ability to continue to live an independent life and maintain their QoL.<sup>126,127</sup>

### Visual Function Questionnaire-25

The primary outcome for TAGS is patient-reported vision-related QoL, as measured by the VFQ-25 at 24 months. The VFQ-25 is primarily a vision-related HRQoL instrument. Our sample size calculations indicated that a study with 190 participants in each arm would have 90% power at the 5% significance level to detect a difference in means of 0.33 of a SD; this translates to 6 points on the VFQ-25.<sup>76-78</sup>

There was a slight reduction in VFQ-25 scores in both arms at 24 months compared with baseline. It would be expected that a reduction in HRQoL would occur as participants age. In the Berlin Ageing Study, the authors concluded that physiological reduction in vision associated with ageing materially affects QoL; however, the authors noted that the correlation with VA was small and small changes in vision do not translate into substantial impairments of daily life.<sup>128</sup>

There was no evidence of a difference in the composite VFQ-25 scores between the trabeculectomy or the medical management arm of the study at any of the time points at which they were measured.

There was a suggestion from the subscale analysis of a reduction in the 'role difficulties' (MD -4.60, 95% CI -8.70 to -0.50;  $p = 0.028$ ) and 'general vision' (MD -3.17, 95% CI -6.03 to -0.32;  $p = 0.029$ ) subscales at 4 months in the trabeculectomy arm. This may reflect some reduction in visual function and activity restriction at this time, which may correspond to recovery from trabeculectomy surgery. This difference disappeared by 12 months, as would be expected following surgery recovery. At the 12-month time point, there is reduction in the 'general health' subscale (MD 4.86, 95% CI 0.23 to 9.49;  $p = 0.040$ ) in the medical management arm. This may reflect the fact that a proportion of those in the medical management arm were aware that their glaucoma was uncontrolled or progressing (0.59, 95% CI 0.38 to 0.910;  $p = 0.018$ ), resulting in the requirement for trabeculectomy or ongoing recovery from the operation. This effect disappeared by 24 months. However, care must be taken when interpreting these results owing to multiple testing.

The VFQ-25 score has been shown to be affected by disease severity in the better and also in the worse eye,<sup>46,129</sup> and is also influenced by severity of glaucoma in both eyes, as measured by binocular VF loss. In patients with advanced glaucoma, there is a disproportionate reduction in VFQ-25 score for each additional 1-unit reduction in VFMD compared with those with less advanced disease.<sup>130</sup> In TAGS, there was no evidence of a difference in the VFMD score and a marginal difference in the VA score between arms; thus, it is not surprising that there was no evidence of a difference in VFQ-25.

We believe that this provides a comprehensive evaluation of vision-related QoL and is sufficient time to capture the short-term differences in effects and to accurately profile the different patient pathways associated with each intervention.

A similar result was observed in the TVT (Tube Versus Trabeculectomy) study, which compared trabeculectomy against the Bearveldt glaucoma drainage device.<sup>51</sup> This study also used VFQ-25. Patients were followed up for 5 years and there was no difference in VFQ-25 at any point in the study.<sup>51</sup> The TVT study, like TAGS, recruited patients with advanced glaucoma in the index eye. A previous primary medicine compared with trabeculectomy study (CIGTS) recruited patients with early glaucoma and used a different patient-reported outcome measure, the Vision Activities Questionnaire, but also found no difference between arms for the duration of the study.<sup>131</sup>

## Secondary outcomes

### Quality of life

#### EQ-5D-5L

There was no evidence of a difference between arms in EQ-5D-5L score at any of the time points measured, suggesting no superiority of either intervention in terms of measures of health status. The value of the EQ-5D-5L in evaluating QoL in glaucoma, and particularly when disease severity changes, is uncertain. Only a small number of studies have evaluated EQ-5D-5L in glaucoma patients and the conclusions have been variable.<sup>124,132-134</sup> Two recently reported RCTs of early glaucoma patients, the LiGHT<sup>59,135</sup> and UKGTS<sup>136</sup> trials, both found poor sensitivity of the EQ-5D-5L to detect change. In the UKGTS study, even when comparing VF progressors with non-progressors, there was no evidence of a difference in EQ-5D-5L results.<sup>136</sup>

#### Health Utility Index version 3

The HUI-3 is a generic patient-reported outcome measure that includes a vision-specific domain; however, there was no evidence of a difference between interventions using this instrument. There is little literature exploring the use of HUI-3 in glaucoma, although one study did demonstrate a difference between cases and controls.<sup>124</sup>



## Glaucoma Utility Index

The GUI is a glaucoma-specific outcome measure that is designed to quantify QoL in glaucoma patients.<sup>14</sup> However, once again, there was no evidence of a difference between the interventions at any time point. This is consistent with a similar observation for GUI from the LiGHT study.<sup>59,135</sup>

## Patient perception of glaucoma getting worse

There was a perception among patients in the medical management arm that their glaucoma was progressing at the 12-month time point. As suggested above, this may coincide with more active glaucoma management involving surgery in some patients in the medical management arm around this time. This effect has disappeared by 24 months. This patient perception is not picked up by any of the composite scores of the instruments used.

The QoL measurement instruments measure binocular vision and, therefore, outcomes are reported at the vision level rather than an individual eye level. This may affect the ability of changes in an eye with poor VFs to influence the QoL score if the VF in the other eye is good. In TAGS in the non-index eye VFMD was  $-6.10$  (SD 7.7) in the trabeculectomy arm and  $-6.13$  (SD 7.1) in the medical management arm and there was no change of MD in either arm over the 24-month follow-up period.

## Clinical effectiveness

### Intraocular pressure

Both of the interventions employed in TAGS are recognised to effectively lower IOP and are recognised by NICE.<sup>65</sup>

In TAGS, the investigators were advised to use the guidance provided by the Canadian perspectives in glaucoma management: setting target IOP range to set the IOP level for individual patients; this suggests an IOP for advanced disease of  $< 15$  mmHg, with reduction of  $\geq 30\%$  from the baseline IOP.<sup>137</sup>

There was a clear reduction in IOP in both arms for the duration of the study from similar baseline values (holding medical management implemented at diagnosis). In the trabeculectomy arm, IOP fell to 12.4 mmHg (SD 5.73 mmHg) at 4 months and remained at around 12 mmHg for the remainder of the study. In the medical management arm, the IOP reduction was initially 4 mmHg lower than that achieved in the trabeculectomy arm [16.4 mmHg (SD 4.12 mmHg) at 4 months and 16.12 mmHg (SD 4.54 mmHg) at 12 months]. There was a further reduction in the medical management arm to 15.07 mmHg (SD 4.8 mmHg) at 24 months, but this reduction was still 3 mmHg lower than that achieved in the trabeculectomy arm. Therefore, for the duration of the study an additional 3–4 mmHg reduction in IOP was achieved in the trabeculectomy arm compared with the medical management arm.

At diagnosis, the IOP was 26.9 mmHg (SD 9.1 mmHg) in the trabeculectomy arm and 25.9 mmHg (SD 8.4 mmHg) in the medical management arm; therefore, the 24-month IOPs represent a reduction of 14.9 mmHg (55%) in the trabeculectomy arm and 10.83 mmHg (42%) in the medical management arm.

The value of medical management in prevention of VF or optic disc progression in patients with ocular hypertension, primary OAG and normal tension glaucoma is well established.<sup>62</sup> Two recent RCTs, both using prostaglandin analogues as primary treatment, as per NICE guidelines,<sup>65</sup> have been undertaken. In the UKGTS,<sup>58</sup> the baseline untreated IOP was 19.6 mmHg (SD 4.6 mmHg) in the medical management arm; by 24 months, an average reduction of 4.0 mmHg (SD 3.4 mmHg) had been achieved, resulting in an IOP of 15 mmHg, mostly on a single medication. The use of prostaglandin monotherapy had a clear benefit in terms of lowering IOP compared with no treatment, and this translated into a statistically and clinically significant reduction in VF progression rate at 24 months.<sup>58</sup> There was a 50% difference in VF progression in the medical management arm compared with the no treatment arm, further establishing the relationship between IOP lowering and VF progression.

The LiGHT trial<sup>59</sup> compared selective laser trabeculoplasty with medical management in the treatment of patients presenting with ocular hypertension and mainly early primary OAG. In the primary OAG group, the baseline IOP was 23 mmHg (IQR 20–27 mmHg). In the medical management arm, IOP fell to a mean of 16.6 mmHg, and only 35% of patients required more than one type of eye drops to achieve this. Despite these results, however, 11 patients required trabeculectomy to prevent further progression.

In the medical management arm of the TAGS trial, a much greater reduction in IOP was achieved in terms of both the absolute IOP reduction and the percentage drop in IOP. This probably reflects the guidance provided for IOP lowering and the recognition that vision is more likely to be preserved in patients with advanced disease if IOP can be reduced.

The IOP lowering achieved in the trabeculectomy arm of the TAGS trial is consistent with current results<sup>61,138,139</sup> reported from the NHS. Kirwan *et al.*'s<sup>61</sup> multicentre service evaluation of augmented trabeculectomies found that the mean IOP achieved at 24 months following augmented trabeculectomy was 12.4 mmHg (SD 4.0 mmHg).<sup>61</sup> Stead and King<sup>138</sup> looked at a group of eyes with advanced glaucoma (mean deviation < -20 dB) and found that, at 24 months, the mean IOP in the cohort was 13.1 mmHg (SD 5.4 mmHg) and the mean number of different types of eye drops required was 0.6. In both of these studies, longer-term follow-up indicated a continued sustained low IOP.

Since the most recently undertaken trial of primary trabeculectomy compared with medical management, CIGTS,<sup>31</sup> which recruited in the early 1990s, there have been significant advances in the technique of trabeculectomy surgery<sup>140</sup> in terms of both anti-metabolite use and post-operative management, which now includes a series of routinely undertaken adjustments to improve IOP control.<sup>141</sup> Therefore, both the safety and the efficacy of trabeculectomy have been improved in this time.<sup>142,143</sup> Similarly, in CIGTS, the primary medical management was initial treatment with a beta-blocker followed by escalating medical therapy, as required. Since CIGTS recruited, several further agents have been introduced, and one type in particular, the prostaglandin analogues, has superior IOP lowering, can be applied once per day and has a low side effect profile and, therefore, is well tolerated, improving both persistence and adherence to the medication.<sup>63</sup> These improvements may reflect that in CIGTS the mean IOP was 15 mmHg in the trabeculectomy arm and 18 mmHg in the medical management arm post treatment; in both cases this was considerably higher than our results. One caveat, however, is that TAGS patients have advanced glaucoma and it is possible that clinicians may have undertaken a more aggressive treatment approach as indicated by consensus guidance to pursue a lower IOP and treat more aggressively, thus aiming for and achieving a lower IOP.

A sustained reduction in IOP is recognised to be the most effective method of preventing further VF loss in glaucoma.<sup>33,34,58,144</sup> In AGIS, long-term follow-up over 8 years indicated that lower IOP in both the predictive analysis (early IOP level behaviour) and the associate analysis (long-term IOP level behaviour) resulted in less VF loss. In the associate analysis, the cohort with the lowest sustained IOP, < 18 mmHg at all follow-up visits, had virtually no VF loss progression. For this arm, this equated to a mean IOP of 12.3 mmHg, which is virtually identical to that achieved for the trabeculectomy arm of TAGS. A difference of 3 mmHg between treatment arms is a clinically important difference and achieving a sustained IOP of 12 mmHg is a clinically important level of IOP reduction for minimising further VF progression.

### **Glaucoma drop usage**

This profile of IOP control is also reflected in the need for glaucoma eye drops. At 4 months, only 61 participants (28%) in the trabeculectomy arm were using eye drops, equivalent to a mean of 0.43 (0.79) different types of eye drops and reflecting the fact that the majority of patients had undergone trabeculectomy and, consequently, were drop free. At the same time point, 210 (96%) participants in the medical management arm were using a mean of 1.77 (0.92) different types of eye drops. At 12 months, eye drop usage in the medical management arm remained unchanged, whereas there was further reduction in the trabeculectomy arm, probably because some patients underwent trabeculectomy as part of treatment

allocation after only 4 months. It is also important to remember that 16 patients declined surgery following randomisation to the trabeculectomy arm and, therefore, remained on eye drops for IOP control. By 24 months, there was a small increase in the number of eye drops in the trabeculectomy arm, suggesting some additional medications required to maintain IOP at a sufficiently low level, and this is consistent with observations from other studies reporting trabeculectomy outcomes.<sup>138,145</sup> By contrast, in the medical management arm, there was a reduction in the mean number of eye drops used and the number of participants using them, reflecting the fact that, during this period, 39 patients (17.3%) required trabeculectomy to control their IOP adequately, following failure of medical management, and subsequently stopped eye drops.

### Visual acuity

There is no evidence of a difference in logMAR VA at baseline between the arms. However, at 4 months the VA in the trabeculectomy arm dropped from 0.15 (SD 0.25) to 0.25 (SD 0.31), whereas it remains unchanged in the medical management arm ( $p < 0.001$ ). This is likely to correspond to some visual reduction experienced by patients undergoing trabeculectomy during the postoperative recovery phase and has resolved by 12 months. At 24 months there has been some further deterioration, VA falling to 0.21 (SD 0.28) in the trabeculectomy arm compared with 0.16 (SD 0.26) in the medical management arm ( $p < 0.006$ ). It is likely that this deterioration is because of the development of cataract in the trabeculectomy arm that has not yet been removed. The development of cataract is well recognised following trabeculectomy<sup>146</sup> and in the CIGTS study cataract extraction was significantly higher in the trabeculectomy arm as opposed to the medical management arm in the first 5 years following randomisation. The hazard ratio for cataract extraction in the trabeculectomy arm compared with the medical management arm was 3.76 (95% CI 2.16 to 6.54;  $p < 0.001$ ) for CIGTS.<sup>147</sup> This difference was clearly visible by 24 months, at which those in the trabeculectomy arm were nearly six times more likely than those in the medical management arm to have had cataract surgery.

### Visual field mean deviation

At 24 months, the mean VFMD was  $-15.15$  in the trabeculectomy arm and  $-15.42$  in the medical management arm with no evidence of a difference (MD 0.18, 95% CI  $-0.58$  to  $0.94$ ;  $p$ -value 0.645). There was no difference in VF progression at 24 months between the arms. To some extent, this is to be expected as 24 months is a relatively short period of time to detect change in glaucoma, especially between arms that have had a good therapeutic response to their interventions. This is particularly true when using a global measure of VF, such as VFMD. In the UKGTS, a difference was demonstrated between arms with a similar IOP difference between treatment arms; however, in UKGTS an intensive VF-testing regime requiring 20 VFs over a 24-month period was undertaken that would not be pragmatic or possible in the context of a publicly funded health system. In addition, for UKGTS they measured individual VF progression using the GPA algorithm, which is not suitable for patients with advanced VF loss. It is possible that extended follow-up for TAGS will reveal differences in VF progression, as was demonstrated in CIGTS with long-term follow-up of patients with more advanced glaucoma<sup>43</sup> and would be expected if lower IOP is maintained in one of the treatment arms.<sup>34</sup>

### Need for cataract surgery

We have estimated cataract formation pragmatically as the need to undergo cataract surgery to improve vision. In the trabeculectomy arm, 28 participants required surgery by 24 months compared with 27 participants in the medical management arm. This is far fewer in the trabeculectomy arm than would be expected from previous studies.<sup>147</sup> In CIGTS, there was a six-fold difference in the need for cataract surgery at 24 months. However, in TAGS there is worsening VA recorded in the trabeculectomy arm at 24 months, which may reflect the development of subclinical cataract in this arm not yet causing sufficient visual reduction to warrant intervention. There may also be some caution on behalf of clinicians and patients to undertake cataract surgery until absolutely necessary because of the risk of compromising successful bleb functioning and causing trabeculectomy failure; therefore, in some cases cataract surgery may be delayed.<sup>148-150</sup>

There was no evidence of a difference between arms for maintaining eligibility to drive at 24 months or eligibility for sight loss registration.

### Safety

In the UK, consultants did not consider medical management to be better or equivalent to primary augmented trabeculectomy when surveyed; however, there was a concern about exposing patients to the risks associated with trabeculectomy and this was the major barrier to carrying out primary surgery. However, clinicians indicated that if robust evidence existed that supported primary surgery they would change their practise accordingly.<sup>35</sup> The perceived 'high risk' associated with trabeculectomy may stem from the National Trabeculectomy Study performed in the late 1990s, which indicated particularly high rates of early complications following trabeculectomy.<sup>151</sup> Improvement in surgical techniques has greatly reduced these perceived risks.<sup>142,143</sup> In addition, virtually all surgery is now carried out by fellowship-trained glaucoma specialists instead of primarily general ophthalmologists, as was the case at the time of the National Trabeculectomy Survey.

One of the main concerns of clinicians is the unexplained irreversible loss of central vision – 'wipe-out' – believed to occur in patients with advanced glaucoma undergoing trabeculectomy.<sup>152</sup> There is no suggestion of unexplained vision loss occurring immediately after surgery in TAGS, which indicates no episodes of wipe-out. In two prospective studies specifically exploring the development of 'wipe-out', no cases of severe, irreversible, unexplained central vision loss were identified, which suggests that 'wipe-out', if it exists, is a very infrequent occurrence.<sup>153,154</sup>

Although visual loss is not uncommon after trabeculectomy, in the majority of cases this is reversible and explained;<sup>153-156</sup> this is the case in TAGS, for which all episodes of visual loss have been identified.

### Vision loss

There were three cases of severe VA loss reported as losing > 10 lines logMAR VA during the course of the trial. All participants were allocated to the trabeculectomy arm. For two of these patients, vision loss resulted from progressive glaucoma damage as a result of inadequately controlled glaucoma. In the third patient, who did not complete the 24-month follow-up, vision reduction was a consequence of central serous retinopathy. There were no cases of severe vision loss because of glaucoma surgery.

### Endophthalmitis

Endophthalmitis is a sight-threatening complication. Following trabeculectomy, it is normally related to a bleb leak or bleb infection. Two patients were reported as having endophthalmitis. However, only one of these was a bleb-related infection. This occurred in a subject originally allocated to the medical management arm who subsequently had a trabeculectomy for uncontrolled IOP. The infection was treated with intravitreal antibiotics and the subject made a good recovery with no vision loss and a satisfactory IOP at 24 months without the need for glaucoma eye drops.

One subject allocated to the trabeculectomy arm developed an endogenous endophthalmitis believed to be related to a diabetic foot ulcer. This subject was also treated with intravitreal antibiotics and made a good visual recovery.

Bleb-related endophthalmitis is a recognised and potentially devastating consequence of trabeculectomy surgery. The frequency of bleb-related endophthalmitis varies: Luebke *et al.*<sup>157</sup> reported 0.004% (7/1816) of trabeculectomies in their consecutive case series<sup>157</sup> and Kim *et al.*<sup>158</sup> found a risk of bleb-related endophthalmitis of 0.005% (9/1959) with a mean follow-up of 54.4 (3.5) years.<sup>158</sup> Several RCTs have reported bleb-related endophthalmitis rates: Wong *et al.*<sup>159</sup> reported no episodes of bleb-related endophthalmitis at 8 years in the Singapore 5-FU study<sup>159</sup> and in CIGTS 0.1% (3/285) of trabeculectomies developed a bleb-related endophthalmitis after an average follow-up of 7.2 years.<sup>160</sup> In both of these studies, trabeculectomies were either unaugmented or augmented with 5-FU, which would be expected

to carry a lower risk for bleb-related problems. In the UK, Kirwan *et al.*<sup>61</sup> reported two cases of bleb-related endophthalmitis within 2 years in their pragmatic multicentre service evaluation cohort of 428 eyes.<sup>61</sup> Alwitry and King<sup>161</sup> undertook a national survey through the British Ophthalmic Surveillance Unit and estimated the rate of bleb-related endophthalmitis in the UK to be 0.17%.<sup>161</sup> In the TAGS trial, 240 trabeculectomies were performed, with one bleb-related endophthalmitis representing an incidence of 1 in 240 (0.4%) at 24 months. In the TAGS trial, the bleb-related endophthalmitis occurred in a patient who had initially been allocated to medical management and subsequently had a trabeculectomy following failed medical management.

### Treatments received

In the trabeculectomy arm, 201 participants (88.5%) received surgery in their index eye and 34 participants (15.0%) received a trabeculectomy in their non-index eye (see *Appendix 3, Table 27*). Of these, four participants did not have a trabeculectomy in their index eye. In the medical management arm, 30 participants (17.3%) received trabeculectomy (see *Table 4*). The reason for participants receiving trabeculectomy in the medical management arm was mainly because of uncontrolled IOP.

Sixteen participants in the trabeculectomy arm declined to have trabeculectomy once allocated to the trabeculectomy arm. It is well recognised that some patients who agree to participate in a trial refuse to have the allocated treatment once randomisation has occurred.<sup>162</sup> In addition, several participants with bilateral advanced glaucoma who were allocated to the trabeculectomy arm did not have surgery performed on their index eye. For these patients, there was a reluctance on the part of patients and patients' clinicians to perform trabeculectomy on the better eye (eye with greater mean deviation value) first and, therefore, in such cases, a decision was made to operate on the worse eye (non-index eye) first and then operate on the index eye when this had settled; however, this did not always occur.

### Economic evaluation

The EQ-5D-5L has been a recommended QoL measure used to estimate QALYs in economic evaluations in the UK. However, a limitation of this generic QoL measure is that it may not be sensitive to small but clinically important changes.<sup>111,112</sup> The GPI and the GUI were developed by Burr *et al.*<sup>55</sup> as a health outcome measure that could be used to estimate preference-based weights in glaucoma.<sup>104</sup> These weights can be used as an alternative to the EQ-5D-5L to estimate QALYs to identify whether or not preference weights from a disease-specific QoL measure are more sensitive to changes in QoL than those from the EQ-5D-5L in individuals with glaucoma. The GUI QoL weight values currently available were estimated based on the responses to a DCE from individuals with self-reported mild or moderate glaucoma, with few responses from those with advanced glaucoma.<sup>104</sup> The aim of the DCE study was to estimate the QoL weights for the GPI in a population with advanced glaucoma and incorporate these values into the economic evaluation.

As expected, participants had a preference for reduced difficulty in the attributes central and near vision, lighting and glare, mobility, and activities of daily living compared with the base level (i.e. severe difficulty). Although some attribute values were estimated to be, on average, negative, there was no evidence that these attribute levels were any different compared with severe difficulty.

The QoL weights were estimated using the results from the logistic regression under the assumption that the health state 111111 (no difficulty with any of the attributes) was equivalent to 1 (perfect health) on the QoL scale. The values for the other attribute levels were anchored on this value to maintain the ratio between the attributes and the levels. Levels with a negative coefficient were assumed to be zero in the estimation of the QoL weights because these levels were close to zero and not statistically significant.

A sensitivity analysis was undertaken incorporating the QoL weights estimated from the DCE and participants' responses to the GUI questionnaire administered at baseline and at 1, 3, 6, 12, 18 and 24 months post randomisation to estimate QALYs and subsequently the cost-effectiveness of surgical

intervention in the management of glaucoma. On average, the GUI produced higher average total QALYs for both interventions than the EQ-5D-5L and HUI-3. There was, however, a smaller difference between treatment arms.

The results of the DCE, support the use of the EQ-5D-5L in individuals with advanced glaucoma. Out of the six attributes valued in the DCE, we found a strong preference for three attributes (central and near vision, mobility, and activities of daily living) with very little utility to be gained from reduced difficulty in the other three attributes. Two of the attributes preferred by individuals with advanced glaucoma are also included in the EQ-5D-5L (mobility and usual activities); therefore, any benefit from an intervention that targets these attributes can arguably be captured by the EQ-5D-5L.

This trial sought to address a paucity of economic evidence for medical compared with surgical interventions in the management of advanced glaucoma.<sup>30</sup> In the economic analysis, the trabeculectomy arm was, on average, more costly and provided more QALYs at 24 months. At 24 months, it was unlikely that trabeculectomy would be considered cost-effective compared with the medical therapy over the range of values for society's willingness to pay for a QALY considered. The driving cost was the initial costs of the trabeculectomy procedure incurred in the first year of the trial in the trabeculectomy arm.

The economic evaluation model suggests that trabeculectomy is likely to be a cost-effective approach compared with medication in patients with severe glaucoma over a lifetime time horizon. The reason for this is that the initial costs (cost of year 1 treatment) are higher for patients assigned to trabeculectomy and these are partly offset in the longer term because these patients receive fewer subsequent procedures and have lower medication use.

It should be noted that there is a small difference in the estimated mean costs and QALYs when comparing the results of the within-trial analysis with those of a 2-year time horizon model-based analysis. These differences are explained partly by the way that we used the trial data to populate our model and the impact that 'random noise' has on the Monte Carlo simulation. A further difference between the trial and the model-based analysis is that the model used age-specific and sex-specific probabilities of death derived from UK life tables, rather than the observed data from obtained from the trial data set.

### **Discrete choice experiment**

The aim of the DCE was to identify the preferences of individuals with advanced glaucoma and update the QoL weights estimated by Burr *et al.*<sup>55</sup> Burr *et al.*<sup>55</sup> estimated their QoL weights from a population with self-reported mild or moderate glaucoma, with only 15% of the sample reporting severe glaucoma. Participants were asked to complete 36 choice-set questions, four of which were rationality tests. The response rate (70% vs. 62%) and number of participants who attempted the choice-set questions ( $n = 308$  vs.  $n = 289$ ) were similar. Our results were comparable to Burr *et al.*<sup>55</sup> in that the strongest preferences were the attributes central and near vision, mobility, and activities of daily living. The ranking of the attribute levels was also similar. Similar to Burr *et al.*,<sup>55</sup> the remaining three attributes (i.e. lighting and glare, eye discomfort, and other effects of glaucoma and its treatment) were not statistically significant in our model but, on average, there were negative preferences. In a sensitivity analysis, we replicated their analysis by combining the levels of these attributes, however, our conclusions did not change and these attributes were not statistically significant. Hence, we can conclude that participants with advanced glaucoma do not have a strong preference for improvements in these attributes (lighting and glare, eye discomfort, and the effects of glaucoma and its treatment). A limitation of combining the attribute levels is that the ratio of preference for that attribute level compared with severe difficulty is lost in the estimation of utility scores. Second, in Burr *et al.*<sup>55</sup> all three levels of lighting and glare (no difficulty, some difficulty and quite a lot of difficulty) were combined but the level no difficulty has a different QoL weight to the other two levels, which were assumed to be zero. This is inconsistent with how they created QoL weights for the other attribute levels that were combined.

### Cost-effectiveness

Within the 24-month time horizon of the trial, medical management was likely to be cost-effective over the range of values for society's willingness to pay for a QALY considered. This recommendation changes when the benefits were extrapolated beyond the time horizon of the trial and are considered across the participant's lifetime. This is important because the median age of glaucoma diagnosis in TAGS is 69 years. Their current average projected life expectancy is 15 years, according to published figures regarding average life expectancy.<sup>119</sup>

For the model-based economic evaluation when a lifetime horizon is taken, trabeculectomy is likely to be considered as cost-effective compared with medical management over the range of values for society's willingness to pay for a QALY considered compared with medication.

There are other studies that have estimated the cost-effectiveness of surgery compared with medical therapy for glaucoma treatment in the UK population. These studies were conducted in different populations of glaucoma patients and gave conflicting results.<sup>112,163-165</sup> Stein *et al.*<sup>112</sup> compared medications with laser trabeculoplasty for the treatment of patients with newly diagnosed mild OAG. They used a Markov model with a 25-year time horizon; the results of this suggested that medication was superior to laser trabeculoplasty, although their analysis assumed optimal medication adherence.<sup>112</sup> Choi *et al.*<sup>113</sup> conducted a cost-effectiveness analysis comparing medication, laser trabeculectomy and trabeculectomy in a South Korean population with mild OAG. Their analysis reported that medication was cost-effective compared with laser trabeculectomy and trabeculectomy.<sup>113</sup> These two studies have limited relevance to our study because they focused on treatments for patients with less severe glaucoma. Only one study was identified that also considered more severe glaucoma, as we have done in TAGS. Guedes *et al.*'s<sup>166</sup> analysis was based on Markov models and aimed to identify the most cost-effective treatment strategy for each severity of glaucoma.<sup>166</sup> The results of this study were similar because this study found that the surgery is cost-effective in participants who are aged < 70 years. Similarly, this study finds that patients who will live for at least 10 years after surgery are more likely to have the benefits outweigh the investment.<sup>166</sup>

### Strengths and limitations

This pragmatic study is representative of what currently happens to patients presenting with advanced glaucoma being managed in the NHS. Consequently, the concluding findings on disease progression, reduction of IOP, vision retention, safety profile of interventions and cost are highly relevant to normal clinical practice.

This trial was unmasked, which allowed the trial to capture any treatment effects on patients' perception, which is clinical reality and reflects the patients experience of the intervention. It answers specific concerns of clinicians regarding the safety of the interventions, which was a major barrier, particularly for consideration of trabeculectomy as a primary procedure.

A common limitation of DCEs is that they can be difficult for participants to understand. However, the majority of those who responded to the DCE questionnaire ( $n = 283$ , 92%) completed all 15 choice-set questions, which suggests that they had a good understanding of the DCE exercise.

Unlike Burr *et al.*,<sup>55</sup> we found negative preferences for 5 of the 18 levels included in the regression model; however, these preferences were not statistically significant. Thus, we have no evidence that the coefficient value is different from the worst state, severe difficulty. We assigned these coefficients a QoL weight of zero where we had no evidence of any difference between these attribute levels and the most severe level (e.g. no difficulty compared with severe difficulty). This assumption potentially created a bias in our QoL weight values as positive coefficients (which were not statistically significant) were assigned a positive QoL weight, albeit close to zero, and it reduced the ratio of preference between the attributes as the negative values were given a slightly higher weighting by assuming that they were zero. However, it is unlikely that this assumption had any implications on our overall results because when

the attribute levels, which were not statistically significant, were combined in a sensitivity analysis the results remained consistent, suggesting that there was no evidence of individuals having a preference for reduced difficulty in these attributes. The second possible bias is that our assumption of assigning a zero value (i.e. levels are equivalent) makes the assumption that evidence of no difference is the same as the there being evidence of no difference in levels. An alternative would be to incorporate the imprecision in estimates into the estimation of QALYs. Although this may be possible, we are unaware of any work that has undertaken this.

There was also an issue with theoretical validity in our model because we found a stronger preference for some difficulty with activities of daily living than for no difficulty with activities associated with daily living, and we had hypothesised that the coefficients would increase with reduced levels of difficulty. A reason for this could be that using a d-efficient design meant that there was no attribute level balance that may have produced this unusual finding. However, a d-efficient design is still recommended because it optimises efficiency as it reduces the standard errors (uncertainty) in the model estimation.<sup>85</sup> Finally, asking participants which alternative; they consider worse is more cognitively challenging than choosing the best alternative; this may explain some of the negative preferences estimated from our model. Further estimation work will be undertaken to explore these negative preferences.

For the economic evaluation, one of the key limitations of the within-trial analysis is the limited time horizon. Primary OAG is a chronic lifelong condition, so the capture of full benefit of any interventions is unlikely to be shown within this time frame. It is also possible that there have been issues with recall for individual participants when completing the resource and QoL questionnaires. A recent study that examined the use of a laser-based intervention and medical management strategy for patients presenting with earlier stage glaucoma was the LiGHT trial.<sup>59</sup> The LiGHT trial assessed selective laser trabeculoplasty versus medical management for glaucoma and ocular hypertension.<sup>59</sup> This study concludes that laser is very likely to be cost-effective within the 3-year trial outcomes. This, potentially, is for a number of reasons. First, a selective laser trabeculoplasty could be a smaller initial intervention cost (the economic results of the trial are yet to be published in full) and that the benefits were examined for an additional year. This would allow the benefits of the initial investments to accrue over a longer time period. It is for this reason that the results of the within-trial analysis should be considered alongside the decision model. Extrapolating the results beyond the initial treatment period could accrue benefits into the future and change the decision regarding which intervention is likely to be cost-effective. It is possible that trabeculectomy may be the most efficient use of resources in a patient with a greater life expectancy who will likely accrue the benefit.

Another consideration is the inclusion of the costs of the non-index eye. When considering the calculation of total costs, the costs for both the index eye and the non-index eye were included. This was the case for a number of reasons. First, the outcome measures of principle interest were not specific to the index eye and when considering vision and QoL the eyes do not work independently of one another. Second, the prognosis of one eye may affect the decisions regarding the management of the other eye. This can be a difficult consideration when carrying out work with vision-related QoL because there is a potential to under value or over value any potential costs. In this study, as shown in *Table 20* within the context of the model, the spread of the severity of glaucoma in the non-index eye is equally spread between the two arms. This means that costs of including the non-index eye should be spread evenly between the two study arms and not affect the marginal difference between the costs.

The main strength of this study is that this model-based economic evaluation was carried out in parallel with the trial-based economic evaluation and was populated with data derived from the trial. All defined parameters in this model-based economic evaluation analysis were based on data collected prospectively as part of TAGS. Moreover, although other economic evaluations exist, the TAGS-based analyses (both the within trial and the model-based analyses) included patients at severe stages of glaucoma only. The results should, therefore, be generalisable across the UK NHS for patients with severe glaucoma.



Using GSS2 for classifying patients (baseline, 12 months and 24 months) into different stages of glaucoma, is another strength because it allowed our study to detect these differences in both cost and utility outcomes between trabeculectomy and medical treatment. Within the model, the severity of glaucoma has been defined based on the state of each eye separately and data on the progression of glaucoma is based on data for both eyes, allowing the modelling of the index eye and non-index eye within the model. Other studies defined health states within their model based on the condition of both eyes together and did not consider each eye separately in the model as we have.<sup>110,111</sup> Although HRQoL and, hence, QALYs are thought to be determined by the quality of vision in the better eye in the case of eye disease,<sup>117</sup> the model structure estimated the chance of unilateral and bilateral progression more precisely over time.

Our evaluation has also repeated the analysis using QALYs based on different measures of utility (EQ-5D-5L, HUI-3 and GUI). The advantage of this is that the EQ-5D-5L is widely used to estimate QALYs in the UK and is the recommended approach by NICE. However, it does not include a specific vision component. The HUI-3, however, is also a generic measure of health status but unlike the EQ-5D-5L has a specific vision component. It should be noted, however, that health state utilities values are derived from a Canadian population rather than a UK population. The GUI is a condition-specific measure for which utilities have been derived directly from TAGs trial conditions. The results of our study showed that using the HUI-3 measure over a patient's lifetime provides the largest difference in QALYs between treatment methods (0.38 additional QALYs of trabeculectomy compared with medical management); QALYs based on the EQ-5D-5L measure are ranked second (with 0.28 additional QALYs of trabeculectomy compared with medical management) whereas the GUI provides the smallest difference in QALYs (0.16 additional QALYs of trabeculectomy compared with medical management).

For the model-based economic evaluation, our analysis has some limitations that need to be considered when interpreting the results. The first limitation is the limited data to extrapolate beyond 2 years; for example, needing further surgery (cataract surgery) to manage complications was not considered in the model because the trial results provide no evidence of a difference between the two arms. Longer-term follow-up, as is planned for TAGS, may further inform the model. Medical therapy is preferred by many patients because it is non-invasive and, from the perspective of the health service, it avoids the initial cost of surgery but may be associated with higher VF loss in the longer term. In part, this may be caused because adherence to medication in the long term may be challenging for patients.<sup>167</sup> Finally, to address uncertainty caused by missing data, we have used multiple imputation data for the model. The results of the multiple imputations suggest that the complete-case analysis may underestimate the difference in effects between the alternatives as a result of those with poorer health outcomes being more likely to withdraw the follow-up.

### **Further research planned**

Further funding has been secured to evaluate clinical and patient-reported outcomes at 5 years to further explore the lifetime experience, patient-reported outcomes and visual loss (VA and VF survival) in this group of participants. These data will be incorporated into an updated economic model once they become available.



## Chapter 8 Conclusions

In summary, this trial shows that treating patients presenting with advanced primary OAG can be undertaken safely with primary augmented surgery. Surgery has a similar effect on patients, HRQoL but is better at reducing IOP, which is likely to reduce further VF progression during the patient's lifetime.

The DCE found similar results to Burr *et al.*<sup>55</sup> in that an individual's strongest preferences were for reduced difficulty in central and near vision, mobility, and activities of daily living. A revised GUI value set from a population with advanced glaucoma is now available.

The within-trial economic evaluation found that, initially, the small incremental change in HRQoL generated by surgery does not offset the additional cost to produce over the range of threshold values for society's willingness to pay for a QALY considered when considering a societal willingness to pay for a QALY threshold. When the benefits for the surgery are extrapolated across the patient's lifetime, the trabeculectomy becomes increasingly more likely to be considered cost-effective.

### Implications for health care

The results of this RCT are widely generalisable. Twenty-seven centres recruited patients with primary OAG, which also included pigment dispersion glaucoma, pseudoexfoliation glaucoma and normal tension glaucoma, and patients from all ethnic backgrounds and adult ages were included. The trial included only patients with advanced disease who were newly diagnosed and, therefore, should be interpreted with caution for patients with less-advanced disease or those who have previously been treated for glaucoma. There are important implications for a resource-limited publicly funded health-care system and for informing future NICE guidelines that have concluded that the evidence supporting treatment options for patients presenting with advanced glaucoma is weak.

The data from this trial support primary surgery as the best primary intervention for patients presenting with advanced glaucoma. The safety of primary trabeculectomy has been demonstrated. There is a clinically important difference in the reduction of IOP achieved with primary surgery, which is likely to reduce the lifetime risk of further disease progression and blindness. Over the 2-year follow-up period, medication had the highest probability of being considered cost-effective at a £20,000 willingness-to-pay threshold. When the results of the trial were extrapolated over the patient's lifetime, trabeculectomy had the highest probability of being considered cost-effective at a £20,000 willingness-to-pay threshold. Further randomised studies would help to confirm these findings and longer-term follow-up of patients enrolled in this study would help to verify the model-based extrapolations reported here.

### Recommendations for research

Long-term follow-up is required because glaucoma is a lifelong condition and lifetime outcomes are essential to fully inform practise. This trial addresses only the first 24-month period following diagnosis; further follow-up is required to further evaluate the patient experience, clinical effectiveness, safety and cost-effectiveness of these interventions in the long term.

It is important to explore the reasons as to why so many people continue to present with advanced glaucoma and it is important to develop strategies to reduce this. Further research into suitable outcome measures to measure QoL for glaucoma is required. Further estimation work is needed to explore the negative preferences reported in the DCE. Further research into cross-walking the VFQ-25 instrument to the EQ-5D-5L is needed to allow comparison between the two measures and to potentially reduce the data collection burden of future trials. Improvements can be made to the methodology for undertaking glaucoma trials to allow differences between arms to be detected in a shorter period of time.



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## Data-sharing statement

All available data can be obtained by contacting the corresponding author.

## Patient data

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

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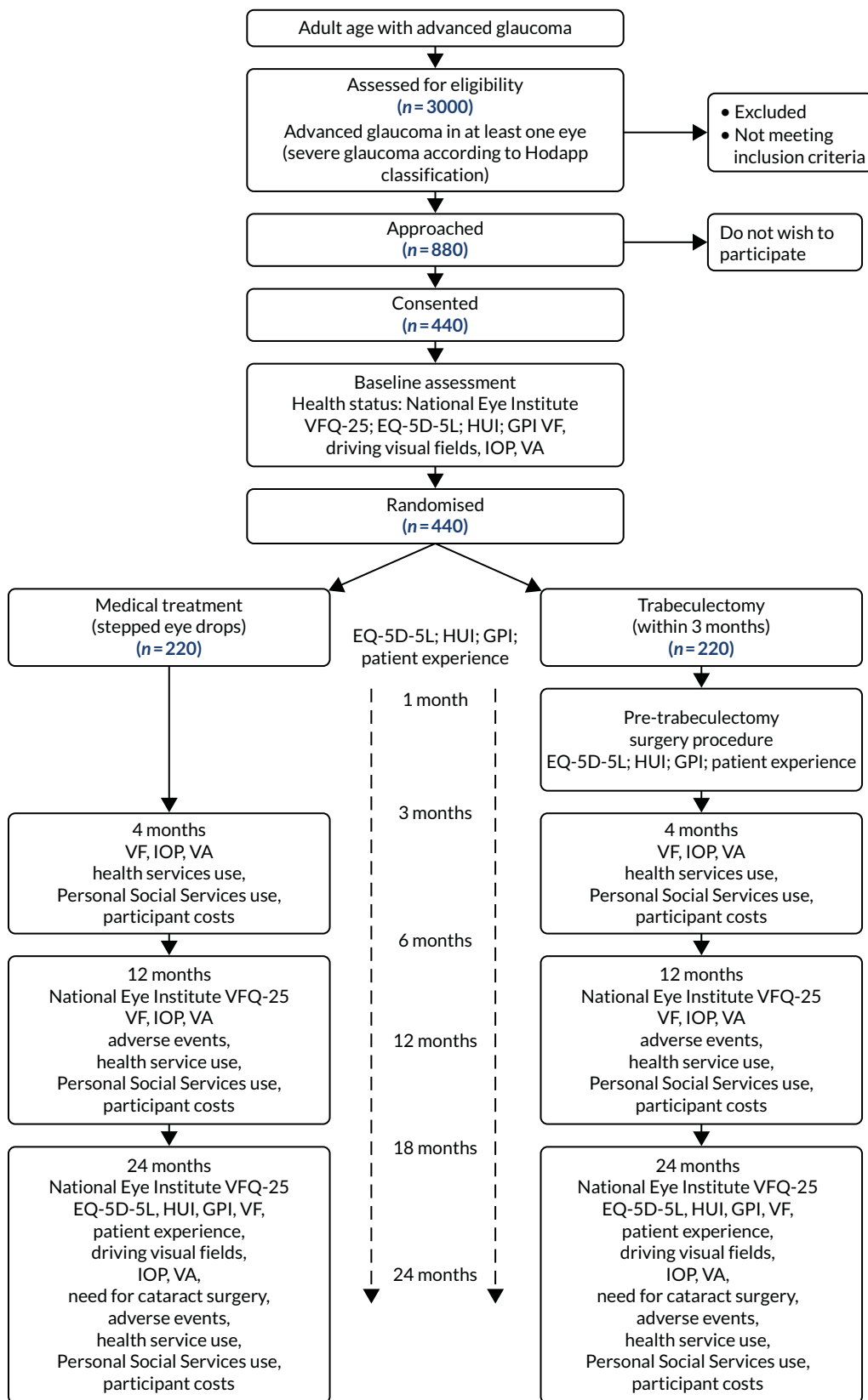
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# Appendix 1 Trial flow diagram







## Appendix 2 Participant characteristics

TABLE 23 Description of excluded patients

Reason <sup>a</sup>	Number of participants (n)	Percentage of total number of participants excluded
<b>Reasons for ineligibility</b>		
Visual fields did not meet criteria	56	24.0
Could not be randomised within 3 months of diagnosis	53	23.1
Secondary glaucomas and primary angle-closure glaucoma	25	10.7
Patient unable to provide informed consent	20	8.7
Unreliable visual fields	14	6.1
Did not meet eligibility criteria	12	5.2
Not advanced glaucoma	11	4.8
Unable to undergo incisional surgery	9	3.9
Non-English speaker	6	2.6
Did not attend appointments	1	0.4
Female who is pregnant, nursing, planning a pregnancy or not using reliable contraception	1	0.4
Other clinical reason	29	12.4
Other non-clinical reason	3	1.3
<b>Reasons for declining to take part</b>		
Patient declined to give a reason	77	27.9
Patient did not want surgery	54	19.6
Lifestyle factors (e.g. work or family commitments)	42	15.2
Did not wish to participate in a trial	40	14.5
Did not wish to be randomised	23	8.3
Had preference for medical or for surgery	23	8.3
Other reasons	37	13.4
a More than one reason is possible.		

TABLE 24 Baseline characteristics for the non-index eye

Characteristic	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Lens status, n (%)		
Phakic	212 (93.4)	206 (91.2)
Pseudophakic	15 (6.6)	19 (8.4)
Missing	–	1 (0.4)
Central corneal thickness, n; mean (SD)	226; 540.6 (38.0)	222; 541.2 (35.6)
Glaucoma eye drops, n (%)		
Prostaglandin analogue	161 (70.9)	159 (70.4)
Beta-blocker	46 (20.3)	36 (15.9)
Carbonic anhydrase inhibitor	33 (14.5)	21 (9.3)
$\alpha$ -agonist	5 (2.2)	2 (0.9)
Ocular comorbidity, n (%)		
Yes	50 (22.0)	48 (21.2)
No	177 (78.0)	178 (78.8)
Ocular comorbidity details, n (%)		
AMD	6 (12.0)	4 (8.0)
Cataract	39 (78.0)	36 (72.0)
Diabetic retinopathy	1 (2.0)	1 (2.0)
Other	8 (16.0)	8 (16.0)
LogMAR VA, n; mean (SD)	224; 0.1 (0.2)	224; 0.1 (0.3)
VFMD (dB), n; mean (SD)	227; -6.1 (7.7)	224; -6.1 (7.1)
IOP (mmHg), n; mean (SD)		
Diagnosis	226; 23.3 (7.6)	222; 22.4 (6.3)
Baseline	222; 18.0 (5.1)	220; 17.9 (4.2)

AMD, age-related macular degeneration.

TABLE 25 Hodapp–Parrish–Anderson classification of glaucoma severity

Classification	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Mean deviation of < -12.00 dB	161 (70.9)	163 (72.1)
> 20 points defective at the 1% level	198 (87.2)	207 (91.6)
A point in the central 5 degrees has a sensitivity of 0 dB	143 (63.0)	129 (57.1)
> 50% of points defective in the pattern deviation probability plot at the 5% level	193 (85.0)	202 (89.4)
Points with 5 degrees of fixation under 15 dB sensitivity in both upper and lower hemifields	42 (18.5)	51 (22.6)

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## Appendix 3 Clinical results

TABLE 26 Details of trabeculectomy procedure

Surgery details	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Received surgery in their index eye	201 (88.5)	39 (17.3)
Surgery clinical report form provided	199	27
<b>Surgeon grade<sup>a</sup></b>		
Consultant	176 (88.4)	25 (92.6)
Fellow	37 (18.6)	5 (18.5)
Other	11 (5.5)	3 (11.1)
Missing	3 (1.5)	0 (0)
<b>Anaesthetist grade<sup>a</sup></b>		
Consultant	120 (60.3)	21 (77.8)
Fellow	16 (8.0)	3 (11.1)
Other	16 (8.0)	3 (11.1)
Missing	58 (29.1)	4 (14.8)
<b>Type of anaesthesia</b>		
Regional block	163 (81.9)	23 (85.2)
General	35 (17.6)	4 (14.8)
Missing	1 (0.5)	0 (0)
<b>Traction suture</b>		
Corneal	184 (92.5)	24 (88.9)
Superior rectus	5 (2.5)	1 (3.7)
Missing	10 (5.0)	2 (7.4)
<b>Conjunctival flap</b>		
Fornix based	186 (93.5)	26 (96.3)
Limbal based	12 (6.0)	1 (3.7)
Missing	1 (0.5)	0 (0)
<b>MMC dose</b>		
0.2 mg/ml	141 (70.9)	23 (85.2)
0.4 mg/ml	42 (21.1)	3 (11.1)
Other	15 (7.5)	1 (3.7)
Missing	1 (0.5)	0 (0)
<b>MMC duration</b>		
3 minutes	151 (75.9)	21 (77.8)
Other	45 (22.6)	5 (18.5)
Missing	3 (1.5)	1 (3.7)

continued

TABLE 26 Details of trabeculectomy procedure (continued)

Surgery details	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>Scleral flap sutures</b>		
Interrupted	163 (81.9)	24 (88.9)
Releasable	86 (43.2)	14 (51.9)
Adjustable	29 (14.6)	3 (11.1)
<b>A/C maintainer</b>		
Yes	61 (30.7)	10 (37.0)
No	137 (68.8)	17 (63.0)
Missing	1 (0.5)	0 (0)
<b>Pre-operative aproclonidine</b>		
Yes	143 (71.9)	20 (74.1)
No	55 (27.6)	7 (25.9)
Missing	1 (0.5)	0 (0)
<b>Peri-operative miochol</b>		
Yes	23 (11.6)	3 (11.1)
No	175 (87.9)	24 (88.9)
Missing	1 (0.5)	0 (0)
<b>Peri-operative viscoelastic</b>		
Yes	36 (18.1)	7 (25.9)
No	162 (81.4)	20 (74.1)
Missing	1 (0.5)	0 (0)
<b>Subconjunctival antibiotic</b>		
Yes	144 (72.4)	23 (85.2)
No	54 (27.1)	4 (14.8)
Missing	1 (0.5)	0 (0)
<b>Subconjunctival steroid</b>		
Yes	175 (87.9)	25 (92.6)
No	23 (11.6)	2 (7.4)
Missing	1 (0.5)	0 (0)
MMC, mitomycin C. a More than one can be present.		

TABLE 27 Trabeculectomy procedure for non-index eye

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Received trabeculectomy in their non-index eye, n (%)	34 (15.0)	13 (5.8)
Time to trabeculectomy (weeks), n; median (IQR)	32; 24.1 (9.2–40.9)	8; 54.7 (27.1–64.1)
<b>Reasons for trabeculectomy,<sup>a</sup> n (%)</b>		
Uncontrolled IOP		6 (46.2)
Visual field progression		3 (23.1)
Missing		5 (38.5)
Trabeculectomy clinical report form provided	34	8
<b>Pre-operation drugs, n (%)</b>		
Carbonic anhydrase inhibitor	8 (23.5)	2 (25.0)
Prostaglandin analogue	26 (76.5)	5 (62.5)
Beta-blocker	14 (41.2)	3 (37.5)
α-agonist	2 (5.9)	0 (0)
<b>Diamox</b>		
Yes, n (%)	1 (2.9)	0 (0)
No, n (%)	32 (94.1)	8 (100.0)
Missing, n (%)	1 (2.9)	0 (0)
Pre-operative IOP, n; mean (SD)	32; 18.3 (6.2)	7; 20.1 (2.7)
<b>Surgeon grade,<sup>a</sup> n (%)</b>		
Consultant	32 (94.1)	7 (87.5)
Fellow	4 (11.8)	1 (12.5)
Other	1 (2.9)	1 (12.5)
Missing	1 (2.9)	1 (12.5)
<b>Anaesthetist grade,<sup>a</sup> n (%)</b>		
Consultant	18 (52.9)	3 (37.5)
Fellow	2 (5.9)	0 (0)
Other	3 (8.8)	0 (0)
Missing	13 (38.2)	5 (62.5)
<b>Type of anaesthesia, n (%)</b>		
Regional block	23 (67.6)	7 (87.5)
General	10 (29.4)	0 (0)
Missing	1 (2.9)	1 (12.5)

continued

TABLE 27 Trabeculectomy procedure for non-index eye (continued)

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>Traction suture, n (%)</b>		
Corneal	31 (91.2)	7 (87.5)
Superior rectus	1 (2.9)	0 (0)
Missing	2 (5.9)	1 (12.5)
<b>Conjunctival flap, n (%)</b>		
Fornix based	33 (97.1)	7 (87.5)
Missing	1 (2.9)	1 (12.5)
<b>MMC dose, n (%)</b>		
0.2 mg/ml	23 (67.6)	4 (50.0)
0.4 mg/ml	8 (23.5)	3 (37.5)
Other	2 (5.9)	0 (0)
Missing	1 (2.9)	1 (12.5)
<b>MMC duration, n (%)</b>		
3 minutes	24 (70.6)	6 (75.0)
Other	9 (26.5)	1 (12.5)
Missing	1 (2.9)	1 (12.5)
<b>Scleral flap sutures, n (%)</b>		
Interrupted	28 (82.4)	6 (75.0)
Releasable	13 (38.2)	4 (50.0)
Adjustable	4 (11.8)	1 (12.5)
<b>A/C maintainer, n (%)</b>		
Yes	6 (17.6)	5 (62.5)
No	27 (79.4)	2 (25.0)
Missing	1 (2.9)	1 (12.5)
<b>Pre-operative lopidine, n (%)</b>		
Yes	21 (61.8)	7 (87.5)
No	12 (35.3)	0 (0)
Missing	1 (2.9)	1 (12.5)
<b>Peri-operative miochol, n (%)</b>		
Yes	4 (11.8)	0 (0)
No	29 (85.3)	7 (87.5)
Missing	1 (2.9)	1 (12.5)
<b>Peri-operative viscoelastic, n (%)</b>		
Yes	6 (17.6)	3 (37.5)
No	27 (79.4)	4 (50.0)
Missing	1 (2.9)	1 (12.5)

TABLE 27 Trabeculectomy procedure for non-index eye (continued)

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>Subconjunctival antibiotic, n (%)</b>		
Yes	25 (73.5)	7 (87.5)
No	8 (23.5)	0 (0)
Missing	1 (2.9)	1 (12.5)
<b>Subconjunctival steroid, n (%)</b>		
Yes	29 (85.3)	7 (87.5)
No	4 (11.8)	0 (0)
Missing	1 (2.9)	1 (12.5)
MMC, mitomycin C. a More than one can be present.		

TABLE 28 Per-protocol analysis for VFQ-25

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>VFQ-25</b>					
Baseline	200; 86.8 (14.1)	185; 87.5 (12.9)			
4 months	190; 84.8 (15.3)	177; 87.2 (12.8)	-1.78	-4.24 to 0.69	0.158
12 months	193; 85.4 (14.3)	171; 87.1 (12.9)	-0.86	-3.34 to 1.62	0.496
24 months	187; 85.3 (14.1)	168; 84.9 (16.4)	0.95	-1.54 to 3.45	0.454
<b>VFQ-25 subscales</b>					
<i>Near activities</i>					
Baseline	199; 84.2 (18.6)	185; 85.2 (16.1)			
4 months	189; 83.7 (18.0)	175; 85.6 (16.2)	-1.30	-5.05 to 2.45	0.498
12 months	193; 84.0 (18.6)	171; 85.5 (17.7)	-0.74	-4.50 to 3.02	0.700
24 months	185; 82.4 (18.6)	167; 83.2 (19.6)	-0.13	-3.93 to 3.68	0.948
<i>Distance activities</i>					
Baseline	200; 88.0 (16.5)	185; 89.5 (14.4)			
4 months	189; 87.6 (16.9)	177; 89.6 (14.3)	-0.88	-4.13 to 2.37	0.594
12 months	193; 88.5 (16.0)	171; 89.2 (15.4)	0.41	-2.86 to 3.68	0.806
24 months	187; 88.2 (16.0)	167; 86.5 (18.9)	2.51	-0.78 to 5.80	0.135
<i>Dependency</i>					
Baseline	200; 93.4 (18.3)	184; 95.0 (14.8)			
4 months	189; 90.6 (20.9)	177; 93.6 (17.2)	-2.33	-5.86 to 1.19	0.194
12 months	192; 92.2 (19.4)	171; 94.8 (13.9)	-1.48	-5.02 to 2.06	0.413
24 months	186; 93.4 (16.1)	167; 92.8 (18.4)	1.73	-1.85 to 5.31	0.344
continued					

TABLE 28 Per-protocol analysis for VFQ-25 (continued)

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<i>Driving</i>					
Baseline	150; 85.2 (28.0)	130; 86.5 (23.6)			
4 months	136; 81.8 (30.8)	127; 84.4 (25.7)	0.49	-7.03 to 8.01	0.899
12 months	138; 81.4 (28.9)	121; 81.5 (28.5)	1.58	-6.02 to 9.17	0.684
24 months	130; 81.8 (28.8)	112; 81.8 (26.6)	2.76	-4.92 to 10.44	0.481
<i>General health</i>					
Baseline	199; 63.1 (23.3)	185; 60.7 (22.2)			
4 months	189; 66.3 (23.6)	176; 64.2 (20.8)	-0.20	-4.71 to 4.31	0.930
12 months	193; 66.2 (23.7)	170; 59.3 (23.2)	5.15	0.61 to 9.68	0.026
24 months	187; 63.5 (25.6)	168; 59.1 (24.7)	2.41	-2.16 to 6.97	0.302
<i>Role difficulties</i>					
Baseline	200; 86.7 (20.2)	184; 88.1 (19.7)			
4 months	190; 81.8 (25.1)	177; 88.2 (19.0)	-6.64	-10.88 to -2.39	0.002
12 months	192; 83.1 (23.2)	171; 86.3 (19.8)	-2.97	-7.24 to 1.30	0.173
24 months	187; 83.0 (22.8)	167; 84.1 (22.4)	-1.25	-5.56 to 3.06	0.570
<i>Mental health</i>					
Baseline	200; 80.8 (21.8)	185; 82.9 (19.1)			
4 months	190; 79.0 (24.1)	177; 84.6 (19.0)	-4.39	-8.40 to -0.38	0.032
12 months	193; 80.0 (21.8)	171; 84.4 (19.0)	-3.29	-7.32 to 0.74	0.109
24 months	187; 80.9 (20.4)	168; 82.5 (21.2)	-0.75	-4.81 to 3.31	0.719
<i>General vision</i>					
Baseline	197; 74.9 (14.8)	184; 73.2 (13.5)			
4 months	189; 71.1 (14.6)	176; 75.0 (12.2)	-4.46	-7.45 to -1.47	0.003
12 months	192; 72.8 (14.6)	170; 74.2 (14.0)	-2.05	-5.06 to 0.95	0.180
24 months	187; 72.9 (13.5)	168; 72.9 (14.9)	-0.73	-3.76 to 2.30	0.637
<i>Social function</i>					
Baseline	199; 94.7 (12.5)	185; 94.7 (12.1)			
4 months	189; 94.9 (12.4)	177; 95.0 (11.3)	-0.23	-3.05 to 2.59	0.871
12 months	193; 94.1 (13.9)	170; 94.7 (11.8)	-0.76	-3.60 to 2.08	0.602
24 months	186; 94.7 (12.6)	168; 92.9 (17.1)	1.36	-1.50 to 4.22	0.350
<i>Colour vision</i>					
Baseline	198; 96.6 (11.4)	183; 96.4 (10.9)			
4 months	187; 97.1 (9.2)	175; 96.9 (10.6)	0.26	-1.81 to 2.33	0.806
12 months	192; 96.1 (11.3)	167; 97.3 (9.1)	-1.11	-3.20 to 0.99	0.300
24 months	186; 95.3 (14.5)	167; 94.6 (16.0)	0.90	-1.20 to 3.00	0.401
<i>Peripheral vision</i>					
Baseline	199; 86.1 (21.4)	185; 87.7 (19.9)			
4 months	188; 85.8 (20.7)	175; 86.1 (19.8)	-0.41	-4.88 to 4.07	0.859



TABLE 28 Per-protocol analysis for VFQ-25 (continued)

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
12 months	193; 86.8 (20.1)	169; 86.5 (20.6)	0.44	-4.06 to 4.93	0.849
24 months	185; 84.9 (19.9)	167; 84.3 (22.4)	0.26	-4.27 to 4.78	0.911
<i>Ocular pain</i>					
Baseline	199; 84.2 (19.3)	185; 85.1 (16.6)			
4 months	190; 81.1 (19.6)	177; 81.1 (18.7)	0.33	-3.10 to 3.75	0.851
12 months	193; 81.3 (20.3)	171; 83.4 (15.4)	-1.46	-4.91 to 1.98	0.405
24 months	187; 81.9 (19.7)	168; 81.0 (18.9)	1.72	-1.76 to 5.20	0.334

TABLE 29 Complier-average causal effect analysis for VFQ-25

Time point	MD	95% CI	p-value
4 months	-1.75	-4.13 to 0.63	0.151
12 months	-0.99	-3.74 to 1.76	0.479
24 months	1.52	-1.27 to 4.30	0.286

TABLE 30 Sensitivity analysis incorporating data from the non-index eye for participants with bilateral disease

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227) N = 271	Medical management (N = 226) N = 270			
<i>Intraocular pressure (mmHg)</i>					
Baseline	266; 19.29 (6.24)	265; 18.97 (5.55)			
4 months	259; 12.87 (6.00)	262; 16.35 (4.05)	-3.74	-4.69 to -2.79	< 0.001
12 months	257; 12.17 (4.50)	248; 16.15 (4.40)	-4.21	-5.17 to -3.25	< 0.001
24 months	246; 12.63 (4.65)	240; 15.12 (4.71)	-2.74	-3.72 to -1.77	< 0.001
<i>LogMAR VA</i>					
Baseline	268; 0.15 (0.25)	267; 0.17 (0.26)			
4 months	250; 0.24 (0.29)	258; 0.16 (0.23)	0.10	0.06 to 0.14	< 0.001
12 months	253; 0.18 (0.25)	249; 0.16 (0.25)	0.04	-0.00 to 0.08	0.077
24 months	239; 0.21 (0.28)	237; 0.16 (0.25)	0.07	0.02 to 0.11	0.003
<i>Visual fields mean deviation (dB)</i>					
Baseline	271; -15.38 (6.93)	270; -15.66 (6.51)			
4 months	251; -14.68 (7.14)	258; -15.09 (6.60)	0.03	-0.74 to 0.81	0.930
12 months	255; -15.14 (7.28)	249; -15.30 (6.71)	-0.17	-0.95 to 0.60	0.663
24 months	241; -15.57 (7.06)	238; -15.84 (6.59)	0.11	-0.68 to 0.90	0.788

N refers to number of eyes.

TABLE 31 Visual fields mean deviation (dB) sensitivity analysis

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>SITA standard only</b>					
Baseline	222; -14.91 (6.33)	219; -15.23 (6.28)			
4 months	208; -14.37 (6.78)	212; -14.85 (6.56)	0.01	-0.73 to 0.74	0.987
12 months	211; -14.84 (6.93)	204; -14.86 (6.49)	0.03	-0.70 to 0.77	0.927
24 months	198; -15.13 (6.68)	195; -15.54 (6.42)	0.24	-0.51 to 0.99	0.536
<b>Eligible visual field at baseline</b>					
Baseline	222; -14.98 (6.29)	221; -15.24 (6.34)			
4 months	207; -14.46 (6.45)	212; -14.78 (6.51)	-0.22	-0.87 to 0.43	0.505
12 months	211; -14.83 (6.75)	205; -14.90 (6.51)	-0.06	-0.72 to 0.59	0.854
24 months	199; -15.12 (6.65)	196; -15.43 (6.32)	0.15	-0.52 to 0.82	0.658

TABLE 32 Eligible to be registered visual impairment at baseline

Visual impairment	Treatment arm, n/N (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
No	214/227 (94.3)	212/226 (93.8)
Sight impaired	10/227 (4.4)	12/226 (5.3)
Severely sight impaired	3/227 (1.3)	2/226 (0.9)

TABLE 33 Safety events: as treated for non-index eye

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of participants with a safety event, n (%)	57 (23.8)	73 (34.3)
<b>SAE</b>		
Number of participants and events, n/N (%)	1/1 (100.0)	0 (0)
Details (n)		
Significant disability	1	-
Expected event	1	-
Classification (n)		
Glaucoma progression despite treatment	1	-
<b>4 months</b>		
Number of participants, n/N (%)	23/234 (9.8)	31/203 (15.3)
Number of events (n)	30	39
Details (n)		

TABLE 33 Safety events: as treated for non-index eye (continued)

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Irreversible loss of $\geq 10$ ETDRS letter <sup>a</sup>	1	–
Drop related	22	19
Ocular surface related	4	17
Non-specific	3	2
Glaucoma progression	–	1
<b>12 months</b>		
Number of participants, n/N (%)	23/233 (9.9)	38/194 (19.6)
Number of events (n)	28	41
Details (n)		
Shallow anterior chamber	2	–
Early bleb leak	1	–
Persistent uveitis	1	–
Ptosis	–	1
Non-specific unrelated uveitis	–	1
Drop related	13	25
Ocular surface related	8	8
Potential AE related to surgery	1	1
Non-specific	–	6
Cataract	1	–
<b>24 months</b>		
Number of participants, n/N (%)	25/228 (11.0)	33/191 (17.3)
Number of events (n)	3	38
Details (n)		
Shallow anterior chamber	1	1
Early bleb leak	2	–
Macular oedema	–	1
Hyphema	2	–
Choroidal effusion	1	–
Iris incarceration	1	–
Drop related	12	16
Ocular surface related	8	7
Non-specific	1	11
Glaucoma progression	–	1
Cataract	1	–
Related to cataract surgery	1	1

<sup>a</sup> Also recorded as a SAE.

TABLE 34 Safety events: as allocated for non-index eye

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Number of participants with a safety event, n (%)	53 (23.3)	77 (34.1)
<b>SAE</b>		
Number of participants and events, n/N (%)	1/1 (100.0)	0 (0)
Details (n)		
Significant disability	1	-
Expected event	1	-
Classification (n)		
Glaucoma progression despite treatment	1	-
<b>4 months</b>		
Number of participants, n/N (%)	18/217 (8.3)	36/220 (16.4)
Number of events (n)	23	45
Details (n)		
Irreversible loss of $\geq 10$ ETDRS letter <sup>a</sup>	1	-
Drop related	9	32
Ocular surface related	10	10
Non-specific	2	3
Glaucoma progression	1	-
<b>12 months</b>		
Number of participants, n/N (%)	25/216 (11.6)	36/211 (17.1)
Number of events (n)	29	40
Details (n)		
Shallow anterior chamber	2	-
Early bleb leak	1	-
Persistent uveitis	1	-
Ptosis	1	-
Non-specific unrelated uveitis	1	-
Drop related	12	26
Ocular surface related	7	9
Potential AE related to surgery	1	1
Non-specific	2	4
Cataract	1	-
<b>24 months</b>		
Number of participants, n/N (%)	21/211 (10.0)	37/208 (17.8)
Number of events (n)	25	43
Details (n)		
Shallow anterior chamber	1	1
Early bleb leak	1	1

TABLE 34 Safety events: as allocated for non-index eye (continued)

	Treatment arm	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Macular oedema	-	1
Hyphema	2	-
Choroidal effusion	1	-
Iris incarceration	1	-
Drop related	12	16
Ocular surface related	4	11
Non-specific	2	10
Glaucoma progression	-	1
Cataract	-	1
Related to cataract surgery	1	1

a Also recorded as a SAE.

TABLE 35 Intraocular pressure, logMAR VA and VFMD for non-index eye

Time point	Treatment arm, n; mean (SD)		Adjusted MD	95% CI	p-value
	Trabeculectomy (N = 227)	Medical management (N = 226)			
<b>Intraocular pressure (mmHg)</b>					
Baseline	222; 17.95 (5.13)	220; 17.86 (4.17)			
4 months	216; 16.77 (4.58)	220; 16.34 (3.78)	0.31	-0.54 to 1.17	0.473
12 months	215; 16.36 (4.89)	209; 16.42 (3.75)	-0.13	-0.99 to 0.74	0.775
24 months	206; 16.08 (4.25)	202; 15.58 (3.76)	0.33	-0.55 to 1.20	0.466
<b>LogMAR VA</b>					
Baseline	224; 0.07 (0.18)	224; 0.09 (0.25)			
4 months	210; 0.07 (0.18)	217; 0.09 (0.23)	0.00	-0.05 to 0.05	0.952
12 months	212; 0.05 (0.19)	209; 0.09 (0.25)	-0.02	-0.07 to 0.03	0.389
24 months	200; 0.06 (0.19)	199; 0.09 (0.23)	-0.02	-0.07 to 0.03	0.455
<b>Visual fields mean deviation (dB)</b>					
Baseline	227; -6.10 (7.69)	224; -6.13 (7.09)			
4 months	212; -5.87 (7.47)	216; -6.03 (6.83)	-0.01	-0.73 to 0.71	0.979
12 months	214; -6.34 (7.74)	208; -6.33 (7.15)	-0.11	-0.83 to 0.61	0.766
24 months	201; -6.80 (7.83)	200; -6.75 (7.44)	-0.17	-0.91 to 0.56	0.644

TABLE 36 Antiglaucoma medication in non-index eye

Time point	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>4 months</b>	<b>N = 217</b>	<b>N = 220</b>
Number of glaucoma eye drops, mean (SD)	1.01 (0.75)	1.60 (0.92)
Number of participants receiving eye drops by glaucoma eye drop type, n (%)		
Prostaglandin analogue	160 (73.7)	193 (87.7)
Beta-blocker	54 (24.9)	74 (33.6)
Carbonic anhydrase inhibitor	31 (14.3)	58 (26.4)
$\alpha$ -agonist	6 (2.8)	11 (5.0)
<b>12 months</b>	<b>N = 216</b>	<b>N = 211</b>
Number of glaucoma eye drops, mean (SD)	0.95 (0.75)	1.69 (0.95)
Number of participants receiving eye drops by glaucoma eye drop type, n (%)		
Prostaglandin analogue	147 (68.1)	182 (86.3)
Beta-blocker	55 (25.5)	92 (43.6)
Carbonic anhydrase inhibitor	32 (14.8)	61 (28.9)
$\alpha$ -agonist	3 (1.4)	16 (7.6)
Pilocarpine	1 (0.5)	0 (0)
<b>24 months</b>	<b>N = 211</b>	<b>N = 208</b>
Number of glaucoma eye drops, mean (SD)	1.00 (0.93)	1.61 (1.03)
Number of participants receiving eye drops by glaucoma eye drop type, n (%)		
Prostaglandin analogue	131 (62.1)	159 (76.4)
Beta-blocker	54 (25.6)	93 (44.7)
Carbonic anhydrase inhibitor	40 (19.0)	69 (33.2)
$\alpha$ -agonist	10 (4.7)	14 (6.7)
Pilocarpine	0 (0)	1 (0.5)

TABLE 37 The number of different bottles of medication: index eye as allocated

Time point	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
<b>4 months</b>	<b>N = 214</b>	<b>N = 218</b>
None	156 (72.9)	10 (4.6)
1	36 (16.8)	108 (49.5)
2	21 (9.8)	93 (42.7)
3	1 (0.5)	6 (2.8)
> 3	0 (0)	1 (0.5)
<b>12 months</b>	<b>N = 211</b>	<b>N = 205</b>
None	173 (82.0)	23 (11.2)
1	17 (8.1)	77 (37.6)
2	20 (9.5)	99 (48.3)
3	1 (0.5)	4 (2.0)
> 3	0 (0)	2 (1.0)
<b>24 months</b>	<b>N = 210</b>	<b>N = 201</b>
None	158 (75.2)	44 (21.9)
1	19 (9.0)	67 (33.3)
2	31 (14.8)	83 (41.3)
3	1 (0.5)	4 (2.0)
> 3	1 (0.5)	3 (1.5)

TABLE 38 The number of different bottles of medication: as treated

Time point	Treatment arm, n (%)	
	Trabeculectomy (N = 227)	Medical management (N = 226)
Treatment received	n = 240	n = 213
<b>4 months</b>	<b>N = 232</b>	<b>N = 200</b>
None	163 (70.3)	3 (1.5)
1	33 (14.2)	111 (55.5)
2	33 (14.2)	81 (40.5)
3	3 (1.3)	4 (2.0)
> 3	0 (0)	1 (0.5)
<b>12 months</b>	<b>N = 231</b>	<b>N = 185</b>
None	190 (82.3)	6 (3.2)
1	10 (4.3)	84 (45.4)
2	28 (12.1)	91 (49.2)
3	2 (0.9)	3 (1.6)
> 3	1 (0.4)	1 (0.5)
<b>24 months</b>	<b>N = 226</b>	<b>N = 185</b>
None	190 (84.1)	12 (6.5)
1	11 (4.9)	75 (40.5)
2	22 (9.7)	92 (49.7)
3	1 (0.4)	4 (2.2)
> 3	2 (0.9)	2 (1.1)



## Appendix 4 Discrete choice experiment

TABLE 39 Baseline characteristics by DCE block

Characteristic	Total (N = 308)	Block, n (%)			
		1 (N = 77)	2 (N = 74)	3 (N = 75)	4 (N = 82)
Age (years), mean (SD)	68.42 (11)	68.01 (12)	69.35 (10)	69.01 (10)	67.40 (11)
Male, n (%)	205 (67)	54 (70)	45 (61)	49 (65)	57 (70)
<b>Ethnicity, n (%)</b>					
White	281 (91)	69 (90)	65 (88)	72 (96)	75 (92)
Asian - Oriental	1 (< 1)		1 (1)		
Afro-Caribbean	19 (6)	6 (8)	6 (8)	3 (4)	4 (5)
Asian: India/Pakistan/Bangladesh	5 (2)	2 (3)	1 (1)		2 (2)
Mixed	1 (< 1)		1 (1)		
Nigerian	1 (< 1)	1 (1)			1 (1)
<b>Level of education, n (%)</b>					
None	18 (6)	4 (4)	5 (7)	3 (4)	6 (7)
Secondary school	144 (47)	29 (38)	34 (46)	42 (56)	39 (48)
College	95 (31)	29 (38)	24 (32)	18 (24)	24 (29)
University	45 (14)	12 (16)	9 (12)	11 (15)	13 (16)
<b>Annual income, n (%)</b>					
< £6000	17 (6)	2 (3)	5 (7)	3 (4)	7 (9)
£6000–10,000	23 (7)	2 (3)	5 (7)	7 (9)	9 (11)
£10,001–15,000	52 (17)	9 (12)	14 (19)	18 (24)	11 (13)
£15,001–20,000	41 (13)	9 (12)	13 (18)	8 (11)	11 (13)
£20,001–25,000	39 (13)	18 (23)	8 (11)	5 (7)	8 (10)
£25,001–30,000	18 (6)	5 (6)	6 (8)	2 (3)	5 (6)
£30,001–35,000	27 (9)	10 (13)	4 (5)	5 (7)	8 (10)
> £35,000	62 (20)	13 (17)	14 (19)	17 (23)	18 (22)
<b>Self-reported time to complete DCE</b>					
Time (minutes), mean (SD)	23.96 (17)	25.84 (20)	22.34 (14)	25.23 (17)	23.03 (16)
Time given in minutes/hours, n (%)	286 (97)				
1.5 days, n (%)	1 (< 1)				
2–3 days, n (%)	1 (< 1)				
3 weeks, n (%)	1 (< 1)				

continued

TABLE 39 Baseline characteristics by DCE block (continued)

Characteristic	Total (N = 308)	Block, n (%)			
		1 (N = 77)	2 (N = 74)	3 (N = 75)	4 (N = 82)
7 days, n (%)	1 (< 1)				
1 week, n (%)	1 (< 1)				
Ages, n (%)	1 (< 1)				
Not long, n (%)	1 (< 1)				
Too long, n (%)	1 (< 1)				
Weeks/month, n (%)	1 (< 1)				
<b>Number of completed choice sets, n (%)</b>					
15	283 (92)	72 (94)	64 (86)	71 (94)	76 (93)
14	6 (2)	2 (3)	3 (4)		1 (1)
13	1 (< 1)		1 (1)		
12	5 (2)	2 (3)		2 (3)	1 (1)
11	4 (1)	1 (1)		2 (3)	1 (1)
7	2 (1)		2 (3)		
6	1 (< 1)		1 (1)		
5	1 (< 1)				1 (1)
2	2 (1)		1 (1)		1 (1)
1	3 (1)		2 (3)		1 (1)

## Appendix 5 Health economic results

### Unit costs

The unit costs utilised in the economic evaluation are described in *Tables 40–43*.

TABLE 40 Unit costs for hospital appointments

Item	Cost (£)	Unit	Reference	Notes
Inpatient	448	Per night	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	Ward costs per night
Outpatient appointment	105.09	Per appointment	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	Consultant-led ophthalmology outpatient costs

TABLE 41 Unit costs for glaucoma procedures

Ophthalmic procedure	Source	HRG code	Unit cost	Comments
Trabeculectomy (day case)	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ92B	1639.44	Very major, glaucoma or iris procedures, with CC score of 0–1
Trabeculectomy (inpatient)	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ92B	2184.07	Very major, glaucoma or iris procedures, with CC score of 0–1
Massage	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ24G	143.29	Minor, glaucoma or iris procedures
Adjustment/suture lysis/releasable release	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ95	143.29	Minor, glaucoma or iris procedures
5-FU injection	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ95Z	149.69	Minor, glaucoma or iris procedures plus unit costs of fluorouracil
Steroid injections	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ95Z	150.16	Minor, glaucoma or iris procedure plus unit prednisolone
Needling plus 5-FU injection	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ94B	149.69	Minor, glaucoma or iris procedures plus unit costs of fluorouracil
Revision of bleb NEC	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ91B	1347.56	Complex, glaucoma or iris procedures, with CC score of 0–1
Reformation of anterior chamber of eye	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ94B	127.90	Intermediate, glaucoma or iris procedures, with CC score of 0
Phaco and IOL	<i>NHS Reference Costs 2017/18</i> <sup>91</sup>	BZ32B	878.61	Intermediate, cataract or lens procedures, with CC score of 0–1

CC, complications and co-morbidities; IOL, intraocular lens; NEC, not elsewhere classifiable.

TABLE 42 Unit costs for glaucoma medications

Glaucoma medication	Dose	Administration	Unit cost (£)	Source	Comments
<b>Prostaglandin analogues</b>					
Saflutan	15 µg/ml	Single-dose unit eye drop	12.20	BNF <sup>168</sup>	Overall costs per box
Latanoprost	50 µg/ml	Eye drop	1.53	BNF <sup>168</sup>	Overall costs per 2.5-ml bottle
Bimatoprost	300 µg/ml	Eye drop	10.30	BNF <sup>168</sup>	Overall costs per 3-ml bottle
Travoprost	40 µg/ml	Eye drop	7.27	BNF <sup>168</sup>	Overall costs per 2.5-ml bottle
Average cost			7.83		
<b>Carbonic anhydrase inhibitors</b>					
Brinzolamide	10 mg/ml	Eye drop	1.89	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Dorzolamide	20 mg/ml	Eye drop	1.55	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Average cost			1.72		
<b>Alpha-2 adrenergic agonists</b>					
Brimonidine	0.2%	Eye drop	1.13	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Iopidine	5 mg/ml	Eye drop	10.88	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Average cost			6.01		
<b>Beta-blockers</b>					
Timolol	0.25%	Eye drop	0.78	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Betoptic	0.5%	Eye drop	1.90	BNF <sup>168</sup>	Overall costs per 5-ml bottle
Average cost			1.34		
<b>Parasympathetic eye drops</b>					
Pilocarpine hydrochloride	1%	Eye drop	20.78	BNF <sup>168</sup>	Overall costs per 10-ml bottle
Average cost			20.78		
<b>Oral glaucoma medications</b>					
Acetazolamide	250 mg	Tablet	16.66	BNF <sup>168</sup>	Overall cost per box (30)
<b>Combination glaucoma medications</b>					
Bimatoprost with timolol (AZARGA)	10 mg/ml	Eye drops	11.05	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Bimatoprost with timolol (Ganfort)	5 mg/ml	Eye drops	14.16	BNF <sup>168</sup>	Overall cost per 3-ml bottle
Brinzolamide with brimonidine (Simbrinza)	2 mg/ml	Eye drops	9.23	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Dorzolamide with timolol (Cosopt)	5 mg/ml	Eye drops	1.50	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Dorzolamide with timolol unit dose (Cosopt)	5 mg/ml	Single-dose unit eye drop	28.59	BNF <sup>168</sup>	Unit dose, 60 doses

TABLE 42 Unit costs for glaucoma medications (continued)

Glaucoma medication	Dose	Administration	Unit cost (£)	Source	Comments
Dorzolamide with timolol (Eylamdo)	5 mg/ml	Eye drop	14.29	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Travoprost with timolol (DuoTrav)	5 mg/ml	Eye drop	13.95	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Average cost			13.25		
<b>Non-glaucoma medications</b>					
<i>Steroid eye drops</i>					
Dexamethasone with hypromellose, neomycin and polymyxin B (Maxitrol)	Dexamethasone 1 mg per 1 g Neomycin (as Neomycin sulfate) 3500 unit per 1 g Polymyxin B sulfate 6000 unit per 1 g	Eye drop	1.68	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Betamethasone sodium phosphate	1 mg/ml	Eye drop	2.32	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Dexamethasone (Maxidex)	1 mg/ml	Eye drop	1.42	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Prednisolone (Pred Forte)	10 mg/ml	Eye drop	1.82	BNF <sup>168</sup>	Overall cost per 5-ml bottle
<i>Antibiotic eye drops</i>					
Azithromycin (azyter)	15 mg per 1 g	Eye drop	1.17	BNF <sup>168</sup>	Unit dose, six doses
Chloramphenicol	5 mg/ml	Eye drop	1.14	BNF <sup>168</sup>	Overall cost per 10-ml bottle
Celluvisc Unit Dose	1%	Single-dose unit eye drop	4.80	BNF <sup>168</sup>	Unit dose, 30 doses
Hylo-Forte unit dose	0.2%	Single-dose unit eye drop	5.60	BNF <sup>168</sup>	Unit dose, 30 doses
Sodium hyaluronate (Vismed Multi)	0.18%	Eye drop	6.87	BNF <sup>168</sup>	Overall cost per 10-ml bottle
<i>Mydriatics</i>					
Cyclopentolate (Mydrilate)	5 mg/ml	Eye drops	8.08	BNF <sup>168</sup>	Overall cost per 5-ml bottle
Atropine	10 mg/ml	Eye drops	15.10	BNF <sup>168</sup>	Unit dose, 20 doses
<i>NSAID</i>					
Bromfenac (Yellox)	900 µg/ml	Eye drops	8.50	BNF <sup>168</sup>	Overall cost per 5-ml bottle
<i>Sympathomimetic</i>					
Phenylephrine	50 µg/ml	Eye drops	11.87	BNF <sup>168</sup>	Unit dose, 20 doses
Average cost of non-glaucoma eye drops			7.27		
BNF, British National Formulary; NSAID, non-steroidal anti-inflammatory drug.					

TABLE 43 Unit costs for community appointments

Item	Unit	Cost (£)	Comments
<b>GP</b>			
GP visit at their practice	Per 9.22-minute appointment	37	PSSRU 2018 <sup>169</sup>
GP home visit	11.4 minutes per appointment	45.98	PSSRU 2015 (most recent information) <sup>170</sup> 11.4 minutes (2015 Health and Social Care) × 2017 hourly rate (£242) (no travel costs)
Telephone triage with GP	Cost per call	8.10	PSSRU 2017 (most recent information) <sup>171</sup> 15.5 minutes × 2015 hourly rate (£67) (not including travel)
<b>Nurse</b>			
Practice nurse consultation	15.5 minutes per consultation	10.84	PSSRU 2018 <sup>169</sup> 15.5 minutes (length of appointment Unit Costs 2015) × 2017 hourly rate (£42)
District nurse	25 minutes per consultation	17.29	PSSRU 2017 <sup>171</sup> 15.5 minutes × 2015 hourly rate (£67) (not including travel)
<b>Optician</b>			
Optometrist in practice	Per examination	21.31	Department of Health and Social Care <sup>172</sup> Eye examination fee (as participants have glaucoma all will be entitled to NHS eye examinations)
Optometrist at home	Per examination	58.87	Department of Health and Social Care <sup>172</sup> Eye examination fee plus domiciliary fee (as participants have glaucoma all will be entitled to NHS eye examinations)
PSSRU, Personal and Social Services Research Unit.			

## Sensitivity analysis use of the Health Utility Index version 3 data to calculate quality-adjusted life-years

TABLE 44 Complete and multiple imputation HUI-3 cost-utility analysis results

HUI-3 data	Treatment arm	Unadjusted cost (£)	Adjusted incremental cost (£)	Unadjusted QALY	Adjusted Incremental QALY	ICER ( $\Delta$ Cost/ $\Delta$ QALY) (£)	Probability cost-effective at threshold (%)			
							£0	£20,000	£30,000	£50,000
Complete case (n = 240)	Trabectomy	3819	2129	1.61	0.06	33,758	0	9	38	76
	Medical management	1691		1.54			100	91	62	24
Imputation (n = 382)	Trabectomy	3688	2040	1.54	0.06	36,130	0	4	32	72
	Medical management	1640		1.48			100	96	68	28

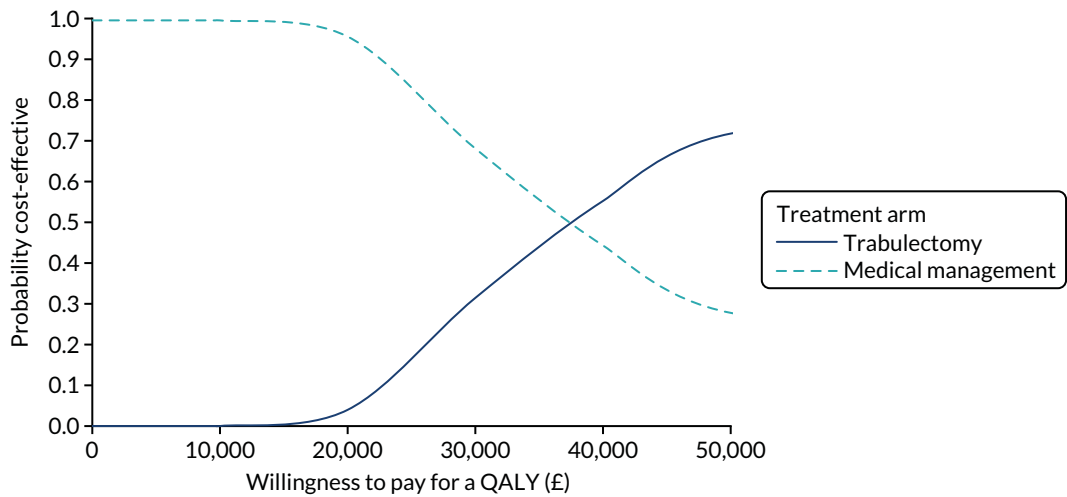


FIGURE 15 Cost-effectiveness curves for the trabulectomy and medical management arms using the results from the imputed HUI-3 sample.

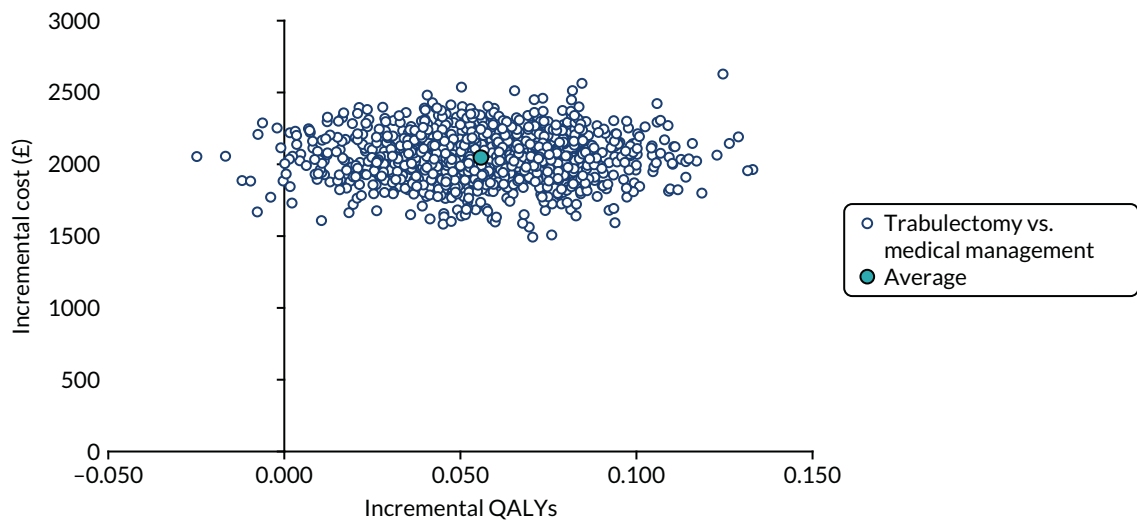


FIGURE 16 Cost-effectiveness plane for the trabulectomy and medical management arms using the results from the imputed HUI-3 sample.



## Sensitivity analysis use of the Glaucoma Utility Index data to calculate quality-adjusted life-years

TABLE 45 Complete and multiple imputation GUI cost-utility results

GUI data	Treatment arm	Unadjusted cost (£)	Adjusted incremental cost (£)	Unadjusted QALY	Adjusted incremental QALY	ICER ( $\Delta$ Cost/ $\Delta$ QALY) (£)	Probability cost-effective at threshold (£) (%)			
							0	20,000	30,000	50,000
Complete case (n = 293)	Trabulectomy	3683	2138	1.67	0.01 <sup>a</sup>	111,117	0	9	38	76
	Medical management	1541		1.64			100	91	62	24
Imputation (n = 398)	Trabulectomy	3617	1995	1.64	0.00	350,149	0	0	0	0
	Medical management	1615		1.62			100	100	100	100

a Adjusted difference is in favour of medication in this instance not surgery.

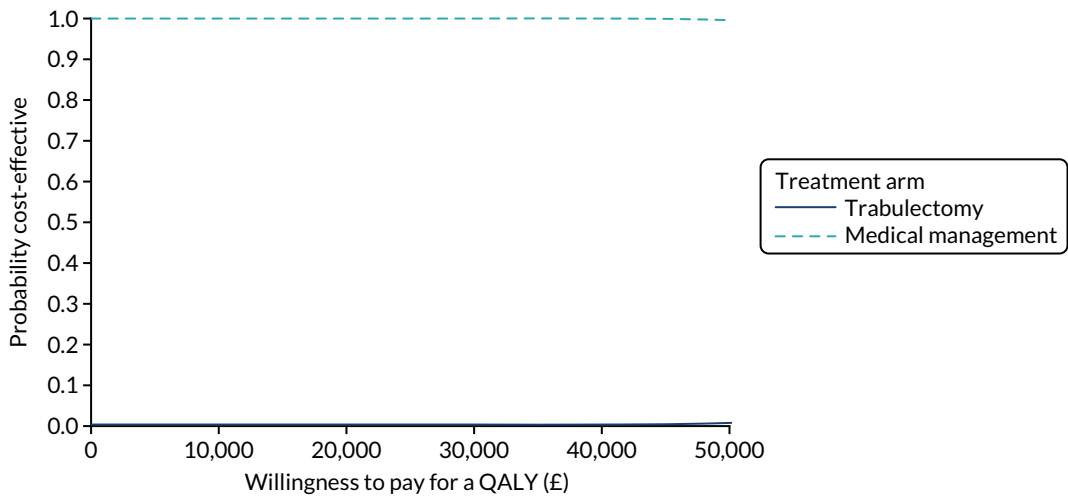


FIGURE 17 Cost-effectiveness curves for the trabulectomy and medical management arms using the results from the imputed GUI sample.

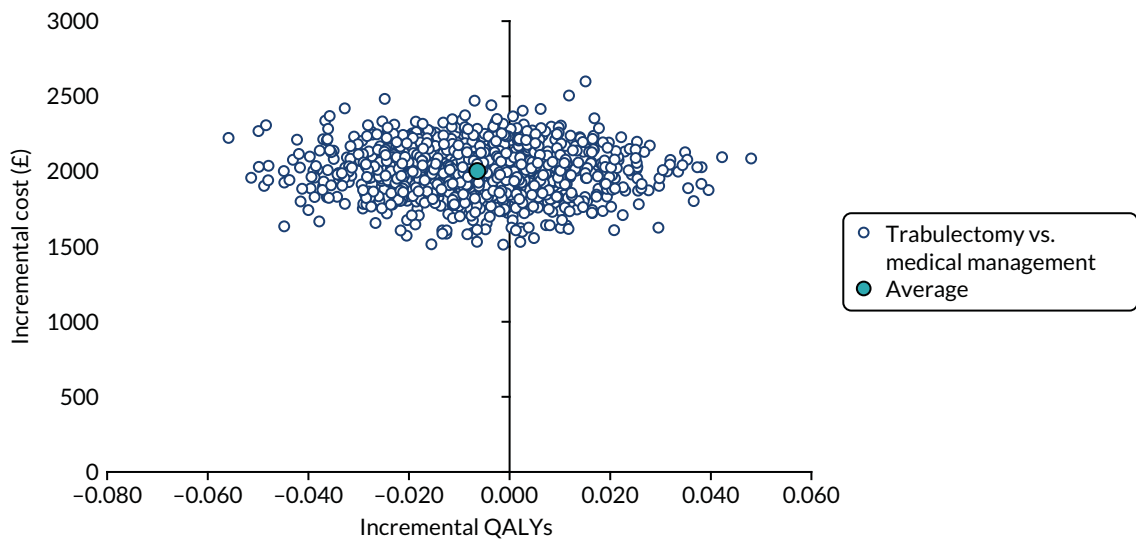


FIGURE 18 Cost-effectiveness plane for the trabulectomy and medical management arms using the results from the imputed GUI sample.

## Sensitivity analysis use of the EQ-5D-5L with the participant time and travel costs

TABLE 46 EQ-5D-5L data with patient time and travel costs included cost-utility results

EQ-5D-5L data with patient time and travel costs included	Treatment arm	Unadjusted cost with TT (£)	Adjusted incremental cost (£)	Unadjusted QALY	Adjusted incremental QALY	ICER ( $\Delta$ Cost/ $\Delta$ QALY) (£)	Probability cost-effective at threshold (£) (%)			
							0	20,000	30,000	50,000
Complete case (n = 290)	Trabulectomy	4453	2412	1.65	0.03	75,347	0	1	2	25
	Medical management	2046		1.59			100	99	98	75
Imputation (n = 403)	Trabulectomy	4419	2359	1.61	0.04	54,197	0	1	5	42
	Medical management	2052		1.56			100	99	95	58

TT, time and travel cost.

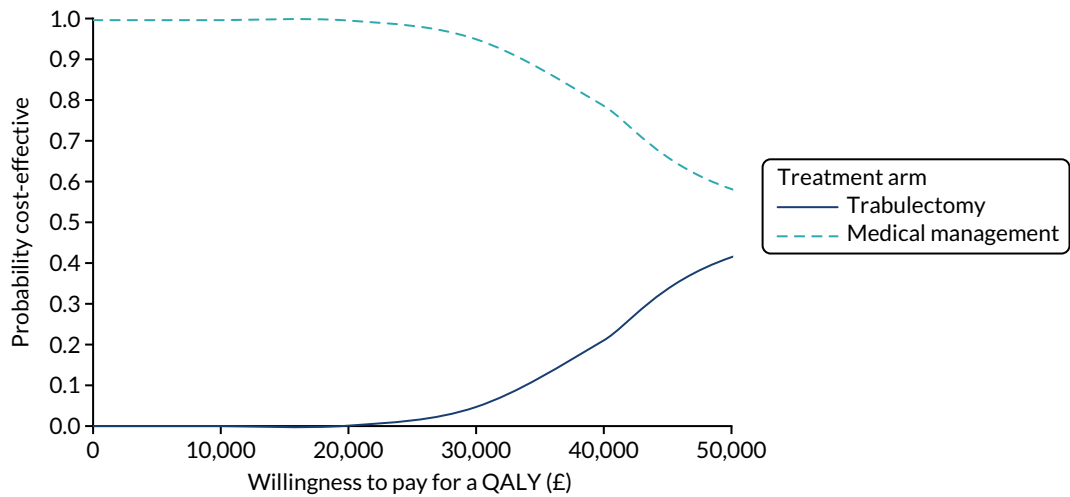


FIGURE 19 Cost-effectiveness curves for the trabulectomy and medical management arms using the results from the EQ-5D-5L using the time and travel data.

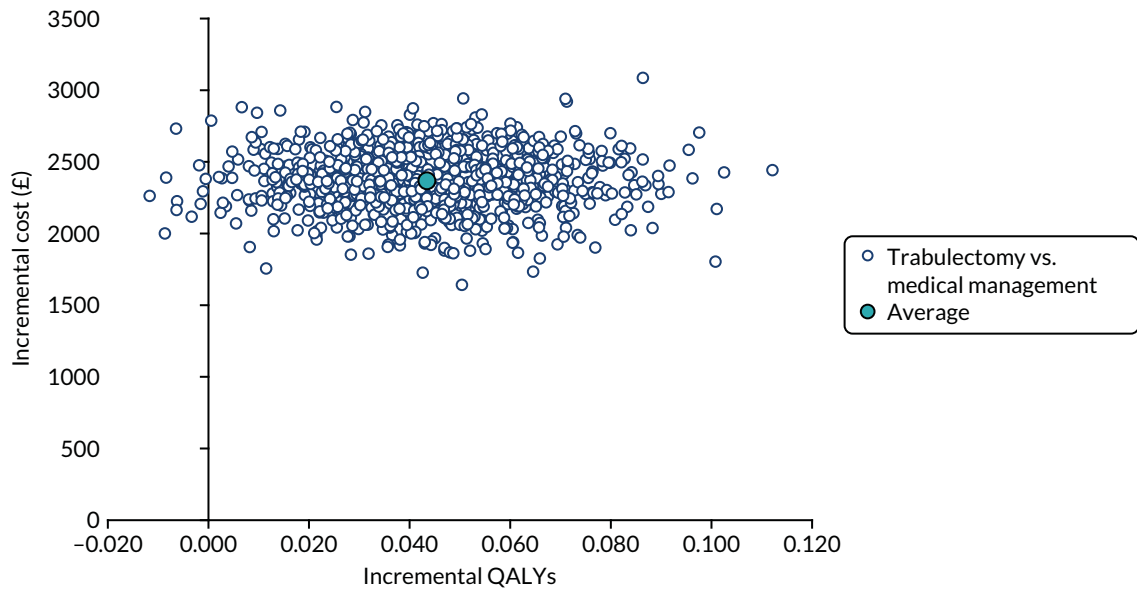


FIGURE 20 Cost-effectiveness plane for adjusted bootstrapped replications for cost-utility analysis for EQ-5D-5L results with time and travel costs.

## Appendix 6 Analysis of pre-trabeculectomy questionnaire utility scores

A measurement of the EQ-5D-5L questionnaire was administered to participants before they underwent a trabeculectomy. This was administered with a view to capture information about the effect of the surgical procedure on the participants. The results of those who completed the pre-trabeculectomy questionnaire in the trabeculectomy arm are summarised in *Table 47*.

*Table 47* summarises the mean values for those who completed a pre-trabeculectomy questionnaire over a pre- and post-surgery period of 6 months. The utility values remain largely stable both pre and post surgery in the participants who undertook the EQ-5D-5L immediately pre surgery in the trabeculectomy arm. There is a very slight decrease in utility values at the 3-month time point (0.01) that could represent post-surgical healing, but this seems to stabilise at the 6-month time point.

**TABLE 47** Summary of the mean utility scores for the pre-trabeculectomy questionnaire in the trabeculectomy arm

Time point	Participants (n)	EQ-5D-5L score	
		Mean	SD
Baseline	204	0.84	0.18
1 month	179	0.85	0.18
Pre trabeculectomy	208	0.85	0.19
3 months	175	0.84	0.17
6 months	176	0.85	0.19



## Appendix 7 Model parameters

### Possible options for model structure

Based on GSS2 classification, we can define states of disease in patients with glaucoma variably, as were provided here in five possible options. Based on GSS2 stages (stage 0, border, stage B, stage 1, stage 2, stage 3, stage 4 and stage 5) and considering two eye health states separately, 64 ( $8 \times 8$ ) eye health states (conditions) are possible theoretically to define for patients. Although most of these 64 conditions (states) are irrelevant in our model because TAGS patients with severe stages of glaucoma (in at least one eye) were included in the study. This means that the indexed eye must be in a severe stage based on HPA classification. In our modified classifications of GSS2 for the model we assumed stage 0, border, stage 1 and stage 2 of GSS2 as non-severe and stage 3, stage 4 and stage 5 of GSS2 as severe. Based on this modified GSS2 classification, only 11 patients (0.02) misclassify (in 11 patients the index eye classified less than stage 3 based on GSS2), which means that the modified classification of the GSS2 for the model is most compatible.

The possible options for the model structure are provided in *Tables 48–52*. The differences between these options are only about the complexity that each one provides for the structure of the model. For example, the first option provides 32 states, of which not all may be necessary, and merging some of these states may provide a simpler and more reasonable structure for the model. Defining many health conditions leads to a very small initial probability of patients for each state, which makes it sensible to define fewer stages as previous related studies have done (EAGLE,<sup>111</sup> GATE,<sup>173</sup> etc.). Moreover, some states (conditions 7, 8 and 16 in the first option, conditions 5, 6 and 9 in the second option) are inconsistent with the assumption of the study as indicated in the TAGS protocol: 'The eye with less severe visual field damage will be nominated the index eye in patients with both eye eligible'. The initial probabilities of these conditions would be zero and some cases may transition to these stages during trial.

The similarity between option 3 and option 4 is that both of them make the model simpler than options 1 and 2. The difference between option 3 and option 4 is that in option 3, the severity of the non-index eye is merged (stages 3–5) but the severity state of the index eye is determined separately, which makes it possible to precisely follow-up for index eye disease progression in the model, which is more consistent with the TAGS objective. On the other hand, in option 4, the severity of the index eye is merged (stages 3–5) but the severity state of the non-index eye is determined separately, which makes it possible to precisely follow-up for non-index eye disease progression, which may not be more important in this study.

**TABLE 48** Option 1: combinations of three conditions of index eye (S3, S4 and S5) with eight conditions of non-index eye (S0, border, SB, S1, S2, S3, S4 and S5)

Condition number	Condition definition
1	Index eye (S3); non-index eye (S0)
2	Index eye (S3); non-index eye (border)
3	Index eye (S3); non-index eye (SB)
4	Index eye (S3); non-index eye (S1)
5	Index eye (S3); non-index eye (S2)
6	Index eye (S3); non-index eye (S3)
7	Index eye (S3); non-index eye (S4)
8	Index eye (S3); non-index eye (S5)
9	Index eye (S4); non-index eye (S0)
10	Index eye (S4); non-index eye (border)
11	Index eye (S4); non-index eye (SB)
12	Index eye (S4); non-index eye (S1)
13	Index eye (S4); non-index eye (S2)
14	Index eye (S4); non-index eye (S3)
15	Index eye (S4); non-index eye (S4)
16	Index eye (S4); non-index eye (S5)
17	Index eye (S5); non-index eye (S0)
18	Index eye (S5); non-index eye (border)
19	Index eye (S5); non-index eye (SB)
20	Index eye (S5); non-index eye (S1)
21	Index eye (S5); non-index eye (S2)
22	Index eye (S5); non-index eye (S3)
23	Index eye (S5); non-index eye (S4)
24	Index eye (S5); non-index eye (S5)

**TABLE 49** Option 2: combinations of three conditions of index eye (S3, S4 and S5) with four conditions of non-index eye (non-severe, S3, S4 and S5)

Condition number	Condition definition
1	Index eye: severe (S3); non-index eye: non-severe (S0 + border + SB + S1 + S2)
2	Index eye: severe (S4); non-index eye: non-severe (S0 + border + SB + S1 + S2)
3	Index eye: severe (S5); non-index eye: non-severe (S0 + border + SB + S1 + S2)
4	Index eye: severe (S3); non-index eye: severe (S3)
5	Index eye: severe (S3); non-index eye: severe (S4)
6	Index eye: severe (S3); non-index eye: severe (S5)
7	Index eye: severe (S4); non-index eye: severe (S3)
8	Index eye: severe (S4); non-index eye: severe (S4)
9	Index eye: severe (S4); non-index eye: severe (S5)
10	Index eye: severe (S5); non-index eye: severe (S3)
11	Index eye: severe (S5); non-index eye: severe (S4)
12	Index eye: severe (S5); non-index eye: severe (S5)



TABLE 50 Option 3: combinations of three conditions of index eye (S3, S4 and S5) with two conditions of non-index eye (non-severe and severe)

Condition number	Condition definition
1	Index eye: severe (S3); non-index eye: non-severe (S0 + border + SB + S1 + S2)
2	Index eye: severe (S4); non-index eye: non-severe (S0 + border + SB + S1 + S2)
3	Index eye: severe (S5); non-index eye: non-severe (S0 + border + SB + S1 + S2)
4	Index eye: severe (S3); non-index eye: severe (S3, S4 and S5)
5	Index eye: severe (S4); non-index eye: severe (S3, S4 and S5)
6	Index eye: severe (S5); non-index eye: severe (S3, S4 and S5)

TABLE 51 Option 4: combinations of one condition of index eye (severe) with four conditions of non-index eye (non-severe, S3, S4 and S5)

Condition number	Condition definition
1	Index eye: severe (S3 + S4 + S5); non-index eye: non-severe (S0 + border + SB + S1 + S2)
2	Index eye: severe (S3 + S4 + S5); non-index eye: severe (S3)
3	Index eye: severe (S3 + S4 + S5); non-index eye: severe (S4)
4	Index eye: severe (S3 + S4 + S5); non-index eye: severe (S5)

TABLE 52 Option 5: combinations of one condition of index eye (severe) with two conditions of non-index eye (non-severe, severe)

Condition number	Condition definition
1	Index eye: severe (S3 + S4 + S5); non-index eye: non-severe (S0 + border + SB + S1 + S2)
2	Index eye: severe (S3 + S4 + S5); non-index eye: severe (S3 + S4 + S5)

## Initial and transition probabilities of defined stages in the model

TABLE 53 Transition to the same and/or higher stages during first year in trabeculectomy arm (n)

Stage	Baseline	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	30	19	9		2	0								
2	76		65	8		1	2							
3	39			32			7							
4	2				2	0		0	0					
5	15					8	2		3	2				
6	11						10			1				
7	5							5	0		0	0		
8	10								7	0			1	2
9	4									4				0
10	0										0		0	
11	11												8	3
12	14													14
	217													

TABLE 54 Transition to the same and/or higher stages during first year in trabeculectomy arm (%)

Stage	Baseline (n)	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	30	0.633333	0.3		0.066667	0								
2	76		0.855263	0.105263		0.013158	0.026316							
3	39			0.820513			0.179487							
4	2				1		0	0						
5	15					0.533333	0.133333		0.2	0.133333				
6	11						0.909091			0.090909				
7	5							1		0	0			
8	10								0.7	0		0.1		0.2
9	4									1		0		
10	0										0			
11	11											0.727273		0.272727
12	14													1
	217													

TABLE 55 Transition to the same and/or higher stages during first year in medical management arm (n)

Stage	Baseline	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	28	19	8		0	1								
2	74		59	3		9	3							
3	46			45			1							
4	3				1	1		0	1					
5	13					9	1		3	0				
6	10						8			2				
7	5							3	2	0	0	0		
8	6								5	0		1		0
9	4									3				1
10	8										7	1		
11	6											5		1
12	13													13
	216													

TABLE 56 Transition to the same and/or higher stages during first year in medical management arm (%)

Stage	Baseline (n)	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	28	0.678571	0.285714		0	0.035714								
2	74		0.797297	0.040541		0.121622	0.040541							
3	46			0.978261			0.021739							
4	3				0.333333	0.333333		0	0.333333					
5	13					0.692308	0.076923		0.230769	0				
6	10						0.8			0.2				
7	5							0.6	0.4	0	0	0		
8	6								0.833333	0		0.166667	0	
9	4									0.75				0.25
10	8										0.875	0.125		
11	6											0.833333	0.166667	
12	13													1
	216													

TABLE 57 Transition to the same and/or higher stages during second year in trabeculectomy arm (n)

Stage	12 months (n)	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	19	16	3		0	0								
2	74		68	2		4	0							
3	40			37			3							
4	4				3	0		0	1					
5	10					9	1							
6	19						16				3			
7	5							5						
8	10								7	1			2	0
9	8									6				2
10	0										0			
11	9												8	1
12	19													19
	217													

TABLE 58 Transition to the same and/or higher stages during second year in trabeculectomy arm (%)

Stage	12 months (n)	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	19	0.842105	0.157895		0	0								
2	74		0.918919	0.027027		0.054054	0							
3	40			0.925			0.075							
4	4				0.75	0		0	0.25					
5	10					0.9	0.1		0	0				
6	19						0.842105			0.157895				
7	5							1	0		0	0		
8	10								0.7	0.1		0.2		0
9	8									0.75				0.25
10	0										0			
11	9											0.888889		0.111111
12	19													1
	217													

TABLE 59 Transition to the same and/or higher stages during second year in medical management arm (n)

Stage	12 months (n)	Stage													
		1	2	3	4	5	6	7	8	9	10	11	12		
1	19	15	2		2	0									
2	66		63	3											
3	48			47			1								
4	1				1										
5	19					15	1		3						
6	13						11			2					
7	3							2	1						
8	12								11	1					
9	5									5					
10	7										7				
11	7											5		2	
12	15														15
	215														



TABLE 60 Transition to the same and/or higher stages during second year in medical management arm (%)

Stage	12 months (n)	Stage												
		1	2	3	4	5	6	7	8	9	10	11	12	
1	19	0.789474	0.105263		0.105263	0								
2	66		0.954545	0.045455		0	0							
3	48			0.979167			0.020833							
4	1				1	0		0	0					
5	19					0.789474	0.052632		0.157895	0				
6	13						0.846154			0.153846				
7	3							0.666667	0.333333		0	0		
8	12								0.916667	0.083333		0		0
9	5									1				0
10	7										1	0		
11	7											0.714286		0.285714
12	15													1
	215													

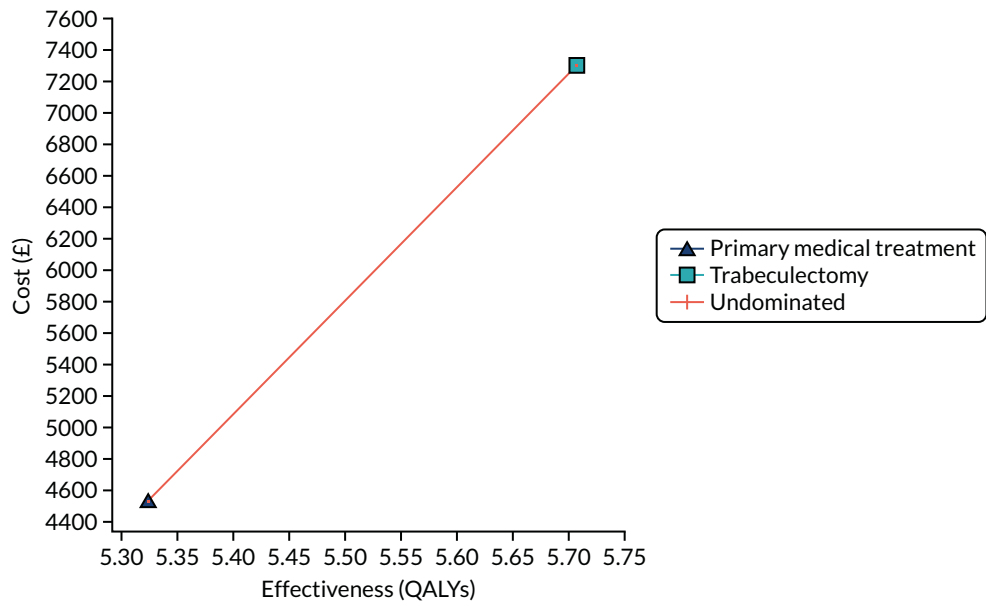


FIGURE 21 Cost-effectiveness analysis for a lifetime horizon (30 years): HUI-3 measure.

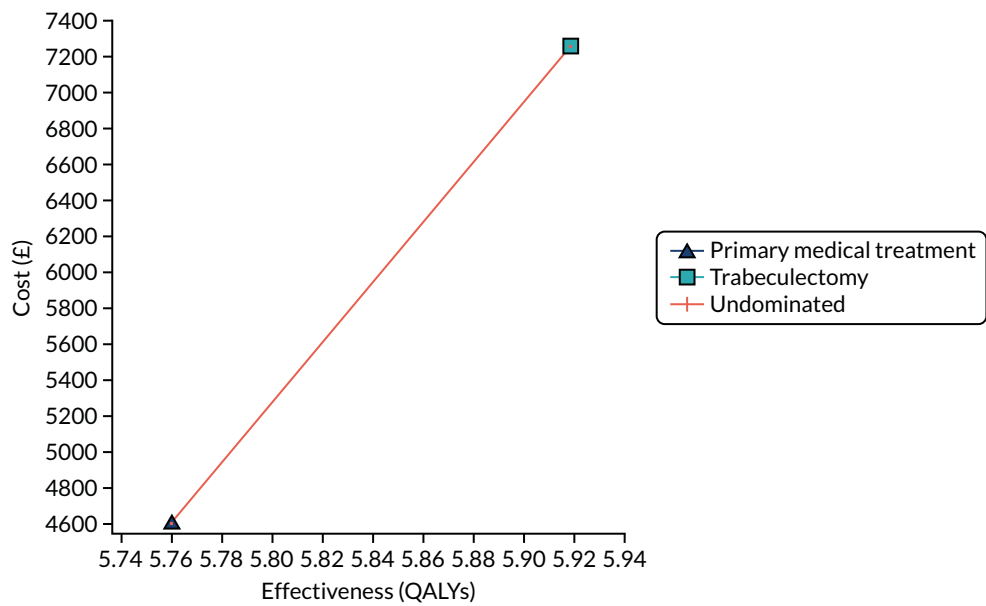


FIGURE 22 Cost-effectiveness analysis for a lifetime horizon (30 years): GUI measure.

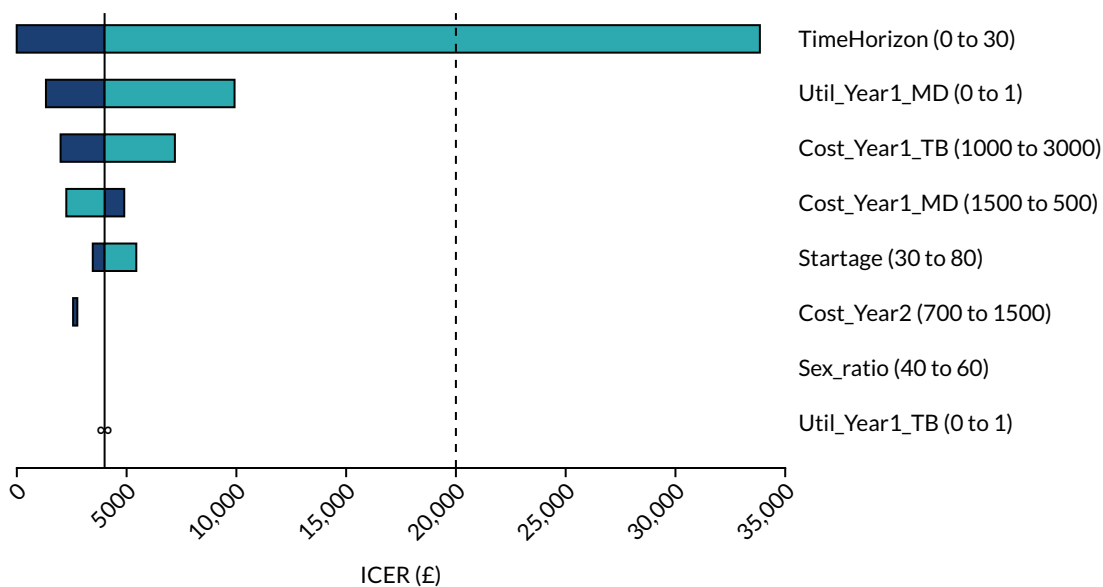


FIGURE 23 Tornado diagram for the main parameters (HUI-3 measure).

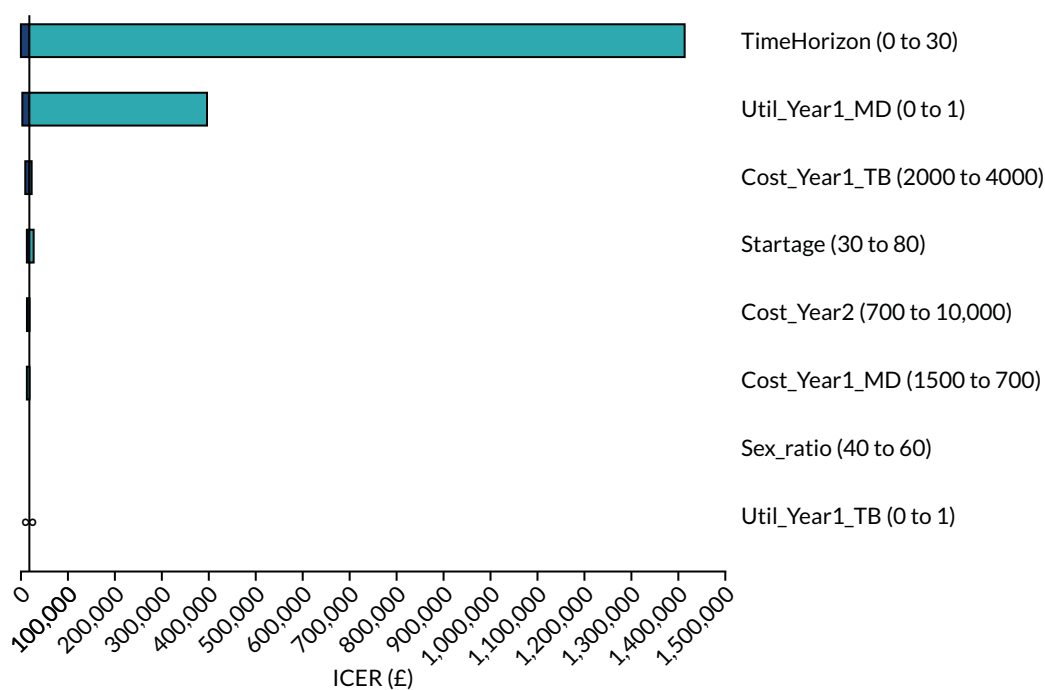


FIGURE 24 Tornado diagram for the main parameters (GUI measure).

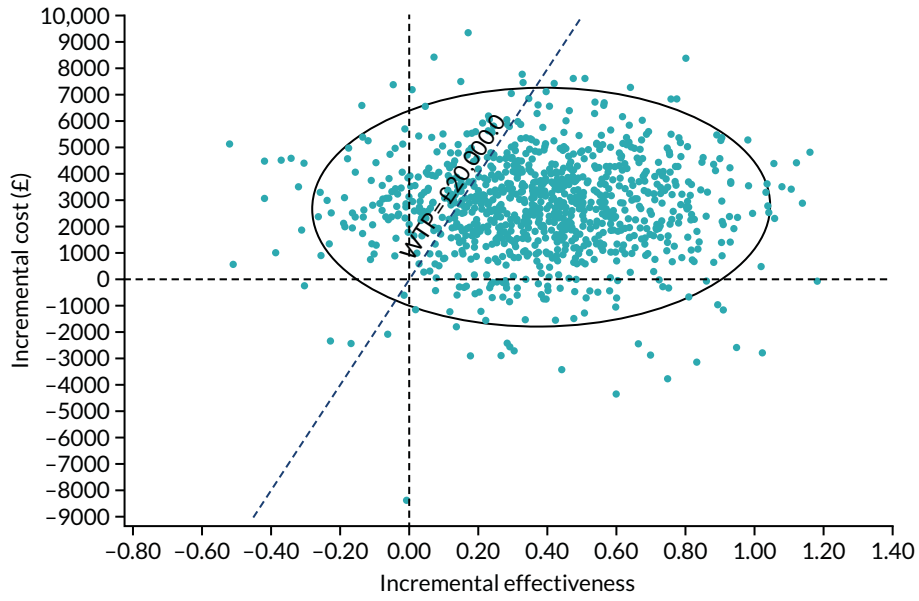


FIGURE 25 Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment (HUI-3 measure). WTP, willingness to pay.

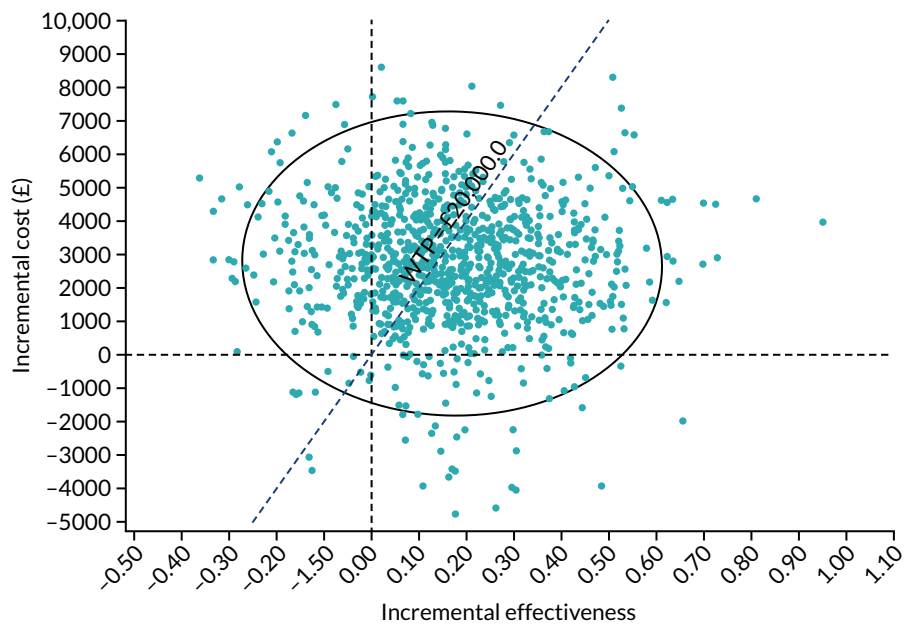


FIGURE 26 Incremental cost-effectiveness scatterplot: trabeculectomy vs. medical treatment (GUI measure). WTP, willingness to pay.

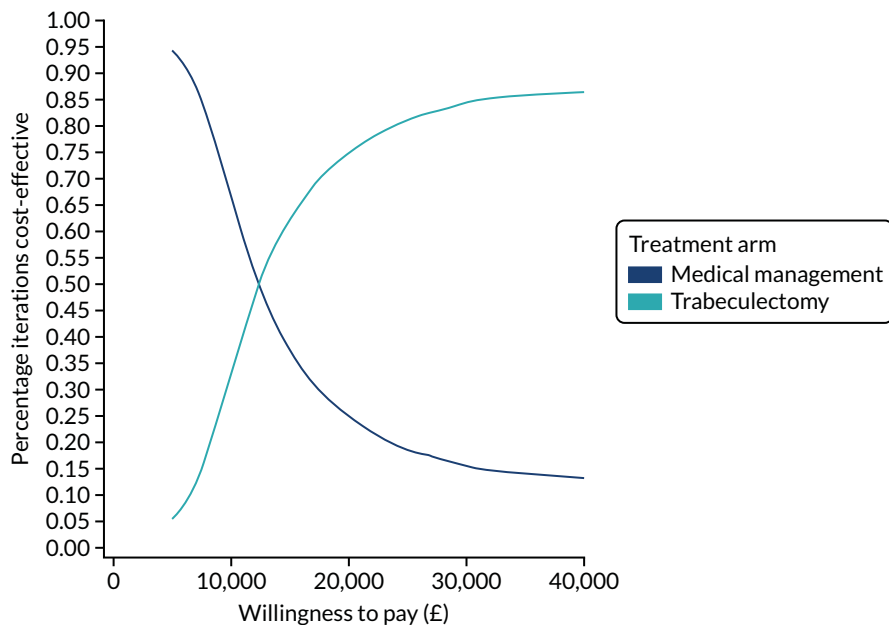


FIGURE 27 Model-based cost-effectiveness acceptability curve for a lifetime horizon (30 years): HUI-3 measure.

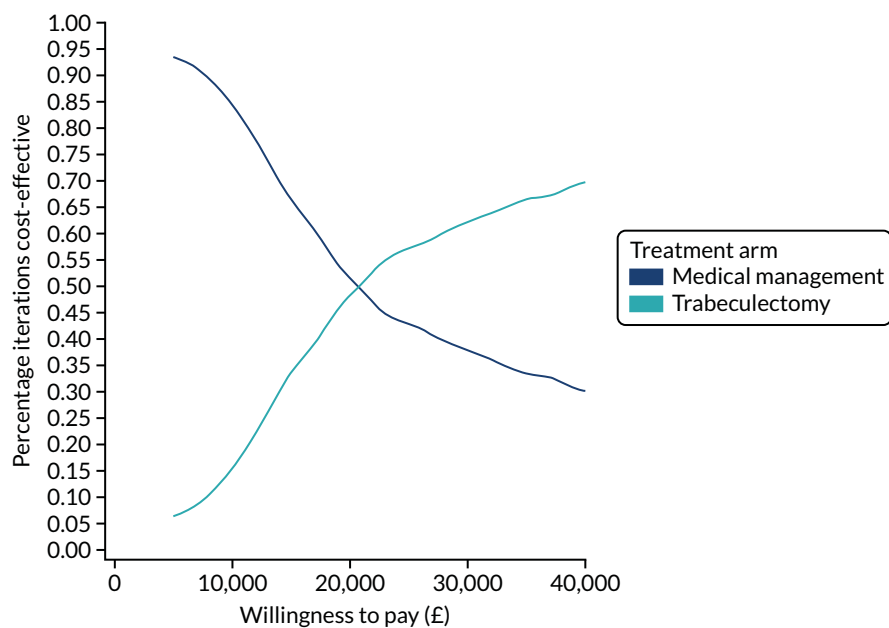


FIGURE 28 Model-based cost-effectiveness acceptability curve for a lifetime horizon (30 years): GUI measure.



## Appendix 8 Protocol changes

**A**mendments to the TAGS protocol during the trial.

### Protocol version 1.1, date issued: 20 November 2013

5.2 Secondary outcomes – TSC requested Esterman-graded VF instead of direct question to participants on driving licence retention.

Redundant abbreviations removed from glossary of abbreviations.

Revision of eligible recruiting centres in section 6.3.1 Overall description of trial participants (see also 7.1).

Removal of reference to female partners of male participants in section 6.3.2 Inclusion criteria.

New section (6.4.3: Recruitment projection) added detailing feasibility pilot study. Subsequent sections renumbered.

Revision to section 6.4.6 (Clinical outcomes) of how eligibility determined from VF tests, Esterman VF at baseline and 24 months replace question about driving licence retention, removal of reference to pregnancies in female partners of male participants.

Revision of section 6.4.6 (Economic outcomes) rephrasing of sentence for clarity.

Revision of section 7.1 (Treatment strategies) to clarify all surgery will be undertaken by senior experienced glaucoma surgeons within 3 months of randomisation and index eye will be operated on first if both eyes eligible.

Addition of corneal decompensation to section 8.1.3 (expected AEs).

Revision of section 8.2.3 on reporting AEs and SAEs to an investigator or a delegate can update missing information following SAE notification and removal of reference to pregnancies in female partners of male participants and investigator or a delegate can notify a pregnancy.

Section 9.0 revised whereby a paragraph was removed and added to new section 6.4; redefinition of restrictions on surgeon involvement; the Statistical Analysis Plan will be available before the second, not first, TSC meeting.

In section 13.1 reference to the Declaration of Helsinki was updated.

### Protocol version 1.2, date issued: 30 June 2014

In section 6.3.1 (Overall Description of Trial Participants) point 5 was corrected to refer to under 15 dB sensitivity rather than –15 dB.

### **Protocol version 1.3 date issued: 6 August 2014**

Appendices A and B amended to highlight need for pre-surgery measures.

### **Protocol version 1.4, date issued: 26 August 2014**

Addition of cataract formation and retinal detachment to expected AEs in trabeculectomy arm.  
Edit to appendix B to highlight need for VF test × 2 at each visit and Esterman at baseline and 24-month visits.

### **Protocol version 2, date issued: 22 October 2014**

Dissociation of identification of the index eye from order of surgery following feedback from sites.

### **Protocol version 3, date issued: 1 March 2016**

Addition of definition for VA AE for loss of vision.

Updated references in section 9.0 and reference list.

### **Protocol version 4, date issued: 4 August 2016**

6.4.6 edited as VFQ-25 not being collected immediately prior to trabeculectomy.

Addition of broad complex tachycardia while under general anaesthetic, and post-operative dizziness to section 8.1.3 expected AEs.

9.6 long-term follow-up funding being pursued during trial.

### **Protocol version 5, date issued: 31 July 2018**

Addition of appendix E detailing long-term follow-up study and update of study information in synopsis.

### **Protocol version 6, date issued: 5 March 2019**

Addition of appendix F detailing substudy to collect genetic material.





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