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Citation: Jones, L., Garway-Heath, D. F., Azuara-Blanco, A., Crabb, D. P., Bunce, C., Lascaratos, G., Amalfitano, F., Anand, N., Bourne, R., Broadway, D. C., et al (2018). Are Patient Self-Reported Outcome Measures Sensitive Enough to Be Used as End Points in Clinical Trials?: Evidence from the United Kingdom Glaucoma Treatment Study. *Ophthalmology*, 126(5), pp. 682-689. doi: 10.1016/j.ophtha.2018.09.034

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Link to published version: <https://doi.org/10.1016/j.ophtha.2018.09.034>

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1 **Title:**

2 Are patient self-reported outcome measures (PROMs) sensitive enough to be used as endpoints
3 in clinical trials? Evidence from the United Kingdom Glaucoma Treatment Study

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20 **Meeting presentation:**

21 The Association for Research and Vision in Ophthalmology, Seattle WA, 2016.

22 United Kingdom and Eire Glaucoma Society, Cheltenham UK, 2016.

23 **Financial support:**

24 DFG-H has received unrestricted research funding from Allergan, Pfizer, the Alcon Research
25 Institute and Santen, equipment loans from Carl Zeiss Meditec, Heidelberg Engineering OptoVue
26 and Topcon; has had advisory roles (compensated) with Aerie, Alcon, Alimera, Allergan, Bausch
27 & Lomb, CenterVue, Quethera, Quark, Santhen and Santhera; and honoraria for lecturing from
28 Allergan Pfizer and Santen. DPC has received unrestricted research funding from Allergan and
29 Santen, and honoraria for lecturing from Allergan and Santen. AA-B declares no competing
30 interests. LJ declares no competing interests.

31 The sponsor or funding organizations had no role in the design or conduct of this research.

32 **Conflict of interest:**

33 No conflicting relationship exists for any author.

34 **Running head:**

35 Patient reported outcome measures in glaucoma clinical trials

36 **Keywords:**

37 glaucoma; PROMs; visual fields; clinical trials

38 **Abbreviations:**

39 **UKGTS** = United Kingdom Glaucoma Treatment Study; **PROM** = Patient Reported Outcome
40 Measure; **GPA** = Guided Progression Analysis; **CI** = Confidence interval; **EQ-5D** = European
41 Quality of Life in 5 dimensions; **SF-36** = Short Form-36; **GQL-15** = Glaucoma Quality of Life-15;
42 **GAL-9** = Glaucoma Activity Limitation-9; **VAS** = Visual Analogue Scale; **AFREV** = Assessment of
43 Function Related to Vision; **IOP** = Intraocular Pressure; **MD** = Mean Deviation; **dB** = Decibels; **VA**
44 = Visual Acuity.

45

46

47 Purpose: The UK Glaucoma Treatment Study (UKGTS) demonstrated the effectiveness of
48 an intraocular pressure-lowering drug in patients with glaucoma using visual field
49 progression as a primary outcome. We now test the hypothesis that responses on patient
50 reported outcome measures (PROMs – secondary outcome measure) differ between
51 patients receiving a topical prostaglandin analogue (Latanoprost) or placebo eye drops
52 in UKGTS.

53 Design: Multi-centre, randomised, triple-masked, placebo-controlled trial.

54 Participants: Newly diagnosed glaucoma patients recruited into the UKGTS with baseline
55 and exit PROM data (n= 182 and n=168 patients from the treatment and placebo group,
56 respectively).

57 Methods: The UKGTS was a multi-centre, randomised, triple-masked, placebo-controlled
58 trial, where patients with newly diagnosed open angle glaucoma were allocated to
59 receive Latanoprost (treatment) or placebo (trial registration number:
60 ISRCTN96423140); the observation period was 24-months. Patients completed general
61 health PROMs (EQ-5D and SF-36) and PROMs specific to glaucoma (GQL-15 and GAL-9)
62 at baseline and at exit from the trial. Percentage change between baseline and exit
63 measurement on PROMs were calculated for each patient and compared between
64 treatment arms. In addition, differences between stable patients (n=272) and those with
65 glaucomatous progression (n=78), as determined by visual field change (primary
66 outcome), were assessed.

67 Main Outcome Measure: PROMs on health-related and vision-related quality of life.

68 Results: Average percentage change on PROMs was similar for patients in both arms of
69 the trial with no statistically significant differences between treatment and placebo

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70 groups (EQ-5D, $p = 0.98$; EQ-5D VAS, $p = 0.88$; SF-36, $p = 0.94$, GQL-15, $p = 0.66$; GAL-9, p
71 $= 0.87$). There were statistically significant differences between stable and progressing
72 patients, as determined by visual fields, on glaucoma-specific PROMs (GQL-15, $p = 0.02$;
73 GAL-9, $p = 0.02$) but not on general health PROMs (EQ-5D, $p = 0.62$; EQ-5D VAS, $p = 0.23$;
74 SF-36, $p = 0.65$)

75 Conclusions: Average change in PROMs on health-related and vision-related quality of life
76 was similar for the treatment and placebo group in the UKGTS. PROMs, specifically those
77 used in the UKGTS, may not be sensitive enough to be used as a primary endpoint in
78 clinical trials when participants have newly diagnosed early stage glaucoma.

79

80 Intraocular pressure (IOP) is currently the only modifiable risk factor for disease
81 progression in glaucoma. All therapies approved for the treatment of glaucoma are
82 licenced on their ability to reduce patients' IOP. Yet, the foremost outcome when treating
83 glaucoma is to maintain what is most important to the patient, vision-related quality of
84 life. ⁽¹⁾ Randomised clinical trials have provided evidence for the visual field preserving
85 benefit of reducing IOP. ⁽²⁻¹²⁾ Recently, the United Kingdom Glaucoma Treatment Study
86 (UKGTS) evidenced the effectiveness of an IOP lowering treatment in patients with
87 glaucoma using visual field deterioration determined by standard automated perimetry
88 as the primary outcome measure over a two-year follow-up period. ⁽¹²⁾

89 Typically, outcome measures in clinical trials are selected on their sensitivity to
90 clinically meaningful changes in disease severity. However, diagnostic test
91 measurements taken in the clinic do not directly capture the impact of glaucoma on the
92 patient's life. ⁽¹³⁾ IOP is not a direct measure of glaucomatous optic neuropathy. Visual
93 fields, however, indicate functional ability, and are therefore more closely associated with
94 vision-related quality of life than IOP. Patient reported outcome measures (PROMs) are
95 instruments derived from standardised, validated questionnaires that are used to
96 measure perceived health status, functional status, or health-related quality of life. Asking
97 a patient directly is an effective way to ascertain how someone feels about their condition
98 and how it might be affecting their well-being. ⁽¹⁴⁾ PROMs can also be readily translated
99 into measures of cost-effectiveness.

100 Use of PROMs in clinical research has increased in recent years, ⁽¹⁵⁾ and this is
101 beginning to be mirrored in glaucoma research, ⁽¹⁶⁾ where a catalogue of vision-specific
102 PROMs are now available. ⁽¹⁷⁾ PROMs are also becoming more frequently used in clinical
103 trials, ⁽¹⁸⁾ including in ophthalmology trials, ^(19- 23). Typically, PROMs are used to
104 complement a more clinical primary outcome in trials. However, The United States Food

105 and Drug Administration endorses the use of PROMs as primary endpoints in glaucoma
106 trials, ⁽²⁴⁾ and this has been implemented in recent glaucoma trials. ⁽²⁵⁻²⁷⁾ An important
107 attribute of a clinical trial outcome measure is to be sensitive enough to detect differences
108 between a treatment and a control group. This is particularly true for glaucoma treatment
109 trials because the disease process is slow and changes to vision can be challenging to
110 measure. Moreover, disease progression in glaucoma is often unnoticeable to the patient
111 in the early stages of disease. ⁽²⁸⁾ A lack of sensitivity may necessitate prolonged trial
112 duration which can add to the delay of drug development. For this reason, the sensitivity
113 of PROMs when used as outcome measures in glaucoma trials should be scrutinised and
114 this is the subject of our study. Specifically, we analyse PROM responses from patients in
115 the UKGTS to test the hypothesis that these measures can determine differences between
116 the groups randomised to treatment or placebo.

117 **Methods**

118 In this study, we analyse the responses on PROMs of patients enrolled into the UKGTS, a
119 multi-centre, randomised, triple-masked, placebo-controlled trial assessing visual
120 function preservation in newly diagnosed open-angle glaucoma patients (trial
121 registration number: ISRCTN96423140). Patients recruited from ten eye clinics
122 throughout the United Kingdom were randomly allocated to receive an IOP reducing
123 prostaglandin analogue Latanoprost (0.005%) or placebo eye drops. The UKGTS, and the
124 subsequent analysis of anonymised data in this study, adhered to the tenets of the
125 Declaration of Helsinki and was approved by local institutional review boards (ethics
126 approval reference: 09/H0721/56). Study participants provided written informed
127 consent.

128 A total of 461 patients from 516 enrolled were analysed in the trial (Latanoprost
129 N = 231, placebo N = 230). Patients in the UKGTS were scheduled to perform a series of
130 11 visual field examinations during a 2-year observation period. Visual field progression
131 was used as the primary endpoint in the trial. Progression analysis was performed in the
132 Humphrey Field Analyser Guided Progression Analysis (GPA) software; a sensitive
133 technique that considers changes at individual points (test locations) in the visual field.
134 Progression was defined as at least three visual field locations worse than baseline at the
135 5% levels in two consecutive reliable visual fields and at least three visual field locations
136 worse than baseline at the 5% levels in the two subsequent consecutive reliable visual
137 fields; the locations identified in the first and second pair were not required to be
138 identical. Details of the trial design and the trial outcome are published elsewhere. (12; 29)
139 In short, the risk of visual field progression was significantly lower in the treatment group
140 than in the placebo group (adjusted hazard ratio 0.44 [95% confidence interval (CI) 0.28-
141 0.69]).

142 PROMs were included as secondary outcome measures in UKGTS. PROMs were
143 self-reported at patients' baseline and final visit and were administered by a trial
144 researcher. In the event of a patient meeting the primary trial endpoint, PROMs were
145 completed upon the patients' withdrawal from the trial. The PROMs used in UKGTS were
146 as follows:

147 **European Quality of Life in 5 dimensions (EQ-5D)** is a classification of general
148 health status. ⁽³⁰⁾ EQ-5D assesses five attributes: mobility, self-care, usual activity,
149 pain/discomfort, and anxiety/depression. We used the three-level measure meaning
150 each dimension has three possible outcomes: no problems, some problems, and severe
151 problems. Patients with no problems across all five attributes will produce a five-digit
152 health status code of 11111. Patients with severe problems will score 33333. Five-digit
153 codes were translated into a single health state score using an existing scoring system
154 which is generated from a UK population sample. ⁽³⁰⁾ Included in the EQ-5D is a visual
155 analogue scale (**EQ-5D VAS**) where patients are asked to score their own health between
156 0 and 100 (where 0 and 100 are worst and the best imaginable health). EQ-5D is the most
157 commonly used general health PROM and is recommended in The National Institute for
158 Health and Care Excellence guidelines for health economic analysis in the United
159 Kingdom. ⁽³¹⁾ Furthermore, following recommendations by the United States Public
160 Health Service, ⁽³²⁾ there now exists a large database of EQ-5D derived health statistics
161 for the American population, too. ⁽³³⁾

162 **Short Form-36 (SF-36)** is another general health instrument featuring 36 items
163 across eight domains relating to: physical functioning, role limitation due to physical
164 problems, emotional problems, bodily pain, general health, social functioning, vitality,
165 and mental health. ⁽³⁴⁾ Responses are made on Likert-type scales and the 36 individual
166 items can be translated to give a global score for general health (ranging 0-100) where

167 lower scores reflect poorer self-reported health. Following the International Quality of
168 Life Assessment Project translation of SF-36 into several languages, ⁽³⁵⁾ this PROM has
169 become frequently used in cost-utility studies. ⁽³⁶⁾

170 **Glaucoma Quality of Life (GQL-15)** instrument has 15-items and is disease
171 specific being designed to assess the impact of glaucoma on vision-related quality of life.
172 ⁽³⁷⁾ The GQL-15 was derived from an initial 62-item pilot questionnaire; the 15-items
173 were included in the final instrument due to their strong relationship with visual field
174 loss in glaucoma patients. ⁽³⁸⁾ GQL-15 has four subscales: central and near vision,
175 peripheral vision, mobility, and glare/dark adaptation. Scoring is based on five-point
176 Likert-type scales where a response of 5 denotes severe difficulty and 1 indicates no
177 difficulty. The measurement scale ranges from 15 to 75 where higher scores represent
178 poorer vision-related quality of life. The instrument has been used in well-designed
179 cross-sectional studies assessing the impact of glaucoma on patients' quality of life. ^(39,40)

180 GQL-15 has previously been subjected to Rasch analysis to produce the 9-item
181 **Glaucoma Activity Limitation (GAL-9)** PROM. ⁽⁴¹⁾ This instrument consists of a subset
182 of nine items from the original GQL-15 and is considered to better reflect the effects of
183 glaucoma on visual function. ⁽⁴¹⁾ GAL-9 has good external validity as scores from the
184 instrument have been shown to correlate well with visual acuity and visual field scores.
185 Furthermore, the GAL-9 is quicker to complete than the GQL-15 because it has fewer
186 items. ⁽⁴¹⁾ In addition to our analysis of GQL-15 responses, we repeat the analysis on the
187 items included in the GAL-9 for patients in the UKGTS.

188 For the data analysis, responses on the PROMs at baseline and exit were
189 transposed into percentage scores. (The exit visit was at 24-months or, for progressing
190 patients, at the visit when progression was confirmed). Differences between these scores

191 were used to detect the degree of change in each PROM between first and last trial visit.
192 For example, no change is indicated by zero and scores greater than 0% indicate
193 worsening on PROMs, i.e. patients report more problems on exit from the trial than at
194 baseline; negative values indicate improvement from baseline. Two-sample independent
195 t-tests were used to determine whether there was a statistically significant difference in
196 change on PROMs between the two trial groups (treatment and placebo).

197 Additionally, we assessed whether statistically significant differences in PROM
198 responses could be observed between patients who remained stable during the UKGTS
199 and those who experienced the primary trial endpoint. We included this additional
200 analysis as it was anticipated that the largest difference in score for health-related and
201 vision-related quality of life would be observed between these two patient groups.

202 **Results**

203 Complete baseline and exit PROM data were available for n=182 (79%) and n=168
204 (73%) of patients with follow-up data in the treatment and placebo arm of the trial,
205 respectively. Average change in scores was similar for both the treatment and placebo
206 groups across all the PROMs (Table 1). There were no statistically significant differences
207 between the trial groups on PROMs relating to general health. Furthermore, there
208 remained no statistically significant differences between the two groups on the
209 glaucoma-specific PROMs. In addition, the distribution in the baseline to exit scores were
210 strikingly similar between the treatment and placebo groups (Figure 1).

211 PROM data were not available at the exit visit for a proportion of patients in the
212 UKGTS. Further analysis of those with missing data indicates that these patients had a
213 similar profile to those with complete data (Table 2). Specifically, as determined through
214 two-sample t-tests, there were no statistically significant differences between these two
215 groups on baseline better eye mean deviation (MD) ($p = 0.12$), worse eye MD ($p = 0.90$),

216 better eye visual acuity ($p = 0.44$), worse eye visual acuity ($p = 0.56$), and age ($p = 0.27$).
217 As a group, patients without exit PROMs reported slightly worse average general and
218 vision-related quality of life at baseline compared to those with exit PROMs. However, the
219 magnitude of these differences was small; it might reflect some patients without exit
220 PROMs being more likely to be people who were unwell at the start of the trial. For
221 example, 32 patients had less than 21-months follow-up in the trial because of ill health
222 and seven patients died during follow-up ⁽¹²⁾.

223 We assessed differences between stable patients ($N=272$) and patients with
224 glaucomatous progression ($N=78$) as determined by the primary visual field outcome.
225 Median (interquartile range) duration between baseline and progression confirmation
226 visit was 465 (278, 553) days, in comparison to the 2-year (730 days) scheduled follow-
227 up for patients remaining stable. No statistically significant differences were found
228 between average responses from stable and progressed patients on PROMs relating to
229 general health (EQ-5D, EQ-5D VAS and SF-36). Average differences between stable and
230 progressed patients were statistically significant when assessing responses on glaucoma-
231 specific PROMs (GQL-15 and GAL-9) (Table 3 and Figure 2). As a group, patients who had
232 progressed on visual fields therefore reported a reduction in glaucoma-specific vision-
233 related quality of life that was different to those who had remained stable on visual fields.
234 Mean (95% CI) scores for the progression patients on the GAL-9 and GQL-15 was 6.5 (2.8–
235 9.2) % and 3.9 (3.2–9.8) % respectively.

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240 **Table 1.** Means (standard deviation) of percentage (%) change scores for the two trial
 241 groups (treatment and placebo) on PROMs between baseline and trial exit in the UKGTS.
 242 Mean (standard deviation) change in worse-eye mean deviation between baseline and
 243 trial exit in the UKGTS. More negative MD indicates improved scores from baseline.

Table 1. Means (standard deviation) of percentage (%) change scores for the two trial groups (treatment and placebo) on PROMs between baseline and trial exit in the UKGTS. Mean [95% confidence interval] difference between the two samples. Mean (standard deviation) change in worse-eye mean deviation between baseline and trial exit in the UKGTS. More negative MD change indicates improved scores from baseline.

PROM	Group		Mean Difference [CI]	p-value
	Treatment N = 182	Placebo N = 168		
EQ-5D	1.7 (15.4)%	1.7 (10.6)%	0.0% [-2.8 to 2.8%]	0.98
EQ-5D VAS	2.1 (12.5)%	1.9 (12.0)%	0.2% [-2.8 to 2.4%]	0.88
SF-36	4.8 (19.8)%	5.0 (22.5)%	0.2% [-4.2 to 4.6%]	0.94
GQL-15	2.7 (7.7)%	3.2 (11.7)%	0.5% [-1.5 to 2.6%]	0.66
GAL-9	3.0 (8.5)%	3.2 (12.8)%	0.2% [-2.1 to 2.5%]	0.87
MD	-0.23 (1.9) dB	0.14 (2.0) dB		0.07

Change from baseline to exit is shown as a percentage (%). Percentages show the average amount of change on each PROM for treatment and placebo group. Positive percentages indicate worsening from baseline.

PROM = Patient reported outcome measure. CI = Confidence interval. EQ-5D = European quality of life in 5 dimensions. VAS = Visual analogue scale. SF-36 = Short form 36. GQL-15 = Glaucoma quality of life. GAL = Glaucoma activity limitation. MD = Mean deviation change in worse-eye. dB = Decibels.

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248 **Figure 1.** Boxplots on the left show change in scores between baseline and exit PROMs
249 for patients in the placebo group (blue) and the treatment group (green) in the UKGTS.
250 Positive scores (higher than 0) indicate worsening from baseline. Boxplots on the right
251 show change in progressing/worse eye MD score between baseline and exit VFs for
252 placebo and treatment groups. (MD is a summary measure used to represent overall
253 reduction in visual field sensitivity relative to healthy aged-matched observers. Lower
254 MD values (more negative) are indicative of greater loss of vision). Boxplots give median,
255 interquartile range, 5th and 95th percentiles (whiskers). Due to large variability in
256 responses, 95th percentile is capped at 40% change for SF-36 analysis (SF-36 placebo 95th
257 percentile = 54.6%; SF-36 treatment 95th percentile = 42.2%).

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269 **Table 2.** Comparison of baseline characteristics between patients in the UKGTS with
 270 PROM data (N=350) and those without PROM data at exit (N=166).

	UKGTS patients with PROMs <i>N = 350</i>	UKGTS patients without PROMs <i>N = 166</i>		p-value
MD (dB)				
Better eye				
Mean	-0.5 (1.2)	-0.8 (1.8)		0.12
Median	-0.5 [-1.3, 0.4]	-0.6 [-1.4, 0.3]		
Worse eye				
Mean	-4.2 (3.3)	-4.3 (3.6)		0.90
Median	-3.3 [-5.6, -2.0]	-3.4 [-5.7, -1.7]		
Best-corrected VA				
Better eye				
Mean	1.0 (0.21)	1.0 (0.24)		0.44
Median	1.0 [1.0, 1.2]	1.0 [1.0, 1.2]		
Worse eye				
Mean	0.9 (0.24)	0.9 (0.25)		0.56
Median	1.0 [0.67, 1.0]	1.0 [0.67, 1.0]		
Age (years)				
Mean	65.8 (9.9)	67.4 (11.9)		0.27
Sex				
Male	188 (53.7%)	85 (51.2%)		
Female	162 (46.3%)	81 (48.8%)		
Baseline PROM				
			Mean difference [CI]	
Mean				
EQ-5D	5 (7.2) %	5 (6.5) %	0 [0 to 3%]	0.53
EQ-5D VAS	81 (15.1) %	75 (18.7) %	6 [2 to 13%]	0.03
SF-36	77 (17.2) %	70 (19.9) %	7 [3 to 14%]	0.002
GQL-15	7 (8.9) %	11 (12.7) %	4 [1 to 10%]	0.003
GAL-9	7 (9.9) %	11 (14.7) %	4 [1 to 10%]	0.01

Data are n (%) or mean (standard deviation) or median [interquartile range]. PROM = Patient reported outcome measure. MD = Mean deviation. dB = Decibels. VA = Visual acuity (decimal). CI = Confidence interval.

272 **Table 3.** Means (standard deviation) of percentage (%) change scores for stable and
 273 progressed patients on PROMs between baseline and trial exit in the UKGTS. Mean
 274 (standard deviation) change in worse-eye mean deviation between baseline and trial exit
 275 in the UKGTS. More negative MD indicates improved scores from baseline.

Table 3. Means (standard deviation) of percentage (%) change scores for stable and progressed patients on PROMs between baseline and trial exit in the UKGTS. Mean [95% confidence interval] difference between the two samples. Mean (standard deviation) change in worse-eye mean deviation between baseline and trial exit in the UKGTS. More negative MD indicates improved scores from baseline.

PROM	Outcome		Mean Difference [CI]	p-value
	Stable N = 272	Progressed N = 78		
EQ-5D	1.5 (13.5)%	2.4 (12.5)%	0.9% [-2.5 to 4.3]	0.62
EQ-5D VAS	1.5 (11.8)%	3.6 (13.5)%	2.1% [-1.0 to 5.2]	0.23
SF-36	4.6 (20.3)%	6.0 (23.6)%	1.4% [-3.9 to 6.7]	0.65
GQL-15	2.1 (7.9)%	6.0 (14.3)%	3.9% [1.5 to 6.3]	0.02*
GAL-9	2.1 (9.1)%	6.5 (14.8)%	4.4% [1.7 to 7.1]	0.02*
MD	-0.22 (1.9) dB	0.55 (2.1) dB		0.003*

Change from baseline to exit is shown as a percentage (%). Percentages show the average amount of change on each PROM for stable and progressed trial outcomes. Positive percentages indicate worsening from baseline.

PROM = Patient reported outcome measure. CI = Confidence interval. EQ-5D = European quality of life in 5 dimensions. VAS = Visual analogue scale. SF-36 = Short form 36. GQL-15 = Glaucoma quality of life. GAL = Glaucoma activity limitation. MD = Mean deviation of worse-eye. dB = Decibels.

* = significant at 0.05 level

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277 **Figure 2.** Boxplots on the left show change in scores between baseline and exit PROMs
 278 for patients remaining stable (purple) and patients with visual field progression (red) in
 279 the UKGTS. Positive scores (higher than 0) indicate worsening from baseline. Boxplots on
 280 the right show change in progressing/worse eye MD score between baseline and exit VFs
 281 for stable and progression groups. Boxplots give median, interquartile range, 5th and 95th

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282 percentiles (whiskers). Due to large variability in responses, 95th percentile is capped at
283 40% change for SF-36 analysis (SF-36 stable 95th percentile = 42.4%; SF-36 progression
284 95th percentile = 53.8%).

285

286 **Discussion**

287 Results from this study show average changes in scores on general health-related PROMs
288 (EQ-5D, EQ-5D VAS and SF-36) to be similar for patients receiving either Latanoprost or
289 placebo eye drops in the UKGTS. Moreover, we did not find any evidence for differences
290 between the two arms of the trial when analysing changes in PROMs specifically relating
291 to vision and glaucoma (GQL-15 and GAL-9). Therefore, PROMs used in the UKGTS
292 measured once at baseline and at 2-year follow-up (or final review, for those exiting early
293 as a consequence of visual field progression) are not as sensitive as serial visual fields,
294 taken over the same time course, in determining treatment differences in disease
295 progression in a trial for glaucoma treatment.

296 There were other interesting findings from our study. Statistically significant
297 differences were observed in average responses between stable and progressed patients
298 on glaucoma-specific PROMs, but this was not the case for general health-related PROMs.
299 This suggests general health-related PROMs are insensitive to treatment-induced
300 changes in glaucoma progression, certainly in the population of patients represented in
301 the UKGTS within the 24-month observation period. Another finding, not directly related
302 to the aim of our study, concerns differences between GAL-9 and GQL-15. When
303 comparing stable and progressing patients, GAL-9 yielded a marginally larger average
304 effect (4.4%) when compared to the GQL-15 (3.9%). As such, we provide supporting
305 evidence that the GAL-9 may be a satisfactory alternative to the GQL-15 when assessing
306 glaucoma-specific vision-related quality of life. The GAL-9 has the added benefit of having
307 fewer items and is therefore less burdensome for the patient to complete.

308 Our results have implications for trial design for glaucoma treatments. The UKGTS
309 highlighted that a relatively short observation period could be implemented when

310 adopting a sensitive change-from-baseline event criterion to identify visual field
311 progression. This was made possible by frequent visual field testing and sensitive
312 statistical methods where measurements that were repeatedly worse than baseline were
313 flagged. Our results suggest that PROMs may not be sensitive enough to be used as
314 outcome measures in glaucoma treatment trials, especially over a relatively short follow-
315 up. Yet, it is important to note in the UKGTS, patients only completed PROMs at baseline
316 and exit visits. The difference in mean deviation (a global measure, in the same sense as
317 a questionnaire score) of the visual fields taken at baseline and final review was also not
318 sufficiently sensitive to identify differences between the treatment and placebo groups.
319 Therefore, the explanation of the inability of the PROM scores to identify treatment
320 differences is that either the PROM scores are insufficiently responsive to the small
321 changes in disease observed over the short trial duration or that the scores are
322 insufficiently precise, or both. Indeed, PROMs administered more frequently during the
323 trial may have reduced the within person variability in responses and increase the
324 likelihood of capturing significant changes. We are aware of at least two ongoing
325 glaucoma trials that are doing this, albeit in different PROMS to the ones used in UKGTS.
326 ⁽²⁶⁻²⁷⁾ Still, the relatively small effects and large variability in our PROM data indicate that
327 even repeat measures may not provide adequate trial power. It is encouraging that our
328 chosen primary end point for the UKGTS, namely visual field progression, was sensitive
329 enough to detect changes that are likely imperceptible to most patients in the early stage
330 of the disease. Longitudinal studies have revealed an association between visual field
331 progression and changes in vision-related quality of life in glaucoma patients ⁽⁴²⁻⁴⁵⁾. Yet,
332 these studies have tended to use global or regional measures of visual field derived from
333 binocular measures. We are unaware of any longitudinal studies reporting changes in
334 quality of life measures that are associated with progression events detected at a visual

335 field test location level using GPA software. Ultimately, it makes sense that trial endpoints
336 are aligned to relevant and meaningful outcomes for the patient, and we have highlighted
337 that disease-specific instruments, like GAL-9 and GQL-15, can track visual field loss
338 amongst glaucoma patients. Moreover, it remains important that all stakeholders are
339 considered when deciding on outcome measures in clinical trials, and that includes the
340 patients themselves. ⁽⁴⁶⁾

341 Other observations on our results are noteworthy. Average changes in PROMs,
342 where they existed, were small and the variability in response between participants was
343 large. For example, the average 6% decline on the GQL-15 in the N=78 patients who were
344 progressing on visual fields is equivalent of a change from 'no difficulty' to 'a little bit of
345 difficulty' on just four of the 15 items on the GQL-15. This small average change in vision-
346 related quality of life suggests that patients experiencing the visual field endpoint do not
347 perceive large changes in visual function, in this cohort with glaucoma mostly at its
348 earliest stage. This is an interesting finding because it has been suggested that placebo-
349 controlled clinical trials for glaucoma treatment can be harmful for those randomised to
350 the placebo arm. ⁽⁴⁷⁾ However, our findings certainly indicate that vision-related and
351 health-related quality of life was similar between patients in the placebo group to those
352 randomised to treatment over the course of the trial. In the case of the UKGTS, all patients
353 were monitored closely over a short trial duration and the criterion for visual field
354 deterioration was proven to be very sensitive. On average, patients progressing, based on
355 visual fields, experience a small or unnoticeable reduction in vision-related quality of life.
356 They certainly do not, on average, experience a change in general health as measured by
357 the general-health PROMs considered in our study and this is particularly noteworthy.
358 These findings support an argument for close monitoring being an alternative to medical
359 treatment in the early stages of the disease, an observation made from the results of

360 previous clinical trials. ^(5, 8) As no statistically significant differences in PROM scores were
361 observed between the treatment and placebo group in UKGTS, our findings might have
362 implications for how health-related and vision-related quality of life are assessed in
363 clinical trials. More objective or 'real-world' assessments of visual disability are
364 emerging, and these have potential for use as trial outcomes that are meaningful to the
365 patient. One such measure, the Assessment of Function Related to Vision (AFREV),
366 requires users to perform visual tasks such as findings objects, using everyday
367 technologies, and reading under various illuminations. ⁽⁴⁸⁾ If used as an outcome measure,
368 tools such as the AFREV may yield more discernible differences between treatment
369 groups in glaucoma clinical trials, but this remains speculation until tested. An added
370 advantage of such objective measures is that, unlike PROMs, they are less reliant on the
371 functional literacy of the patient. Offering definitive guidance on the use of PROMs or
372 visual fields, or a combination of the two, as outcome measures for glaucoma trials is
373 beyond the remit of this study. These issues are complicated because, for example,
374 PROMs are derived from the individual, who has two eyes, and the visual field outcome
375 is derived from just one eye (the first showing progression), and in the UKGTS just 11%
376 (n = 10) of progressing patients had visual field progression in both eyes. PROM
377 performance in glaucoma is likely driven by the least affected eye but this is dependent
378 on the stage of glaucoma ^(49, 50); in the UKGTS, almost 50% of participants had glaucoma
379 in only one eye. Furthermore, the visual field progression outcome occurred in one eye
380 only in almost 90% of participants with identifiable progression (94 of 461 subjects) and
381 in 73% of these, the progression was in the worse eye. Thus, the person-level PROM
382 outcome would be expected to be less sensitive to glaucoma deterioration than eye-based
383 measures of visual function. For example, standard automated perimetry will detect
384 changes in sensitivity that may be unnoticed by the patient, whereas PROMs will likely be

385 more responsive to central visual field loss. This does not mean that PROMs do not have
386 a role in treatment trials; they may have a more important role in identifying adverse (or
387 even beneficial) effects of interventions on the person that they have in identifying
388 disease modifying effects.

389 The study was not without limitations. In some cases, not all patients completed
390 PROMs at baseline or exit from the trial and so no comparable data were available for
391 analysis. Yet, patients with and without PROM data had similar demographic and visual
392 function profiles. One key limitation comes from patients possibly being aware of the
393 status of their glaucoma progression (stable or worsening) at the time of completing exit
394 PROMs. This is certainly true for patients withdrawn early from the trial because visual
395 field progression had occurred. If, for example, a patient was told they were exiting the
396 trial because their clinically measured vision was getting worse, then that would likely
397 influence self-report of quality of life. If this were the case, one might expect knowledge
398 of glaucoma progression status to affect general health-related, as well as vision-related,
399 quality of life, but there were no differences in the EQ-5D or SF36 between those who
400 progressed and those who did not. As previously discussed, the design of the UKGTS
401 meant that patients completed PROMs at only two time points. This is obviously different
402 to the frequent collection of visual field data (primary outcome). Our results are also
403 limited to apply to only a UK population of newly diagnosed patients, most of whom were
404 at the earliest stage of the disease. We cannot say how PROMs may change over a period
405 of 24-months in people with more advanced disease. Patient's vision-related quality of
406 life may decrease more quickly when visual field loss is already quite advanced. ⁽⁵¹⁾

407 In conclusion, patients randomised to treatment or placebo in the UKGTS returned
408 similar responses to PROMs at baseline and final visits of the trial. It is accepted that no

409 single PROM covers all aspects of patients' vision-related quality of life, ⁽⁵²⁾ and our
410 findings at least emphasise the importance of appropriate PROM selection when
411 designing and implementing clinical trials. Even if PROMs cannot capture the disease
412 modification effect of an intervention, that certainly does not mean that they are not
413 useful if they can capture other consequences of an intervention including, for example,
414 side effects or inconvenience of treatment regimens. In the UKGTS differences in PROM
415 responses only emerged when comparing stable and progressed patients on instruments
416 that were specific to glaucoma. As such, we suggest PROMs alone, administered at the
417 start and end of a 24-month trial assessing disease progression, may not be sensitive
418 enough to be used as the primary endpoints in glaucoma clinical trials assessing disease
419 progression.

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