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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

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Manuscript Details

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Abstract

Purpose: The UK Glaucoma Treatment Study (UKGTS) demonstrated the effectiveness of an intraocular pressure-lowering drug in patients with glaucoma using visual field progression as a primary outcome. We now test the hypothesis that responses on patient reported outcome measures (PROMs – secondary outcome measure) differ between patients receiving a topical prostaglandin analogue (Latanoprost) or placebo eye drops in UKGTS. **Design:** Multi-centre, randomised, triple-masked, placebo-controlled trial. **Participants:** Newly diagnosed glaucoma patients recruited into the UKGTS with baseline and exit PROM data (n= 182 and n=168 patients from the treatment and placebo group, respectively). **Methods:** The UKGTS was a multi-centre, randomised, triple-masked, placebo-controlled trial, where patients with newly diagnosed open angle glaucoma were allocated to receive Latanoprost (treatment) or placebo (trial registration number: ISRCTN96423140); the observation period was 24 months. Patients completed general health PROMs (EQ-5D and SF-36) and PROMs specific to glaucoma (GQL-15 and GAL-9) at baseline and at exit from the trial. Percentage change between baseline and exit measurement on PROMs were calculated for each patient and compared between treatment arms. In addition, differences between stable patients (n=272) and those with glaucomatous progression (n=78), as determined by visual field change (primary outcome), were assessed. **Main Outcome Measure:** PROMs on health-related and vision-related quality of life. **Results:** Average percentage change on PROMs was similar for patients in both arms of the trial with no statistically significant differences between treatment and placebo 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 = 0.87). There were statistically significant differences between stable and progressing patients, as determined by visual fields, on glaucoma-specific PROMs (GQL-15, p = 0.02; GAL-9, p = 0.02) but not on general health PROMs (EQ-5D, p = 0.62; EQ-5D VAS, p = 0.23; SF-36, p = 0.65). **Conclusions:** Average change in PROMs on health-related and vision-related quality of life was similar for the treatment and placebo group in the UKGTS. PROMs, specifically those used in the UKGTS, may not be sensitive enough to be used as a primary endpoint in clinical trials when participants have newly diagnosed early stage glaucoma.

Taxonomy	Patient-Reported Outcome, Glaucoma
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Submission Files Included in this PDF

File Name [File Type]

Jones et al UKGTS PROM Ophthalmology Cover letter.docx [Cover Letter]

R to R_Jones et al. Ophthalmology_final.docx [Response to Reviewers]

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20th June 2018

City, University of London
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Dr. Stephen McLeod
Editor-in-chief
Ophthalmology

Dear Dr. McLeod

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

On behalf of all authors, we would be grateful if the above manuscript would be considered for publication in *Ophthalmology*.

The objective of this original research was to test the hypothesis that responses on patient reported outcome measures used in the United Kingdom Glaucoma Treatment Study will differ between patients receiving a topical prostaglandin analogue (Latanoprost) or placebo eye drops.

This manuscript has not been submitted elsewhere prior to our submission to *Ophthalmology* and we believe our work fits within the scope of this journal.

We thank you for your time and look forward to hearing from you.

Sincerely,

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Manuscript ID: OPHTHA_2018_1420

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

Suggestion, Question, or Comment from the Editor	Author's Response	Change in the Manuscript
It would be very helpful to the reader to define progression in this manuscript rather than referencing a previous publication. Also, the authors should describe whether the amount of change required to declare visual field progression has been associated with changes in QOL in previous studies (it likely has, but it will provide better background for the PROM descriptions).	<p>We thank the editor for their suggested revisions to the manuscript. We now include the definition used to determine visual field progression in the study. (1)</p> <p>We are unaware of any studies reporting changes in measures of quality of life (vision-related, or glaucoma-specific, or general) that are associated with progression events detected at a pointwise level using GPA software. We have added this point to the discussion (2) and expanded on it by adding references to studies that have used well-designed cohort studies to explore the relationship between changes in visual field measures in individuals and their self-reported QoL. These studies tend to use summary measures of the visual field (MD or mean sensitivity) and binocular measures to boot. Evidence suggests scores on QoL metrics tend to be driven by the binocular visual field or by the better-eye visual field (Skalicky et al., 2016; Arora et al., 2013), and in the UKGTS the majority of patients reached the trial outcome in the worse (most affected) eye only.</p>	<p>(1) Line 131: "Visual field progression was used as the primary endpoint in the trial. Progression analysis was performed in the Humphrey Field Analyser Guided Progression Analysis (GPA) software; a sensitive technique that considers changes at individual points (test locations) in the visual field. Progression was defined as at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields; the locations identified in the first and second pair were not required to be identical."</p> <p>(2) Line 332: "Longitudinal studies have revealed an association between visual field progression and changes in vision-related quality of life in glaucoma patients ⁽⁴²⁻⁴⁵⁾. Yet, these studies have tended to use global or regional measures of visual field derived from binocular measures. We are unaware of any longitudinal studies reporting changes in quality of life</p>

		<p>measures that are associated with progression events detected at a visual field test location level using GPA software.”</p> <p>42. Medeiros FA, Gracitelli CP, Boer ER, et al. Longitudinal changes in quality of life and rates of progressive visual field loss in glaucoma patients. <i>Ophthalmology</i>, 2015; 122: 293-301.</p> <p>43. Abe RY, Diniz-Filho A, Costa VP, et al. The Impact of Location of Progressive Visual Field Loss on Longitudinal Changes in Quality of Life of Glaucoma Patients. <i>Ophthalmology</i>, 2016; 123: 552-7.</p> <p>44. Peters D, Heijl A, Brenner L, et al. Visual impairment and vision-related quality of life in the Early Manifest Glaucoma Trial after 20 years of follow-up. <i>Acta Ophthalmologica</i>, 2015; 93: 745-752.</p> <p>45. Diniz-Filho A, Abe RY, Cho HJ, et al. Fast visual field progression is associated with depressive symptoms in patients with glaucoma. <i>Ophthalmology</i>, 2016; 123: 754-759.</p>
<p>The original study was powered to look at differences between treatment and placebo groups of 11% vs 24% progression. The study was not powered to look for differences in PROM measures. What would be a clinically meaningful difference in PROM score? The manuscript deals with change in score, which makes it difficult to know where these participants are falling on the PROM score metric(s). What PROM difference would have been detectable with 80% power or more? Is that difference clinically significant?</p>	<p>The editor has rightly pointed out that PROMs were secondary outcomes in the UKGTS and were not used to power the study. Our report is an analysis of the relative sensitivity of PROMs by assessing if differences could be detected between the treatment and placebo groups of the UKGTS. We found no statistically significant difference here, thus our findings indicate PROMs to be less sensitive measures. However, an important caveat to this finding is that PROM data were collected at baseline and trial exit, only. It is indeed possible that more frequent administration of these PROMs may provide different results whereby more discernible differences between the groups are identified. We already made this point but we now further highlight it in the discussion to make it clear.</p> <p>Interestingly, the Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE)</p>	<p>Line 324: “Indeed, PROMs administered more frequently during the trial may have reduced the within person variability in responses and increase the likelihood of capturing significant changes.”</p>

<p>The issue of non-significant findings must be considered in the context of study power.</p>	<p>randomised control trial comparing lens extraction to laser peripheral iridotomy (Azuara-Blanco et al., 2016) used a margin of 5% change in EQ-5D score as a clinically important difference. In our study, the average difference between treatment arms on the EQ-5D was 0.0% [95% CI - 2.8 to 2.8%] and so would not be considered clinically significant. However, as glaucoma is a chronic progressive disease, small changes over a small amount of time are likely to become larger differences eventually. So even small changes may become clinically meaningful later in time if the patient continues to progress. In the previous iteration of the manuscript we did not report the 95% confidence intervals around the differences between the groups and these have now been added to Table 1 and 3.</p> <p><i>Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. The Lancet, 2016; 388(10052): 1389-97.</i></p>	
<p>The authors do not report on differences within each treatment group between progressors and non-progressors. This might be understandable given the relatively small number of progressors. However, there could be confounding, as the original study found a protective effect of treatment on progression. The reason this is important is that such a large percentage have missing data. The authors compare baseline characteristics between those with</p>	<p>We appreciate the effort the editor has gone to when considering this comment. We have split our response to address the two questions that are asked.</p> <p>Q1. The main UKGTS outcome paper stated that 15.2% of patients in the Latanoprost group progressed and 25.6% of the placebo group progressed. Based on the n=350 in our study, it would be anticipated that 71 patients with progression would be included in this analysis. However, we analyse the data of 78 progression patients. Thus, the editor is questioning the representativeness of our study sample. We agree that when reporting outcomes on only a subset of data (in this case, the 350 with PROMs), it would be important to consider how representative the sample is. Yet, we would argue that the inclusion of 78 progression patients as opposed to the expected 71 is not likely to be meaningfully different and is unlikely to have any</p>	<p>(1) Line 315: 'Our results suggest that PROMs may not be sensitive enough to be used as outcome measures in glaucoma treatment trials, especially over a relatively short follow-up. Yet, it is important to note in the UKGTS, patients only completed PROMs at baseline and exit visits.'</p> <p>Line 391: 'In some cases, not all patients completed PROMs at baseline or exit from the trial and so no comparable data were available for analysis. Yet, patients with and without PROM data had similar demographic and visual function profiles.'</p> <p>(2)</p>

<p>and without PROM data, but this skirts the question of whether those with missing data might have been more likely to progress. A crude examination of this possibility might be gleaned from the data: the expected number of progression events (if results from original trial held in this subgroup) would be 15.2% of those in the treatment group (n=182) and 25.6% of those in the control group (n=168); i.e., 28 in the treatment group and 43 in the placebo group, for a total of 71. This report includes 78 cases of progression. Might this indicate somewhat differential follow-up by treatment group? What would be the implications for the results? The percentage of missing data in the treatment arm is somewhat higher than for the placebo arm (lines 194-195) – might this mean that those with progression are somewhat over-represented in the subgroup with PROM data?</p>	<p>implications on the results. This is supported by the following calculation. In the main Lancet outcome paper, we report 94 participants had visual field deterioration consistent with glaucomatous progression in 461 patients (20.3%). (This is identical to the result of the editor's nice calculation of an expected 71 from 350 [20.3%].) In our sample of patients with PROM data, we ended up with 78 participants with visual field progression from 350 patients (22.2%). These two proportions (20.3 vs 22.2%) are not statistically different. (Chi Square Test for how likely it is that any observed difference between the sets arose by chance gives P=0.51). So we don't think those with progression are over-represented in the subgroup with PROM data</p> <p>The missing data and the fact that data were captured at only baseline and exit are key caveats to this study, and we have attempted to address this in the discussion. (1)</p> <p>Q2. The percentage of missing data in the treatment arm is somewhat higher than for the placebo arm (lines 194-195) – might this mean that those with progression are somewhat over-represented in the subgroup with PROM data?</p> <p>We have now included the 95% CI around the proportion of patients with complete data for the Latanoprost and placebo groups (2). These estimates suggest that there is not a large difference (certainly not statistically different because the CIs overlap considerably) between the two groups and so it is unlikely that this will have an impact on our main findings.</p>	<p>Line 203: 'Complete baseline and exit PROM data were available for n=182 (79%; 95% CI 73 to 84%) and n=168 (73%; 95% CI 67 to 79%) of patients with follow-up data in the treatment and placebo arm of the trial, respectively.'</p>
<p>The table comparing baseline characteristics of those with and without complete PROM data should include information on baseline</p>	<p>We have now amended Table 2 to include average baseline scores on PROMs.</p>	<p>See Table 2.</p>

<p>scores for the various PROM measures. In addition, they should include the absolute PROM scores at final assessment for each group.</p>		
<p>Was there any additional information such as change in comorbidities or development of cataract, etc, that might also have affected the PROM changes?</p>	<p>This is indeed an important factor to consider as comorbidities may have an influence on PROM responses. However, as noted in the main outcome paper, a total of 11 patients had less than 21-months follow-up due to ocular comorbidities, including cataract, angle closure, and uveitis (6 in Latanoprost group; 5 in placebo group). Thus, these patients were not included in our main PROM analysis. As the number of patients with comorbidities is similar between the groups, it is not likely that this will impact our main finding. It would be possible to perform a statistical analysis to assess this using clinical measures, such as change in VA, however reductions in VA would not necessarily represent comorbidity. In addition, it is important to note that VA change worse than <20/60 in either eye was a non-glaucomatous endpoint and no patient reached that endpoint.</p>	
<p>The authors mention the limitation of the PROM being given earlier to participants who progressed. However, there is no description of how much earlier, nor is there any adjustment for it. The discussion mentions the possibility of introducing bias into the PROM assessment by the participant's learning of their disease progression before the PROM was administered: this was</p>	<p>The trial was designed to evaluate the primary outcome of time to progression, and PROMs were a secondary outcome. If progression was identified, confirmation visits were scheduled. The fact that confirmation visits were scheduled would mean the patient would likely be aware of their disease progression. The decision to collect PROM data at the exit visit was in line with the ethical standards for the trial and this was to ensure patients' care would not be affected. We agree that a description of how much earlier progressing patients exited the trial is an important addition. We have now added the average time duration between first baseline visit and progression confirmation visit (for the first eye).</p>	<p>Line 226: "Median (interquartile range) duration between baseline and progression confirmation visit was 465 (278, 553) days, in comparison to the 2-year (730 days) scheduled follow-up for patients remaining patients."</p>

<p>quite surprising as it is difficult to imagine that the clinical trial did not take steps to prevent this possibility.</p>		
<p>The authors make a good point (line 253): "...changes in PROMs specifically relating to vision and glaucoma (GQL-15 and GAL-9). Therefore, PROMs measured once at baseline and at 2-year follow-up (or final review, for those exiting early as a consequence of visual field progression) are not as sensitive as serial visual fields, taken over the same time course, in determining treatment difference". However, (line 278): "...important to note in the UKGTS, patients only completed PROMs at baseline and exit visits. The difference in mean deviation (a global measure, in the same sense as a questionnaire score) of the visual fields taken at baseline and final review was also not sufficiently sensitive to identify differences between the treatment and placebo groups." In other words, if there is a relatively short time between baseline and final assessments, neither PROMs nor MD would be sensitive –</p>	<p>In the UKGTS, glaucomatous progression was determined via HFA GPA whereby individual points of the visual field can be assessed for localised loss of sensitivity. Assessment of all of the points in the visual field is likely to be more sensitive to changes in disease than global parameters, such as the MD (Bryan et al., 2013). Previous research has established the MD to be an unsuitable method of determining visual field progression, since this metric takes the average deviation of all the measured points compared to age-corrected normative value (Heijl & Åsman, 1995). Our rationale for including an assessment of MD for patients in the UKGTS was simply to provide context of a global measure not being sensitive enough to detect changes between treatment arms. The relevance of our finding is that PROMs, when used as a global measure, were also not as sensitive as serial visual fields (where pointwise data are assessed) at determining differences between the two treatment arms in the trial.</p> <p><i>Bryan SR, Vermeer KA, Eilers PH, et al. Robust and censored modeling and prediction of progression in glaucomatous visual fields. Investigative Ophthalmology & Visual Science. 2013; 54: 6694–700.</i></p> <p><i>Heijl A, Åsman P. Pitfalls of automated perimetry in glaucoma diagnosis. Current Opinion in Ophthalmology. 1995; 6: 46–51.</i></p>	

so why make the conclusion that the authors emphasize about PROMs being not sufficiently sensitive to use in a clinical trial? They certainly aren't saying that about MD.		
One point that seems a bit overstated (line 264): "... concerns differences between GAL-9 and GQL-15. When comparing stable and progressing patients, GAL-9 yielded a larger average effect (4.4%) when compared to the GQL-15 (3.9%). As such, we provide supporting evidence that the GAL-9 is a satisfactory alternative to the GQL-15 when assessing glaucoma-specific vision-related quality of life. The GAL-9 has the added benefit of having ..." The difference between 4.4 and 3.9 doesn't seem very striking. GAL-9 and GQL-15 scores should be highly correlated and perhaps with GQL-15 you are gaining some additional information that is not constrained to be unidimensional (as in the Rasch-scaled version). How much additional time is needed to do 6 additional questions?	<p>We agree with the editor that the difference between 4.4 and 3.9 is not particularly striking. We have now amended the paper to state that the difference is marginal.</p> <p>We did not analyse the instrument sub-scores and so cannot be sure if additional information is lost when using GAL-9 over GQL-15. Yet, the GAL-9 showed no disadvantage as compared with the GQL-15 in this study. Shorter questionnaires are usually preferred by the patient, and 67% extra time would be needed for the GQL-15 over the GAL-9.</p>	Line 304: "When comparing stable and progressing patients, GAL-9 yielded a marginally larger average effect (4.4%) when compared to the GQL-15 (3.9%)."
Line 267 – change "is" to "may be"	The sentence has now been amended.	Line 306: "As such, we provide supporting evidence that the GAL-9 may be a satisfactory alternative to the

		GQL-15 when assessing glaucoma-specific vision-related quality of life.”
Line 291 “... namely visual field progression, was sensitive enough to detect changes that are likely imperceptible to most patients.” If the changes are imperceptible, how relevant would most PROM items be?	We agree with the editor and this was indeed one point we were attempting to emphasise. We present findings that visual field metrics (certainly with analysis at a visual field location level as used in GPA) are more sensitive to disease progression than PROMs and are therefore more useful, at least when assessing patients with early stage glaucoma. In the case of the UKGTS, we demonstrate that using visual field outcomes do not show a reduction in QoL even when patients are randomised to no treatment. We have now amended the discussion to emphasise that our findings refer to the sensitivity of PROMs in the early stages of disease.	Line 329: “It is encouraging that our chosen primary end point for the UKGTS, namely visual field progression, was sensitive enough to detect changes that are likely imperceptible to most patients in the early stage of the disease.”
The discussion can be shortened; in particular, lines 342-348 could be deleted.	We have now removed this aspect of the discussion section.	

Suggestion, Question, or Comment from Reviewer #1	Author’s Response	Change in the Manuscript
The main conclusion is that "PROMs may not be sensitive enough to be used as a primary endpoint in clinical trials". This is a generalization that is probably true, but cannot be supported by this study, since the authors didn't test every possible PROM. It is also specific to clinical trials that look at the rate of functional progression; they may be useful for other trials in similar populations (e.g. drug tolerance studies). More care is needed to	<p>We thank the reviewer for their constructive comments on how this manuscript can be improved.</p> <p>We have tried to ensure that the present study highlights that, although PROMs were not sensitive at detecting changes in the UKGTS, PROMs can be useful when determining treatment consequences. We have reworded the discussion to attempt to highlight this. (1)</p> <p>In addition, some changes have been made to the phrasing used in the paper. (2)</p>	<p>(1) Line 413: “Even if PROMs cannot capture the disease modification effect of an intervention, that certainly does not mean that they are not useful if they can capture other consequences of an intervention including, for example, side effects or inconvenience of treatment regimens.”</p> <p>(2) Line 76: “PROMs, specifically those used in the UKGTS, may not be sensitive enough to be used as a primary endpoint in clinical trials when participants have newly diagnosed early stage glaucoma.”</p>

<p>ensure that the conclusion accurately reflects what can actually be concluded from this study, both in the paper and the abstract.</p>		<p>Line 294: “Therefore, PROMs used in the UKGTS measured once at baseline and at 2-year follow-up (or final review, for those exiting early as a consequence of visual field progression) are not as sensitive as serial visual fields...”</p> <p>Line 418: “As such, we suggest PROMs alone, administered at the start and end of a 24-month trial assessing disease progression, may not be sensitive enough to be used as the primary endpoints in glaucoma clinical trials assessing disease progression.”</p>
<p>Given a large enough sample size, any two groups will be significantly different. I highly recommend reading "An Applied Statistician's Creed" by Nester (Appl Statist 1996)... When reporting a negative result then, it is imperative to report not just the statistical significance of the comparison, but also the 95% confidence interval for the difference between the groups; and preferably a sample size calculation showing how many people would be needed for this difference to be significant. That is likely to be an unfeasibly large sample size in this case, which will make a much stronger case against use of PROMs than merely lack of a significant difference.</p>	<p>We have now added the 95% confidence intervals for the differences between the groups (see Table 1 and 3). Despite adding these CIs the mean difference (effect) between the treatment and placebo group are all less than 0.5% (for EQ5D the effect was exactly zero!). Therefore, a post-hoc power calculation is unlikely to be useful. A power calculation can be used to determine the required sample size of a hypothetical future study assessing similar outcomes, although the utility of such calculations is debated (Hoenig & Heisey, 2001). A post hoc power calculation to determine the number of individuals that would be needed to detect a difference of 0.5% on the GQL-15 between patients randomised to treatment or placebo where alpha is set to 0.05 and power at 80% indicates a staggering 3723 individuals would be required in both arms of the trial. We have not included this because the sample size calculation for our study was based on the visual field change criteria in the UKGTS (for which there was a sample size calculation in the main outcome paper).</p> <p>We have, however, attempted to demonstrate the clinical effect of the observed change in PROMs in our study to</p>	<p>Line 343: “Average changes in PROMs, where they existed, were small and the variability in response between participants was large. For example, the average 6% decline on the GQL-15 in the N=78 patients who were progressing on visual fields is equivalent of a change from ‘no difficulty’ to ‘a little bit of difficulty’ on just four of the 15 items on the GQL-15.”</p>

	<p>emphasise the fact patients reaching the trial end point are unlikely to be strongly impacted by glaucomatous progression.</p> <p><i>Hoenig JM, Heisey DM. The abuse of power: the pervasive fallacy of power calculations for data analysis. The American Statistician. 2001; 55: 19-24.</i></p> <p>We also think our effect sizes and SDs in published Table 1 will be particular useful for other researchers who might want to generate sample size calculations for studies using these PROMS.</p>	
<p>The authors note that the PROMs were only measured twice, rather than at every visit. With the data at their disposal, they should be able to estimate the test-retest variability in each score (by subtracting the average change). This would then allow the authors to perform a sample size calculation for what would be expected if the data were to be collected on every visit (on the assumption of a constant rate of underlying change in PROM score), which would be a useful addition to the results.</p>	<p>We agree with the reviewer that this would be interesting. However, it may not be valid to assume that tests repeated up to 2-years apart may not have the same repeatability as those repeated, say, 3-months apart. Yet we think this could be the subject of further work. So, for example, someone designing a study where GQL-15 is an outcome could use the valuable data from our tables. We reiterate, the average change in PROMs in our study was very small, in some cases 0% (non-existent) when comparing placebo to the Latanoprost group. We know of at least two ongoing glaucoma clinical trials that are collecting PROM data at several time points throughout the trial, and it will be interesting to see what differences are observed in these studies. We have now added to our speculation about more frequent PROM measurements in the discussion and pointed the reader towards these trials that will report soon.</p>	<p>Line 324: “Indeed, PROMs administered more frequently during the trial may have reduced the within person variability in responses and increase the likelihood of capturing significant changes. We are aware of at least two ongoing glaucoma trials that are doing this, albeit in different PROMS to the ones used in UKGTS”. (26-27)</p> <p>26. King AJ, Fernie G, Azuara-Blanco A, et al Treatment of Advanced Glaucoma Study: a multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma—study protocol <i>British Journal of Ophthalmology</i> 2018;102:922-8.</p> <p>27. Vickerstaff V, Ambler G, Bunce C, et al. Statistical analysis plan for the Laser-1st versus Drops-1st for Glaucoma and Ocular Hypertension Trial (LiGHT): a multi-centre randomised controlled trial. <i>Trials</i>. 20; 16:517.</p>
<p>It is well known that PROM scores are driven largely by central vision; while visual field progression is more commonly seen in the mid-periphery, due to the spatial distribution of test locations (especially in the HFA 24-2 field that was used in the UKGTS). I would ask the authors to comment on this discrepancy, but also to</p>	<p>Certainly our findings do not imply that PROMs will not be useful in similar studies. The purpose of the presented study was to assess PROMs as outcomes in trials for glaucoma progression. For that reason, it is perhaps not necessary to perform this sub analysis as we already show that glaucoma-specific PROM results were different when comparing progressing and stable patients:</p>	<p>Line 383: “Thus, the person-level PROM outcome would be expected to be less sensitive to glaucoma deterioration than eye-based measures of visual function. For example, standard automated perimetry will detect changes in sensitivity that may be unnoticed by the patient, whereas PROMs will likely be more responsive to central visual field loss.”</p>

report and compare the rates of central field progression in each group (maybe using the rate of change of the mean of the central 4 locations, or something along those lines?). If the treatment and placebo groups had equal rates of central progression, then that would explain the results entirely without implying that PROMs were not useful for similar studies.	<p><i>“No statistically significant differences were found between average responses from stable and progressed patients on PROMs relating to general health (EQ-5D, EQ-5D VAS and SF-36). Average differences between stable and progressed patients were statistically significant when assessing responses on glaucoma-specific PROMs (GQL-15 and GAL-9) (Table 3 and Figure 2). Patients who had progressed on visual fields therefore reported a reduction in glaucoma-specific vision-related quality of life that was different to those who had remained stable on visual fields. Mean (95% CI) scores for the progression patients on the GAL-9 and GQL-15 was 6.5 (2.8–9.2) % and 3.9 (3.2–9.8) % respectively.”</i></p> <p>We have now further emphasised this point by adding the confidence intervals to Table 3 and we have clarified further by adding a comment in the discussion to reflect on this fact.</p>	
n=10 participants showed progression in both eyes. Would it be possible to repeat the main analysis using this an outcome measure for 'progression', instead of single eye progression? Or is the number too low to generate meaningful results?	Our findings already demonstrate that there is a difference when comparing progressed to stable patients on glaucoma-specific instruments. Unfortunately a sample of 10 is too small to perform a meaningful analysis.	
Were there any differences in PROM scores at baseline between the groups?	<p>A good suggestion. We have now added baseline PROM scores to Table 2. Statistically significant differences were observed between average baseline PROM scores in those with and those without comparable PROM data on the EQ-5D VAS (p=0.03), SF-36 (p=0.002), GQL-15 (p=0.003), and GAL-9 (p=0.01) whereby those without comparable data gave worse scores at baseline.</p> <p>As a group, participants without exit PROMS reported slightly worse general and vision related quality of life at</p>	Line 218: “As a group, patients without exit PROMs reported slightly worse average general and vision-related quality of life at baseline compared to those with exit PROMs. However, the magnitude of these differences was small; it might reflect some patients without exit PROMs being more likely to be people who were unwell at the start of the trial. For example, 32 patients had less than 21 months follow-up in the trial because of ill health and seven patients died during follow-up ⁽¹²⁾ .”

	<p>baseline compared to those with exit PROMS. However, the magnitude of these differences was small (we have added 95% CIs for the differences to the table). It is well known that PROM responses are affected by personality factors and health, such as depression. We speculate that a number of those without exit PROMS were more likely to be people who were unwell at the start of the trial. For example, 32 participants had less than 21 months follow-up in the trial because of ill health and seven participants died during follow-up. We do not think this finding influences our main results.</p> <p>We have now included detail about this this finding in the results section.</p>	<p>12. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. <i>The Lancet</i>. 2015;385:1295-304.</p>
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Suggestion, Question, or Comment from Reviewer #2	Author's Response	Change in the Manuscript
<p>The trial is a landmark trial, and this particular finding with respect to generic and glaucoma-specific PROMs is of relevance to all glaucoma trials. It would be good to have a little more data on exactly how the PROMs were administered to the trial participants - for example, was this the task of a specific trial researcher (eg nurse) or were they administered by the treating clinicians. The importance of this is that if the PROM is administered by the treating clinician, then there is the potential for bias. It would also be helpful to know if the patients were assessed for functional literacy before filling in the PROMs.</p>	<p>We thank the reviewer for their positive comments about the manuscript. We agree that PROMs administered by patients' treating clinician may incur biases the likes of demand characteristics. PROMs were administered in clinic and this was the role of a trial researcher within each recruitment site and all study personnel were masked to the treatment allocation. As such, the treating clinician's role in data collection was limited and hence reduced the likelihood of such biases. We have now stated that PROMs were administered by a trial researcher (1).</p> <p>Although 'educational level' was included in the main outcome paper baseline characteristic, patient's functional literacy was not assessed during the recruitment period. We agree with the reviewer that knowledge of patients' literacy abilities is an important aspect of clinical research. We have now added to the discussion to reflect this (2). In this instances, the intention was for the trial sample to be</p>	<p>(1) Line 143: "PROMs were self-reported at patients' baseline and final visit and were administered by a trial researcher"</p> <p>(2) Line 371: "An added advantage of such objective measures is that, unlike PROMs, they are less reliant on the functional literacy of the patient."</p>

	generalisable and as such, inclusion criteria did not specify specific functional literacy criterion.	
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Title:

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

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Conflict of interest:

No conflicting relationship exists for any author.

Running head:

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 Quality
41 of Life in 5 dimensions; **SF-36** = Short Form-36; **GQL-15** = Glaucoma Quality of Life-15; **GAL-9** =
42 Glaucoma Activity Limitation-9; **VAS** = Visual Analogue Scale; **AFREV** = Assessment of Function
43 Related to Vision; **IOP** = Intraocular Pressure; **MD** = Mean Deviation; **dB** = Decibels; **VA** = Visual
44 Acuity.

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

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

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

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

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

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

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

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

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

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

Use of PROMs in clinical research has increased in recent years, ⁽¹⁵⁾ and this is beginning to be mirrored in glaucoma research, ⁽¹⁶⁾ where a catalogue of vision-specific PROMs are now available. ⁽¹⁷⁾ PROMs are also becoming more frequently used in clinical trials, ⁽¹⁸⁾ including in ophthalmology trials, ^(19- 23). Typically, PROMs are used to 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.

Methods

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

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

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

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

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

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

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

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

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

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

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

Results

Complete baseline and exit PROM data were available for n=182 (79%; 95% CI 73% to 84%) ~~79% (N = 182)~~ and n=168 (73%; 95% CI 67% to 79%) ~~73% (N = 168)~~ of patients with follow-up data in the treatment and placebo arm of the trial, respectively. Average change in scores was similar for both the treatment and placebo groups across all the PROMs (Table 1). There were no statistically significant differences between the trial groups on PROMs relating to general health. Furthermore, there remained no statistically significant differences between the two groups on the glaucoma-specific PROMs. In addition, the distribution in the baseline to exit scores were strikingly similar between the treatment and placebo groups (Figure 1).

PROM data were not available at the exit visit for a proportion of patients in the UKGTS. Further analysis of those with missing data indicates that these patients had a similar profile to those with complete data (Table 2). Specifically, as determined through two-sample t-tests, there were no statistically significant differences between these two

groups on baseline better eye mean deviation (MD) ($p = 0.12$), worse eye MD ($p = 0.90$), better eye visual acuity ($p = 0.44$), worse eye visual acuity ($p = 0.56$), and age ($p = 0.27$).

As a group, patients without exit PROMs reported slightly worse average general and vision-related quality of life at baseline compared to those with exit PROMs. However, the magnitude of these differences was small; it might reflect some patients without exit PROMs being more likely to be people who were unwell at the start of the trial. For example, 32 patients had less than 21-months follow-up in the trial because of ill health and seven patients died during follow-up⁽¹²⁾.

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

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 (standard deviation) change in worse-eye mean deviation between baseline and 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
	<i>Treatment</i> <i>N = 182</i>	<i>Placebo</i> <i>N = 168</i>		
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.

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

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

Table 2. Comparison of baseline characteristics between patients in the UKGTS with 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.				

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 (standard deviation) change in worse-eye mean deviation between baseline and trial exit 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
	<i>Stable</i> <i>N = 272</i>	<i>Progressed</i> <i>N = 78</i>		
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

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

283 percentiles (whiskers). Due to large variability in responses, 95th percentile is capped at
284 40% change for SF-36 analysis (SF-36 stable 95th percentile = 42.4%; SF-36 progression
285 95th percentile = 53.8%).

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Discussion

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

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

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

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

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

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

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

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

~~The UKGTS had a strong experimental design. The trial was the first to use a placebo group to measure the effects of IOP reduction. Furthermore, only a single treatment was evaluated – prostaglandin analogue eye drops were the only intervention used in the trial. In addition, patients in the UKGTS were newly-diagnosed, meaning their glaucoma had not been treated previously. As such, there were no influences from previous treatments, which may have had an impact on patients’ health-related and vision-related quality of life.~~

—The study was not without limitations. In some cases, not all patients completed PROMs at baseline or exit from the trial and so no comparable data were available for analysis. Yet, patients with and without PROM data had similar demographic and visual function profiles. One key limitation comes from patients possibly being aware of the status of their glaucoma progression (stable or worsening) at the time of completing exit PROMs. This is certainly true for patients withdrawn early from the trial because visual field progression had occurred. If, for example, a patient was told they were exiting the trial because their clinically measured vision was getting worse, then that would likely influence self-report of quality of life. If this were the case, one might expect knowledge of glaucoma progression status to affect general health-related, as well as vision-related, quality of life, but there were no differences in the EQ-5D or SF36 between those who progressed and those who did not. As previously discussed, the design of the UKGTS meant that patients completed PROMs at only two time points. This

is obviously different to the frequent collection of visual field data (primary outcome). Our results are also limited to apply to only a UK population of newly diagnosed patients, most of whom were at the earliest stage of the disease. We cannot say how PROMs may change over a period of 24-months in people with more advanced disease. Patient's vision-related quality of life may decrease more quickly when visual field loss is already quite advanced.⁽⁵¹⁾

In conclusion, patients randomised to treatment or placebo in the UKGTS returned similar responses to PROMs at baseline and final visits of the trial. It is accepted that no single PROM covers all aspects of patients' vision-related quality of life,⁽⁵²⁾ and our findings at least emphasise the importance of appropriate PROM selection when designing and implementing clinical trials. Even if PROMs cannot capture the disease modification effect of an intervention, that certainly does not mean that they are not useful if they can capture other consequences of an intervention including, for example, side effects or inconvenience of treatment regimens. In the UKGTS differences in PROM responses only emerged when comparing stable and progressed patients on instruments that were specific to glaucoma. As such, we suggest PROMs alone, administered at the start and end of a 24-month trial assessing disease progression, ~~are~~may not be sensitive enough to be used as the primary endpoints in glaucoma clinical trials assessing disease progression.

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Précis

Patients randomised to receive treatment or placebo eye drops in a glaucoma clinical trial responded similarly on PROMs. Statistically significant differences in average responses were observed between stable and progressed patients on disease-specific PROMs.

Title:

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

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No conflicting relationship exists for any author.

Running head:

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 Quality
41 of Life in 5 dimensions; **SF-36** = Short Form-36; **GQL-15** = Glaucoma Quality of Life-15; **GAL-9** =
42 Glaucoma Activity Limitation-9; **VAS** = Visual Analogue Scale; **AFREV** = Assessment of Function
43 Related to Vision; **IOP** = Intraocular Pressure; **MD** = Mean Deviation; **dB** = Decibels; **VA** = Visual
44 Acuity.

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

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

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

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

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

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

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

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

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

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

Use of PROMs in clinical research has increased in recent years, ⁽¹⁵⁾ and this is beginning to be mirrored in glaucoma research, ⁽¹⁶⁾ where a catalogue of vision-specific PROMs are now available. ⁽¹⁷⁾ PROMs are also becoming more frequently used in clinical trials, ⁽¹⁸⁾ including in ophthalmology trials, ^(19- 23). Typically, PROMs are used to 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.

Methods

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

A total of 461 patients from 516 enrolled were analysed in the trial (Latanoprost N = 231, placebo N = 230). Patients in the UKGTS were scheduled to perform a series of 11 visual field examinations during a 2-year observation period. Visual field progression was used as the primary endpoint in the trial. Progression analysis was performed in the Humphrey Field Analyser Guided Progression Analysis (GPA) software; a sensitive technique that considers changes at individual points (test locations) in the visual field. Progression was defined as at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields; the locations identified in the first and second pair were not required to be identical. Details of the trial design and the trial outcome are published elsewhere. (12; 29)

In short, the risk of visual field progression was significantly lower in the treatment group than in the placebo group (adjusted hazard ratio 0.44 [95% confidence interval (CI) 0.28-0.69]).

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

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

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

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

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

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

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

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

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

Results

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

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

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

We assessed differences between stable patients ($N=272$) and patients with glaucomatous progression ($N=78$) as determined by the primary visual field outcome. Median (interquartile range) duration between baseline and progression confirmation visit was 465 (278, 553) days, in comparison to the 2-year (730 days) scheduled follow-up for patients remaining stable. No statistically significant differences were found between average responses from stable and progressed patients on PROMs relating to general health (EQ-5D, EQ-5D VAS and SF-36). Average differences between stable and progressed patients were statistically significant when assessing responses on glaucoma-specific PROMs (GQL-15 and GAL-9) (Table 3 and Figure 2). As a group, patients who had progressed on visual fields therefore reported a reduction in glaucoma-specific vision-related quality of life that was different to those who had remained stable on visual fields. Mean (95% CI) scores for the progression patients on the GAL-9 and GQL-15 was 6.5 (2.8–9.2) % 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
	<i>Treatment</i> <i>N = 182</i>	<i>Placebo</i> <i>N = 168</i>		
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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Figure 1. Boxplots on the left show change in scores between baseline and exit PROMs for patients in the placebo group (blue) and the treatment group (green) in the UKGTS. Positive scores (higher than 0) indicate worsening from baseline. Boxplots on the right show change in progressing/worse eye MD score between baseline and exit VFs for placebo and treatment groups. (MD is a summary measure used to represent overall reduction in visual field sensitivity relative to healthy aged-matched observers. Lower MD values (more negative) are indicative of greater loss of vision). Boxplots give median, interquartile range, 5th and 95th percentiles (whiskers). Due to large variability in responses, 95th percentile is capped at 40% change for SF-36 analysis (SF-36 placebo 95th percentile = 54.6%; SF-36 treatment 95th percentile = 42.2%).

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).

Table 2. Comparison of baseline characteristics between patients in the UKGTS with 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.				

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 (standard deviation) change in worse-eye mean deviation between baseline and trial exit 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
	<i>Stable</i> <i>N = 272</i>	<i>Progressed</i> <i>N = 78</i>		
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

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

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%).

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Discussion

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

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

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

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

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

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

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

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

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

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

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

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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 (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	Group		Mean Difference	p-value
	<i>Treatment</i> <i>N = 182</i>	<i>Placebo</i> <i>N = 168</i>		
EQ-5D	1.7 (15.4)%	1.7 (10.6)%	0.0%	0.98
EQ-5D VAS	2.1 (12.5)%	1.9% (12.0)%	0.2%	0.88
SF-36	4.8 (19.8)%	5.0% (22.5)%	0.2%	0.94
GQL-15	2.7 (7.7)%	3.2% (11.7)%	0.5%	0.66
GAL-9	3.0 (8.5)%	3.2% (12.8)%	0.2%	0.87
MD	-0.23 (1.9)	0.14 (2.0)		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. 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.

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

	UKGTS patients with PROMs <i>N</i> = 350	UKGTS patients without PROMs <i>N</i> = 166		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.				

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 (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	p-value
	<i>Stable</i> <i>N = 272</i>	<i>Progressed</i> <i>N = 78</i>		
EQ-5D	1.5 (13.5)%	2.4 (12.5)%	0.9%	0.62
EQ-5D VAS	1.5 (11.8)%	3.6 (13.5)%	2.1%	0.23
SF-36	4.6 (20.3)%	6.0 (23.6)%	1.4%	0.65
GQL-15	2.1 (7.9)%	6.0 (14.3)%	3.9%	0.02*
GAL-9	2.1 (9.1)%	6.5 (14.8)%	4.4%	0.02*
MD	-0.22 (1.9)	0.55 (2.1)		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. 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.

* = significant at 0.05 level

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