Author's response to reviews

Title: A Prospective, Longitudinal, Observational Cohort Study Examining How Glaucoma Affects Quality of Life and Visually-Related Function Over 4 Years: Design and Methodology

Authors:

Michael Waisbourd (mwaisbourd@willseye.org)
Samantha Parker (sparker@willseye.org)
Feyzahan Ekici (feyzahah@gmail.com)
Patricia Martinez (pmartinezlehman@gmail.com)
Rachel Murphy (tub98500@temple.edu)
Katie Scully (kscully@villanova.edu)
Sheryl S. Wizov (swizov@willseye.org)
Lisa A. Hark (lhark@willseye.org)
George L. Spaeth (gspaeth@willseye.org)

Version: 3 Date: 6 July 2015

Author's response to reviews: see over
Dear Reviewers,

Thank you for taking the time and effort to review our manuscript. We truly appreciate your constructive comments and believe that your comments have helped to improve our papers. Please see our responses below, which are highlighted on the revised version of the manuscript.

Reviewer 1

General Comments:

First of all, I believe this study is well designed and what the authors aimed to elucidate is novel. However, I would like to raise some minor concerns.

COMMENT 1: The patients enrolled in this study had minimum 2-year diagnosis of glaucoma, so I think they had undergone at least one VF test before they were enrolled. However, because of learning effect of VF test, the number of VF tests, before they enrolled, should be referred to.

REPLY: We added the following to the methods section: “The patients enrolled in this study had minimum 2-year diagnosis of glaucoma, therefore all study patients had already underwent at least two VF examinations prior to their baseline assessment.” (Page 8, Line 163)
**COMMENT 2:** The age of the patients ranged from 21 to 85; therefore some of them might have suffered from dementia. Neurological disease, which is included in the exclusion criteria, may include it, but I still believe the authors should refer to dementia in Table 1 because it would have affect not only the QoL (or VRQoL, and so on) of the patients but also the accuracy of the results.

**REPLY:** We included dementia in the exclusionary criteria in the revised Table 1 as suggested. (Page 20)

**COMMENT 3:** Page 8, line 184: Time is treated as a categorical data in this study, according to the manuscript, but I am wondering why it is not treated as a continuous variable. As far as I know, visual field impairment associated with glaucoma is irreparable, which means it is progressive. So I could not understand the rationale of treating it as a categorical variable ignoring the time course deterioration of visual field defect.

**REPLY:** We will be modeling time both as continuous and categorical variable, in two separate models, as appropriate. E.g., we will compare outcomes between each year, and we will also investigate trajectories over time.

**COMMENT 4:** Page 9, line 199-201: I could not understand this sentence. For example, what “extension of GCMM” means and how it contributes to “multiple outcome trajectories.” I suppose that the authors employed an extended GCMM model for multiple outcome trajectories somehow. Please clarify and elaborate this sentence.
REPLY: Growth curve mixture models typically look for classes that differ with respect to the trajectory of a single outcome. We will use an extension of GCMM that allows for jointly modeling multiple outcome trajectories and identifying classes based on these multiple outcomes.

We added the following paragraph to the test: “In order to determine whether changes in VRQoL are associated with changes in clinical measures of vision and performance-based measures of visual function, an extension of GCMM will be used to model to simultaneously model multiple outcome trajectories and identify classes based on the joint consideration of multiple outcomes.” (Page 9, Line 207).

COMMENT 5: Page 9, line 208-210: The authors calculated confidence interval based on a linear model. However, with reference to page 8, line 183-184, linear and quadratic curves are also employed. I understand that quadratic regression (second order linear regression) is a kind of linear (as in linear algebra) regression, but I think it is somewhat confusing for some ophthalmologists.

REPLY: The reviewer is correct that linear regression can include quadratic terms. The linearity is in the coefficients of the model, not in the shape of the curve. We are unsure at this stage what shape the curves will take. Ideally, for simplicity of interpretation, a linear curve will be sufficient, however, a quadratic curve or a saturated model may be necessary.
COMMENT 6: I recommend that the authors should discuss the usefulness of employing non-linear regression in page 8; otherwise this sentence should be deleted.

REPLY: Our goal in comparing linear, quadratic, and saturated models (where we treat time as a categorical variable) is to determine an adequate representation of the trajectory of the outcome over time. Ideally, a linear model will be sufficient. However, it is possible that some outcomes may deteriorate more rapidly initially followed by a plateau or may stabilize and then rapidly decline. In these cases, a quadratic curve may more accurately represent the shape of the outcome trajectory. Failure to correctly model the trajectory can lead to errors in classification of subjects in the mixture models.

We added the following: Our goal in these analyses is to identify the most parsimonious model that adequately represents the shape of the outcome trajectory over time. Ideally, a linear model will be sufficient. It is possible, however, to imagine scenarios where a quadratic term may be required (e.g., initial decline followed by stabilization). (Page 9, Line 191)

Reviewer 2

General Comments:

Overall, this study represents a promising effort to clarify the relationship between glaucoma-related vision loss, function, and quality of life. The longitudinal nature of the study is a particular strength. This paper is, overall, well-written.
COMMENT 1: Background, third paragraph. Several relevant studies examining glaucoma, quality of life, and function are not referenced in this paper and probably should be, either here or in the discussion section.

REPLY: References 7-15 were added to the introduction as suggested, including the following: The Los Angeles Latino Eye Study, Salisbury Eye Evaluation, The Early Manifest Glaucoma Trial, The Collaborative Initial Glaucoma Treatment Study, and more recent studies by Weinreb/Medeiros and Ramulu. (Page 3, Line 67)

COMMENT 2: Methods/Design, research instruments, paragraph 4, line 126. Reference 29 should be sited here. In that reference, you explain that the test is intended to be useable on any relatively normal computer used with decent lighting. Are lighting conditions standardized in this study? Do all subjects take the test on the same computer? Please also specify lighting conditions (and if they are consistent) for Pelli-Robson contrast sensitivity testing.

REPLY: As suggested the SPARCS reference was cited; lighting conditions and the computer used are now mentioned: “The SPARCS test is a new method of measuring contrast sensitivity. It is performed on any standard computer with Internet access. [26] In this study, the SPARCS test was administered on the same computer, with standardized lighting conditions.” The Pelli-Robson lighting conditions were also specified: “The chart is mounted on a white wall with the patient sitting 1 meter in distance from the chart; the luminance of the test is at 85 candelas/m² (cd/m²), with the accepted range being between 60 to 120 cd/m².[25]” (Page 6, Line 124)
**COMMENT 3:** Methods/Design, Statistical analysis: Overall, this section could be less detailed. I expect that most of the audience for this paper will be physicians and some of this section is too technical for that audience. Some of the details can be saved for later publications (it will be easier to understand when it is explained alongside a presentation of the results).

**REPLY:** We agree that the statistical analysis is quite detailed, however we wanted to include as much detail as possible, as a reference for future publications.

**COMMENT 4:** Methods/Design, Statistical analysis, first paragraph: Given that the stated goal of the study is to examine vision-related function and quality of life over time, I would not consider ‘clinical measures of vision’ a primary outcome variable. I would describe these measures as ‘primary exposure/demographic variables’.

**REPLY:** We changed the order in which the outcome measures appear in the text to emphasize that vision-related functions and quality of life over time are the main focus of this study. We still believe that clinical measures of vision are important outcome measures, and therefore kept them in the revised manuscript. (Page 8, Line 172)

**COMMENT 5:** Methods/Design, Statistical analysis, second paragraph: line 176. I think you mean “all pairs of outcome variables and demographic variables.”

**REPLY:** The sentence was changed as suggested. (Page 8, Line 181)
COMMENT 6: Methods/Design, Statistical analysis, third paragraph: consider using a latent trait model (i.e. Rasch analysis) to analyze questionnaire data. This could be useful especially as the questionnaire items are not weighted.

REPLY: Since we will be calculating subscale scores on a validated instrument, we believe latent trait model is not necessary for this comparison.

COMMENT 7: Methods/Design, Missing data paragraph: the last sentence is confusing. What do you mean by a sensitivity analysis?

REPLY: Sensitivity analysis will involve comparison between the intent to treat population (all patients, including those with missing data,) and the per protocol population (which includes patients with complete data at all visits,) to investigate the impact of missing data on statistical results.

COMMENT 8: Discussion, first paragraph: probably more accurate to say “the overall health and well being of my patients”

REPLY: The sentence was changed as suggested. (Page 11, Line 239)

COMMENT 9: Discussion, second paragraph: probably more accurate to say “cognitive decline or other physical ailments in addition to their visual impairment.”
REPLY: The sentence was changed as suggested. (Page 11, Line 244)

COMMENT 10: Discussion, third paragraph: probably more accurate to say “VRQoL is an elusive term, the meaning of which may…”

REPLY: The sentence was changed as suggested. (Page 11, Line 1251)

COMMENT 11: Background, second paragraph, line 59. Change ‘their’ to ‘a’ unless you have a specific reference.

REPLY: Done.

COMMENT 12: Methods/Design, participants, paragraph 6, line 102. Delete “general”.

REPLY: Done.

COMMENT 13: Methods/Design, research instruments, last paragraph, line 162. Delete comma after “in addition to”

REPLY: Done.

COMMENT 14: Methods/Design, Statistical analysis, fifth paragraph: clause from line 200-201 (an extension of GCMM…) is missing a verb.
REPLY: The sentence was restructured as suggested (Page 9, Line 209)

COMMENT 15: Table 2, item 3: delete the comma after “one character in each sign”

REPLY: Done.

COMMENT 16: Table 3: the line spacing of this questionnaire is awkward and makes it harder to read. Also, the columns are strangely distributed across two pages – this won’t be an issue for the HTML version, I suppose, but the table should either fit in one page or read like normal text (follow the first column to the end of the page, then read the second column, then turn the page, etc). A question mark is needed at the end of item 10. In Part 2, “Next Questions” should be lower case.

REPLY: The table was reformatted as suggested. The revised Table 3 is now read like normal text. A question mark was added to the end of item 10 and “Next Questions” in Part 2 was changed to lower case letters. (Pages 21-22)

COMMENT 17: Methods/Design, Statistical analysis, sixth paragraph: It is not clear to me how the sample size of 161 was determined to be sufficient. Is this the total number that could be recruited during a particular time period? I am surprised that there is no sample size formula (even an approximation) that can be used with GCMM. Similarly, I am confused by the sentence “for illustration, we estimated precision for class sizes of
20, 60, and 100)- what do you mean by precision and how does this tie into your sample size calculation? What were your results for these precision calculations?

**REPLY:** The difficulty in determining adequate sample size is driven by the lack of pre-specified hypothesis testing in GCMM and the complexity of the models. The analysis is more exploratory in nature, and, thus, we attempted to demonstrate that under certain circumstances we would get reasonably precise estimates of the slopes (with precision defined by the width of the confidence interval).

Sample size was changed to 160. We added the following to the text: “Table 5 shows the width of the confidence interval for the slopes for NEI-VFQ-25 Total Score and LogMAR VA. For reference, a slope of 1 would indicate a 12-unit change in the NEI-VFQ over 12 months. A slope of 0.01 for LogMAR would indicate a change of 0.12 units over 12 months. The calculations given in Table 5 assume an intra-subject correlation of 0.2. Higher values within subject correlation would result in less precision while lower correlation would result in increased precision. (Page 10, Line 223)

See Table 5 on the next page.
### TABLE 5. Sample Confidence Intervals for Slopes of NEI-VFQ-25 and Visual Acuity.

<table>
<thead>
<tr>
<th>Number of subjects per class</th>
<th>Effective Sample Size N*4.5/(1+(4.5-1)*0.2)</th>
<th>Distance from slope estimate to the two-sided 95% confidence limits for the class-specific slope.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEI-VFQ (Std. Dev=17)</td>
<td>LogMAR VA (Std. Dev=0.2)</td>
</tr>
<tr>
<td>20</td>
<td>53 +/- 0.28</td>
<td>+/- 0.0033</td>
</tr>
<tr>
<td>60</td>
<td>159 +/- 0.16</td>
<td>+/- 0.0019</td>
</tr>
<tr>
<td>100</td>
<td>265 +/- 0.12</td>
<td>+/- 0.0014</td>
</tr>
</tbody>
</table>

**COMMENT 18:** Table 1: The last two bullets are somewhat vague and subjective.

Precise reasons for patient exclusion (visually significant cataract, dementia, etc) should be recorded and included in later publications [this is not a revision, rather a comment for the study going forward]

**REPLY:** Thank you for your valuable comment.