Author's response to reviews

Title: The Glaucoma Initial Treatment Study: Comparing the effectiveness of selective laser trabeculoplasty with topical medication as initial treatment: study protocol for a randomized controlled trial

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

Thank you very much for the opportunity to revise our manuscript. We have addressed the reviewers’ and editorial comments point by point and highlighted the changes in the manuscript using track changes.

We hope that the revised paper is now suitable for publication in Trials. Please let us know if you require any further amendments.

Kind regards,

Ecosse Lamoureux

Reviewers’ report:

1. The discussion section is missing. Parts of the introduction could be moved to the discussion section.

Response: As advised, we have added a discussion section (page 17-18).

2. Background, Page 3, last paragraph: “Whilst the exact mechanism underlying the effectiveness of laser trabeculoplasty remains uncertain, it induces trabecular endothelial cell division and, in some instances, may create burns which result in contraction and subsequent stretching of the trabecular meshwork”. The authors should provide a more accurate description of recent theories on the presumed underlying mechanisms of SLT for example the cellular/macrophage and biochemical signaling with loosening cellular adhesion in the trabecular meshwork. Thermal burns may occur in ALT, not SLT, which is the main focus of this study.

Response: As advised by the reviewer a more accurate description of recent theories on the presumed underlying mechanisms of SLT, for example, the cellular/macrophage and biochemical signalling with loosening cellular adhesion in the trabecular meshwork has been provided to the revised manuscript (page 4-5). We have also added 2 new references (Alvarado 2010a, Alvarado 2010b).

3. Objectives and Hypotheses, Page 5, 2nd paragraph: “We hypothesise that treatment with SLT, compared with topical medication, will ... show greater IOP reduction...” Based on previous studies, you should expect similar, not greater, IOP reduction compared with medications. Perhaps more modest IOP reduction with SLT since the initial step is treatment over 180 degrees and only completing the other 180 later as needed.
**Response:** We thank the reviewer for their comment. The manuscript has been updated and page 6 now reads ‘We hypothesise that treatment with SLT, compared with topical medication, will improve overall and glaucoma-specific QoL parameters, show comparable IOP reduction and demonstrate less ocular and systemic side effects, including less frequent ocular surface disease.’

4. Figure 1: The abbreviations 6/52, 12/52 and 3/12 are not clear. It would be more easily read as “6 weeks”, “3 months” etc.

- Figure 1: Please explain more clearly what “exit ¥” means.

**Response:** As advised, the abbreviations have been expanded for clarity. The manuscript has been updated to clearly explain what Exit means in Figures 1 and 2. Page 9 of the revised manuscript now reads ‘If patients have crossed over with both treatment regimens, they will exit the trial with further management at the discretion of the treating doctor (Figure 1 and 2).’

5. Page 7 – “Initial 180# treatments of approximately 50 applications will be applied inferiorly from the 3 to 9 o’clock position.” Why not performing 360 degrees SLT first, which is probably more likely to result in greater IOP reduction?

We thank the reviewer for their comment. There are currently no international standards of how SLT should be performed, including the extent and energy levels. The rationale for performing 180 degrees of treatment first is so that patients are not over-treated in the first SLT session itself and our clinical experience in Australia is such that initial 180 degree SLT is often sufficient to provide good IOP control.

**Statistics comments for manuscript id: 1933252901149666**

#1 Use of inferential tests at baseline.

In the statistical analysis plan section it is stated that:

“Analyses will be performed for all variables at baseline to detect potential bias in recruitment.”

From a methodological and statistical points of view, p-values for baseline comparisons in randomised studies are questionable. Randomisation eliminates assignments bias and tend to produce comparable groups, balances known and unknown covariates on average across treatment groups. In fact, use of statistical tests to compare the balance and/or values of baseline characteristics between the study groups is currently considered as inappropriate or at least as illogical1,2,3,4,5,6,7,8,9,10. Such significance tests assess the probability that observed baseline differences could have occurred by chance; however, we already know that any differences are caused by chance. Such hypothesis testing is superfluous and can mislead investigators and their readers11. Rather, comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred7. Baseline imbalance in itself should not be considered an appropriate reason to include a baseline measure as a covariate in randomised clinical trials12,13. Furthermore, adjustment for variables because they differ significantly at baseline is likely to bias the estimated treatment effect14.

Thus, it is strongly recommended to amend this part accordingly and to also delete the following sentence: “The comparison of means will be carried out using Student’s t test, the Mann-Whitney
test, analysis of variance or the Kruskall-Wallis test as appropriate. The difference in proportions between the two treatment groups will be carried out using Chi-square statistics.”

Response: We agree with Reviewer 2 that baseline imbalance in itself should not be considered an appropriate reason to include a baseline measure as a covariate. A pronounced baseline imbalance is not expected *a priori* in a randomised trial: if the randomisation process works correctly, any observed imbalance must always be a random phenomenon. We will compare the baseline characteristics by treatment groups. These comparisons will be made by assessing the prognostic relevance of the difference observed, not through hypothesis testing. Baseline summaries with respect to the main covariates will be presented and discussed from a clinical point of view, irrespective of whether a statistical test indicated a “statistically significant difference” between treatment groups. If we find a strong baseline imbalance in a variable, we will include this variable as a covariate in a sensitivity analysis to allow assessment of the robustness of the conclusions drawn from the primary analysis. We have updated this section on page 12.

#2 Primary outcome and multiplicity issues.

It is stated that “Our primary endpoint will be health-related QoL (HRQoL)”, but it is unclear which of the test will be the primary one. It should be clearly stated which is the predefined one or a strategy to handle multiplicity should be put in place to control the type-1-error rate. This is considered a major issue which should be clarified in the protocol manuscript.

Response: Since patient-centred measurements will recur on the same patients, *longitudinal HRQoL* data will be analysed using multivariate generalized estimating equation (GEE) or generalized linear mixed models (GLMMs). The Glaucoma Outcome Assessment Tool (GOAT) is considered to be the predefined primary outcome. We specify this on page 12. We will use traditional and IRT techniques to validate the data in this sample.

To handle multiplicity in the multiple regression models, Bonferroni adjustment will be used. This has been added in the statistical analysis section (page 13).

#3 Randomisation plan, stratification and subgroups analyses

It is stated that: “*Randomisation, per person, will be stratified by clinical centre and type of glaucoma*”.

This is fully acceptable and the use of the type of glaucoma is not only acceptable but also strongly recommendable as per the randomisation design. However, the appropriateness of including the variable “optic disc changes” in the analysis (either for adjustment or stratification) is not understood. If this is a baseline variable, then it might be considered whenever it is also used in the randomisation design, otherwise it is strongly discouraged.

Response: We agree with the reviewer that including ‘optic disc changes’ in the analysis plan is confusing. Therefore, we have amended this sentence as follows: Analyses for the primary (HRQoL) and secondary outcomes (clinical efficacy) will be stratified for baseline types of glaucoma (POAG and XFG), VF (MD), and optic disc changes.

#4 Handling of missing data.

The authors should note that GEE only is applicable when the missing completely at random
(MCAR) assumptions holds and that even that mixed models are applicable in more restrictive assumptions when missing are at random (MAR), both approaches strongly rely on their assumptions and they may lead to different results. If the authors are convinced that missing data will be MAR, then it should be justified and discussed in the plan: the primary model/strategy for the primary analysis should always be predefined before hand and there should not be room for interpretation for the analysis of the primary outcome.

**Response:** We will examine the missing data mechanism (probability distribution of missingness) to determine whether it is missing completely at random (MCAR), missing at random (MCR) or missing not at random (NMAR). This has been added in the statistical analysis section (page 13).

**#5 Minor points**

**#5.1** In “OBJECTIVE(S) AND HYPOTHESIS(ES)” it is stated that “We are implementing a multicentre prospective randomised controlled trial (RCT)...” While it is formally correct to include the word “prospective”, it might be misleading for some readers. Actually, all randomised trials, as per the definition of what is randomisation, are prospective. I suggest to delete “prospective”

**Response:** As advised, the word prospective has been deleted throughout the paper.

**#5.2** In line with issue #1 the statement “Cox proportional hazards method will be used to adjust for confounders.” is not considered appropriate in clinical trials. Randomisation is a stronger and a more reliable tool than any post-hoc adjustment. If the authors intention is to conduct a series of sensitivity analyses to assess the robustness of the results, then that would be fine. However, they should note that the use of covariates apparently imbalanced is per se a risk and an opportunity to increase the type-1-error beyond the intended 5% level.

**Response:** We will conduct a series of sensitivity analyses to assess the robustness of the results if we find a significant difference between treatment groups. Additionally, we will handle multiplicity in the Cox proportional hazards regression model and Bonferroni adjustment will be used (page 12).

**#5.3** The use and interpretation of explanatory variables should be taken with lots of caution. Even if the intention is exploratory, this should be dealt in more detail to avoid room for bias in the interpretation, which in principle it is not considered needed in the protocol, but please consider this point when elaborating the Statistical Analysis Plan document. You may also decide to delete any information regarding this analyses in the protocol manuscript but please, do not spare room to redefine the analysis of the primary outcome. Which one of the HRQoL variables (otherwise how to handle multiplicity issues), fully prespecification of statistical model and justification, including type, variables included, etc.

**Response:** We have amended our analysis plan to avoid using explanatory variables and a data-driven approach. Instead, we will adjust for pre-defined variables that we consider are associated to the primary outcome (HRQoL) from the literature. These include clinical variables (e.g. baseline glaucoma severity, visual field, visual acuity, optic disc changes, duration of glaucoma), and sociodemographic variables (e.g. age, gender). We have added this to the statistical analysis section (page 13).

As specified in our response to point #2 above, we consider The Glaucoma Outcome Assessment Tool (GOAT) to be the primary HRQoL outcome.