Author's response to reviews

Title: Cost-Effectiveness of Monitoring Stable Glaucoma Patients in Shared Care: an Economic Evaluation alongside a Randomized Controlled Trial

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Author's response to reviews: see over
Submission of revised manuscript (MS: 9206910473385012)

Dear Miss Hayley Hewitt,

Thank you for the opportunity to revise our manuscript entitled “Cost-Effectiveness of Monitoring Stable Glaucoma Patients in Shared Care: an Economic Evaluation alongside a Randomized Controlled Trial” (MS: 9206910473385012). The comments of the reviewers were positive, stimulating and very helpful to further improve the manuscript.

Enclosed, we send you a revised version of the paper with changes marked in the text. A reply to the editor in which the comments of the reviewers are addressed, is added.

The most import change made is the addition of paragraphs about the methods used in the clinical trail, and the bootstrap exercise to reflect the uncertainty around the costs and quality of care of this intervention. These and further changes are addressed in the point-by-point reply to the comments.

Yours sincerely,
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Enclosed: response to editor (see below), revised manuscript with changes marked
Dear editor,

Please find the point-by-point response on the concerns of the reviewers in this letter.

The first reviewer had the following comments:

1.1. The first comment concerns the reporting of the study. The reference to the report of the clinical trial study was in insufficient detail to find the report. The first reviewer stated that if this reference was accessible then this manuscript could be reported as an economic evaluation alongside the trial and then only the main trial design and findings should be reported in brief only.

We have made the report available on the website of our institute [1] and we provided more information about the trial design (see comments 2 to 5) in the methods section as well.

1.2. The reviewer would like more information about the power of the study and wondered whether we have performed a sample size calculation.

We did not perform a power calculated prior to the start of the study, as the assumptions with regard to the mean and standard deviation of the outcome parameter were hard to derive from other research. We had problems with the selection of a single appropriate outcome measure as well, since we could not use progression as parameter. However, we performed a post-hoc power analysis using our data to estimate the power (certainty) of our conclusion. We performed this analysis using two outcome parameters since quality of care has multiple dimensions: the stability of the patient according to the practitioner and the overall mark regarding patient satisfaction. The power of the study was >99% based on the stability outcome when using 5% as an acceptable difference, and >99% based on the overall mark when using a difference of 0.5 (on a 1-10 scale) as an acceptable difference between the treatment groups as well. This explanation has been included in the revised version of the manuscript.

1.3. The reviewer asked for more details of the randomisation method in terms of allocation method and concealment.

We describe this in the methods section in more detail now.

1.4. We were asked to clarify for the GFU group as to who conducted the monitoring.

The GFU group was monitored by optometrists, ophthalmic technicians level 1, and ophthalmic technicians level 2. We described this more explicitly in the methods section now.
1.5. **The reviewer asked for a description of the primary outcome and the times of measurement.**

In this research about shared care in glaucoma, you would like to compare the progression rate of the two groups. However, as discussed in the manuscript, we are not able to measure progression due to the limited study duration of 30 months (since glaucoma is a slowly progressive, chronic illness). Alternatively, we therefore used different outcomes without making a distinction between primary and secondary outcome measures. Our outcomes were: compliance to the protocol; patient satisfaction; mean difference of the IOP; results of the examinations; number of treatment changes. We also used a composed outcome measure: stability according to the practitioner which reflects the opinion of the practitioner whether the time till next visit should be significantly shorter than the time from the last visit. This involves information about changes or asymmetry in IOP, outcomes of the GDx and visual field tests, visual acuity, changes in medication, co-morbidity and other risk factors. We measured the outcome measures every visit. The outcomes and their times of measurement have been described in more detail in the methods section now as well.

1.6. **The reviewer observed a possible contradiction in our inclusion criteria.**

“Inclusion criteria 5 states that vision had to be >20/100 and or patient had no visual field loss—does this mean only those without glaucoma were included? This needs to be clarified. If this is the case it needs to a limitation in the discussion in that this follow up service relates to those at risk of glaucoma and not those with stable glaucoma.”

Inclusion criterion 5 only says that there should not be CENTRAL visual field loss. Patients with glaucoma were therefore included in our study, except for patients with advanced glaucoma that involved the central visual field within the central 10º. We excluded those patients, since these patients required more specialized care. We have added the specification “the central 10º” in the inclusion criteria to avoid misunderstandings.

1.7. **Results: Details of the patient flow are required in a CONSORT diagram, if not published elsewhere, for easy reference.**

We have visualized the patient flow in a CONSORT diagram as a part of the article in Figure 1. It would also be possible to provide this in an appendix.

1.8. **The reviewer was of the opinion that the writing style was rather conversational and she felt it would benefit from editing and deleting unnecessary words.**
We edited the manuscript ourselves and hopefully the style has reached an acceptable level now. If you would like us to edit the manuscript externally, we are willing to do so.

The second reviewer had the following minor comments:

2.1a. *The reviewer suggested to add the duration of the study and to add that IOP was the only clinical outcome considered in the abstract.*
We added a description of the outcomes measures used and the follow-up duration of this study in the abstract now.

2.1b. *According to the reviewer, we should also reflect upon the modest cost savings of approximately 10% in the abstract.*
The costs savings are about 10% indeed, but we don't think that these cost savings are modest. In particular from the hospital perspective, a 13% cost reduction is substantial, considering that glaucoma care is standard eye care that has been provided in by the glaucoma specialists for a long time. Besides, the Rotterdam Eye Hospital already has an active policy on patient logistics and cost-effectiveness, which puts an extra cost reduction of 13% in an other perspective.

2.2a. *This comment addressed the number of stable glaucoma patients vs. patients with risk for glaucoma.*
All patients were recruited from the glaucoma outpatient clinics and comprised 5 subgroups of glaucoma patients. The clinicians who decided whom to refer to the GFU did so, on their own discretion. It is unclear how large each subgroup was. Some clinicians stated that they only referred people with ocular hypertension or with a positive family history; whereas others stated that they sent people with outright glaucoma, deemed stable, as well.

2.2b. *We were asked to describe the way to select the target pressure for glaucoma patients as only target pressure for subjects at risk had been described.*
The target pressure was determined by the individual clinicians in all patients, where they took in consideration: the age of the patient, the appearance of the optic disc, the level of intraocular pressure, any co-morbidity and any other risk factors. Only when there were no explicit risk factors, the target pressure for patients at risk for glaucoma
was set on 30. We added this information to the inclusion criteria regarding target pressure.

2.3  The reviewer would like to see a description of the protocol and wondered whether the technicians in the GFU used Goldmann tonometry.
We added a table with the description of the protocol used in the GFU. All health care professionals used Goldmann Applanation Tonometry to measure the intraocular pressure at all times.

2.4. The reviewer asked for clarification about the 3 different types of personnel within the GFU.
The GFU group was monitored by optometrists, ophthalmic technicians level 1, and ophthalmic technicians level 2. We described this more explicitly in the methods section now.

2.5. The reviewer suggested modelling the ability of GFU to detect conversion or progression of glaucoma and the additional cost associated with missing progression. The model could eventually inform us about the number of patients that the GFU would need to miss for the shared care scheme not to be cost-effective.
In our study we compared the costs and effects of treating stable glaucoma patients in a Glaucoma Follow up Unit vs. usual care. We focused on the compliance of the GFU employees to the protocol and patient satisfaction, as progression could probably not be measured during the relatively limited follow-up duration of this study for stable glaucoma patients. So, we do not have reliable information about the probability and consequences (valued in money and quality of life) of missing progression by the GFU, and the number of patients that might progress during the waiting time which would have increased if the GFU was not established. Although the idea of modeling the consequences of missing progression (in both treatment groups), is interesting, our study does not provide the information to build such a model and fill it with adequate data.

2.6. The reviewer asked whether we would consider building a model to estimate the CEA of not using imaging at all or using IOP only.
We would like to build a model if we would have data about the consequences of refraining from imaging at all or using IOP only, but we have not collected that information.
2.7. The final minor comment of this reviewer is the suggestion to update the reference for estimating progression of glaucoma.

We added a reference to recent work of Heijl and Quigley. And we did a structural literature review to provide more evidence regarding the quality of care by optometrists in shared care projects as suggested by reviewer 3. The reference of Azuara-Blanco et al that was suggested by this reviewer was included in that review.

The third reviewer had the following comments:

3.1. He would like to see all the issues around the original randomized controlled trial explained together in a concise manner.

Based on this comment and the comments of this reviewer 1, more information about the trial is given in the methods section and a consort diagram has been included. More information is also available in a report of the study as well [1, 2].

3.2. The reviewer asked whether the stable glaucoma patients and the individuals with risk factors for glaucoma were analysed separately.

We did not analyse these sub-groups separately, because it was hard to distinguish the groups of patient who were only at risk, suspect glaucoma patients and glaucoma patients. Besides, patients could shift from one group to another (one way only) during the study period. However this analysis will probably not influence the results, because there are no differences at baseline between the two groups with regard to target pressure, intraocular pressure and age.

3.3. The reviewer asked for a definition of glaucoma in the methods section.

Although primary open-angle glaucoma was the most prevalent type of glaucoma, we included all types of glaucoma patients: primary and secondary glaucoma, open-angle and angle-closure glaucoma, high and normal pressure glaucoma. Eyes were considered to be glaucomatous if they had typical thinning or notching of the neuroretinal rim of the optic nerve head, with or without disc haemorrhages, visual field defects, peripapillary atrophy and/or an elevated IOP.

We provided this information in the methods section.

3.4. According to the reviewer, we should provide a definition of “no other significant ocular disease was present”.

The somewhat vague description of this exclusion criterion was used to keep the referral protocol as simple as possible to facilitate the referral of patients (to the GFU, for inclusion in this study). In a preceding pilot study, an extensive list of inclusion and exclusion criteria (including a list of co-morbidities) had been provided, which had lead to hardly any referrals to the GFU. With this simple referral protocol that could be easily memorized by all clinicians, the number of referrals was substantial in relatively little time.

3.5. This reviewer asked for more information about the randomisation methods. This information has been added to the methods section.

3.6. This comment concerns the evidence of equivalence of the groups concerning the quality of the provided care on which we based our decision to perform a cost-minimisation analysis instead of a cost-effectiveness analysis.

In our manuscript we explained that we did not expect progression to occur within the time horizon of our study. Presenting a cost-effectiveness ratio with final health outcomes, could therefore elicit a misinterpretation of the outcomes of the study. However, we measured the quality of care in our study. We therefore did not use a strict cost-minimisation analysis. If there was a difference in quality of care between the two groups within the study period, we probably would have found it.

To meet the concerns of the reviewer, we performed a structural literature review in pubmed, searching for publications about the quality of care of optometrists (or technicians) in shared glaucoma care. The search query was: glaucoma, and co-management or shared care in the title or abstract. We have found 34 articles of which 13 presented data about the quality of care by optometrists. Only one reported a variation in individual performances of optometrists, which makes education and accreditation an essential prerequisite for co-management. [10] All other articles reported either good quality of care by optometrists, comparable inter- and intra-observer variability in optic disc assessments between optometrists and ophthalmologists, or high levels of agreement between optometrists and a research clinic reference or ophthalmologists.

The reviewer also asked how we measured an equal quality of care. We performed a bootstrap analysis to reflect on the uncertainty around the cost and quality of care results. It showed that the quality of care was equal in 80.5% of the bootstrap replications, when a difference of 5% in the number of stable visits was acceptable. This was confirmed by a post-hoc power calculation. Our study had a power of more than 99% either based on the outcome “stability” when using 5% as an acceptable
difference or on the overall mark when using a difference of 0.5 as an acceptable difference between the treatment groups.

Moreover, we did not find any statistical differences in the baseline characteristics of the patients in the two groups and the differences in quality of care as reported in more detail now in our manuscript. However, the reviewer is right that the absence of a statistical difference is not necessarily equal to the absence of a clinical meaningful difference. We therefore also searched for literature about clinical relevant differences in glaucoma. The IOP is the outcome that is reported most. According to the literature a difference of more than 2mmHg is considered to be a clinical relevant difference in IOP. In our study the mean difference between the groups was much lower: 0.4 mmHg OD, and 0.0 mmHg OS. This does also confirm our conclusion of equal effectiveness.

3.7. The reviewer states that we should provide a rationale when we choose one particular perspective and treat the rest as sensitivity analyses.

We chose on purpose for multiple perspectives to provide different decision makers with relevant information from their own perspective. Besides, we are not in favour of using sensitivity analysis as means to reflect the different perspectives, as sensitivity analysis serves another purpose; to measure the sensitivity of the results for variation in parameter values.

3.8. Sensitivity analysis: this reviewer would like to see a scenario with worst case for GFU and best for Glaucoma specialists. Moreover, the reviewer asked us to run a threshold analysis considering a higher number of visits for GFU and alternatively fewer for glaucoma specialist.

We already provided a worst case scenario for the GFU and best for the Glaucoma specialists, based on the duration of a visit. If we understand the reviewer correctly, he would like us to vary the time between two visits in favour of the glaucoma specialists to see when the GFU is no longer cost-effective. This will imply a shorter time to the next visit for the GFU and that is not a clinically plausible situation. Besides, an increase in the number of GFU visits per year (or a shorter follow-up period) is not likely, as the number of visits was stable during our study.

3.9. The reviewer wondered whether we have considered running stochastic analysis. For instance, using bootstrapping methods for their RCT selected outcome measure and costs. This would enable to avoid the issue of “equal” effectiveness.

We had not considered that yet, because of a lack of a single clinical effectiveness outcome that represents the quality of care on the long term. Nor did we have
information about QALY’s that are often used in cost-effectiveness planes and acceptability curves.

We consulted the clinical co-author to identify the best quality of care parameter to use in the bootstrap analysis. We considered the variable stable according to the practitioner (whether the time to the next visit should or should not be significantly shorter than the time from the previous visit) as best quality of care parameter. It is a good outcome of the short term effectiveness that involves information about changes or asymmetry in IOP, outcomes of the GDx and visual field tests, visual acuity, changes in medication, co-morbidity and other risk factors. Since quality of care has more dimensions, we also used the overall mark as indicator of patient satisfaction as outcome. These two quality of care parameters were compared with the societal costs associated with this intervention.

The bootstrap analysis showed that the GFU is cost saving in 88% (stability) and 89% (overall mark) of the bootstrap replications. Using a 5% difference in stability as acceptable, the GFU and Glaucoma specialists provide an equal quality of care in 80.5% of the bootstrap replications. For the overall mark, this percentage is 99.5% using a 0.5 point difference as an acceptable difference.

3.10. Due to the limitations about transferability of their results to other settings, the reviewer thinks that our conclusion is too strong.

Given the results of the uncertainty analysis we added, it seems likely that establishing a GFU reduces health care costs with no loss in quality of care. Whether the GFU is sustainable in the Rotterdam Eye Hospital and implementable in other hospitals will indeed partly depend on future negotiations between health insurers and ophthalmologists. We therefore reformulated our conclusion.

Minor revisions:

3.11. Page 7: CVZ should be defined.
This has been done - Health Care Insurance Board.

3.12. Page 8: DBC should be defined.
This has been done as well - Diagnosis Treatment Combinations.

3.13. Page 10: the authors stated “data from a comparable group of patients were imputed to the missing values”. “Comparable” should be defined as well as the method used for imputation (e.g. multiple imputations?).
We added some explanation about the methods of imputation in the method section.

3.14. The reviewer stated that the study duration section should be part of the methods and not the results.
In accordance with this comment, the section “Study duration” was moved to the methods section.

Reference