*Comparative Effectiveness Research Review Disposition of Comments Report*

**Research Review Title:** *Treatment of Glaucoma: Comparative Effectiveness*

Draft review available for public comment from September 14, 2011 to October 12, 2011.

**Research Review Citation:** Boland MV, Ervin AM, Friedman D, Jampel H, Hawkins B, Volenweider D, Chelladurai Y, Ward D, Suarez-Cuervo C, Robinson KA. Treatment for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review No. 60. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 12-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

## Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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*Published Online: April 2012*

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Executive Summary | This AHQR document attempts to achieve a worthy goal: to evaluate the safety and relative effectiveness of existing treatments in glaucoma. In the process, the report also comments on the quality of evidence underpinning glaucoma treatment. One purpose of such a report is to inform physicians and those paying for treatments about the value of providing treatment. In addition, such a report can guide goals for future research and ensure such research is not unreasonably idealistic so that future grant reviewing bodies can focus funding appropriately. | NA |
| Public comment/ AAO-AGS | Executive Summary | The analytic framework of the report confuses the desired result of treatment--reducing the burden of visual impairment and improving vision-related QOL in a population--with reducing the burden of visual impairment and improving QOL in an individual. In the former instance, if treatment stops or slows vision loss in a sufficiently large number of individuals, the overall visual and QOL status of the population will improve. Conversely, in the latter instance, an individual can do no better than hold steady or deteriorate more slowly. In this analytic framework, there is the implied expectation that treatment should improve visual function and improve QOL in individuals or a group of individuals in a trial, which is an unrealistic goal. What the documents reviewed show that treatment should decrease progression to visual impairment and slow deterioration of QOL relative to no treatment; it should be explicitly stated as such to avoid any confusion. Interestingly, the first two sentences of the Discussion on page 46 state the desired result of treatment, but this phraseology is not carried forward to the Abstract or Executive Summary, nor throughout other sections of the report. | There is no such expectation regarding improvement in QOL in the design of this review. The focus of this review is on comparative effectiveness so we were looking for evidence either that treatment resulted in better QOL and less visual impairment than no treatment or that one treatment was superior in this regard to another treatment. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Executive Summary | Even if properly reworded as described above, the analytic framework of the document obfuscates the goal of appropriately designed studies: to document the results of treatment compared with no treatment to slow worsening of vision and deterioration of quality of life. This is an unrealistic goal on two counts. First, no U.S. institutional review board (IRB) would approve a treatment study in glaucoma with a no treatment control arm. It would be considered unethical to withhold treatment. The Early Manifest Glaucoma Treatment (EMGT) was performed abroad, where the IRB-equivalent agreed to the argument that if patients would not have known they had glaucoma but for the study, that an untreated arm would be tolerated only as long as visual field deterioration did not occur. Even so, visual field deterioration may precede measurable QOL deterioration or of the manifestation of visual impairment. Second, visual impairment as defined in this analytic framework requires a visual acuity of 20/70 or worse or a visual field of 20 degrees or worse. Only the most advanced, nearly endstage, glaucoma patients reach that level, and to allow a patient or study subject to deteriorate to that level untreated in a study would be unethical. Visual impairment as a study endpoint would also be unreliable, as this definition would define patient failure at a time when visual acuity and visual field measurements are most variable | It is clear that the studies needed to answer the key questions related to QOL and PRO may be difficult but that is not to say that they are impossible. Because we realized this issue at the outset, we explicitly allowed for non-randomized designs in KQ5 which would allow us to bridge the gap between the intermediate outcomes and QOL/PRO. |
| Public comment/ AAO-AGS | Executive Summary | Three Key Questions that derive from this analytic framework are consequently flawed. KQ1 is focused on severe visual impairment, which is not an appropriate measure on ethical or practical grounds as reasoned above. Visual field deterioration is more appropriate. It is well known that visual impairment usually does not appear de novo in glaucoma; it reaches that level by gradual deterioration through earlier stages of visual field loss. Moreover, the NEI-funded Latino Eye Study (a population-based study based in Los Angeles) (McKean-Cowdin R, Wang Y, Wu J, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Ophthalmology. 2008 Jun; 115(6):941-948), | We disagree that visual field loss alone is a final outcome in glaucoma. It is accepted that glaucoma patients are asymptomatic through much of their disease course, despite the presence of visual field loss. While it is logical that visual disability would not occur without the vision loss due to glaucoma, it has still not been demonstrated that treatment prevents patients from reaching the point of disability at a lower rate than if they had not been treated. While treatments have been shown to reduce the rate of visual field loss, they also have some rate of vision loss due to complications, both in the short and long term. It is the balance of the benefits and harms that needs to be better evaluated. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Executive Summary | It is appropriate to consider early visual field deterioration as a direct measure of visual impairment, rather than as a disconnected, indirect measure that requires research to link it to damage as stated in KQ5. This research has been performed. The discussion on page 48 states that "it is likely that even alternative definitions [of visual impairment] would not have resulted in the identification of any appropriate studies." This statement would not be correct if visual field deterioration was accepted as direct evidence. Finally, KQ2 asks if treatment improves patient-reported outcomes. Vision-related quality of life in an aged population, which glaucoma afflicts, declines over time. Glaucoma treatment can at best slow quality of life deterioration in the affected population | We are unaware of justification for considering early visual field deterioration as a measure of impairment. |
| Public comment/ AAO-AGS | Executive Summary | ES9, KQ1, bullet 2<br>Visual acuity is not a suitable primary outcome for studies of glaucoma because it is lost only in end stage disease | Visual acuity is not a primary outcom but was considered since there is little consistency in the reporting of vision-related outcomes in clinical trials. |
| Public comment/ AAO-AGS | Executive Summary | ES10, Surgical Treatment KQ4<br>An important conclusion about 4c on page 64 is not brought forward to ES | All of the key points from KQ4c are present in the ES. |
| Public comment/ AAO-AGS | Executive Summary | ES 11, Future Research para 2<br>The problem is not that glaucoma takes years or decades to cause visual impairment, but that to allow a placebo-controlled arm to progress to vision impairment is unethical. | There is nothing in the report suggesting that subjects would need to be randomized to no treatment for their entire disease course to address the questions of visual impairment and PRO. |
| Peer Reviewer #1 | Executive Summary | Page ES12<br>the main results from key question 1 seem contradictory. There is a statement that studies addressing secondary outcomes (which we find out from the text consists of changes in visual acuity and visual field loss) are too short in duration to answer this question; however, the next main result states that no single treatment has a greater effect on visual acuity than any other treatment.<br>Strength of evidence: How can there be a low level of evidence rating for the surgical outcomes when there are no conclusions to be drawn from these studies? (see comment above in relation to this also). | The latter part of the discussion deals only with the evidence that is available, namely reporting of visual acuity over the short term. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #1 | Executive Summary | Page 40, Key question 4c Key Points; Page ES13, Table A Key Question 4 Main Results and Strength of Evidence: The conclusion stating that "Treatment of ocular hypertension with medicines preserves visual fields better than no treatment" is being included in the medical vs. surgical section of the report when it seems to fit into the CE on medical treatments; it's also being given a SOE rating of insufficient in the table, which does not seem consistent with the conclusion that was drawn from 5 RCTs. Please clarify.<br>There are several Key Points on Page 40 that are not included in Table A. There was enough evidence to make conclusions here, so the SOE rating of 'Insufficient' for Medical vs. Surgical in Table A seems inappropriate. Please clarify | The study in the table is not the OHTS trial from which this recommendation was drawn. The OHTS was included in a systematic review which was analyzed in this section of the document. Additional text was added to KQ4a to point to this section for discussion of the OHTS.<br>We revised Table A |
| Peer Reviewer #1 | Executive Summary | After the description of all these studies, it is not clear why only 1 trial is being included in the number of studies here or why the SOE rating is insufficient, when there are a number of Key Points on page40 and the Conclusions statement on page 42 says that "both medical and surgical treatments decrease the risk of incident or worsening of visual field loss, but initial surgery may be more effective in this regard." Please clarify. | The text and summary table have been revised |
| Peer Reviewer #1 | Executive Summary | Page ES10, Key Question 1 conclusions statement<br>Is there some wording that could be included to provide some clarity as to what trabeculectomy is being compared to here? Does trabeculectomy potentially reduce the risk of vision loss compared with all medical interventions, or only specific ones? | Trabeculectomy was not compared to particular agents across (or frequently within) these studies so nothing more can be said about which medications this applies to. |
| Public Comments/ Beth Kneib | Executive Summary | where it states "symptoms that affect day to day function and quality of life" insert before the word "symptoms" the words "causing vision impairment that results in..." | This section of the ES has been revised. |
| Public Comments/ Beth Kneib | Executive Summary | there is no mention of loss of visual field (peripheral or other defects) under the "potentially serious" or "less likely to be serious" adverse events. | Given that peripheral vision loss is part of the disease, it is difficult to discriminate that caused by treatment from that caused by disease. It is therefore not reported as a complication in any studies we found. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public Comments/ Richard Chapell | Executive Summary | future research As will be discussed under "Future Research" below, the role of preservatives in topical ocular medications in the incidence of adverse events and consequently on adherence to treatment is becoming increasingly apparent. We suggest adding: "Another specific area that would benefit from additional research is the impact of preservatives on ocular surface health and medication adherence and persistence. Due to the limited availability of preservative-free first-line treatments, this issue has been largely ignored, however due to findings from existing research and the expected increased availability of preservative-free eye drops in the near future, there is a need for clinical trial and real world assessments." | We agree that factors related to medication adherence are important in glaucoma and as those factors are better understood, they might play a role in future reviews. |
| Public Comments/ Richard Chapell | Executive Summary | "Similar effect than" should be "similar effect to" | This correction has been made. |
| Public Comments/ Richard Chapell | Introduction | Please describe the various surgical treatments more fully, either within the introduction or in the glossary section of the appendix. If the descriptions remain in the appendix, please refer the reader to the appendix in the text. In addition, please include a sentence or two describing the mechanisms of action of the various medical treatments. Page 1: "Characterized by a typical appearance" Please consider revising this phrasing. While the current phrasing is correct, the reader may be confused, wondering whether the authors meant "atypical". | We added a section describing the various treatments and have reworded the first paragraph. |
| Public Comments/ Richard Chapell | Introduction | Several issues of great importance to the understanding of glaucoma are not addressed in the Background section of the Introduction. The primary issue is that glaucoma is not so much a diagnosis as a description of symptoms. While IOP is an important risk factor, it is not the only one. Many factors influence the development of glaucoma, including genetic, environmental and behavioral factors, yet studies concentrate on IOP because it is easy to measure. Many patients develop glaucoma without elevated IOP, especially in Japan (Iwase et al., 2004) and among Japanese-Americans (Pekmezci et al., (2009). To complicate matters further, IOP varies according to a circadian rhythm, and may be normal at the time of the office visit, only to rise to potentially dangerous levels at other times of the day (Barkana et al., 2006). | The points regarding the role of IOP and other risk factors are clearly important but not in the context of this report which focuses on the effect of treatment which, to this point, does not vary appreciably based on our understanding of differing risk factors in individuals. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public Comments/ Richard Chapell | Introduction | Please expand the discussion of glaucoma to include discussion of known and unknown factors that may influence the development of glaucoma. This is important, as it will feed into subsequent discussions of the applicability of the included studies and the need for future research in these areas. While many of these factors are discussed in the companion review on screening for glaucoma, not all readers will see both reviews. Please include a brief summary or the findings of that review here, and refer readers to the companion review for further information. Barkana et al., (2006) Arch Ophthalmol 124:793 Iwase et al., (2004) Ophthamol 111:1641 Pekmezci et al., (2009) 127: 167 | A complete discussion of "known and unknown" risk factors for glaucoma is outside the scope of this report. As mentioned above, the focus is on the effect of treatment which currently does not vary based on those risk factors. We agree that future glaucoma research might benefit from considering the role of risk factors. |
| Public Comments/ Richard Chapell | Introduction | Here and throughout the document, clinical specialty-specific terminology is used without definition. While some of the surgical procedures mentioned are described in the appendix, even there, the descriptions are brief and insufficiently informative. The reader, who may be a pharmacist or other healthcare professional with limited exposure to the conventions of ophthalmology, needs to understand what is being compared. | More extensive descriptions of the surgical interventions have been added and there is an appendix of terms. |
| Peer Reviewer #3 | Introduction | "..may therefore.." is incorrect. This is no doubt that preservation of visual field correlates to prevention of visual disability. These two words need to be deleted and the sentence rewritten. If the authors intend to say that the extend of visual field loss as measured by standard achromatic perimetry has an unclear correlation with visual disability, then they should state it clearly. | It is the uncertainty that current treatments actually modify the risk of ultimate visual disability that is in question. We have rewritten this sentence to clarify this point. Again there are no studies showing that treatment reduces the risk of visual disability. |
| Peer Reviewer #3 | Introduction | Many studies exist that demonstrate that medical therapy slows the rate of visual function decline. This is our surrogate for visual impairment, both because of the need for longer duration studies and a lack of an endpoint measure for "visual impairment." The statement could say that sufficient evidence exists to support the use of medical therapy to prevent or slow loss of visual function as measured by standard perimetry." | This point is explicitly included later in that same paragraph of the abstract. |
| Peer Reviewer #3 | Methods | OHTS was 15 yrs in duration. Is this "too short?" | Given that subjects started the study with no evidence of glaucoma, and that most of the control group remained untreated for ~5 years, there was little chance of finding a difference in rates of visual impairment or patient reported outcomes. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #3 | Methods | The problem with the search strategies is detailed - the keywords for quality of life and visual impairment were not included, and targeted literature searches were not performed for each key question. A more inclusive literature search would have yielded up to 2000+ articles. | As is standard practice for the development of comprehensive searches, we did not include terms for outcomes in the search strategies (see for example Chapter 6, Section 6.4.2 of the Cochrane Handbook). Similarly, we chose the conduct a broader, more sensitive search, versus question specific searches. We retrieved and considered any studies suggested via peer review, none of these were eligible. |
| Peer Reviewer #4 | Methods | There appears to be a significant gap or discrepancy in the basic literature searches performed for this report. Instead of performing a separate literature search with specific keywords tied into each key question, it appears from the documentation that one gigantic literature search to find articles that were relevant for each key question. The problem with this approach is that articles are missed, because they would not be indexed necessarily with the more general keywords or MESH terms for the one large search. To see the number of articles that were missed, I updated the original treatment searches adding quality of life keywords and visual impairment/visual acuity keywords. As of October 6, the original search in PubMed retrieves 6487 references. The modified search to include Quality of Life, Visual Impairment, and Visual Acuity terms retrieve 9232 references. The total difference is 2,745 references, which is restricted to PubMed only and not the other database. Many of these articles might have been excluded through further examination, but it doesn't appear that this was performed. | As is standard practice for the development of comprehensive searches, we did not include terms for outcomes in the search strategies (see for example Chapter 6, Section 6.4.2 of the Cochrane Handbook). Similarly, we chose the conduct a broader, more sensitive search, versus question specific searches. We retrieved and considered any studies suggested via peer review, including the two specified in this and following comments. These two articles are not eligible for inclusion in this review. |
| Peer Reviewer #4 | Methods | Also, there is not a search string for the Cochrane Library in the Treatment appendix as there is in the Screening Appendix. | Thank you for noticing, the Cochrane search string has been added. |
| Peer Reviewer #4 | Methods | For the quality of life search, I would suggest running a broader, separate search with concepts such as those suggested below and with expanded study types (not restricted to RCTs). Study types restrictions could be added to this search once decided upon.ality of life search, I would suggest running a broader, separate search with concepts | As is standard practice for the development of comprehensive searches, we did not include terms for outcomes in the search strategies (see for example Chapter 6, Section 6.4.2 of the Cochrane Handbook). Similarly, we chose the conduct a broader, more sensitive search, versus question specific searches. We retrieved and considered any studies suggested via peer review |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #4 | Methods | For large studies such as AGIS, CIGTS, EMGT, etc., I would run searches to guarantee that all reports from these studies have been gathered. This should be done using Corporate Author and keyword searches. The Corporate Author search alone is not reliable. For example, a systematic literature review of MEDLINE, EMBASE Psychiatry and Global Health databases was conducted on March 16 2010, and included indexed publications up until the end of December 2009. The searched used the following quality of life key words or phrases: quality of life, functional consequences, performance, real world, functional ability, every day, daily living, daily life, behavior, behavior, activities of daily living and independent living. The initial literature search yielded a total of 294 papers for QoL and glaucoma. Using their filtering criteria, they found 51 suitable papers. | Thank you for your suggestion. We identified no additional studies addressing our review questions. The general question of “QOL and glaucoma” was not included in our review. |
| Public Comments/ Richard Chapell | Methods | The reviewers do not appear to have paid adequate attention to external validity. This is especially important for this review, as it does not include a Key Question on patient subgroups. Threats to external validity include differential distribution of racial groups among studies (Rudnicka et al., 2006), exclusion of patients with known hypersensitivity to medications or preservatives (See Baudouin, 2008), as well as the presence or absence of genetic markers. Please add a discussion of the applicability of the reviewed studies to the discussion of each key question and, if necessary, modify the Strength of Evidence rating accordingly. Baudouin (2008) Acta Opthamol. 86:716 Rudnicka et al., (2006) Invest Ophthalmol Vis Sci. 47:4254 | Specific subgroups were considered for each of the Key Questionsand discussed, as warrantedfrom the available evidence. |
| Public Comments/ Richard Chapell | Methods | Please define the various outcome measures. Systematic reviews are read by a variety of stakeholders with different levels of understanding of the topic. The review should be accessible to all. How are visual acuity or impairment defined and measured? How is visual field assessed, and what constitutes a defect? What is a Snellen fraction? What are hypotony and hyphema? What is meant by "phakic"? Again, the glossary appendix contains insufficient detail. Most importantly, the distinction between visual field and visual acuity must be made clear. As the review demonstrates, the efficacy of glaucoma treatments on these two outcomes is quite different. The reader should come away from the review with a full understanding of that difference and its importance | The audience for this version of the report is not the general public but we will add additional terms to the Glossary. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ Pfizer | Methods | Pfizer agrees that a comprehensive evaluation of the treatments for open-angle glaucoma (OAG) is particularly important given that this condition affects over 2.5 million people in United States.1 Pfizer supports the effort to ensure that credible and appropriate evidence on the risks and benefits of treatment for OAG is available to patients and providers. In this spirit, we respectfully submit the following comments on the draft questions that were posted on April 22, 2010, and recommend that AHRQ consider<br>1) Stratifying the key questions by variables known to impact treatment responsiveness. The draft questions do not explicitly acknowledge that there are a number of variables that may impact the effectiveness of OAG treatments when used in real-world settings. These variables include patient characteristics such as age, race, presence of co-morbid ocular or other medical conditions, severity of OAG, whether the patient has received previous OAG treatments (and in what sequence), patient preferences, and treatment adherence.<br>2) Extending the minimum length of study follow-up period beyond one year. Due to the chronic and slow progression of glaucoma, it is difficult to measure outcomes associated with glaucoma treatment. In some instances it can take between six months to ten years to discover an adverse event associated with ocular surgery. To account for the long-term nature of glaucoma treatment and to capture all of the associated outcomes, it is critical for AHRQ to include studies with follow-up periods longer than one year wherever possible.<br>3) Conducting an evaluation of treatment-associated harms by subpopulations and severity | What are such variables? We would have included discussion of such factors, should they be part of included studies. These issues are included in the methods. There is not enough evidence on any of them to draw any conclusions.<br>We considered all studies and the 1 year term was a MINIMUM for certain categories. There was no maximum duration.<br>This would require that such harms be reported with enough detail to do so. If the included studies were to report harms in a more systematic fashion, this might be possible. |
| Public comment/ Pfizer | Methods | We encourage AHRQ to account for variability in OAG treatment-associated risks and harms by patient population and often extend beyond the eye. Research indicates that certain treatments used to reduce intraocular pressure can exacerbate preexisting conditions such as asthma, chronic pulmonary disease, and chronic renal insufficiency.10 To prevent unnecessary adverse events, it is critical that patients and providers are aware of the wide range of risks associated with taking glaucoma medication and how these risks are directly linked to specific patient characteristics. Thus, in Key Question 6, we recommend that AHRQ comprehensively evaluate the risks and harms associated with OAG treatment by subpopulation | These risks were evaluated as part of KQ6. |

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| Public comment/ Pfizer | Methods | In addition, we suggest that AHRQ assess the severity of the risks and harms associated with OAG treatments. For example, the researchers of the Tube Versus Trabeculectomy (TVT) Study found that although there were no significant differences in the incidence of intraoperative complications between patients receiving shunt surgery and patients receiving trabeculectomy, the severity of the intraoperative complications varied significantly.11 The severity of complications may vary in patients receiving different types of treatments (e.g., surgery vs. medication) as well. For example, a hyphema following an intraocular operation may be considered less serious than a hyphema that occurs in relation to a medication. It is important for AHRQ to take these types of differences into account, especially when evaluating treatments with potentially similar outcomes. | This would require that such harms be reported with enough detail to do so. If the included studies were to report harms in a more systematic fashion, this might be possible. |
| Public comment/ Pfizer | Methods | 4)Comparing the effectiveness both within and across treatment modalities | These comparisons (medicine v. medicine, medicine v. surgery, etc.) were made wherever there was evidence to support them. |
| Public comment/ Pfizer | Methods | 5) Further defining and expanding outcomes used to evaluate treatments responsiveness | The primary outcomes were very explicitly defined in the Methods. |
| Public comment/ Pfizer | Methods | There is a significant amount of evidence indicating that variables such as these directly affect a given treatment's effectiveness. 2,3,4 For example, data suggest that diabetes may be a risk factor for developing glaucoma and that patients with both diabetes and glaucoma can be less responsive to intraocular pressure lowering treatments than other patient populations.5,6 Given that glaucoma typically impacts an older population that may be at higher risk for diabetes (as well as other metabolic disorders), it is critically important that the impact of co-morbid conditions are taken into account when assessing treatment effectiveness. | These issues are included in the methods. There is not enough evidence on any of them to draw any conclusions. Furthermore, the role of diabetes in glaucoma is unclear at best (note that it was very beneficial in the OHTS study). |
| Public comment/ Pfizer | Methods | Another patient-related variable that likely impacts real-world assessments of effectiveness is adherence to a prescribed treatment. Many glaucoma patients, including the elderly and those with arthritis, have difficulty self-administering ophthalmic solutions into the eye and, as a result, may not consistently adhere to their medication regiments.7 Medication adherence can be a key determinant of a treatment's effectiveness and should be accounted for in AHRQ's review. | These issues are included in the methods. There is not enough evidence on any of them to draw any conclusions. |

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| Public comment/ Pfizer | Methods | In order to reflect real world practice and account for these important patient characteristics, we encourage AHRQ to stratify all of the key questions posed by variables known to impact treatment responsiveness. Ultimately, if real world variables such as these are not considered, the value of the final comparative effectiveness review to patients and providers will likely be significantly reduced. | These issues are included in the methods. There is not enough evidence on any of them to draw any conclusions. |
| Public comment/ Pfizer | Methods | Pfizer encourages AHRQ to evaluate the effectiveness of OAG treatments within treatment modalities (e.g., prostaglandin analogs versus parasympathomimetics), as well as across different types of treatment modalities (e.g., trabeculectomy versus prostaglandin analogs). As the questions are currently phrased, it is unclear how treatments will be evaluated. It is also important for AHRQ to evaluate how the sequencing of therapies impacts treatment effectiveness. For example, trabeculectomies may be less effective in patients that are already prescribed prostaglandin analogs. To better inform patient and physician decision making, it is critical that AHRQ's review assesses the benefits and harms of all the available treatment options against one another and accounts for the sequencing of therapies. | These comparisons (medicine v. medicine, medicine v. surgery, etc.) were made wherever there was evidence to support them. |
| Public comment/ Pfizer | Methods | To account for the diverse population represented by OAG patients and the diverse impact glaucoma has on patients' lives, we encourage AHRQ to define and expand the outcomes evaluated as part of this review. Most critically, we suggest that the authors clearly define a priori the "intermediate outcomes" in key question 5. Based on current treatment objectives, we assume that the primary intermediate outcome of interest is intraocular pressure, but other variables may also be considered | Both the intermediate and final outcomes are clearly defined and depicted in the figure of the analytic framework. |
| Public comment/ Pfizer | Methods | Additionally, while we commend AHRQ for noting the importance of patient-reported outcomes (such as vision-related quality of life and patient preferences) in the background materials associated with the key questions strongly suggest that AHRQ also explicitly incorporate additional measures such as vision-related functional loss, treatment convenience, and unwanted side effects.12 Finally, we encourage AHRQ to incorporate the impact of glaucoma on patient caregivers, who are often responsible for providing physical, emotional and economic help to OAG patients.13 Outcomes such as these provide a more comprehensive view of the multidimensional impact OAG treatment has on patients and associated stakeholders | If such outcomes had been reported as part of appropriately controlled studies, they would have been included in the review. |

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| Peer Reviewer #2 | Results | The results for the key questions that were primarily reviewed are sufficient. The results for key questions that rely entirely on other reviews, and are stated as such, should either be deleted or explained more clearly in the results section. | |
| Peer Reviewer #2 | Results | Several reference codes were not turned into endnotes. Please ensure that they were entered correctly. | This was corrected |
| Peer Reviewer #3 | Results | The amount of detail could have been greater. As in the methods section, there appear to be studies related to visual impairment and quality of life that could have been included, particularly about the linkages between visual impairment and visual field loss and quality of life which have been described in several articles | We have added text describing the cross-sectional studies that link visual impairment to visual field loss due to glaucoma. Because of their design, these studies do not address the question of whether treatment modifies the risk of visual disability and so they cannot be used to address the key questions in the analytic framework. |
| Peer Reviewer #4 | Results | For key question 1, the proportion of participants with moderate, severe, and profound visual impairment as defined in the International Classification of Diseases, Clinical Modification, 9th Revision (ICD-9-CM).9 The ICD-9 criteria define moderate visual impairment as best corrected visual acuity of between 20/70 and 20/160, severe visual impairment as acuity between 20/200 and 20/400 or a visual field of 20 degrees or less, and profound visual impairment as an acuity of 20/500 to 20/1000 or no more than 10 degrees of visual field. The form of visual impairment that is prevented early in the course of glaucoma is loss of visual field, loss of color perception, and loss of contrast sensitivity. Only in the latest stage of glaucoma does loss of central vision characteristically occur. Visual field loss constitutes visual impairment under all Federal insurance and entitlement programs and under the laws of all 50 states. The same holds true for visual disability as defined in the European Union overall and on a country-specific basis as well. Thus, many individuals are ineligible to drive, are disqualified from both military and civilian employment (as well as active duty in the US Public Health Service) and qualify for Social Security Disability Insurance and Medicaid benefits without meeting the definition of visual impairment identified in this document. If one includes loss of visual field in the definition of visual impairment as is done in all 50 states and all Federal programs, then there is very strong evidence from several government-funded multicenter clinical trials that treatment of both overt glaucoma and of ocular hypertension significantly decreases the likelihood of visual impairment. | The definitions of disability used in the report were included to potentially standardize outcomes across studies. We would have considered any measures of visual disability, however. We disagree that any of the major glaucoma trials has shown a link between treatment of glaucoma or ocular hypertension and visual impairment. As we state in the report, IOP lowering has been shown to reduce the risk of visual field loss but has not shown a change in rates of visual disability. |

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| Peer Reviewer #4 | Results | The report describes this approach towards patient-reported outcomes: We considered participants' mean total or relevant item/subscale scores as measured by any validated questionnaire, e.g., National Eye Institute Visual Functioning Questionnaire (NEI-VFQ), for the following patient-reported outcomes among the treatment groups of interest: Primary outcome Vision-related quality of life (vision-related functional loss as well as the impact of functional loss on activities of daily living) Secondary Outcomes - Treatment convenience - patient satisfaction patient preference values or utility values -adherence to medical treatment. However, it seems important that additional quality of life outcomes, such as patient symptoms and patient attitudes/beliefs, should also be considered as secondary outcomes. | Again, these outcomes were specified in the hope we would be able to standardize reporting across studies but we would have been accepted any PRO. |
| Peer Reviewer #4 | Results | The statement contained in the report, "The Early Manifest Glaucoma Trial (EMGT) was the only study to compare QOL before treatment and after treatment, and found no difference." Is inaccurate. The EMGT did not include a quality of life instrument in their original design. The NEI-VFQ was not available at the time of initial study randomization; instead it was made available in 1996, 3 years after the beginning of the trial. On initial Swedish version was first pilot tested in 10 patients, then backtranslated into English, thirdly compared with the original English version, and fourthly retranslated into Swedish. Then the quality of life instrument was introduced at 3 years and 6 years after randomization began. Thus, it cannot be described precisely as comparing quality of life before and after treatment. Only about half of EMGT patients were drivers, which could be a critical difference between this population and a U.S. population, accounting for the lack of good internal consistency and reliability for the driving subscale of the NEI-VFQ. Nevertheless, as noted by the authors: "The EMGT finding of an association between vision-related quality of life and visual function (VA or MD) is consistent with other reports and suggests that, even at early stages, glaucoma can have a modest effect on vision-targeted HRQOL. Because EMGT patients had early disease and the disease has a protracted clinical course, longer follow up would be needed to evaluate the long-term effects of initial treatment on HRQOL." (Hyman LG, Komaroff E, Heijl · et al. Treatment and vision related quality of life in the Early Manifest Glaucoma Trial. Ophthalmology 2005; 12:1505-13.) | We corrected the summary of the EMGT and QOL in the report. As with other studies, the design of the QOL assessment in the EMGT prevents one from drawing conclusions regarding the impact of treatment. It is ony posisble to say that there is some relationship between visual field loss and QOL. We have added text to the report to discuss the latter point. |

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| Peer Reviewer #4 | Results | The Collaborative Initial Glaucoma Treatment Study provided a comprehensive evaluation of quality of life before treatment and after treatment, and as reported in Table 9 Summary of Evidence for Key Question 2, found important differences in quality of life before treatment and after treatment: symptoms decreased after treatment in both the medication and treatment groups, fear of blindness declined after treatment in both the medication and treatment groups and in general, glaucoma patients reported high levels of satisfaction with their initial treatment. These are quality of life, patient-reported outcomes from a randomized controlled trial that should be given more consideration. | These results are indeed discussed along with the key point that the assessment of QOL was done after diagnosis but before treatment. Because of this, it is not possible to say anything about whether treatment modified the baseline concern about blindness (which was likely near 0 before diagnosis). What we learn from CIGTS is that both medical and surgical treatments impact concerns in a similar manner after diagnosis. |
| Peer Reviewer #4 | Results | Patient utilities have also been found to be diminished for patients with glaucoma. In one study, the authors reported: “Glaucoma subjects and suspects rated the utility of their vision as 0.72 and 0.71, respectively, on a 0 to 1 scale, and blind subjects rated the utility of their visual state as 0.54. This can be compared with a report by Torrance and Feeny of utility values of 0.90 for mild angina, 0.64 for home dialysis, and 0.39 for blindness and a report by Bass et al. of utility value of 0.68 for vision in a cohort of patients about to undergo cataract surgery.” Jampel HD, Schwartz, Pollack I et a. Glaucoma patients’ assesssment of Their Visual Function and Quality of Life.” J Glaucoma 2002: 11:154–163) | NA |
| Peer Reviewer #4 | Results | Also missing is the discussion of indirect linkages with quality of care, i.e., a large body of evidence linking visual field loss with health-related quality of life as measured with standardized questionnaires such as the NEI-VFQ. This is further detailed in my response to Key | We have added text describing the cross-sectional studies that link visual impairment to visual field loss due to glaucoma. Because of their design, these studies do not address the question of whether treatment modifies the risk of visual disability and QOL |

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| Peer Reviewer #4 | Results | The document indicates that the literature search would be updated in September 2011, but there is no further mention of additional studies being considered. One article was published which provides additional evidence on intraocular pressure fluctuation. Musch DC, Gillespie BW, Niziol LM et al. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology 2011; 118:1766-73. The authors concluded, "Our findings are consistent in identifying 3 measures of IOP control or variation during treatment—the range of IOP, the SD of IOP, and the maximum IOP—as important measures to consider in reviewing a patient's record of IOP measurements over time. Our findings support the hypothesis that increased IOP fluctuation (SD or range of IOP) as well as high IOP (maximum IOP) are important predictors of progressive VF loss and considering their risk of progressive VF loss." | The updated search will be included in the final report. The specific reference to the CIGTS report, while important to the understanding of IOP in glaucoma, does not address any of the key questions in the analytic framework. |
| Peer Reviewer #4 | Results | The document does not mention several articles that demonstrate links between visual field loss and the final outcomes of vision-related QOL and between visual impairment and the final outcomes of vision-related QOL. | We have added text describing the cross-sectional studies that link visual impairment to visual field loss due to glaucoma. Because of their design, these studies do not address the question of whether treatment modifies the risk of visual disability and QOL |
| Public comment/ AAO-AGS | Results | For Key Question 1, visual acuity is not an appropriate outcome measure except to answer Key Question 6, because it is affected so late in the course of glaucoma. | Acuity is a secondary outcome and is included because it is reported by some studies of treatment. |
| Public comment/ AAO-AGS | Results | Key Question 1<br>Since the GRADE methodology resulted in an "insufficient" evidence grade for all glaucoma RCTs other than those for medical therapy, it would be helpful to understand how close each RCT came to reaching the necessary threshold, since it is not productive to reject these well-planned and well-conducted studies out of hand | The EPC Strength of Evidence rating system, similar to the GRADE system, rates body of evidence, not single studies. Specific details about the studies, including assessment Risk of Bias, are provide in the evidence tables. |
| Public comment/ AAO-AGS | Results | Key Question 1 - Page -41-39-38<br>The Burr (2004) summary does not capture the correct conclusions regarding visual acuity, IOP, and "n" of each of the trials it reviewed and reported. | We are unclear is this is a comment on the Burr (2004) review or our conclusion. This text, as all sections of the report, has been reviewed and revised, where necessary. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question 1- Page 38<br>detailed analysis of primary studies. In a document of this importance, it is inappropriate to rely solely on systematic reviews that may lose important detail “in translation.” Furthermore, one has to read the fine print to discover that RCTs covered in systematic reviews were not reanalyzed for this report! This is much less transparent then AHRQ conveyed was its intention. Hence, the inappropriate conclusion that “no RCTs studied” the variable in question is reached | Where possible we did not duplicate effort but instead systematically identified and summarized high-quality systematic reviews. Please see Whitlock et al (PMID 18490690) and specific AHRQ-EPC guidance on this practice (PMID 21433402). We have revised text to clarify the summary of existing systematic reviews in relation to summaries of individual studies. |
| Public comment/ AAO-AGS | Results | Key Question 3a<br>The draft report correctly points out that prostaglandin analogs (PGA) are the most effective agents for lowering IOP. The report also notes that all 3 PGAs effectively lower IOP, and multiple studies indicate that bimatoprost reduces IOP to a greater extent than travoprost and latanoprost. The report does not note that the PGAs are well tolerated with a favorable side-effect profile, thereby making the PGAs first line therapy for glaucoma | The evidence regarding medical therapies is reported and appropriate conclusions have been drawn. Determining "first line therapy" was not in the scope of the project. |
| Public comment/ AAO-AGS | Results | Key Question 3a<br>The document comments on the value of fixed combination therapy, specifically dorzolamide/timolol. There is no mention of the newer fixed combination brimonidine/timolol, which is another effective and widely used combination. | There were no studies of brimonidine/timolol relevant to the key questions. If such studies existed, they would have been included. |
| Public comment/ AAO-AGS | Results | Key Question 3a- Diurnal studies<br>The AHRQ document briefly discusses the effects of IOP-lowering medications on diurnal IOP. Although they correctly note that there are few data on this subject, publications by Weinreb et al. shed light on this topic. These include: Ophthalmology. 2010 Nov; 117(11):2075-9, Ophthalmology. 2009 Mar; 116(3):449-54 and Am J Ophthalmol. 2004 Sep; 138(3):389-95. | The relevant studies of the impact of medical therapy on diurnal IOP were included. The studies mentioned in the comment are not comparative in nature and do not address our key questions. |
| Public comment/ AAO-AGS | Results | Key Question 4a<br>More details from both the Ocular Hypertension Treatment Study (OHTS) and the Early Manifest Glaucoma Trial (EMGT) need to be included. Current studies such as EMGT and OHTS provide evidence of the benefit of glaucoma treatment. Visual field progression as well as optic nerve change can be slowed with treatment. Both OHTS and EMGT showed that treatment reduces the risk of progression of glaucoma in half. In OHTS, the probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group after 5 years of follow-up. Treatment reduced the visual filed abnormality by 55% and optic disc deterioration by 64%. (reworded according to hazard ratios). | These conclusions of the OHTS and EMGT are indeed mentioned prominently in the report. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question 4a<br>Visual field deterioration directly compromises quality of life. Goldberg et al. showed that there was a correlation between increasing severity of disease as demonstrated by the mean defect at visual field test and poor quality of life reported by patients. (Goldberg I, Clement C, Chiang TH, et al. Assessing Quality of Life in patients with Glaucoma Using the Quality of Life-15 Questionnaire. J Glaucoma 2009; 18:6-12.) | Again, this study is a cross sectional one that does not address the relationship of treatment to visual impairment or quality of life. |
| Public comment/ AAO-AGS | Results | Key Question 4a<br>Nine studies which mention worsening (on Page 22) of visual field measures have small numbers of incidence. For instance, in Dirk's study, only one patient worsened (original article could not be located); in Melamed's study, 2 subjects worsened; in Berry's study, 3/35 patients in the betaxolol group and 2/43 patients in the timolol group worsened. One study which was not mentioned in the report is a recent report from the Low-Pressure Glaucoma Treatment Study. In this study, application of brimonidine 0.2% twice a day was found superior to timolol 0.5% for preventing visual field progression in patients with low-pressure glaucoma during the 4 years of treatment. In this study, intraocular pressure reduction was similar between the groups. Krupin T, Reviewer #3n JM, Greenfield DS, et al; Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011 Apr; 151(4):671-81. Epub 2011 Jan 22. Erratum in: Am J Ophthalmol. 2011 Jun; 151(6):1108 | The inadequacy of the studies mentioned is clearly pointed out in the report and no conclusions are drawn from them. The LoGTS study results were published after the initial search but was included in the updated search conducted in 2011. |
| Public comment/ AAO-AGS | Results | Key Question 4a<br>Although the document mentions that OHTS and EMGT studies proved that medical treatment decreases the risk of progression by 50% (Page 23), its emphasis is mostly on the inadequacy of glaucoma treatment studies. The report should leave room for monitoring modalities other than IOP reduction in light of mounting evidence that there can be glaucoma progression regardless of IOP level or control. The results of the Low-Pressure Glaucoma Treatment Study and the fact that Prata (2009) showed that three medicines--timolol, brimonidine and travoprost--improve visual function and that this was independent of intraocular pressure control. These findings illustrate that comparative effectiveness of medical treatment of glaucoma may not be confined to IOP reduction, and that possibly there are unidentified effects of the medicines | The comment brings up the potential benefit of "neuro-protection" but there are, as yet, no comparative studies demonstrating such a clear effect. |

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| Public comment/ AAO-AGS | Results | Key Question 4a<br>The AHRQ document minimizes the evidence of effectiveness of treatment against no treatment, although it gives limited credit to large RCTs such as OHTS and EMGT. Unfortunately, this statement may discredit the use of medicines to prevent the worsening of the visual impairment in an era where practicing clinicians are trying to improve adherence to the use of glaucoma medication. In the Friedman et al study, 44.4% of 196 patients missed once at night glaucoma treatment 25% or more of the time during the 3-months of study, despite the fact that medication was provided free-of-charge. Among those who missed the drops, they more likely agreed with the statement that glaucoma treatment would “not do much” rather than the statement that “glaucoma treatment will keep my vision from getting | The conclusion that medical therapy slows visual field damage is clear and in no way minimized. |
| Public comment/ AAO-AGS | Results | Key Question 4a<br>The report could undermine the evidence and the patient’s conviction that treatment helps, a fact that has been established by numerous clinical trials and years of clinical experience. | We are unsure where this conclusion comes from. The link to improvements in intermediate outcomes is made clear, even if the links to final outcomes do not yet exist. |
| Public comment/ AAO-AGS | Results | Key Question3b<br>There are many glaucoma procedures for which no systematic review exists and that this should not detract from the potential utility of those other procedures. For instance, viscocanalostomy and deep sclerectomy are the only non-penetrating procedures for which a meta-analysis was available. Other procedures (but not all available procedures) are discussed in the detailed analysis of primary studies. | No RCTs other than those reviewed or included in the search were available for the other treatments. |
| Public comment/ AAO-AGS | Results | Key Question3b<br>With regard to the variations of trabeculectomy surgery, there is strong evidence supporting the use of mitomycin C (MMC)and for the timing of mitomycin application. Concentration of mitomycin is not discussed in the report.(Lee SJ, Paranhos A, Shields MB. Does titration of mitomycin C as an adjunct to trabeculectomy significantly influence the intraocular pressure outcome? Clin Ophthalmol. 2009; 3:81-7). Aside from use of antifibrotic agents, other variations of trabeculectomy technique are reviewed, including location of surgery, fornix versus limbus based conjunctival incision surgery, and use of adjustable sutures versus laser suture lysis. Additional variations of trabeculectomy exist, including use of releasable sutures, type of incision closure, use of fibrin glue, and size and shape of trabeculectomy flap. It is difficult to account for all possible variations in technique, which may prove equally valid. | No RCTs other than those reviewed or included in the search were available for the other treatments. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question3b<br>We are confused why deep sclerectomy (rarely used in this country) is discussed twice, once in the section on "trabeculectomy compared to trabeculectomy variants and other glaucoma procedures" and then again in "other glaucoma operations." Other similar procedures are not discussed, including Trabectome and endocyclophotocoagulation, which presumably belong at least in the section on combined cataract and other (non-trabeculectomy) glaucoma surgery. Unfortunately, there are no randomized controlled trials for these procedures | No RCTs other than those reviewed or included in the search were available for the other treatments. |
| Public comment/ AAO-AGS | Results | Key Question3b<br>Aqueous humor shunts are not discussed at all in the "Primary Studies" section, although a randomized controlled trial does exist in the Tube Versus Trabeculectomy study (TVT). Although TVT does include patients who have previously failed trabeculectomy, it should not have been excluded based on the criteria provided. Although the data available may not be sufficient to draw strong conclusions about the procedure, this primary study should be included in the review. (Am J Ophthalmol. 2009 Nov; 148(5):670-84. Three-year follow-up of the tube versus trabeculectomy study. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL; Tube Versus Trabeculectomy Study Group.) | The recent studies of glaucoma drainage devices were not relevant to this review because they a significant proportion of the subjects had something other than the forms of open angle glaucoma specified in the methods and did not analyze the open angle subjects separately. Text to this effect has been added to the discussion of KQ3b. |
| Public comment/ AAO-AGS | Results | Key Question3b<br>It is important to remember that target intraocular pressures of glaucoma patients vary greatly and therefore the amount of pressure lowering required for a specific patient is tailored to that individual. With this in mind, the conclusion that "trabeculectomy lowers intraocular pressure more than non-penetrating surgeries" should not be taken out of context. There is likely a place for non-penetrating surgeries in the treatment of glaucoma for many patients who need lesser amounts of pressure reduction. Likewise, the conclusion that use of MMC results in lower intraocular pressures needs to be considered in context of the higher risk profile of surgery with MMC used, and that this may not always be necessary. | The statement we have made does not imply a preference for one approach over another. It summarizes the evidence in the literature. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question 4b<br>Curiously, the entire published bibliography from the pivotal Advanced Glaucoma Intervention Study (all 14 papers) (AGIS) and from the recent 3-year results of the Tube Versus Trabeculectomy study (2 papers) was eliminated from consideration in this review. The reasons for this exclusion specified for the AGIS study were: “Other (specify): AGIS” (pgs.189-190 of appendix) or “OAG can’t be analyzed separately” (pgs. 235-236 of appendix). The reason for exclusion of the Tube Vs. Trabeculectomy study was: “Data not abstractable” (pgs. 248-249 of appendix). Since these are extremely important studies to consider, perhaps this was a methodological oversight in literature review. | While an important study, the AGIS enrolled subjects with angle closure glaucoma and did not analyze the OAG group separately. We have added some text to the discussion of KQ3b to address the AGIS. |
| Public comment/ AAO-AGS | Results | Key Question 4b<br>The AGIS reported in paper #7 that lowering IOP had a beneficial effect slowing or halting the progression of visual field damage with either laser trabeculoplasty or trabeculectomy in patients with advanced disease over the 7 years of follow-up. This fact was supported by subsequent papers 10 years after enrollment | While an important study, the AGIS enrolled subjects with angle closure glaucoma and did not analyze the OAG group separately. |
| Public comment/ AAO-AGS | Results | Key Question 4b<br>Blindness from glaucoma is not uncommon (Blindness in Patients with Treated Open-Angle Glaucoma, Chen, P, Ophthalmology 2003, 110:726–733; Management and prognosis of end-stage glaucoma, William E Gillies, Anne MV Brooks, and Nicole T Strang, Clinical and Experimental Ophthalmology 2000, 28: 405–408; The Probability of Blindness from Open-angle Glaucoma, Matthew G. Hattenhauer, Douglas H. Johnson, Helen H. Ing, David C. Herman, David O. Hodge, Barbara P. Yawn, MD, Linda C. Butterfield, Darryl T. Gray, Ophthalmology 1998, 105:2099–2104). Prevention of the visual field loss in glaucoma avoids development of blindness which occurs in its advanced stages. Patients benefit the most from early intervention to prevent much of the vision loss (see attached studies below on quality of life and glaucoma). | The articles cited are well known but do not address the relationship of treatment to the final outcomes of visual impairment and quality of life. The fact that these two populations were retrospectively identified from subjects being treated at some point and still went on to blindness is, in fact, concerning with regard to the assertion that treatment leads to less blindness. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question 4b<br>In addition to the prospective, randomized, controlled AGIS and TVT studies that documented successful IOP control and visual field preservation by surgical intervention in advanced glaucoma, other retrospective and prospective studies have shown that surgical intervention to lower IOP is successful in preventing late stage visual field loss and progressive optic disc damage, if low enough IOPs can be obtained for use over years and decades (The Long-term Outcome of Glaucoma Filtration Surgery, Christine E. Parc, Douglas H. Johnson, Jessica E. Oliver, Matthew G. Hattenhauer, David O. Hodge, Am J Ophthalmol 2001,132:27–35; Understanding the Importance of IOP Variables in Glaucoma: A Systematic Review, Marla B. Sultan, Steven L. Mansberger, and Paul P. Lee, Surv Ophthalmol 2009, 54:643--662; Otago Glaucoma Surgery Outcome Study Long-term Results of Trabeculectomy—1976 to 1995, Anthony C. B. Molteno, Nicola J. Bosma, John M. Kittelson, Ophthalmology 1999, 106:1742–1750; Five year follow-up optic disc findings of the Collaborative Initial Glaucoma Treatment Study, Parrish RK, Feuer, WJ, Schiffman, JC, Lichter, PR, Musch, DC, CIGTS optic disc study group, Am J Ophthalmol 2009, 147:717-724). AHRQ should review their methodology and include these reports that demonstrate a demonstrable benefit of surgical intervention for IOP control, when necessary, and subsequent prevention of glaucoma blindness | The Parc and Molteno studies are retrospective in nature, and therefore can't be used to determine the effect of treatment. The Parc article actually reports a rate of blindness of 46% at 10 years after surgery and found no difference in the IOP of eyes going blind and no going blind. The latter finding may call into question the effectiveness of treatment. In the Molteno study only 60% of subjects retained useful vision 15 after surgery. |
| Public comment/ AAO-AGS | Results | Key Question 1c<br>This question is best answered by randomized clinical trials comparing the visual impairment outcomes of medically versus surgically treated glaucoma patients. Due to the difficulty and expense of conducting such a trial, only a few have been funded. However, in order to evaluate outcomes in medicine, we must rely on surrogate measures that have been established by evidence based studies. In glaucoma, there is strong evidence that visual impairment (and quality of life) correlates well with visual field loss and glaucomatous optic nerve damage, and that lowering of IOP significantly slows such damage. | We agree that there is some correlation between visual field loss and QOL/PRO but this link is not consistent across studies and may be limited to later-stage disease. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public comment/ AAO-AGS | Results | Key Question 1c<br>Perhaps the most critical trial that was designed specifically to answer this question is the Collaborative Initial Glaucoma Treatment Study (CIGTS). There are many papers from this study group, which was a prospective, randomized, longitudinal study with up to 10 years of follow up. Please consider including thethe latest publication along with earlier CIGTS work.(Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R; CIGTS Study Group. Intraocular Pressure Control and Long-term Visual Field Loss in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology. 2011 Sep; 118(9):1766-73. Epub 2011 May 20) | The results of the CIGTS are included and support the conclusion that medical and surgical treatments are similarly effective. |
| Public comment/ AAO-AGS | Results | Key Question 1c<br>The study was the first of its kind to include quality of life measures in the comparison between the two groups. The initial report concluded that there was no significant difference in visual field progression between the medicine and surgery groups, and that the medically treated group had less quality of life issues associated with localized ocular discomfort. Later studies supported surgical intervention in cases with more advanced glaucoma at baseline, showing better preservation of visual field in those patients who had initial surgery, rather than medical therapy | The results of the CIGTS are included and support the conclusion that medical and surgical treatments are similarly effective. |
| Public comment/ AAO-AGS | Results | Key Question 1c<br>This study clearly meets the Level I criteria for grading of evidence, being a large, well conducted, randomized clinical trial. Thus, there is good evidence that more stringent control of IOP, whether it is obtained by medical or surgical treatment, results in slower progression of visual field loss in glaucoma patients. Surgical treatment does allow for more stringent control, and should be undertaken in patients with fluctuating IOP levels. There are many studies that have shown the direct association between visual field loss and visual disability and quality of life in glaucoma patients using validated quality of life measures. Therefore, there seems to be clear support for surgical intervention in the treatment of glaucoma, especially if IOP control is inadequate or there is progression of visual field or optic nerve damage, or if glaucoma damage is already advanced. | The results of the CIGTS are included and support the conclusion that medical and surgical treatments are similarly effective. |

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| Public comment/ AAO-AGS | Results | Key Question 3c<br>Include a study that evaluated 24-hour IOP control in patients with advanced OAG treated by trabeculectomy with MMC versus maximum tolerated medical therapy (Konstas AG, Topouzis F, Leliopoulou O, et al. 24-hour intraocular pressure control with maximum medical therapy compared with surgery in patients with advanced open-angle glaucoma. Ophthalmology 2006; 113(5): 761-5). Investigators in this prospective observational study measured IOP at 6 am, 10 am, 2 pm, 6 pm, 10 pm, and 2 am in patients treated successfully with one treatment option (patients were matched by IOP at 10 am). The results suggested that 24-hour range of IOP for the surgical group was 2.3 +/- 0.8 mm Hg versus 4.8 +/- 2.3 mm Hg for the medical group. The study suggested that a well-functioning trabeculectomy provides a statistically lower mean, peak, and range of IOP for the 24-hour day than maximum tolerated medical therapy in patients with advanced OAG. | This is an observational study, not RCT, and therefore is not eligible. |
| Public comment/ AAO-AGS | Results | Key Question 4c<br>We note several observations regarding the studies discussed in the paper. Meir (2005) conducted a meta-analysis of five RCTs concerning the treatment of OHT and open-angle glaucoma (OAG). Treatment of OHT and OAG was found to lead to better preservation of VF compared with observation. Greater mention of the OHTS trial may be warranted in this section. | This statement reflects the conclusions in the report. |
| Public comment/ AAO-AGS | Results | Key Question 4c<br>Burr (2004) performed a review of four RCTs comparing the medical and surgical treatment of mostly early open-angle glaucoma. Of these four trials, only the CIGTS uses current medicines and surgical techniques. Their results showed that at 5 years, the medical and surgical groups showed no difference in VF progression once the adjustment was made for the incidence of cataract surgery in the surgical group. However, the surgical group did report more quality of life symptoms in tasks relating to visual acuity and ocular symptoms. Also, as the author points out, there is no formal economic analysis comparing trabeculectomy, laser modalities, and topical medicines. | This statement reflects the conclusions in the report. |

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| Public comment/ AAO-AGS | Results | Key Question 4c<br>The de Moura review examines laser trabeculoplasty and OAG. However, this review only examines argon laser trabeculoplasty (ALT). Selective laser trabeculoplasty (SLT) is a more current laser modality that may have similar intraocular pressure outcomes and less adverse effects compared with ALT. There are no formal studies examining SLT and the outcomes of VF progression or optic nerve damage. | This statement reflects the conclusions in the report. |
| Public comment/ AAO-AGS | Results | Jay (1989) conducted an RCT comparing surgical and medical therapy for patients with primary OAG with IOP greater than 25. Surgical therapy showed better preservation of visual field, but this result may not apply in patients with new OAG with lower baseline IOP. | This study, which had major methodological flaws and in which most of the data could not be clearly abstracted, was included in an existing systematic review. As such we did not include it in our review. However, we do discuss this study briefly in the relevant section. |
| Public comment/ AAO-AGS | Results | Key Question 4c<br>Migdal (1986) compared trabeculectomy, laser trabeculoplasty and medicine for patients with primary OAG. Trabeculectomy showed better preservation of VF compared with the other two modalities. The medicines in this trial included timolol, sympathomimetics,and pilocarpine; the latter two are not commonly used in OAG currently. | This statement reflects the conclusions in the report. |
| Public comment/ AAO-AGS | Results | Key Question 4c<br>There is a conclusion that "Trabeculectomy first may lead to better preservation of visual field than medicines first in more advanced glaucoma." The Summary of evidence from systematic reviews described several trials where primary trabeculectomy and medical interventions are compared in glaucoma patients and many statistical results from these studies are presented. Would it be possible to do a metaanalysis of some kind so that we can communicate to clinicians with conclusive statistics that "trabeculectomy first may lead to better preservation of visual field than medicines first in advanced glaucoma?" | The individual studies included were too heterogeneous to conduct a meta-analysis |

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| Public comment/ AAO-AGS | Results | Key Question 4c<br>An important study was omitted from this discussion. (Five-year follow-up optic disc findings of the Collaborative Initial Glaucoma Treatment Study. (Parrish RK 2nd, Feuer WJ, Schiffman JC, Lichter PR, Musch DC; CIGTS Optic Disc Study Group. Am J Ophthalmol. 2009 Apr; 147(4):717-72). This study shows better preservation of the optic nerve with initial surgery versus initial medical treatment. In the multiple studies that were reviewed, medication and surgery were equal or there was a slight advantage to surgery in preventing progression of visual field loss. The quality of the evidence was variable. CIGTS was the best study, by a large margin, that relates to question 4C, and is limited mainly by its recruitment of milder glaucoma. CIGTS shows no difference in preservation of visual field loss, medication versus surgery. By and large, the findings of this report mirror the findings of the multiple CIGTS reports. Many of the studies reviewed are more than 20 years old and did not make use of current surgical techniques | CIGTS was included and details abstracted |
| Public comment/ AAO-AGS | Results | Key Question2<br>The lack of a demonstrated beneficial effect in patient-related outcomes after glaucoma treatment should not be interpreted as evidence against treatment for this blinding disease. The characteristics of glaucoma are such that judgment regarding treatment efficacy cannot be entirely based on patient-reported outcomes. Unlike cataracts, where surgical treatment results in an immediate and clearly apparent improvement in patient-reported outcome, glaucoma has the following unique features that pose challenges in using patient-reported outcomes as an endpoint in assessing the value of treatment: 1. Early glaucomatous visual field damage is asymptomatic. 2. The natural history of untreated glaucoma is irreversible worsening of visual function; however this takes years to become manifest on tests and it may take even longer for patients to perceive significant deterioration. 3. The goal in glaucoma treatment is to stabilize, not reverse, optic nerve damage. Effective treatment of glaucoma with field loss would halt progression of an existing (often asymptomatic) visual field defect. In pre-field loss glaucoma, effective treatment would prevent the development of a visual field defect. In both cases, the benefit of treatment is not captured by patient-reported outcomes. | The relevant text has been modified to address this comment. Patient reported outcomes are not the only final outcome, however. |

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| Public comment/ AAO-AGS | Results | Key Question2<br>There is ample evidence of the benefit of treating glaucoma. It is recognized that visual field damage is linked with decrease in vision-related quality of life and also results in impairment of several activities such as walking, reading and driving (See Systematic Review, Ramulu P. Glaucoma and Disability). Which tasks are affected, and at what stage of disease? Curr Opin Ophthalmol. 2009;20:92-98). It is also known that intraocular pressure reduction decreases visual field progression – given the effect of visual field defects on quality of life, stabilization of damage would minimize further impairment related to visual field damage. | We certainly understand the reviewer's logical thought process that a. if treatment prevents visual field loss, and if b. visual field loss is associated with worsening patient reported outcomes, then treatment should reduce worsening patient reported outcomes. However, this indirect line of reasoning cannot serve as proof in the context of this report. |
| Public comment/ AAO-AGS | Results | Key Question2<br>Obtaining direct evidence regarding improvement in patient-related outcomes after glaucoma treatment is a difficult task from logistic and ethical standpoints. The ideal study would include treated and untreated arms, similar to the EMGT, but with longer follow-up and current treatments in order to detect differences in vision-specific QOL measures. With our knowledge of the benefit of reducing intraocular pressure and the effects of visual field damage on quality of life, it would be ethically unreasonable to include an untreated group that is observed until visual field deterioration is advanced enough to be perceived by the patient. | There are alternative study designs that could be used to evaluate the impact of treatment on the final outcomes of visual impairment and QOL. Had such studies been completed, our search would have found them. |
| Public comment/ AAO-AGS | Results | Key Question2<br>The draft report cited the EMGT as the only trial to compare quality of life before and after treatment. But the EMGT did not assess quality of life at the beginning of the trial, but only 3 years and 6 years after randomization. Even so, the EMGT did find an association between visual function (visual acuity or mean deviation (MD) with vision-related quality of life, and that even at early stages, glaucoma can affect health-related quality of life. Also, the documented literature search strategy does not appear to include keywords using quality of life terms; thus there are many quality of life studies that do not appear to have been included in the literature review. | The document has been revised accordingly, i.e. the first sentence under "Quality of Life" on page 51 has been deleted. There are many studies that have examined the association between visual function and HRQOL. Unfortunately, none of them bear upon the question of the effect of treatment upon HRQOL. |
| Public comment/ AAO-AGS | Results | Key Question2<br>It is not useful to say that QOL did not improve with treatment, because it is not supposed to. Stability is the expectation. It is also unfair to say there was no treatment effect, since neither treatment group in at least two studies worsened as might be expected if natural history had been allowed to run its course. | The key points related to KQ2 have been revised |

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| Public comment/ AAO-AGS | Results | Key Question2<br>outcomes QOL. The CIGTS study measured QoL before treatment and at intervals after treatment and reported their findings. CIGTS made use of perhaps the most thorough assessment of HR-QoL of any large trial funded by the NEI. The Visual Activities Questionnaire was used throughout the study, the Symptom Impact Glaucoma total score decreased in both treatment groups over time, and worry about blindness diminished substantially over time | The results of CIGTS are highlighted in the report and are used to support the conclusion that there is no clear difference in treatments (medical vs. surgical) with regard to PRO/QOL. |
| Public comment/ AAO-AGS | Results | Key Question2<br>EMGT was designed to discontinue patient participation if VF deterioration occurred. Thus, no patient was allowed to progress until QoL measures declined. | NA |
| Public comment/ AAO-AGS | Results | Key Question2<br>The fear of blindness results has an alternate explanation. The VF failed to deteriorate in either group, so patient confidence was restored. | This conclusion assumes that patients appreciated their visual field defects at the outset and there is no evidence for this. |
| Public comment/ AAO-AGS | Results | Key Question2<br>CIGTS found weak correlation between visual field results and QOL measures in early glaucoma. | NA |
| Public comment/ AAO-AGS | Results | Key Question2<br>Patient Reported Outcomes (PROs) are by definition study outcomes that are reported by the patient, and are perceived by the patient to be important. As a consequence, the most prominent PRO tends to be quality of life. Therefore, these comments will focus on PRO. There are two types of Quality of Life (QoL) measures: function- and preference-based.1 Function-based instruments assess a patient's ability to perform functions in investigator defined domains. The most common measures of function based QoL in vision are the NEI-VFQ2 (measuring vision specific domains) and the SF-123 (a generic QoL instrument that is a shorter version of the older SF-36). Preference-based instruments measure the value that the patient puts on his/her quality of life. Preferences can be assessed using direct methods (i.e., the standard gamble or time-tradeoff) or indirectly using survey instruments (i.e., the EQ-5D or Health Utilities Index). | NA |

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| Public comment/ AAO-AGS | Results | Key Question2<br>The document argues that there is no good evidence that treatment results in improved PRO outcomes. This appears to be based on the fact that no randomized trial of treatment has reported a statistically significant change in scores on the VFQ, SF-12 or other instrument. CIGTS evaluated the relationship between VFQ scores and treatment response and found that there was no significant difference over time between randomization groups.4 However, CIGTS also did not find that there was a difference in visual field results between treatment groups so it is not surprising that QoL would not be different.5 The EMGT also examined the relationship between VFQ scores and treatment group and did not find a significant difference in changes over time.6 But while the EMGT investigators found a statistically significant difference in progression between patients who were treated and those in the untreated group, the mean difference seen between the treated and untreated group in EMGT (i.e., less than 3 dB) at five years is arguably less than a clinically significant difference.7 As the difference is not clinically significant, it is unlikely that the patient's perception of the difference in quality of life would be noticeable | We agree that the EMGT results help to point out the complex relationship between visual field loss and quality of life. |
| Public comment/ AAO-AGS | Results | Key Question2<br>However, the AHQR document seems either to be unduly dogmatic or discounts the results from cohort studies that have found an association between visual field loss and worse QoL. Multiple studies have shown that the NEI-VFQ scale scores are lower for people with visual field loss. Jampel et al. found a positive correlation between visual field loss and worse visual field scores in 191 people with glaucoma. In particular, they found a 5 point reduction in the VFQ composite score between people with glaucoma and glaucoma suspects.8 In people with retinal disease, a five point reduction in the NEI-VFQ is considered to be clinically significant, and comparable to people with a 15 letter loss in visual acuity.9 In a sample of 537 people with POAG and OHT, van Gestel and colleagues demonstrated that for every dB loss in visual field, there is nearly a two point loss in the VFQ composite score.10 Hyman6 and Wren4 found that people with greater loss of visual field had lower VFQ composite scores, albeit in studies with a negative finding concerning treatment effect. McKean-Cowdin and colleagues evaluated the relationship between longitudinal visual field loss and VFQ score.11 For each dB of MD lost, 0.5 points were lost on the VFQ composite score, and more than one point on the Dependency and Driving Scales | We don't argue that glaucoma vision loss does not lead to poorer QOL scores, just that treatment has not been shown to prevent QOL decrement. |

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| Public comment/ AAO-AGS | Results | Key Question2<br>Similar loss of QoL was found in preference-based measures. Among 99 people with glaucoma, Lee et al. found a 15 point loss in utility between those with mild and severe glaucoma. In the context of the utility elicitation exercise, this indicates that people with severe glaucoma are on average willing to accept a risk of blindness 17 points greater than people with mild glaucoma.12 Saw13 had similar findings in a sample from Singapore. Using the EQ-5D, a multi-attribute utility survey, Kobelt14 found that the initial diagnosis resulted in a 7 point drop in QoL, and people with advanced glaucoma had a 13 point drop in QoL. Using the same instrument van Gestel reported similar findings.10 Given the clear evidence of loss of quality of life seen in these cross-sectional and longitudinal analyses, it is reasonable to ask why the AHRQ team indicated there was no evidence that treatment prevents a loss of QoL (or other PROs). For most people, glaucoma is a slowly progressive disease. In the CIGTS study, the average loss of visual field is less than ½ dB over seven years. Only 5% of participants experienced sufficient loss of visual field to be classified as visually impaired. In OHTS and AGIS the average loss of visual field at seven years was approximately 2 dB, but in OHTS there was an untreated arm; and in AGIS entrance criteria required people to have IOP that was difficult to control. In spite of this, the average participant's visual field loss (after seven years) did not qualify as clinically significant (i.e., not worse than 3 dB). | We don't argue that glaucoma vision loss does not lead to poorer QOL scores, just that treatment has not been shown to prevent QOL decrement. |
| Public comment/ AAO-AGS | Results | Thus, it is not surprising that no study has shown that PROs are significantly improved by treatment. The vast bulk of people in clinical trials do not experience sufficient progression to experience a loss of QoL. Yet, there is considerable evidence to show that people who have loss of visual field, even in small increments, have a lower QoL. It does not take an extensive extrapolation of the available data to construct a model that bridges these empirical findings. 1. Treatment reduces intraocular pressure. IOP reduction reduces the probability of progression. This has been shown in EMGT (for people with early glaucoma) and in OHTS (for ocular hypertensives and glaucoma suspects). 2. People with more advanced disease have worse PROs (notably QoL). This occurs even before subjectively defined "visual impairment" is experienced. 3. Thus, treatment is beneficial by helping individuals preserve QoL. | As the comment correctly points out, it requires extrapolation of cross-sectional data to reach the conclusion that treatment must result in less reduction in QOL. Such extrapolation has proven incorrect in the context of treatments of other diseases. We share the reviewers' frustration that we only have indirect evidence linking treatment with preservation of HRQOL. We have added another bullet to the Key Points on p 74, to acknowledge this possible link.Since there are unlikely to be any future trials with a "no treatment" or placebo arm, it will not be possible to determine if treatments improve patient-reported outcomes, but interventions that are more effective than others in preventing vision loss ought to be more effective at maintaining desirable patient-reported outcomes than less effective treatments. |

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| Public comment/ AAO-AGS | Results | As the preparers of the AHRQ document noted, the only way to "prove" this is through the implementation of an extraordinarily large and lengthy randomized trial. Such a study (given our current study funding infrastructure) would not be an appropriate or logical use of social resources. More importantly, it would take years to collect sufficient study end points, while in the meantime thousands of patients (non-study participants who are denied treatment) would experience visual impairment and loss of quality of life---people who would otherwise be treated but for the lack of an RCT to support a policy. | The assertions made in this comment are outside the scope of this review (i.e., we are not proposing 'policy') |
| Public comment/ AAO-AGS | Results | Key Question5<br>The first step is to establish that glaucoma patients have documented visual disabilities that interfere with activities of daily living and to be able to reliably record these findings in a statistical manner. This has now been well established with validated testing strategies and questionnaires. Patients with glaucoma report detectable decrements in vision-targeted HRQoL issues, and the findings are most dramatic in patients with severe field loss. The Los Angeles Latino Eye Study demonstrated that greater severity of visual field loss in persons with POAG impacts vision-related QoL. The study also determined that both losses and gains in visual field produce clinically meaningful changes in vision-specific HRQoL. The Salisbury Eye Evaluation Project found that glaucoma is associated with slower reading and increased reading impairment with advanced bilateral field loss. There is an obvious increased economic load to society because the cost of glaucoma management increases with disease severity. In addition, the overall burden for families with individuals with glaucoma includes increased risk of nursing home admission, depression, falls and/or accidents, injury and fractures in the elderly with glaucoma (based on Medicare beneficiaries). | The LALES study was a cross-sectional population based study so there are no conclusions about "losses" or "gains" in visual field. We again agree that there is cross sectional evidence relating visual field loss to disability and QOL but not evidence about the impact of treatment on that relationship. |
| Public comment/ AAO-AGS | Results | We are concerned that this document sets research goals that are currently not feasible. As pointed out, it is unethical to let untreated glaucoma progress to visual impairment. It is highly unlikely that review committees for funding sources would approve studies of the type suggested by this report. It is also not necessary to answer KQ5 since the progression of early visual field loss to visual impairment has already been demonstrated by those patients who discontinue treatment, fall out of follow-up, and return 10 years later with substantially diminished vision. | This report has no official role in setting future research goals and the Future Research section is merely recommendations that are derived from the gaps found as part of the review. Again, there is nothing that requires monitoring of subjects to the point of blindness. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #1 | Results | Key Question2<br>It seems contradictory that there are a number of studies that address the improvement of patient-reported outcomes allowing for the conclusions described in the Key Points, yet the strength of evidence is insufficient. | |
| Peer Reviewer #1 | Results | Key Question3b<br>First bullet states that Trabeculectomy lowers IOP. Is there a comparator that is missing here? Also, considering bullets 4 and 6, this statement seems redundant. Is there some wording that could possibly be included to make this statement more specific? | We have revised the summary points for glaucoma surgery to more accurately reflect the summarized evidence. |
| Peer Reviewer #1 | Results | Key Question 6a- Page26-23<br>The statement that the overall strength of evidence is "insufficient to make firm determination of differential harms for one therapy compared to another" is contradictory to all the conclusions that are made in the Key Points on page 23 for the harms associated with medical treatments. Additionally, it is unclear how these conclusions were drawn from just a list of the SRs and primary studies included. There is no mention of metaanalysis in order to draw the conclusions stated in the Key Points. | Comparison of differential harms of medical versus surgical treatment would require that those harms be reported systematically by studies in which two or more treatments were being compared. Given the heterogeneity in individual studies, it is not possible to compare harms (or benefits) across the studies that were included in the review. |
| Peer Reviewer #1 | Results | The Grading of Evidence paragraph is a copy of the paragraph from KQ6a on page 26. In addition, the grading of evidence paragraph is in direct contradiction to the Conclusions paragraph below it that describes several comparisons where there seems to be enough evidence that those conclusions can be drawn regarding different treatments. However, there are no details on how these overall conclusions were drawn. A description of the studies included precedes this paragraph, but there is no description or metaanalysis showing how these conclusions were then made based on these studies. | |
| Peer Reviewer #1 | Results | Key Question 6c- Page 42-43;<br>In the Conclusions statement, it says 'The evidence is conclusive…", however, there are only descriptions of the RCTs included without a description or metaanalysis indicating how these conclusions were drawn. Additionally, it is unclear how these conclusions can be drawn, yet there are too many variables in the reported outcomes to allow for strength of evidence grading. | |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #1 | Results | All KQ6<br>The discussions of all three sections of Key Question 6 (a-c) are simply a systematic review of systematic reviews and primary studies. How can the results be communicated to clinicians without some sort of metaanalysis of these studies for the harms data? How are we supposed to claim that one treatment has fewer side effects without giving clinicians an overall odds ratio or p-value or number needed to harm, etc.? It is going to sound like the conclusions are just an estimation of the literature without any statistics to back them up. If the data truly cannot lend itself to metaanalysis, perhaps there could be some ranges of the results of the studies that reported on a specific outcome? | The individual studies included were too heterogeneous to conduct a meta-analysis. This problem would be avoided if trials of glaucoma treatments would report harms in a more systematic way. |
| Peer Reviewer #3 | Discussion | The discussion discounted the patient-reported outcome of reduced fear of blindness but this belief may be very important for patient mental well-being. | Indeed, but the CIGTS protocol did not assess PRO before diagnosis and there was no untreated group so it is not possible to say that treatment itself was responsible for the changes in fear of blindness. |
| Public Comments/ Mariela Shirley | Discussion | No data on traumatically-induced glaucoma and how treatment may differ given sub-population(s). No mention regarding timing of medication vs trabeculectomy vs more invasive surgical procedures relative to extent of visual field loss. No mention of duration of effects regarding lowering of IOP and how treatment should be modified for those cases 'resistant' to change--that is, what indicators should be used to determine the next level of care needed and timing of this? For example, individual treated with numerous medications for a 10 year period of time, followed by trabeculectomy, followed by glaucoma implant---what determines this progression re treatment? Timing of trabeculectomy vs implant relative to ethnicity/race matter? Younger samples of glaucoma patients may lend themselves to longitudinal studies. | These are all interesting questions, none of which have evidence to address them directly at this time. Most of them currently fall to the individual clinician to make a determination. Traumatic glaucoma is outside the scope of this review. |
| Public Comments/ Richard Chapell | Discussion | Many systematic reviews prepared under the Effective Healthcare program include a section discussing the limitations of the current review. Please consider adding such a section to this review. The limitations of the review include: ? Does not consider variability among patients (genetic, environmental, psychological) ? Does not consider development of glaucoma among patients with "normal" IOP. ? Does not address interactions between treatments (e.g. the effect of prior use of topical medications on outcomes of surgical treatment [Broadway et al., 1994].) Broadway et al.,(1994) Arch Opthamol. 12: 1446. | These are all interesting questions, none of which have evidence to address them directly at this time. Most of them currently fall to the individual clinician to make a determination.<br>genetic, environmental, psychological variability are outside the scope of this review |

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| Public Comments/ Beth Kneib | Discussion | RE: Key Question 5 Conclusions and Discussion - when referring to clinical treatment for OAG, it is recommended that there be a comment indicating that available treatment for visual impairment resulting from OAG is clinical vision rehabilitation, and this treatment option differs from the surgical and pharmaceutical treatment for OAG. This will clarify the statement made by the authors where they reported "a lack of direct or indirect links between treatment and visual impairment". This could also be reflected in the Exec Summary. | Potential treatments for visual impairment are themselves outside the scope of this report. |
| Public Comments/ Beth Kneib | Discussion | A growing body of evidence suggests that there may be a link between adverse events associated with ocular medications and the presence of preservatives in ocular solutions. Topical formulations containing preservatives are associated with statistically significant increases in inflammatory markers in patient tears (Manni et al., 2005) and associated symptoms of irritation (Pisella et al., 2002). These adverse events may affect persistence and adherence to dosing regimens (Chawla 2007) and thus may affect the overall effectiveness of the treatments. Moreover, preservatives can lead to corneal or conjunctival damage (Reviewed in Baudouin, 2008). For this reason, there are at least two preservative-free medical treatments currently under FDA review (Tafluprost-PF and Cosopt-PF). This issue will be of increasing interest as additional preservative-free solutions come onto the market. This issue should be addressed in any future updates of the current review. The Future Research Needs section of the review is organized around the PICOT framework. However, the "C" of PICOT, "Comparisons" is omitted. We suggest that the section be expanded to include a listing of the comparisons that are recommended for future research, including within-class comparisons of medications such as preservative-free v. preservative-containing IOP-reducing medications. Baudouin (2008) Acta Ophthamol. 86:716 Chawla et al (2007) Acta Ophthamol Scand. 85:464 Manni G et al. (2005) Am J Ophthalmol. 139:72. Pisella et al. (2002) Br. J. Ophthamol 86:418 | Preservatives are outside of the scope of this report |

| Commentator & Affiliation | Section | Comment | Response |
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| Public Comments/ Beth Kneib | Discussion | Need research for traumatically induced glaucoma in younger samples (even those in their 4th decade). Need research on timing of surgical interventions and longitudinal progression re IOP and visual field loss/stabilization. Need a NATIONAL RCT that includes private practitioners as well as those in academic settings-- perhaps pairing private practice settings with academic institutions. While optimal IOP is as low as possible, there need to be better definitions/standards re what is "normal". More research on timing of surgical procedures relative to visual field changes is needed. Need more research on the duration of improvements; again a longitudinal study of younger populations would help. | Traumatically induced glaucoma is outside of the scope of this report |
| Public Comments/ Beth Kneib | Discussion | P. 51 under "Lack of Association Between Treatment & Visual Impairment: Population" - the bullet point stating "patients with moderate visual loss from glaucoma, i.e. at risk for visual impairment" is clinically inaccurate. Patients with moderate visual loss HAVE visual impairment (as per current ICD-9 diagnosis coding and referencing Key Question 1 p. ES5) and are at risk for further PROGRESSION of visual impairment. All patients with a diagnosis of glaucoma are AT RISK for visual impairment (regardless of acuity or field status at time of initial diagnosis). Accuracy with this important clinical and population-health language is needed to positively impact and strengthen future research. P. 51 under "Lack of Association Between Treatment & Visual Impairment: Outcomes" - the bullet point stating "all studies of glaucoma treatments should routinely include measures of visual impairment" can be strengthened by including the language "accepted clinical and/or vision-related quality of life " in front of the word "measures". This will assist researchers in appropriately developing aims and selecting outcomes measures for future studies | Text has been revised |
| Peer Reviewer #2 | Future Research Needs | The results are clearly stated. The future research section could be more specific in terms of the new research that is most definitively needed, perhaps even prioritized. | We have revised the future research section but it is outside the scope of this review to prioritize the research that is needed. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public Comments/ Richard Chapell | Future Research Needs | A growing body of evidence suggests that there may be a link between adverse events associated with ocular medications and the presence of preservatives in ocular solutions. Topical formulations containing preservatives are associated with statistically significant increases in inflammatory markers in patient tears (Manni et al., 2005) and associated symptoms of irritation (Pisella et al., 2002). These adverse events may affect persistence and adherence to dosing regimens (Chawla 2007) and thus may affect the overall effectiveness of the treatments. Moreover, preservatives can lead to corneal or conjunctival damage (Reviewed in Baudouin, 2008). For this reason, there are at least two preservative-free medical treatments currently under FDA review (Tafluprost-PF and Cosopt-PF). This issue will be of increasing interest as additional preservative-free solutions come onto the market. This issue should be addressed in any future updates of the current review. The Future Research Needs section of the review is organized around the PICOT framework. However, the "C" of PICOT, "Comparisons" is omitted. We suggest that the section be expanded to include a listing of the comparisons that are recommended for future research, including within-class comparisons of medications such as preservative-free v. preservative-containing IOP-reducing medications. Baudouin (2008) Acta Ophthamol. 86:716 Chawla et al (2007) Acta Ophthamol Scand. 85:464 Manni G et al. (2005) Am J Ophthalmol. 139:72. Pisella et al. (2002) Br. J. Ophthamol 86:418 | We agree that the areas of ocular surface changes due to glaucoma drops and adherence with topical medications are important topics and would benefit from further investigation. On the other hand, there is currently no evidence linking either of these to any of the outcomes in the analytic framework so there is no place for us to comment. |
| Public Comments/ Mariela Shirley | Future Research Needs | Need research for traumatically induced glaucoma in younger samples (even those in their 4th decade). Need research on timing of surgical interventions and longitudinal progression re IOP and visual field loss/stabilization. Need a NATIONAL RCT that includes private practitioners as well as those in academic settings--perhaps pairing private practice settings with academic institutions. While optimal IOP is as low as possible, there need to be better definitions/standards re what is "normal". More research on timing of surgical procedures relative to visual field changes is needed. Need more research on the duration of improvements; again a longitudinal study of younger populations would help. | Traumatic glaucoma is outside the scope of this review. |

| Commentator & Affiliation | Section | Comment | Response |
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| Public Comments/ Beth Kneib | Future Research Needs | P. 51 under "Lack of Association Between Treatment & Visual Impairment: Population" - the bullet point stating "patients with moderate visual loss from glaucoma, i.e. at risk for visual impairment" is clinically inaccurate. Patients with moderate visual loss HAVE visual impairment (as per current ICD-9 diagnosis coding and referencing Key Question 1 p. ES5) and are at risk for further PROGRESSION of visual impairment. All patients with a diagnosis of glaucoma are AT RISK for visual impairment (regardless of acuity or field status at time of initial diagnosis). Accuracy with this important clinical and population-health language is needed to positively impact and strengthen future research. P. 51 under "Lack of Association Between Treatment & Visual Impairment: Outcomes" - the bullet point stating "all studies of glaucoma treatments should routinely include measures of visual impairment" can be strengthened by including the language "accepted clinical and/or vision-related quality of life " in front of the word "measures". This will assist researchers in appropriately developing aims and selecting outcomes measures for future studies. | The point of including that population recommendation is to maximize the chance of finding differences in QOL measures. Studies that start with suspected or early glaucoma are unlikely to reach significant differences in QOL in any reasonable amount of time. |
| Peer Reviewer #3 | Applicability | The conclusions are not really useful for practice and policy decisions, because treatment of glaucoma is linked to improved quality of care and reduced visual impairment. | We stand by the conclusion that treatment has not been definitively linked to either of these (quality of life and reduced visual impairment) |
| Peer Reviewer #2 | General Comments | The focus of the report is clinically meaningful. The target population is appropriate and defined. The key questions are explicitly stated. | None |
| Peer Reviewer #3 | General Comments | The report is limited in its clinical meaningfulness because of the gaps in studies considered for quality of life and visual impairment | While there are studies relating quality of life and visual impairment to vision loss due to glaucoma, there are no studies that assess the impact of treatment on those outcomes. |
| Peer Reviewer #3 | General Comments | Overall the document is well-written and I have no major comments regarding the bulk of the work, which followed a set of guidelines that appear to be standard for this type of work. However, I think that there is a major flaw that requires correction. This does not involve the data itself, but, rather, how the data are presented and executive summary statements are worded. | See specific responses below. |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #3 | General Comments | As with any chronic disease, often with a 30 year duration for an individual patient, it is difficult to relate data that is collected in the short term (<10 yrs) to long term impact. In glaucoma, our best surrogate measures for visual disability are derived from visual field testing, for which there is a slowly developing consensus that visual impairment (as measured in terms of falls, fractures, driving accidents, etc) likely worsens as visual field indices deteriorate. The executive summary, which is what most readers will cite (and actually read), makes it seem that there is little evidence that glaucoma treatment (medical, laser, or surgery) prevents visual impairment. Nothing could be further from the truth. | While it is true that there is evidence relating treatment to a decrease in vision loss due to glaucoma, there is no evidence that those same treatments prevent the final outomce of visual impairment which is something else entirely. |
| Peer Reviewer #3 | General Comments | The use of phrases such as "insufficient evidence" suggests that current treatment paradigms may be incorrect or deleterious can be very harmful to patients as policy makers and policy development may think that current treatments are ineffective or do not prevent or delay vision loss. The review should carefully state that currently available data is limited because of the long duration that most individuals suffer from the disease. In fact, where data is available (eg OHTS), the data supports current consensus- and evidence-driven treatment paradigms (all of which, of course, can be improved) and better long-term outcomes. | We use this term in the usual manner as related to systematic reviews - to indicate that the available evidence is not adequate in some way to draw conclusions regarding a particular topic. We are very clear regarding where current treatments have been demonstrated to be effective. |
| Public comment/ AAO-AGS | General Comments | “Relative to persons with no visual impairment (VI), persons with bilateral mild and unilateral or bilateral moderate/severe VI report greater difficulties in performing most vision-dependent daily activities and experience vision-related dependency and poorer vision-related mental health.” Varma R, Wu J, Chong K. et al. Impact of severity and bilaterality of visual impairment on health-related quality of life. Ophthalmology. 2006 Oct; 113(10):1846-53. | We added text related to the cross sectional studies of visual disability and visual field loss but again, these studies do not address the question of whether treatment modifies this relationship. |
| Public comment/ AAO-AGS | General Comments | “Relative to persons with no visual impairment (VI), persons with bilateral mild and unilateral or bilateral moderate/severe VI report greater difficulties in performing most vision-dependent daily activities and experience vision-related dependency and poorer vision-related mental health.” Varma R, Wu J, Chong K. et al. Impact of severity and bilaterality of visual impairment on health-related quality of life. Ophthalmology. 2006 Oct; 113(10):1846-53. | We added text related to the cross sectional studies of visual disability and visual field loss but again, these studies do not address the question of whether treatment modifies this relationship. |
| Peer Reviewer #1 | General Comments | iIOP should be IOP or defined as a new acronym. | This was a typographical error<br>We corrected |
| Peer Reviewer #1 | General Comments | First sentence of the Outcomes paragraph is an incomplete sentence. | We made this correction |
| Peer Reviewer #1 | General Comments | in the second bullet under Key Question 1, Should be "…this question given **that** glaucoma is…" | We made this correction |

| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #1 | General Comments | Have consistent nomenclature. For example, on page 2, the key questions are broken out in parts a, b, and c; however, these designations are not found in the executive summary. | The a,b,c designations are used to delineate the three categories of comparison (medical, surgical, medical-surgical) used in the report |
| Peer Reviewer #1 | General Comments | second bullet of Key Question 3 Main Results, this wording is awkward: "The combination dorzolamide/timolol has similar effect than prostaglandins." | We made this correction |
| Peer Reviewer #1 | General Comments | 4th bullet under Key Question 3b, Trabeculectomy misspelled. | We made this correction |
| Peer Reviewer #1 | General Comments | the statement "…patients prefer the treatment that is less frequently applied" is awkward. Perhaps clearer wording such as "…patients prefer the treatment they do not have to apply as often" or "…the treatment that does not have to be applied as often is preferred by more patients." | We made this correction |