

**American Academy of Ophthalmology and the
American Glaucoma Society Joint Comments on:
Comparative Effectiveness of Treatment for Glaucoma, xx-EHC-XXX**

The American Academy of Ophthalmology is the world's largest association of eye physicians and surgeons—Eye M.D.s—with more than 19,000 members in the U.S. The American Glaucoma Society (AGS), is an organization of over 500 ophthalmologists who specialize in glaucoma care and surgery. The Academy and the AGS appreciate the opportunity to comment upon this draft document. These two organizations have brought together world-renowned glaucoma experts and researchers to analyze and review this draft document, resulting in a broad-based consensus. The deadline for the review of this type of document is wholly inadequate given the amount of data and literature included and more importantly excluded from this report. **Even with the short amount of time to review, we believe that there are gaps in the document that warrant reconsideration in the examination and weighing of the overall effectiveness of treatment for glaucoma for the American public. Given the short time allotted for review we strongly encourage AHRQ to meet with representatives from our groups so that additional information can be provided and considered for this review.**

Patients with glaucoma have been demonstrated in several studies to have reduced quality of life and difficulties with a variety of activities of daily living. These disabilities include increased risk of fractures and falls, slower reading speed, greater reading impairment, decline in mobility, loss of independence, loss of ability to drive and increased social isolation. Studies have shown increased resource utilization associated with greater disease progression for these patients. A computer-simulation model found that the cost of routine office-based identification and subsequent treatment of primary open-angle glaucoma was comparable to other health interventions, about \$20,000 per quality-adjusted life year (QALY). Early disease detection and treatment may prevent these [medical](#) and social impediments at a substantial cost savings to the health care and social welfare system.

Important concerns in our assessment of the AHRQ review of glaucoma treatment are highlighted below:

- **There is more evidence on the linkage between quality of life and glaucoma treatment than was presented in the draft document.**
- **Visual acuity and visual field loss with health-related quality of life are not described anywhere in the document. Glaucoma treatment has been demonstrated to reduce visual field progression and is also linked to improvement or preservation of health-related quality of life.**

- The analytic framework of the report is flawed since it appears to confuse the desired result of treatment--reducing the burden of visual impairment and improving QOL in a population--with reducing the burden of visual impairment and improving QOL in an individual.
- The review evaluates treatment with respect to a decrease in rate of progression to visual impairment and slow deterioration of QOL *relative to* no treatment. This should be explicitly stated.
- The goal of any appropriately designed study of an intervention should be to document the results of that treatment compared with no treatment. The outcomes in the case of glaucoma should be a slowing in the rate of worsening of vision and deterioration of quality of life.
- Importantly lost in this review is the research limitation that we believe no U.S. institutional review board would approve a treatment study in glaucoma with a no treatment control arm.
- Many of the key questions that derive from this analytic framework are flawed. We examine these flaws later in this document.
- The RCTs covered in systematic reviews were not analyzed separately.
- The AHRQ document minimizes the evidence of effectiveness of treatment against no treatment. This type of report may cause a disbelief in the use of medicines to prevent the worsening of the disease in an era where practicing clinicians are trying to improve adherence to the use of glaucoma medication.
- An important factor missed by the reviewers is that there is no single treatment that is appropriate for a broad class of glaucoma patients. Intraocular pressures of glaucoma patients vary greatly and the amount of pressure lowering required for a specific patient needs to be tailored to that individual.
- There was a systematic oversight in the methodology for selection of the studies to include in this EPC review with many key studies excluded.
- The lack of a demonstrated beneficial effect in patient-related outcomes after glaucoma treatment should not be interpreted as positive evidence against treatment for this potentially blinding disease.
- Finally, this document sets research goals that are not feasible. It is unethical to let untreated glaucoma progress to visual impairment. In fact, it is unethical to keep patients in a placebo control arm once progression of visual field outcome measures has been documented. It is highly unlikely that institutional review boards or review panels for funding organizations would approve studies of the type suggested by this report.

Our specific comments and feedback on the questions posed follow.

There is more evidence on the linkage between quality of life and glaucoma treatment than was presented in the draft document. The Early Manifest Glaucoma Trial was cited in the document as “...the only study to compare QOL before treatment and after treatment, and found no difference.” (p. 45) However, it did not assess quality of life at the beginning of the trial, but only at 3 years and 6 years *after* randomization and quality of life measures were not included in the initial study design. The Collaborative Initial Glaucoma Treatment Study (CIGTS), a randomized controlled trial, studied quality of life measures extensively in patients before and after treatment. This trial reported a reduction in symptoms after treatment, and a decrease in the fear of blindness, which are two patient-reported outcomes.

There are other linkages between visual acuity and visual field loss with health-related quality of life not described in the document. The Los Angeles Latino Eye Study (LALES), a large population-based study, demonstrated that the National Eye Institute-Visual Function Questionnaire (NEI-VFQ)-25 was sensitive to differences in visual acuity, with a 5 point change in the NEI-VFQ 25 equivalent to a 1 or 2 line difference in visual acuity. Using a definition of mild visual impairment as 20/40 or worse, an association between health-related quality of life and visual impairment was found. LALES reported that patients with bilateral mild visual impairment reported greater difficulties in performing activities of daily living dependent on vision. LALES also reported that visual field loss is associated with health-related quality of life, and that even early visual field loss is related to decrements in health-related quality of life. A loss of more than 5 dB (decibels) in visual field and no visual acuity impairment was associated with a loss of vision-specific health-related quality of life of 3.7 points. Therefore, **glaucoma treatment which has been demonstrated to reduce visual field progression is linked to improvement or preservation of health-related quality of life.**

➤ **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.

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.

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.

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), showed that even early visual field impairment can cause quality of life

deterioration. 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.

Specific comments on the Executive Summary are as follows:

Page ES9, KQ1, bullet 2: Visual acuity is not a suitable primary outcome for studies of glaucoma because it is lost only in endstage disease.

Page ES10, Surgical Treatment KQ4: An important conclusion about 4c on page 64 is not brought forward to ES.

Page ES10, Medical v Surgical Treatment KQ4: An important conclusion about 4c on page 64 is not brought forward to ES.

Page ES 11, Future Research para 2: 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.

➤ **Results**

Medical Treatment of Open-Angle Glaucoma

Key Question 1a: What is the comparative effectiveness of medical treatments for reducing visual impairment?

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.

Page 12, para 2. 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.

Page 38 and 39 and 41. 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.

Page 38, 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 than AHRQ conveyed was its intention. Hence, the inappropriate conclusion that “no RCTs studied” the variable in question is reached.

Key Question 3a: What is the comparative effectiveness of medical treatments for lowering intraocular pressure?

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 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.

Studies of Diurnal Intraocular Pressure

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.

Key Question 4a What is the comparative effectiveness of medical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

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 field abnormality by 55% and optic disc deterioration by 64%. (reworded according to hazard ratios).

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.)

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, Liebmann 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.

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 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

worse.” (Friedman DS, Okeke CO, Jampel HD, et al. Risk factors for poor adherence to eyedrops in electronically monitored patients with glaucoma. *Ophthalmology*. 2009 Jun; 116(6):1097-105. Epub 2009 Apr 19.)

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.

➤ Surgical Treatment

Key Question 3b: What is the comparative effectiveness of laser and other surgical treatments for lowering intraocular pressure?

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.

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.

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.

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.)

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.

Key Question 4b: What is the comparative effectiveness of laser and other surgical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

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.

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.

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).

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.

➤ **Medical versus Surgical Treatment**

Key Question 1c: What is the comparative effectiveness of medical versus surgical treatment for reducing of visual impairment?

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.

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 the 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 initial was designed to evaluate the impact of primary medical versus surgical treatment on the control of IOP and

preservation of visual field loss in glaucoma. 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.

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.

Key Question 3c: What is the comparative effectiveness of medical versus surgical treatment for lowering intraocular pressure?

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.

Key Question 4c: What is the comparative effectiveness of medical versus surgical treatment for preventing or slowing the progression of optic nerve damage and visual field loss?

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 and medications. There may be too much reliance on one study (CIGTS) to make their ultimate conclusions.

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.

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.

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.

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.

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.

Key Question 2 Does treatment of OAG improve patient-reported outcomes?

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.

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.**

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.

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.

Page 43, Key Question 2. 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.

Page 45, 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.

Page 47, line 2. EMGT was designed to discontinue patient participation if VF deterioration occurred. Thus, no patient was allowed to progress until QoL measures declined.

Page 47, para 2. The fear of blindness results has an alternate explanation. The VF failed to deteriorate in either group, so patient confidence was restored.

Page 47, detailed analysis para 1. CIGTS found weak correlation between visual field results and QOL measures in early glaucoma.

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).¹

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.

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.

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

It is notable in all of these cases, there was a loss of QoL even before visual impairment is reached. In most cases, the diagnosis of glaucoma resulted in a loss of QoL.

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).

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 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.

Key Question 5 Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?

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).

Detecting and treating glaucoma at an earlier stage in order to prevent these HRQoL issues has been evaluated in two studies. The first, the OHTS clearly demonstrated that lowering IOP in ocular hypertensive patients significantly reduced the conversion to glaucoma. There was less optic nerve damage and visual field damage in the treated group. In addition, patients at high risk for glaucoma suffered greater damage by waiting to treat as opposed to patients who were low risk. Second, the EMGT-demonstrated progression was less frequent in treated patients with POAG than non-treated, thus reducing visual field and disc impairment in the treated group. In addition, the EMGT demonstrated that visual function affected vision-targeted quality of life. There are not a plethora of studies that demonstrate reducing IOP improves HRQoL issues because an untreated control group would be required. In general, society would currently not allow for untreated study arms when failure to treat can cause blindness.

Page 51 ff. 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.