UNIVERSITY OF BIRMINGHAM

Literature search on the long-term prognosis for optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and/or field loss in patients with primary open-angle glaucoma

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

October 2006

For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1 Aims

The aims of this report were to address the following questions submitted by the Driver Medical Group:

1.1 Primary questions

What is the long-term rate of progression in primary open-angle glaucoma?

1.2 Secondary questions

Are there any conditions of the disease that are associated with lower or static progression rates?

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of Request)

2 Background

Glaucoma is a group of diseases, which are characterised by progressive optic nerve damage, leading to specific structural abnormalities of the optic nerve head and patterns of visual field loss. Primary open-angle glaucoma (POAG) occurs in people with an open anterior chamber drainage angle with no secondary identifiable cause. POAG is mostly associated with increased intraocular pressure, but it can also occur in the absence of elevated intraocular pressure and this is referred to as normal-tension glaucoma (NTG). There is no consensus as to whether NTG is a subtype of POAG or a separate entity but for the purpose of this report NTG is reported as a sub-type of POAG. The upper range of normal intraocular pressure (IOP) is 21mmHg.

The DVLA require defects associated with glaucoma to be reviewed at least every three years and licenses are removed once a defect is outside the required visual field standard. The minimum field of vision requirement is defined as a field of at least 120˚ on the horizontal and no significant defect in the binocular field which reaches within 20˚ of fixation above or below the horizontal meridian. Due to the progressive nature of glaucoma, once a license has been removed due to defects associated with glaucoma, consideration is not given for relicensing. The DVLA are currently reviewing whether relicensing consideration should be given in cases where the disease is no longer liable to progression and whether repeat license reviews are necessary in cases where defects are considered acceptable for driving and they and not liable to further progression.

Further background information is given in the documentation supplied by the Drivers Medical Group contained in Appendix 1 – Details of Request.

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by e-mail (Appendix 2 – Outline methods)

Briefly these were:

- To undertake a search for studies looking at the long-term rate of progression of POAG, focussing on optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and field loss.
- To initially search for existing systematic reviews.
- To concentrate on large, well conducted, cohort studies reporting the long-term prognosis for optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and field loss in different sub-groups of primary open-angle glaucoma patients (e.g. split by patient characteristics, sub-types of the condition and treatments) so comparisons could be made.
- Methodological quality of such studies was to be commented upon.
- Where appropriate and possible, data on relevant outcomes was to be extracted and tabulated.

3.1 Searches

3.1.1 Existing reviews

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 3 – Search strategies)

3.1.2 Primary studies

Searches were undertaken for cohort studies in MEDLINE, EMBASE and the Cochrane Library. The search strategy employed MeSH headings and text terms for open angle glaucoma and progression, with terms for appropriate study designs. The strategy was developed iteratively and modified accordingly.

The detailed search strategies can be found in Appendix 3 – Search strategies.

Searches were predominantly undertaken by an information specialist with additional searches by a research reviewer. Both interacted to ensure searches were conducted appropriately.

An information specialist and a research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that adhered to the following broad criteria were obtained in full for further scrutiny:

Design: Systematic review or cohort study

Population: POAG (including normal tension glaucoma)

Outcomes:	Rate of progression of disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer or visual field loss
Exclusion:	Studies reporting on mainly closed-angle glaucoma or secondary open-angle glaucoma patients Studies with a sample size less than 50 subjects

Full copy articles were assessed for their match to the questions being addressed (external validity) and the most informative articles (large, prospective cohort studies with long-term follow-up, reporting on all the outcomes of interest or systematic reviews of randomised-controlled trials comparing glaucoma treatments) were subjected to further scrutiny and reporting.

The reference lists of the most relevant articles were also checked in order to identify further relevant papers.

4 Results

The searches retrieved around 300 papers. The titles and abstracts were scanned and 34 papers were thought to be relevant and were requested in full. From these papers, eight studies were thought to offer the best evidence and these have formed the basis of the report. Ideally we would like to have identified a large, well conducted cohort study that assessed all the factors of interest in the same population of patients, however no such study was found. Instead, we have identified a series of observational studies assessing the rate of progression in untreated POAG populations and treated populations. We also found studies on possible risk factors for the progression of POAG (prognostic factors) and three systematic reviews of randomised controlled trials assessing the effect of different treatments on either the rate of progression or surrogate outcomes.

Studies were excluded for reasons such as unrepresentative population to the UK (e.g. Japanese population), mixed glaucoma populations with results not reported for each sub-type of glaucoma, advanced POAG population, inappropriate analyses, small sample sizes, inappropriate study designs and irrelevant outcomes (e.g. errors in visual field measurements).

4.1 Rate of progression in primary open-angle glaucoma

4.1.1.1 Treated primary open-angle glaucoma population

The Canadian Glaucoma Study[1] offered the best available evidence on the rate of progression of POAG in a treated population. The cohort study followed-up 248 patients (91% European derived) with early to moderate POAG every 4 months for a median of 5.3 years (follow-up range of 0.3 to 8.7 years). Newly diagnosed patients were targeted for a ≥30% reduction IOP and previously diagnosed patients entered the study at a physician-defined target IOP. IOP was maintained, whether progression had occurred or not, using the following treatment steps:

- Step 1: Topical monotherapy
- Step 2: Adjunct topical therapy

- Step 3: Argon laser trabeculoplasty
- Step 4: Systemic carbonic anhydrase inhibitors
- Step 5: Primary filtration surgery
- Step 6: Secondary filtration

Progression was defined as visual field change determined by standard automated perimetry and visual field change was defined by glaucoma change probability analyses based on total deviation (dB difference between the observed threshold at a visual field location and the corresponding age-matched normal value). They found a cumulative progression rate of 11.3% at 2 years, 21.5% at 4 years, 33.1% at 6 years and 43.5% at 8 years. This means that 56.5% of patients did not progress at all in the 8 years of follow-up.

These results are considered to be applicable to the UK POAG population as the majority of the participants are from European descent and the treatments used in Canada are similar to those in the UK.

4.1.2 Treated compared to untreated primary-open angle glaucoma population

We identified a well conducted systematic review[2] which combined data from randomised controlled trials assessing the rate of progression of POAG in an IOP lowering treatment group (medical or surgical) compared to an untreated control group. They identified two studies[3,4] that met their inclusion criteria. Heijl et al compared laser trabeculoplasty, betaxolol and latanoprost treatments to observation in 255 POAG patients, including 132 NTG patients. Within 6 years, 58 out of the 129 treated patients (45%) and 78 out of the 126 control patients (62%) had deterioration of visual field or optic disc. The Collaborative Normal Tension Glaucoma Study Group compared any medication or surgery to observation in NTG patients only. Within 5 years, 22 out of the 66 treated patients (33%) and 31 out of the 79 control patients (39%) had deterioration of visual field or optic disc. Combining the results of the two studies showed treatment to be significantly effective at preventing glaucoma progression (defined as deterioration of visual field or optic disc), giving a hazard ratio of 0.65 (95%CI 0.49-0.87, p=0.003), i.e. treated POAG patients are 35% less likely to progress than untreated POAG patients. A sub-group analysis was conducted to determine the effect of treatment on patients with NTG alone. There was a small sample size and the results were non-significant (HR=0.70, 95%CI 0.48-1.02, p=0.06).

4.1.3 Untreated primary open-angle glaucoma

We did not identify any cohort studies assessing the rate of progression in untreated POAG patients. This was not surprising due to the ethical issues of following-up a group of patients denied treatment for a long period of time. We did identify a cross-sectional study conducted in the UK[5] which compared the average age at diagnosis of patients who presented with early stage disease to the average age at diagnosis of those who presented with end stage disease. As both groups were at the diagnosis stage, neither had commenced treatment. The difference in average age was used to indicate the average time taken for untreated POAG to progress to blindness after early field defects appear. Case notes from 177 subjects (74 with early disease and 103 with end stage disease) attending the Tennent Institute of Opthalmology or Glasgow Eye Infirmary with POAG were used.

The results show a mean difference in age of 5.9 years (p=0.0001, t-test) which implies that untreated POAG takes an average of 6 years to progress from early stage to end-stage disease. They also conducted a sub-

group analysis on intraocular pressure (IOP) at diagnosis. This showed that patients with an IOP at diagnosis of 21-25 mmHg had a mean difference of 14.4 years between early stage and end stage disease ($p<0.00001$, t-test), patients with an IOP at diagnosis of 26-30 mmHg had a mean difference of 6.5 years ($p=0.029$, t-test) and patients with an IOP of >30mmHg had a mean difference of 2.9 years ($p=0.17$,non-significant,t-test). This implies that the greater the untreated IOP at diagnosis, the faster the rate of progression of POAG.

These results will be confounded as patients who present at end stage glaucoma will be very different in health seeking behaviour characteristics compared to those who present with early stage glaucoma. These results are not as robust as cohort studies which follow-up the same group of patients over time to determine the rate of the progression. This study is merely comparing the average age of two groups of POAG patients presenting with different stages of the disease at diagnosis, in order to give an estimation of the rate of progression. In addition, the difference observed could be due to selection bias with older patients being more likely to be included in the study if they were diagnosed at end-stage rather than early stage disease.

4.2 Factors affecting the rate of progression of primary open-angle glaucoma

4.2.1 Treatments

Currently there are many medical and surgical treatments available for POAG, all of which act by lowering IOP. Randomised controlled trials offer the best form of evidence to assess whether any differences in rates of progression exist between different treatments. Many randomised controlled trials have been conducted on the comparative effectiveness of different treatments for POAG. Therefore we looked for well conducted systematic reviews which combined the results of randomised controlled trials addressing the same treatment-related question. We identified three POAG treatment-related systematic reviews which were thought to be relevant to factors affecting the rate of progression of POAG and details are reported below.

4.2.1.1 Medical treatment compared to surgery

A Cochrane Collaboration systematic review assessing the relative rate of progression of medical and surgical treatments of open-angle glaucoma was identified.[6] The review was well conducted and included four trials, three of which were conducted in the UK and one in the US. The total number of participants in the three trials was 888, all of which had newly diagnosed open-angle glaucoma and no prior treatment for the condition. The studies all measured visual field progression using visual field analysers (perimeters) but the methods of perimetry, definitions of progression and analysis of outcome differed between the trials. All of the trials were randomised and the allocation sequence was adequately concealed. However only one of the four studies conducted an intention-to-treat analysis so attrition bias may have been introduced. The results of the studies were not combined quantitatively as the studies used different medications, surgical techniques and methods of measurements of visual field loss as the studies were conducted at different times when different guidelines existed (1968, 1988, 1994 and 2001). Three of the studies compared initial medical treatment compared to initial trabeculectomy and one study compared initial medical treatment versus primary Scheie's procedure.

The most recent trial and hence the most relevant to today's practice included participants with mild open-angle glaucoma. At the 5 year follow-up, it found progressive visual field loss to be about 26% more likely in medically treated patients compared to surgically treated patients (OR=0.74) (after adjustment for baseline visual field score, age, gender, race, diagnosis, diabetes, time in the study and cataract surgery). However, this result was not statistically significant (95% CI 0.54-1.01) and it is not clear why the results are adjusted for all the parameters mentioned above, as the trial is randomised and hence these parameters should be balanced between the two groups. In addition, the trial was conducted in the US and 44% of the participants were non-whites therefore the results may not be applicable to the average UK population.

The remaining three trials were all conducted in the UK and assessed patients with moderately advanced glaucoma. The results seemed to suggest that surgery (trabeculectomy or Scheie's procedure) was associated with a lower progressive visual field loss than medical treatments. However these trials may have been subjected to detection and attrition bias as the majority did not use intention-to-treat analysis and there have been changes to the medical and surgical treatments since the trials were conducted.

4.2.1.2 Comparison of medical treatments

No systematic reviews assessing the comparative rate of progression of medical treatments for POAG were identified. However a well-conducted systematic review assessing the IOP lowering effects of commonly used drugs to treat POAG and ocular hypertension was identified.[7] Treatments for glaucoma act by reducing IOP with the aim of reducing the rate of progression, therefore it is likely, (but not certain) that IOP reduction and rate of progression will be closely associated and therefore IOP reduction could be a surrogate outcome for rate of progression.

The systematic review included 27 randomised controlled trials which were generally of high methodological quality and included populations representative of the UK. The included trials were a combination of head-to-head and placebo-controlled trials, assessing a variety of β-blockers, prostaglandins, α_2 adrenergic agents and carbonic anhydrase inhibitors. The pooled absolute and relative change in IOP from baseline for each drug suggest that bimatoprost, travoprost and timolol are the most effective drugs at reducing IOP. However it is not clear whether this finding would translate into these drugs being the most effective at reducing the rate of progression of glaucoma.

4.2.2 Sub-types of primary open-angle glaucoma

Rasker et al[8] assessed the rate of progression of glaucoma (defined as rate of visual field loss) for an average of 9 years in 227 patients with newly detected disease who were recruited from a hospital in Amsterdam. Of these, 68 patients had POAG, 34 patients had NTG and 125 patients had ocular hypertension (results not commented on for the purpose of this review). Patients were diagnosed with POAG and NTG if they had an arcuate scotoma within the central 30˚ or a nasal step on at least 2 examinations, a glaucomatous optic disc, an open angle and IOP during day-time without medication and during the study of 22mmHg for NTG and greater than 22mmHg for POAG. Patients with POAG were treated when diagnosed. Patients with NTG received treatment if their IOP exceeded 18mmHg, visual field

worsened or glaucomatous changes to the optic head occurred. Visual fields were obtained annually with automated perimetry and the estimation of progression was based on clusters of deteriorating points.

The mean rates of visual field progression were 2.5% (+/-1.8%) per year in POAG patients and 3.7% (+/-3.3%) per year in NTG patients. The difference in the rate of visual field loss did not differ significantly between NTG and POAG patients. No significant associations were found between rate of visual field loss and optic disc hemorrphages and initial visual field loss.

Although no differences between POAG and NTG and no associations between visual field loss and prognostic factors were detected, it does not mean that they do no not exist as the study may have been too small to detect significant differences. The method of selecting participants was not reported so it is not clear whether selection bias was introduced.

4.2.3 Prognostic factors

Large, prospective, cohort studies with long-term follow-up offer the best form of evidence when assessing risk factors affecting the rate of progression. Ideally, we would have liked to have identified such a study which also assessed a variety of pre-specified, possible prognostic factors and measured all the outcomes of interest (optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and field loss) so we could compare rates of progression in different sub-groups of POAG patients. However, we did not find a study that fulfilled all of the criteria above.

The relevant studies identified were generally poorly reported and tended to only assess one outcome of interest. Most were retrospective studies, with moderate sample sizes and length of follow-ups. The majority did not conduct multivariate analyses (adjustment for multiple confounders), which can lead to confounded results, especially in POAG where many prognostic factors are interrelated. Also, they did not take into account differences in the glaucoma treatments administered between the exposure groups, which is also likely to significantly confound results. This was particularly apparent in studies which compared the mean IOP levels of stable POAG patients to that of progressive POAG patients[9-11] as those patients perceived to be at high risk of progression may be treated more intensively to reduce IOP than those perceived to be at low risk.

We have reported the results of only two of the relevant cohort studies[12,13] as these were the only studies believed to conduct multivariate analyses. Caution should be taken when interpreting the results due to the issue mentioned above concerning treatment choices confounding results. Caution should also be taken when comparing results from the different studies due to differences in the study populations, definitions of progression and methods of measurements.

4.2.3.1 Prospective cohort study

Martus et al[12] conducted a prospective cohort study assessing differences in predictive factors for progression between sub-types of open-angle glaucoma. This study was thought to offer the most relevant and robust evidence, however only the progression of glaucomatous optic nerve damage was assessed. 300 (517 eyes) Caucasian patients with chronic open-angle glaucoma were identified from the Erlangen

Glaucoma Register in Germany. All patients had POAG and a visual acuity of 20/25 or better, and at day of examination had an IOP ≤21mmHg. POAG was diagnosed in 289 eyes, which was defined as having at least one office measurement and a history of an IOP greater than 21mmHg. NTG was diagnosed in 178 eyes, which was defined as having maximal IOP readings ≤21mmHg in at least two 24-hour pressure profiles and no other reason for optic nerve damage than glaucoma. Secondary open-angle glaucoma (SOAG) was diagnosed in 50 eyes. The results are reported separately for open-angle glaucoma (OAG) with elevated IOP (POAG and SOAG) and open-angle glaucoma with normal IOP (NTG). Although the SOAG patients are not relevant to this review, the study reports that similar results were obtained for both POAG and SOAG patients.

Patients were admitted into hospital for follow-up measurements which were conducted at 6 months and at 1 yearly intervals following this 6 monthly measurement. IOP in a circadian curve with measurements at 5pm, 9pm, midnight, 7am and noon were taken, and white-on-white perimetry and stereophotography of the optic nerve head were undertaken. The median follow-up was 4.1 years (follow-up range of 0.5 years – 10.9 years).

After 8 years, the Kaplan-Meier estimate for progression of glaucoma (defined as loss of neuroretinal rim) was 32.5% (95% CI 23.9% - 41.02%) of the total study population. Progression was observed in 20.8% of 178 eyes with NTG and 16.8% of 339 eyes with OAG with elevated IOP. A multivariate analysis showed temporal horizontal neuroretinal rim area and presence of visual field loss at baseline to be significant prognostic factors for OAG patients with elevated IOP to have increased progression. For patients with NTG, the multivariate analysis showed presence of initial optic disc haemorrhages as the only predictive factor for increased glaucoma progression.

These results should be interpreted with caution for the following reasons. The paper does not state how the Erlangen Glaucoma Register was compiled and if all the patients on the register were approached to participate in the study or whether a sample was used. Therefore it is impossible to determine whether selection bias may have been introduced. Also, the level of IOP was not taken into account in the analysis, therefore the results may have been confounded by IOP. However the authors state that the participants were under relatively good control of IOP.

4.2.3.2 Retrospective cohort study

Spry et al[13] conducted a retrospective cohort study assessing the risk factors for progressive visual field loss in treated POAG, using historical ophthalmic data from the case notes of 108 subjects, taken at the Bristol Eye Hospital between 2001-2002. POAG was defined as a clinical case-note diagnosis of POAG which included visual field status and optic nerve head appearance made by the monitoring clinician and a pre-treatment IOP measurement of ≥22mmHg. All other glaucomas, including pseudoexfoliative, pigmentary and NTG were excluded. Progressive glaucomatous visual field loss was defined using the Advanced Glaucoma Intervention Study visual field defect scoring system. The following exposures were assessed to determine whether they were significant prognostic factors: maximum recorded IOP, IOP reduction, IOP variation during study, treatment duration, baseline cup-to-disc ratio, baseline visual field status, visual field loss within

5˚ of fixation at baseline, parapapillary atrophy, disc haemorrhage during study, age at baseline, gender, high myopia, positive family history of chronic glaucoma, diabetes, systemic hypertension and possible vasospasm. Visual field tests were performed, on average, every 8 months and the mean duration of follow-up was 3.6 years.

Only 19 subjects (17.6%) showed progressive glaucomatous visual field loss during the study and the majority of these (15 subjects) were found to be unilateral. The most significant prognostic factors found in the unadjusted analysis were then analysed in a multivariate Cox proportional hazards model. The only factor found to be significantly associated with rate of progression was increasing age (Hazard Ratio=1.07, 95%CI 1.01-1.12, p-value=0.022). This implies for each additional year of age in the age-group 40-87 years, there will be a 7% increase in risk of progression. This result should be interpreted with caution as it was only adjusted for gender and maximum IOP observed, so it may still have been confounded by other risk factors which were not recorded in the case notes.

The sample size of the study will have been too small to detect moderate differences in progression rates for possible prognostic factors as only 19 subjects showed progressive visual field loss. The non-significant associations may be a product of the small sample size rather than concrete evidence that these possible prognostic factors are not prognostic.

5 Conclusion

The evidence surrounding rates of progression of POAG and prognostic factors is poor. The majority of the observational studies identified are too small and confounded by treatment to reliably determine prognostic factors. However, it is clear from the evidence found that not all patients with POAG progress and treatments for POAG are effective at reducing the rate of progression. There was insufficient evidence to determine whether NTG is associated with a worse prognosis than POAG.

5.1 Limitations of this report

This is not a systematic review but a rapid assessment for relevant literature. Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, the searches for the latter were restricted to observational studies reporting outcomes related to the progression of POAG. To aid comprehensiveness the reference lists of relevant articles were scanned for further studies.

A large cohort study with long-term follow-up and analyses adjusted for possible confounders was needed to reliably determine prognostic factors and make comparisons between progression rates in different sub-types of glaucoma. In light of such a study not being found, we had to report the findings of smaller cohort studies which were insufficiently powered and had several confounders and therefore may not offer reliable findings.

6 References

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7 van der Valk R, Webers CA, Schouten JSAG, Zeegers MP. Intraocular pressure-lowering effects of all commonly used glaucoma drugs. *American Academy of Opthalmology* 2005; 112:1177-1185.

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7 Appendices

7.1 Appendix 1 – Details of Request

ARIF REQUEST FORM

Date of Request 04 / 08 / 06

Lead Medical Adviser Issuing request

Name – Dr Claire Jenkins
Secretary to Vision Panel

Contact details

Drivers Medical Group
DVLA
Sandringham Park
Swansea Vale
Llansamlet
Swansea
SA7 OAA

[redacted]

[redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

Glaucoma is considered to be a progressive condition for licensing purposes. Defects secondary to glaucoma are therefore reviewed at least every 3 years. Once a defect is outside the required standard, the licence is removed and consideration can not be given as an 'exceptional case', to allow subsequent relicensing. If under certain conditions the disease can be considered to be no longer liable to progression such consideration could be given.

2. Please give a background to the question. Why has DMG raised this problem?

Since the introduction of the consideration as exceptional cases for static defects, there have been challenges from those whose licenses have been removed because of defects secondary to glaucoma.

In addition, if a defect can be considered to be acceptable for licensing and not liable to further progression, repeated fields tests could be avoided.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues*, which might be important for the problems, you describe.

a) Chapter 6 Visual Disorders – At a Glance Guide to the Current Medical Standards of Fitness to Drive February 2006.
b) Report of the European Working Group on Driving and Vision.
c) MONASH report on driving and chronic medical conditions.
d) MEDRIL Workshop II Report.

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Mr M H Miller (Chairman)
MD FRCS FRCOphth
Consultant Ophthalmic Surgeon
73 Harley Street
London W1G 8QJ
[redacted]

5. What is the nature of the target population of the issue detailed above? E.g. age, profile, vocational drivers, young drivers, other co-morbid features.

Group 1 licence holders – all ages.

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

The opportunity to avoid repeated licence review and field testing.
The opportunity to consider future relicensing for those drivers who have debarring defects.

What is the latest date that an ARIF response would be of value 31 / 10 / 06

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to:- **Dr David Moore**
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
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Please ring 0121 414 3166 or 6767 if you have any queries, or you want to check the progress with your request.

7.2 Appendix 2 – Outline methods

- The report will focus on the long-term rate of progression of primary open-angle glaucoma, focussing on optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and field loss.
- In addition, where data is available, patient characteristics, sub-types of primary open-angle glaucoma and treatments that are associated with lower progression rates will be reported.
- MEDLINE (1966-2006), EMBASE (1980-2006) and the Cochrane Library (2006 Issue 3) will be searched using a comprehensive search strategy.
- The identified studies will be screened by an analyst for relevance.
- Cohort studies which report the relevant outcomes will be selected and the most robust commented upon.
- Ideally we would like to find a large cohort study that reports the long-term prognosis for optic disc damage, loss of neuroretinal rim, defects of the retinal nerve fibre layer and field loss in different sub-groups of glaucoma patients so comparisons can be made.
- In the first instance, studies conducted in the UK or a population similar to the UK will be searched for, as prognosis may vary according to treatments used and ethnicity.
- Methodological quality of these studies will be discussed.
- Data on relevant outcomes will be extracted and reported.

7.3 Appendix 3 – Search strategies

7.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines

- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products

7.3.2 Primary studies protocol

Database: Cochrane Library (Wiley) 2006 Issue 3

#1 glaucoma
#2 MeSH descriptor Glaucoma explode all trees
#3 prognosis
#4 MeSH descriptor Prognosis explode all trees
#5 progression
#6 MeSH descriptor Disease Progression explode all trees
#7 (#1 OR #2)
#8 (#3 OR #4 OR #5 OR #6)
#9 (#7 AND #8)

Database: Ovid MEDLINE(R) 1966 to September Week 4 2006
Search Strategy:

1 exp Glaucoma/ or glaucoma.mp.
2 prognosis.mp. or exp Prognosis/
3 exp Disease Progression/ or progression.mp.
4 retinal damage.mp.
5 exp Vision Disorders/ or exp Visual Fields/ or field loss.mp.
6 or/2-5
7 1 and 6
8 exp Case-Control Studies/ or case control.mp.
9 exp Cohort Studies/ or cohort.mp.
10 cross-over.mp. or exp Cross-Over Studies/
11 or/8-10
12 7 and 11

Database: Ovid MEDLINE(R) 1966 to September Week 4 2006
Search Strategy:

1 glaucoma.ti.
2 progress$.ti.
3 prognos$.ti.
4 or/2-3
53 1 and 4

Database: EMBASE (Ovid) 1980 to 2006 Week 40
Search Strategy:

1 glaucoma.ti.
2 progression.ti.
3 prognosis.ti.
4 or/2-3
5 1 and 4
6 exp COHORT ANALYSIS/ or cohort.mp.
7 exp Case Control Study/ or case control.mp.
8 cross-over.mp.
9 or/6-8
10 5 and 9
11 limit 1 to "prognosis (sensitivity)"
12 9 and 11

Internet sites searched 12/10/2006 :

TRIS Online (National Transportation Library)
TRL
UNESCO
Highways Agency
CARE Europe

US Driving Assessment Symposia
Monash University Accident Research Centre
NHTSA (National Highway Traffic Safety Association)