THE UNIVERSITY
OF BIRMINGHAM

Literature Search on
the Prognosis / Natural History of Treated Diabetic Retinopathy

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

October 2005

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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Warning

This is a confidential document.

Do not quote without first seeking permission of the DVLA and ARIF.

The information in this report is primarily designed to give approved readers a starting point to consider research evidence in a particular area. Readers should not use the comments made in isolation and should have read the literature suggested. This report stems from a specific request for information, as such utilisation of the report outside of this context should not be undertaken. Readers should also be aware that more appropriate reviews or information might have become available since this report was compiled.

1 Aims

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

1.1 Primary Questions

1. How can visual field impairment secondary to Diabetic Retinopathy (DR) be evaluated, in relation to driving and what is the best practical framework for assessment?

2. What is the prognosis of DR with and without laser treatment and to what extent is this linked to diabetic control?

3. Do retinal scars enlarge and cause further impairment after laser treatment and do different types of laser have different ongoing effects on visual impairment in this respect? What are the implications for:
   - type and subsequent field loss
   - type and scar enlargement

4. What is the range for the rate of progression in terms of functional vision loss: best, worst and mean? How can this be anticipated or evaluated in an individual case?

5. Can stable retinal defects be defined in diabetic retinopathy and if so how?

6. How well do changes in retinal appearance correlate with
   - (a) visual function?
   - (b) the size/location of a field defect measures by perimetry?

After discussion with the Drivers Medical Group, the question became:

What is the prognosis/natural history of treated diabetic retinopathy?

2 Background

Background information is given in the documentation supplied by the Drivers Medical Group contained in 7.1 Appendix 1 – Details of Request.

3   Methods

To address the question raised by the driving medical group, outline methods are listed as follows:

- To undertake a search for studies looking at the prognosis and or natural history of the diabetic retinopathy, laser treatment of diabetic retinopathy, diabetic retinopathy and driving.
- To initially search for existing systematic reviews on the above topics.
- To start by searching for articles published 2000-2005, and then work back to 1966 on the above topics.
- To concentrate on primary studies on a cohort of diabetes patients who were given laser treatments.
- Methodological quality of such studies was to be commented upon.
- Where appropriate and possible data on relevant outcomes was to be extracted and tabulated.
- Data analysis would depend on information identified.

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 (7.2 Appendix 2 – Search strategies)

3.1.2   Primary Studies

Searches were undertaken for primary studies in MEDLINE(Ovid) and the Cochrane library.The search strategy employed MeSH headings and text terms for diabetic retinopathy and laser treatment and a filter to identify prognostic studies. Searches were also undertaken into diabetic retinopathy and driving and the natural history of diabetic retinopathy. The strategy was developed iteratively and modified accordingly.

Searches were initially conducted from 2000-2005 and then extended back to 1966.
The detailed search strategies can be found in 7.2 Appendix 2 – 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: Long term (> 1 year) follow-up of a defined cohort of diabetic patients.
Population: Diabetic patients who received laser treatment for diabetic retinopathy.
Outcome: Visual acuity, visual field defects, qualitative or quantitative description of severity states of retinopathy, the expected number of years before vision impairment or death.
Exclusions: Study designs only assessing the best way of assessing visual field defects,
Studies only of prognosis of diabetic retinopathy without treatment.

Full copy articles were assessed for their match to the questions being addressed and the most informative articles (closest match to population [Section 1.1 Primary Questions], longest follow-up) 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 focus of the results is on visual acuity and visual field defects. The results of the searched articles have been studied and summarized into the following subsections:

- Nature and quantity of literature available
- Quality of literature available
- An example of modelling found in the literature

4.1   Nature, quantity and quality of the studies found

107 potentially relevant references were found from the searches. The titles and abstracts were read for relevance and twenty eight full papers were ordered. From this, 9 studies have been used in this report. The remaining 19 studies were excluded because patients did not have laser treatment or the follow up times were less than one year.

The nine included studies are all cohort studies where patients are treated with laser photocoagulation and followed up for more than one year. Some studies compared treated to untreated patients, we have given the results for treated patients here. Most of the studies give very little information about the patients, for example, their ages, how long they had diabetes, severity of diabetes, smoking status etc. They mostly just give visual information about the patients. Therefore it is very difficult to tell whether all the patients were in similar stages of disease progression and whether the results from one study are comparable to another. They also give little information about the actual treatment used, such as type of laser, the spot size and number of burns. None of the studies discuss blinding of treatment outcome assessment. Most of the studies do mention losses to follow up and the reasons for losses, such as deaths or inability to trace records.

The treatment settings and the baseline and follow-up visual acuity and visual standards required for a UK driving licence are summarized in Tables 1 and 2. (see below). There were no studies that gave both visual acuity and visual field results independently. One study (Mackie et al 1995) assessed both visual fields and visual acuity but gave a categorical outcome on ability to pass the visual standards required for a UK driving licence. One of the studies in table 2 (Pearson et al 1998) compared visual field measurement by the chairman of the Visual Standards Sub-committee of the DVLA to four consultants.

Table 1 shows that visual impairment and blindness tended to develop more often in eyes treated for proliferative retinopathy compared to those treated for severe non-proliferative retinopathy. Compared to the

baseline, about 20% of patients had moderate visual loss in the treated or better eye (if the patients received bilateral treatment) at follow up. In 5-15 years follow up, about 40-90% of photocoagulation treated patients maintained visual acuity in a level of >20/40 that is required by the DVLA for holding a Group 1 driving license. There was no apparent significant difference between argon and xenon treatment, in the only study to compare both (Yassur et al, 1980). The visual acuity of argon-treated eyes did not change much, whilst the visual acuity of xenon-treated eyes had very wide variations during the follow-up period. These wide variations might not reflect the effect of xenon treatment, but may have been more due to vitreous haemorrhage or macular oedema as the xenon-treated eyes had more vitreous haemorrhage from choroidal neovascularisation than argon-treated eyes during the follow-up period.

Table 2 shows that up to 17% of diabetic patients failed DVLA visual acuity and/or binocular field test after photocoagulation treatment, and that 40 to 50% of patients failed DVLA monocular field test. These are very different from early reports that 80% of patients who have had photocoagulation for proliferative diabetic retinopathy will fail the DVLA field test (Mackie et al 1995). As larger spot sizes were used in earlier studies, this implies that the use of large laser spot size (>500 micron) or burn area is probably associated with an increased risk of DVLA visual field test failure. Two studies showed a significant association between visual field loss and total burn area (Hulbert et al 1992, and Mackie, et al 1995). These results demonstrated that 16-32% of the variation of visual field loss could be explained by total burn area. Reduction in the risk of DVLA visual field test failure can be achieved by using small burns (preferably less than 200micron spot size), avoiding major vessels and retina within the temporal arcades and applying 3000 to 3500 burns. Although a definition for the minimum visual field for safe driving is available, its interpretation remains somewhat subjective. Substantial differences in the assessment of driving visual fields following photocoagulation were observed between consultants and the chairman of the Visual Standards Sub-Committee (Pearson et al 1998).

Table 1 Results from cohort studies of laser treatment - visual acuity results

Study	Population	Patients	Number Followed up (eyes)	Age at onset of diabetes (years)	Diabetes duration (years)	Severity state	Visual Acuity (VA)	Types	Number of burns	Spot size	Follow up (years)	Pathology	Visual Acuity (VA)	Note
				Baseline				Treatment				Outcome		
Lövestam-Adrian et al, 2003	Type 1 diabetes	344	40	14±8	18+10	SNPDR	20/50 to 20/20	PRP			10	VH (5%) CNV (35%)	>20/40 (90%)	Significant different P=0.056
			41	15±10	22+13	PDR	20/200 to 20/20					VH (29%)	>20/40 (75%)	
George 1991	Diabetes	151	19	15-50 mean 33		DR	>20/40 (95%)	Argon			3-5		>20/40 (79%)	
											10		>20/40 (37%)	
											15		>20/40 (58%)	
			32	15-48 mean 30			>20/40 (94%)	Xenon			3-5		>20/40 (63%)	
											10		>20/40 (41%)	
											15		>20/40 (41%)	
Chew et al, 2003	Diabetes type 1 (26%) type 2	214	71		<10(15%) 10-19 (64%)	NPDR (39%) SNPDR (43%)	>20/20 (57%) >20/40 (91%)	PRP			16	NPDR (38%) SNPDR (13%)	>20/20 (42%) >20/40 (84%)	In better eye

	(36%) Mixed (38%)				>19 (20%)	PDR (18%)	<20/200 (0)					PDR (49%)	<20/200 (1%)	
Yassur et al, 1980	Diabetes	67	45		18	PDR CNV		Argon	Manual of operation in diabetic retinopathy	Manual of operation in diabetic retinopathy	4	CNV grade decrease 71% same 18% increase 11%	Not change much	No significant difference on effect of CNV between Argon and Xenon
			22					Xenon				CNV grade decrease 64% same 23% increase 13%	Very wide variation	

PRP, Panretinal photocoagulation; SNPDR, Severe non-proliferative diabetic retinopathy; PDR, Proliferative diabetic retinopathy; CNV, Choroial neovascularization; VH, Vitreous haemorrhage; DR, Diabetic retinopathy

**Table 2. Results from cohort studies of laser treatment - visual standards required for a UK driving licence**

Study	Population	Patients	Number Followed up (eyes)	Baseline Severity state	Baseline Visual Acuity (VA)	Treatment Types	Treatment Number of burns	Treatment Spot size	Follow up (years)	Outcome Visual field (VF) defects	Note
Pearson et al, 1998	Diabetes	60	21 binocular field	PDR	>20/40 in treated or better eye	PRP(1)			>1	5% Fail* by chairman 2.5% Fail by consultants	Comparison of visual field measurements
			34 binocular field			PRP(2)				12% Fail by chairman 14% Fail by consultants	
			86 monocular field			PRP(1)				43% Fail by chairman 52% Fail by consultants	
Mackie et al 1995		100	100	PDR		Argon	>3000	200	4	4% Fail* due to VA, not VF 9% Fail due to VF, not VA 17% Fail due to VA and VF	19% of VF failures is attributable solely to the treatment
Hulbert et al, 1992		31	21	PDR		Xenon	2500-3500	200-500	4	11% Fail*	
PRP, Panretinal photocoagulation; PDR, Proliferative diabetic retinopathy; PRP(1), Panretinal photocoagulation for one eye, PRP(2), Panretinal photocoagulation for two eyes. * Fail to meet visual standards required for a UK driving licence.											

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4.2 Modelling the natural history of the treated diabetic retinopathy

There were two models of the prognosis of diabetic retinopathy found during the searches that were used to generate detailed prognosis of diabetic retinopathy because of the lack of evidence from studies. One (Craig et al 1999) estimated how many years a patient would remain in the severity state 2 (Background Diabetic Retinopathy) before death. The cohort results are shown in Table 3 but the model will not be discussed further here.

The second model is shown in Figure 1 below (Liu et al. 2003). This model is of interest and is included in the report as it gives an indication of what can be achieved with the results of a cohort study. The model used data from a cohort of 795 patients with diabetes mellitus and evaluated the rates of transition between the severity states of diabetic retinopathy after treatment. The severity states use the classification systems shown in Appendix 3. The cohort results are summarised in Table 3 below.
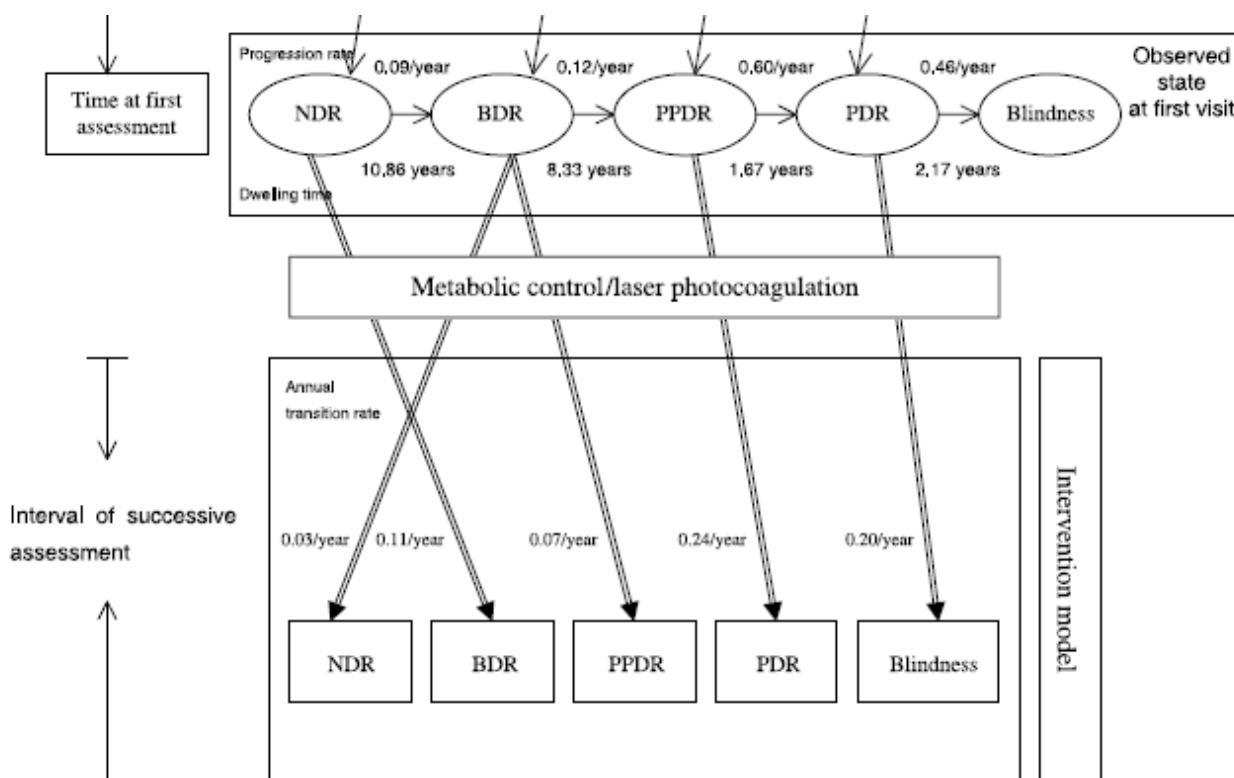
Reproduced from Liu and colleagues 2003

The model shows that, if no treatment is given, 9% of people may move from the state of No Diabetic Retinopathy (NDR) to a state of Background Diabetic Retinopathy (BDR) in one year (0.09/year) and 12% of people move from the state of Background Diabetic Retinopathy (BDR) to Pre-Proliferative Diabetic Retinopathy (PPDR) on one year (0.12/year) and so on through the other two severity states of Proliferative Diabetic Retinopathy and Blindness. This can be seen in the top line of the model. The lower line in that top box gives us the average dwelling time in each severity state. So it is estimated that it would take 10.86 years on average for a person to move from No Diabetic Retinopathy to Background Diabetic Retinopathy. It is estimated that it would take an average of 8.33 years for a person to move from Background Diabetic Retinopathy to Pre-Proliferative Diabetic Retinopathy, and so on. Please note that there are no estimates of

precision around these numbers so they could vary considerably if another cohort of patients was used in the model. Therefore considerable caution needs to be applied if using data from this model.

The bottom box of the model shows us what may happen with treatment. So, instead of 9% moving from NDR to BDR, 11% would move instead. This would be expected because of retinal damage from the treatment itself. The main difference with treatment is flowing from the PPDR group where only 24% go onto the next stage of PDR with treatment but 60% progress to this state without treatment. Again, there is no estimate of precision around these numbers and they may vary considerably if a different cohort was used.

There is little other evidence in the other studies identified to corroborate adequately the cohort results in the Liu model. However, the most reliable estimate would use results from all of the nine studies included in Tables 1 and 2 and may also require contacting the authors for further information. This work is outside the scope of the current review.

Table 3. Progression rates, transition rates, and the simulated expected number of years before vision impairment or death (Liu et al 2003)

Study	Population	Patients	Follow up (years)	Treatment Yes/No	Model	Variable	Severity state change				Note
							NDR->BDR	BDR->PPDR	PPDR->PDR	PDR-> Blindness	
Liu et al, 2003	Diabetes mellitus	795	7			Progression rate	0.09/year	0.12/year	0.60/year	0.46/year	
				No	Markov	Dwelling time	11 year	8 year	2 year	2 year	23 years from NDR to blindness, 12 years from BDR to blindness
				Yes		Transition rate	0.11/year	0.07/year	0.24/year	0.20/year	
Craig et al, 1999	Diabetes type 1	996 (year 1) 891 (year 5) 765 (year 11)	5-11	Yes At PDR, assumption of 40% of response to the treatment	Markov chain Monte Carlo (MCMC)	Expected number of years before vision impairment or death	Suppose a 30 years old diabetes patient, duration of diabetes 8 years, in severity state 2, the simulation results showed the expected number of years of the treated patient before vision impairment or death is between 27 to 31 with 95% posterior probability, and between 25 to 29 if no treatment is given				The expected number of years might depend on the assumed parameters

4.3   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 specific years. To aid comprehensiveness the reference lists of relevant articles were scanned for further studies. Citation checking of relevant articles identified further studies in this and other time frames.

5   Conclusion

We found 9 relevant cohort studies with a follow up of greater than one year. They investigated the natural history and the prognosis of the treated diabetic retinopathy. The results are not all that helpful in determining which patients with treated diabetic retinopathy will be able to pass the visual standards required for a UK driving licence. This is mainly because very little information is given about the patients enrolled in the cohort studies apart from their visual function. We also cannot distinguish from these studies the difference between the natural history of the disease and the effect of treatment causing loss of vision over time. There is also very little evidence on the effects of the different types of laser, and none on the effect of the size of laser spots and the number of the burns on visual outcomes. To reliably link visual outcomes to the outcome of failure to meet the DVLA driving standards is also problematic.

It is clear from the model described above that laser treatment can slow the progression of diabetic retinopathy. However, the relationship between treatment response and the underlying patient and treatment characteristics has not yet established. The model was overly simplified, for example, they had no estimates of precision or variability around point estimates. A comprehensive model is needed to accurately evaluate the prognosis and natural history of diabetic retinopathy. Also, in order to effectively assess the prognosis and natural history of diabetic retinopathy, it is essential to accurately detect and grade the severity stages of diabetic retinopathy.

6 References

6.1 Main References

Blankenship G, Fifteen-year Argon Laser and Xenon Photocoagulation Results of Bascom Palmer Eye Institute's patients participating in the Diabetic Retinopathy Study. Ophthalmology, 1991; 98(2) 125-128.

Chew EY et al, The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy, Ophthalmology, 2003:110(9), 1683-1689.

Craig, BA et al. A Bayesian Approach To Modelling The Natural History Of A Chronic Condition From Observations With Intervention, Statistics In Medicine, 1999: 18:1355-1371.

Garg SK, et al, The use of the Markov process in describing the natural course of diabetic retinopathy. Arch Ophthalmology. 1990 Sep; 108(9): 1245-7.

Harvey WJ, Diabetic retinopathy classification and clinical features. CE Optometry 2000; 3:(2). 51-56.

Hulbert MF et al, Passing the DVLC Field Regulations Following Bilateral Pan-retinal Photocoagulation in Diabetics. Eye, 1992; 6, 456-460.

Liu, WJ et al. Assessing progression and efficacy of treatment for diabetic retinopathy following the proliferative pathway to blindness: implication for diabetic retinopathy screening in Taiwan. Diabetes UK. Diabetic Medicine. 2003: 20, 727-733.

Lövestam-Adrain M, et al, Type 1 diabetes patients with severe non-proliferative retinopathy may benefit from panretinal photocoagulation. Acta ophthalmologica Scandinavica, 2003; 81(3), 221-5.

Mackie SW et al, How much blame can be placed on laser photocoagulation for failure to attain driving standards? Royal College of Ophthalmologists, Eye, 1995 9: 517-525.

North R, The effect of diabetes mellitus and its management upon visual functions. CE Optometry 2000; 3(2), 66-71.

Pearson AR et al, How good are we at assessing driving visual fields in diabetics? Royal College of Ophthalmologists, Eye, 1998, 12, 938-942.

Raynor M & Turne G, Treatment of diabetic retinopathy. CE Optometry 2000; 3:62-5.

Yassur, Y et al. Optic disc neovascularisation in diabetic retinopathy: II. Natural history and results of photocoagulation treatment. British Journal of Ophthalmology, 1980, 64, 77-86.

7 Appendices

7.1 Appendix 1 – Details of Request

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ARIF REQUEST FORM

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| Date of Request | | 15 | / | 06 | / | 05 |

| Lead Medical Adviser Issuing request | Name – Dr Claire Jenkins
          Secretary to Vision Panel |

| Contact details | Drivers Medical Group ██████████
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1. Without worrying about the structure of the question, state in full the nature and context of the problem.

We need to know:

1.   How can visual field impairment secondary to Diabetic Retinopathy (DR) be evaluated, in relation to driving and what is the best practical framework for assessment?

2.   What is the prognosis of DR with and without laser treatment and to what extent is this linked to diabetic control?

3.   Do retinal scars enlarge and cause further impairment after laser treatment and do different types of laser have different ongoing effects on visual impairment in this respect? What are the implications for:

- type and subsequent field loss
- type and scar enlargement

4. What is the range for the rate of progression in terms of functional vision loss: best, worst and mean?

How can this be anticipated or evaluated in an individual case?

5. Can stable retinal defects be defined in diabetic retinopathy and if so how?

6. How well do changes in retinal appearance correlate with
   a) visual function?
   b) The size/location of a field defect measures by perimetry?

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

Since 2002, drivers with de-barring field defects have been allowed to apply to be considered as "exceptional cases". Where it is confirmed that there is no progressive element to their defect, and they have made full functional adaptation to the defect, entitlement can be restored, following completion of a satisfactory driving assessment. This concession is not offered where the cause of the defect is a condition that is considered to be progressive in behaviour. The scarring following laser treatment for diabetic retinopathy has up to now been considered to be potentially progressive. In addition there is opinion that the retinopathy itself may be progressive. Some patients and their Consultants challenge this position on the grounds that: -

(a) laser treatment arrests the progress of diabetic retinopathy and/or

(b) with modern more precise laser treatment the scarring that is produced is minimal and not prone to further progression.

(c) Perimetry is not an appropriate method of evaluating functional visual fields

A Diabetic Retinopathy Workshop is proposed for November 2005. One of the key points we need to cover at the Workshop is "the natural progression of diabetic eye disease and retinopathy specifically, with the aim of establishing whether there are parameters that can be applied to establish a stable condition.

The major issues in which DVLA needs a consensus view are the natural history and progression of DR in order to determine the frequency and nature of medical review and the most appropriate method of assessing the extent of visual field defects.

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 3 Visual Disorders – At A Glance guide to the current Medical Standards of Fitness to Drive February 2005.

(b)   Chapter 6 Visual Disorders – At A Glance guide to the current Medical Standards of Fitness to Drive February 2005.

Minutes of the Secretary of State for Transport's Honorary Medical Advisory Panel on Driving and Visual Disorders.

(c)   21 April 2005
(d)   16 December 2004
(e)   10 June 2004
(f)   2 December 2003
(g)   15 May 2003
(h)   29 January 2002
(i)   30 April 2002
(j)   24 June 2002
(k)   14 November 2002
(l)   29 October 2001
(m)   19 July 2001

Minutes of the Secretary of State for Transport's Honorary Medical Advisory Panel on Driving and Diabetes Mellitus.

(n)   9 March 2005
(o)   6 October 2004
(p)   10 March 2004
(q)   5 November 2003
(r)   5 March 2003
(s)   1 May 2002
(t)   2 October 2002
(u)   31 October 2001

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

Professor Brian M Frier (Chairman)

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Consultant Physician and Diabetologist

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Mr M H Miller (Chairman)

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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 drivers of all ages

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

A clear understanding of the natural progression of:

(a)   A visual field defect secondary to diabetic retinopathy alone

(b)   A visual field defect secondary to laser treatment of diabetic retinopathy.

This has major implications for allowing re-instatement of driving entitlement after a de-barring field defect
has developed in a driver who has had laser treatment for diabetic retinopathy.

What is the latest date that an ARIF response would be of value

14	/	10	/ 05

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: d.j.moore@bham.ac.uk

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
                   Edgbaston
                   Birmingham
                   B15 2TT

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 – Search strategies

7.2.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES
(Feb 2005)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

A. Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

B. 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.

C. NHSCRD (WW Web access)
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

D. Health Technology Assessments and evidence based guidelines(WW Web access)
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages:www.ncchta.org/nice/)
- 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)

E. Clinical Evidence

F. Bandolier

G. TRIP Database

H. Bibliographic databases

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

I. Contacts

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

7.2.2 Primary studies protocol

Search strategy: Diabetic retinopathy – prognosis and natural history of treated disease

♦ **Sources searched:**

Cochrane – CDSR, DARE, HTA, CENTRAL, NHS EED

MEDLINE (Ovid) 2005 August week 4

ARIF databases

Additional sites as listed on ARIF protocol (Clinical Evidence, Bandolier, Effectiveness Matters, NICE, NCCHTA, CRD, AHRQ, NZHTA, SBU, CCOHTA

Guidelines – National Guidelines ClearingHouse, NeLH guidelines

Extra documentation provided by DVLA

Additional internet searches - Merck Manual, GP Notebook, eMedicine, TRIP, Scottish Medicines Consortium, Health Evidence Bulletin Wales

♦ **Search Strategies:**

Search strategy used on Cochrane Library (Wiley internet version) 2005 Issue 3

Subject: Laser treatment of diabetic retinopathy

#1 (diabetic next retinopathy)
#2 DIABETIC RETINOPATHY/
#3 (#1 or #2)
#4 (laser* next treat*)
#5 LASERS/
#6 (#4 or #5)
#7 (#3 and #6)

Search Strategy used on Ovid MEDLINE(R) <1966 to August Week 3 2005 :

Subject: Prognosis of treated disease

Database: Ovid MEDLINE(R) <1966 to August Week 4 2005>
Search Strategy:

1   diabetic retinopathy.mp. or Diabetic Retinopathy/ (13644)
2   macular oedema.mp. (453)
3   maculopathy.mp. (1547)
4   ((proliferative or background) adj (retinopathy or maculopathy)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1474)
5   or/1-4 (15434)
6   laser$.mp. or LASERS/ (88675)
7   5 and 6 (1884)
8   limit 7 to "prognosis (optimized)" (190)
9   limit 7 to "prognosis (specificity)" (107)
10 from 9 keep 1-107 (107)

Subject: Diabetic retinopathy and driving

Database: Ovid MEDLINE(R) <1966 to August Week 4 2005>
Search Strategy:

1   diabetic retinopathy.mp. or Diabetic Retinopathy/ (13644)
2   macular oedema.mp. (453)
3   maculopathy.mp. (1547)
4   ((proliferative or background) adj (retinopathy or maculopathy)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1474)
5   or/1-4 (15434)

6   laser$.mp. or LASERS/ (88675)

7   5 and 6 (1884)

8   driv$.tw. (76401)

9   road$.tw. (10225)

10   or/14-15 (85078)

11   7 and 10 (19)

12   from 11 keep 6-10,12-13,16-19 (11)

Subject: Natural history of disease and treated disease

Database: Ovid MEDLINE(R) <1966 to August Week 4 2005>

Search Strategy:

1   diabetic retinopathy.mp. or Diabetic Retinopathy/ (13644)

2   macular oedema.mp. (453)

3   maculopathy.mp. (1547)

4   ((proliferative or background) adj (retinopathy or maculopathy)).mp. [mp=title, original title, abstract,
name of substance word, subject heading word] (1474)

5   or/1-4 (15434)

6   laser$.mp. or LASERS/ (88675)

7   5 and 6 (1884)

8   natural history.mp. or exp Natural History/ (20668)

9   8 and 7 (24)

10   8 and 5 (23)

11   9 or 10 (40)

12   from 11 keep 1,2,5,7,11

7.3 Appendix 3 – Classification of diabetic retinopathy

Many classification systems have been proposed to quantify the lesions seen in the diabetic eyes. No single classification system has been able to fully encompass the variation of expression of retinal lesions. Recent classification systems include VAHEX, Hammersmith grading system and the modified Airlie-House classification system. The modified Airlie-House classification system classifies the severity of lesions seen in eyes into having mild to moderate non-proliferative, moderate to severe non-proliferative, and proliferative changes. It is now the basis of most classification systems. The modified Airlie-House classification system and its possible links with severity of diabetic retinopathy and visual acuity have been put together by ourselves and are summarized in the table below.

Table of comparison of Airlie -House classification to severity states and visual acuity

Modified Airlie-House	Severity states (Harvey 2000)	Grades of severity states (Craig et al 1999)	Commonly used alternative (Liu et al. 2003)	Qualitative description (Harvey 2000)	Quantitative description (Craig et al 1999)
	No retinopathy present	1	No diabetic retinopathy	a	A
Mild to moderate non-proliferative	Non-proliferative retinopathy	2	Background diabetic retinopathy	b	B
Moderate to severe non-proliferative	Mild non-proliferative retinopathy	3	Preproliferative diabetic retinopathy	c	C
Proliferative	Active proliferative retinopathy	4	Proliferative diabetic retinopathy	d	D
	Severe visual impairment	5	Advanced diabetic eye disease	e	E

a. Microaneurysms, intraretinal haemorrhages, hard exudates, macular oedema.
b. Cotton-wool spots, venous changes, intraretinal microvascular abnormalities.
c. Neovascularisation of the disc, Neovascularisation of the retina, pre-retinal haemorrhages, vitreous haemorrhages, tractional retinal detachment, neovascularisation of iris/angle.
d. Proliferation of new, week-walled vessels.
A. Visual acuity (VA) better than 20/200, and retinopathy severity levels (RL, ranging from 10, no disease; to 85, end-stage proliferative retinopathy) RL <15
B. VA better than 20/200, and 15 <= RL <= 37
C. VA better than 20/200, and 38 <= RL <= 59
D. VA better than 20/200, and 60 <= RL <= 84
E. VA worse or equal to 20/200, or RL = 85