Guidelines for the

Management of Diabetic Retinopathy

Prepared by the Australian Diabetes Society for the Department of Health and Ageing

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The NHMRC
The National Health and Medical Research Council (NHMRC) is Australia's leading funding body for health and medical research. The NHMRC also provides the government, health professionals and the community with expert and independent advice on a range of issues that directly affect the health and well being of all Australians.

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Disclaimer
This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (up to 31 August 2007). They are not meant to be prescriptive.

These guidelines can be downloaded from the National Health and Medical Research Council website: www.nhmrc.gov.au/publications.

Foreword

The National Health & Medical Research Council developed *Clinical Practice Guidelines for the Management of Diabetic Retinopathy*, published in 1997[1]. This information has now been updated to include literature that has been published up to September 2007. The objective of these guidelines is to assist practitioners in making decisions about the appropriate health care of patients with diabetes.

Considerable evidence now shows that diabetes is becoming a more frequent problem in our community so that detecting diabetic eye disease is critically important, since there are well-developed and proven strategies to prevent visual loss.

One of the earliest randomised controlled clinical studies to show the success of a particular treatment investigated photocoagulation therapy for diabetic retinopathy. Findings from the Diabetic Retinopathy Study were reported in 1976, showing that appropriate laser treatment would dramatically reduce the risk of blindness.

Further major prospective trials have now shown that the control of diabetes, and more recently, the control of hypertension in patients with diabetes, will reduce the risk of visual loss from diabetic eye disease.

The period since 1997 has witnessed the introduction of newer modalities to investigate patients with diabetic eye disease, such as Optical Coherence Tomography and newer treatments such as intravitreal triamcinolone. A variety of agents aimed at inhibiting pathways leading to diabetic retinopathy (e.g. protein kinase C) or the induction of retinal angiogenesis (e.g. vascular endothelial growth factor) are also being evaluated in clinical trials at this time.

Each of the guidelines has been linked to measures of the quality of the evidence available on that subject.

Changes in the attitudes and practices of optometrists and ophthalmologists following the release of the 1997 *Guidelines*[1], were documented in a series of reports by the Working Group on Evaluation of NHMRC Diabetic Retinopathy Guidelines[2-5]. Although well distributed and apparently well received, there appeared to be few changes in the referral pattern by optometrists[3;4]. However, the proportion of persons with known diabetes examined with dilated fundoscopy by optometrists reportedly increased[4]. There were also few changes in ophthalmic practice documented as a result of the *Guidelines*. Some change in accordance with recommendations was apparent in the co-management of macular oedema and cataract[5] and in fluorescein angiography[3;5]. These evaluations, however, were conducted one to three years after release of the *Guidelines*. Longer-term analysis of changes in practice[6] will be important and are planned in association with these revised Guidelines.

This background research work was undertaken in Professor Paul Mitchell's University of Sydney department of ophthalmology at Westmead Hospital in Sydney. The information provided in these guidelines was submitted for public consultation and the Committee has examined all these submissions before producing the final document. The Committee feels that this is an important review of a disease becoming progressively more common, yet still a major cause of avoidable blindness and visual impairment in Australia.

Associate Professor Justin O'Day
June 2008

C. Summary of the [illegible]ies

Table 1 summarises guidelines [illegible]ined in this document. Readers should consult the relevant section of the document for further details and a presentation of the evidence for each guideline. Guidelines regarding intervention or treatment are accompanied by a Quality of Evidence rating (Levels I-IV). A Level I rating indicates that the guideline is based on the highest quality evidence, whereas a Level III or IV rating indicates that the statement or recommendation is based on lower quality evidence.

Table I: Summary of guidelines for the management of diabetic retinopathy with level I to IV evidence

Guidelines	*Evidence Level*
I. Diabetes and diabetic retinopathy	
1. Undertake a multidisciplinary approach in all patients with diabetes to achieve optimal glycaemic control (target HbA_{1c} levels 7.0% or lower) and to adequately manage blood pressure (target systolic blood pressure less than 130 mmHg) and serum lipids (target LDL cholesterol of less than 2.5 mmol/L and a target triglycerides of less than 2.0 mmol/L).	**I (glycaemic control)[13;14]; II (blood pressure control)[14-16]; II (blood lipid control)[17-19]**
II. Screening for diabetic retinopathy	
2. Ophthalmologists, optometrists and other trained medical examiners should use dilated ophthalmoscopy or slit lamp biomicroscopy with a suitable lens (e.g. 78 D), to detect presence and severity of DR and DME, with adequate sensitivity and specificity.	**Systematic review of diagnostic accuracy studies[20] (dilated ophthalmoscopy) and individual diagnostic accuracy study (slit lamp biomicroscopy)[21]**
3. In the absence of a dilated fundus examination by a trained examiner, use non-mydriatic (or mydriatic) photography with adequate sensitivity, specificity and low technical failure rate to detect presence of DR.	**Systematic review of diagnostic accuracy studies[20] and individual diagnostic accuracy studies[22-26]**
4. Ensure that all people with diabetes have a dilated fundus examination and visual acuity assessment at the diagnosis of diabetes and at least every 2 years.	**I[14;27]**
5. Screen children with pre-pubertal diabetes for DR at puberty.	**IV[27]**
6. Examine higher-risk patients (longer duration of diabetes, poor glycaemic control, blood pressure or blood lipid control) without DR at least annually.	**I[14]**
7. Examine patients with any signs of NPDR annually or at 3- to 6-monthly intervals, depending on the DR level.	**IV[27]**
8. Refer to an ophthalmologist urgently (within 4 weeks) if there is any	**IV[27;28]**

unexplained fall in visual acuity, or if there is any suspicion of DME or PDR.	
9. All cases of mild or moderate NPDR, should be followed closely to detect signs of sight-threatening retinopathy.	IV[29;30]
10. Conduct comprehensive eye examinations on pregnant women with diabetes during the 1st trimester and follow women with DR throughout their pregnancy.	IV[31]
11. Women with gestational diabetes do not need ophthalmic surveillance after delivery, unless diabetes persists.	IV[31]
12. Perform FA if diffuse DME is present, and use the angiogram to identify sources of perimacular leakage and non-perfusion, to guide focal and grid laser treatment.	II[32-34]
13. Use FA to assess signs of likely macular ischaemia.	II[35;36]
III. Management of diabetic retinopathy	
Laser treatment	
14. For high-risk PDR, perform PRP as soon as possible.	II[37]
15. For earlier PDR stages, commence PRP after any maculopathy is stabilised	II[37]
16. Consider PRP for severe NPDR, particularly if there is T2DM, poor follow-up compliance, impending cataract surgery, renal disease, pregnancy, severe disease in the fellow eye or evidence of retinopathy progression.	II[38]
17. For less severe retinopathy, balance benefits of laser against the small risk of damage to vision from laser treatment.	II[37]
18. For all eyes with CSME, apply standard focal/grid macular laser treatment to areas of focal leak and capillary non-perfusion.	II[37;39]
19. For DME not meeting CSME criteria, consider either laser treatment or deferral, depending upon progression of signs, the status of the fellow eye, or ability to follow closely, and warn patients of potential risks.	II[37;39]
20. For eyes with both PDR and CSME, but without high-risk PDR, delay PRP until focal or grid macular laser treatment is completed.	II[37;39]
21. Review patients closely after completion of laser treatment. If high-risk characteristics do not regress or re-develop, perform additional laser treatment.	II[37]
22. Warn patients about the adverse effects of laser treatment.	II[37;39]
Vitrectomy	
23. Consider vitrectomy within 3 months for T1DM patients with severe vitreous haemorrhage in eyes suspected to have very severe PDR.	II[40-42]
24. Also consider early vitrectomy for eyes with severe PDR, not responding to aggressive and extensive PRP.	II[40;42]
25. Consider vitrectomy to relieve macular or other retinal traction in	IV[42-44]

advanced PDR cases, in an attempt to salvage some vision. Such cases, if left untreated, will mostly develop severe visual loss or blindness.	
26. Consider vitrectomy in eyes with chronic or diffuse DME that is non-responsive to laser treatment, or if related to vitreomacular traction.	III-1[45-48]
27. Warn patients about the adverse effects of vitrectomy surgery.	II[40;49]
Medical and Ancillary Therapies	
28. Strive to achieve optimal glycaemic control (HbA_{1c} levels less than 7%) in all patients with diabetes in order to reduce the development and progression of DR	I[13;14]
29. Consider adjunctive blood-pressure-lowering therapy in patients with DR. Any lowering of systolic and or diastolic blood pressure is beneficial. In patients with DR, aim to keep systolic BP <130 mm Hg.	I[50-53]
30. Consider lowering blood lipids to reduce diabetes macrovascular complications and to reduce progression of DME.	II[18;54]
31. Consider lowering blood lipids in patients with extensive hard exudate deposition.	III-3[55-57]
32. Consider using intravitreal triamcinolone (IVTA) for DME that persists after focal/grid laser treatment.	II[58]
33. Also consider IVTA for cases of extensive macular hard exudate deposition, or as an adjunct to PRP for PDR.	III-3[59-64]
34. Warn patients having IVTA about the high incidence of secondary intraocular pressure rise, development of posterior subcapsular cataract, risk of intraocular infection, and the need for treatment of these adverse effects, as well as recurrence of the DME.	II[58]
Management of Cataract	
35. Carefully assess DR in patients with significant cataract. Attempt to treat any DME with focal/grid laser, before cataract surgery, if possible.	III-3[65]
36. Once DR is stable, consider cataract surgery to improve vision in diabetic patients. If cataract is moderate to advanced, consider surgery to adequately assess need for laser or to permit laser.	IV[66-68]
Special Groups	
37. Conduct annual screening for Aboriginal or Torres Strait Islander groups with diabetes.	IV[69]

Table II: Summary of consensus good practice points for the management of diabetic retinopathy

Good Practice points	
II	**Screening for diabetic retinopathy**
1.	Always assess visual acuity at the time of DR screening
2.	Apply DR severity scales to determine need for referral, follow-up and treatment.
3.	Use FA in selected patients with PDR, or after PRP therapy for PDR to assess response
III	**Management of diabetic retinopathy**
Laser treatment	
1.	Complete as much PRP as possible before considering vitrectomy surgery, in order to minimise post-operative complications.
Vitrectomy	
2.	Use OCT to confirm the presence and severity of DME and to monitor its response to treatment.
Management of Cataract	
3.	Consider delaying cataract surgery until DR and DME signs are stabilised
IV	**Costs and co-ordinated care for diabetic retinopathy**
7.	Screen for DR as part of the systematic and integrated care of people with diabetes, where possible.

Table III: Summary of key points in the management of diabetic retinopathy

Diabetes

- There are two common types of diabetes, type 1 (T1DM) and type 2 (T2DM) with some overlap in age at onset, together with intermediate forms.

Epidemiology and Trends for Diabetes in Australia and Worldwide

- The global prevalence of diabetes among adults aged ≥ 20 years was estimated in 2000 to be around 171 million (2.8% of the world's population), and is expected to rise to 366 million (4.4% of the estimated world population) by the year 2030.
- Asia is expected to be home to 61% of the total global projected number of people with diabetes by 2010, not only because it is the most populous continent on earth, but also because of increased urbanisation and improved life expectancy. India, China and the U.S.A. are expected to have the highest numbers of people with diabetes in 2030.
- In 2002, the AusDiab group reported a diabetes prevalence of 8.0% in adult men and 6.8% in adult women from an Australian nationwide cross-sectional survey. These data reveal that the prevalence of diabetes has more than doubled since 1981. An additional 16% of adults had impaired glucose tolerance or impaired fasting glucose.
- Diabetes is around twice as prevalent in Aboriginal as in non-Aboriginal Australians. One report indicated that the prevalence of diabetes in the Aboriginal population increased from 12% to 21% between 1983 and 1997.

Diabetic Retinopathy, Definition and Types

- Diabetic retinopathy (DR) is defined as the presence of typical microvascular signs in a person with diabetes; these signs are non-specific and may also be seen frequently in people without diabetes.
- DR is categorised as 'non-proliferative' (NPDR) or 'proliferative' (PDR). The latter stage is associated with a high risk of visual loss. Diabetic macular oedema (DME) represents thickening near the foveal area, can occur in either stage and is a very frequent cause of impaired vision.

Prevalence and Incidence of Diabetic Retinopathy in Australia and Worldwide

- Overall, between 25 and 44% of people with diabetes have some form of DR at any point in time. A recent large meta-analysis pooling data from 8 population-based studies of older groups reported an overall DR prevalence of 40%. The prevalence of sight-threatening retinopathy (PDR or CSME) varies principally with the known duration of diabetes, with some influences from age and type of diabetes.
- Projections from these data indicate that around 300,000 Australians have some DR and that 65,000 have sight-threatening retinopathy (PDR or CSME).
- From earlier reports from the WESDR study to more recent reports from the UKPDS, Liverpool DR Study, and the BMES, the prevalence and incidence of DR appear to have decreased.
- The most recent Australian DR prevalence data derive from the AusDiab Study, which found an overall DR prevalence of 25.4%, with PDR in 2.1%.
- Few Australian DR incidence data are available, with recent (2004) annual incidence lower at 4.5% in the BMES compared to 8.0% in the 1985 Newcastle study.
- Typical retinopathy lesions are also found in older persons without diabetes (possibly due to hypertension and other conditions), with the prevalence varying from 7.8% (BDES) to 9.8% (BMES).

Pathogenesis of Diabetic Retinopathy

- Many biochemical pathways link the altered glucose metabolism seen in diabetes directly to development and progression of DR.
- DR has a multifactorial pathogenesis, involving many pathways linked to glycaemia (aldose reductase, protein glycation, protein kinase C activation, angiotensin enzyme expression, vascular endothelial growth factor expression, and others). New therapies may target these pathways.
- These biochemical changes are accompanied by increased blood retinal barrier permeability and initially by increases in retinal blood flow.
- Widened venular calibre is a marker of retinopathy severity.

Risk Factors associated with Diabetic Retinopathy

- All people with diabetes are at risk of developing retinopathy.
- Duration of diabetes is the strongest factor determining DR prevalence.
- The most important systemic factors associated with increased risk of DR are:
- Other documented risk factors include:
  - Glycaemic control – evidence from RCT (DCCT, UKPDS) and large cohort studies (WESDR); any lowering of HbA1c will assist in reducing the development and progression of DR. For patients with DR, the target for HbA1c levels should be 7.0% or lower.
  - Blood pressure – evidence from RCT (UKPDS) and cohort studies (WESDR); any lowering of blood pressure will assist in reducing the development and progression of DR. For patients with DR, the target for systolic blood pressure should be less than 130 mmHg.
  - Blood lipids – evidence from both RCT (ETDRS) and cohort studies (WESDR). Normalising blood lipid levels may reduce cardiovascular risk and also DR, particularly DME.
- The DR risk associated with hyperglycaemia and hypertension is continuous, with no evident glycaemic or blood pressure threshold.
- Other documented risk factors include:
  - Renal impairment
  - Pregnancy
- Candidate genes (ALR2, RAGE, TGF-beta1, VEGF, eNOS, MTHFR, IGF-1 and vitamin D receptor genes) – evidence from case-control studies.

Grading of Diabetic Retinopathy

- The modified Airlie House classification (Wisconsin system) has become the basis for detailed grading of DR and was used in all the major studies of risk factors and trials of laser and other treatments, including the DCCT, UKPDS, DRS and ETDRS studies. It was based on grading seven 30° stereoscopic fields. Newer cameras now mostly utilise wider fields, so that two- to four-field photography is likely to be sufficient to document DR in current clinical practice.
- The ETDRS study quantified the risk of retinopathy progression associated with the severity of individual lesions from masked photographic grading.
- The presence of IRMA, H/Ma and VB were strong predictors of progression from NPDR to PDR.
- The ETDRS classified DR into the following categories: None, Minimal NPDR, Mild NPDR, Moderate NPDR, Severe NPDR, PDR, High-Risk PDR.
- The International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale proposes five levels for grading of DR, based on risk of progression: None, Mild NPDR, Moderate NPDR, Severe NPDR or PDR. Presence and severity of DME is classified separately. The World Health Organisation grading system stresses referral urgency: STR

requiring immediate referral, lesions needing referral as soon as possible, and lesions that could be reviewed in a few months.

- It is important to detect DME in the assessment of DR, as this is the most frequent cause of decreased vision from retinopathy. Both macular oedema (ME) and clinically significant macular oedema (CSME), defined by proximity of these signs to the foveal centre, are best assessed using slit lamp biomicroscopy or by grading stereoscopic macular photographs.
- Optical coherence tomography may be also used to provide valuable confirmation and quantification of the clinical grading for DME.

Examinations, Sensitivity and Specificity in Detecting Diabetic Retinopathy

- Stereoscopic seven-field fundus photography by a trained grader is the gold standard method of detecting DR. It is mainly a research tool and is rarely performed in routine practice.
- Clinical examinations to detect DR may use slit lamp biomicroscopy, ophthalmoscopy or retinal photography. Pupils should normally be dilated. An exception is non-mydriatic photography with adequate photographic quality and sensitivity.
- Dilated slit lamp biomicroscopy is used in routine clinical practice to assess the presence and severity of DR.
- The level of sensitivity needed by the examination or screening test cannot be defined unequivocally. Screening examinations or tests should aim for a sensitivity of at least 60% (as defined in earlier studies), though higher levels are usually achievable. It is considered that mild DR missed at one visit would likely be detected at the next. Specificity levels of 90-95% and technical failure rates of 5-10% are considered appropriate for both measures.
- Dilated direct or indirect ophthalmoscopy by ophthalmologists, optometrists, or other trained medical examiners, or fundus photography by trained personnel, generally meet screening sensitivity guidelines.
- Clinical assessments to screen for DR should include measurement of visual acuity and a dilated fundus examination. Examiners need adequate sensitivity and specificity in performing assessments. Alternately, retinal photographic screening (which may be non-mydriatic) with adequate sensitivity should be performed. Technical failure, however, should prompt a referral for clinical assessment.
- Non-mydriatic digital retinal photography is increasingly used in screening DR. Its usefulness may be limited by reduced sensitivity for screening and detecting DR and by technical failure with ungradeable photographs caused by small pupils and media opacities. Adequate training of staff is very important. DME may be difficult to detect using this method when few exudates are present.
- Patients should be referred promptly for dilated fundus examination if non-mydriatic photographs cannot be graded.
- Digital photography has allowed screening services to reach rural and remote areas via tele-ophthalmology.
- People with diabetes present to a variety of examiners, including general practitioners, general physicians, endocrinologists, optometrists and ophthalmologists. All are potentially able to screen for DR.

Safety of Pupil Dilation

- Pupil dilation using 0.5 to 1.0% tropicamide is safe and markedly increases the sensitivity of DR screening, so should be considered mandatory in performing ophthalmoscopy or slit lamp biomicroscopy.
- Two large Australian population studies (MVIP and BMES) showed high levels of patient acceptance for pupil dilation. These and other population studies have also confirmed the safety of pupil dilation.
- Although practitioners should be aware of the potential to induce acute angle closure glaucoma from use of mydriatic drops, its incidence is rare (1 to 6 per 20,000 people) and

tropicamide alone has not been reported to cause this.

Frequency of Examinations and Referral

- A large, multicentre RCT has shown that timely laser treatment will prevent vision loss from PDR and DME.
- Early detection of sight-threatening retinopathy by regular eye exams is the key to reducing visual loss and blindness from DR.
- Persons with diabetes should have a dilated fundus examination by a trained examiner, with adequate sensitivity and specificity, at the time of diagnosis of diabetes and at least every two years thereafter, if no DR is found.
- Alternately, retinal photographic screening, that may be non-mydriatic, with adequate sensitivity, should be performed. Technical failure should prompt referral for a dilated fundus examination.
- Once DR is detected, further examinations should be conducted annually or at 3-12 monthly intervals depending on the level of DR. Any visual symptoms should prompt a further referral.
- It is important to measure the visual acuity of both eyes, at the time of DR screening.
- Children with pre-pubertal diabetes onset should be screened at puberty, unless other considerations indicate the need for an earlier examination.
- Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and, if DR is found, they need close follow-up throughout pregnancy. This does not apply to women who develop gestational diabetes.
- Referral to an ophthalmologist should be urgent (within 4 weeks) if DME or PDR is suspected or if an unexplained fall in visual acuity is recorded.

Role of Fluorescein Angiography in Assessing Diabetic Retinopathy

- Fluorescein angiography (FA) is not appropriate to screen for DR.
- Routine use of FA should be guided by clinical experience, as there is little evidence to provide firm guidelines.
- The presence of CSME is the principal justification for FA in DR patients. It may not be needed to guide treatment if DME is occurring from a well-defined ring of hard exudates or from focal maculopathy. Nevertheless, FA should be performed whenever diffuse macular oedema is present, in order best to identify sources of perimacular leakage and non-perfusion, guiding focal and grid laser treatment.
- FA can determine presence of macular ischaemia.
- FA may be warranted in selected cases of severe NPDR to assess severity of retinal ischaemia, to detect subtle NVE or in assessing patients with PDR before PRP. It may also be warranted in certain cases to determine adequate regression of DR after laser treatment.
- FA has a small risk of significant side effects. Frequent adverse reactions include mild transient reactions that require no medical management such as nausea (5-10%), vomiting (1.3%), dizziness (0.6%), and itching (0.5%). Moderate adverse reactions, defined as transient but requiring some medical intervention, include urticaria, syncope, thrombophlebitis or local tissue necrosis from extravasation of injected fluorescein and occur rarely. Severe adverse reactions, such as anaphylaxis or cardiac arrest, were reported in 1:20,000 FA procedures. Deaths occurred in 1:50,000-200,000 FA procedures. A number of FA-related deaths have been reported in Australia.
- It is important to have resuscitation equipment and medications readily available wherever FA is performed.

New Modalities to Assess the Severity of Diabetic Retinopathy

- Ophthalmoscopy, slit lamp biomicroscopy, fundus photography and fluorescein angiography (FA) have traditionally been used to assess the severity of DR.
- Optical Coherence Tomography (OCT) provides an effective qualitative and quantitative method of examining the eye, particularly in detecting early macular thickening, and also in following progression or regression of macular oedema over the course of treatment. OCT has good reproducibility and accuracy for the measurement of retinal thickness with an axial resolution in the order of 10μm or better with newer instruments. OCT also correlates reasonably with both biomicroscopic examination and FA in CSME.
- Heidelberg Retinal Tomography (HRT) and the Retinal Thickness Analyzer (RTA) are two other modalities that have the potential to provide an indirect measure of retinal thickness in order to quantify diabetic macular oedema. Both techniques have acceptable reproducibility and an axial resolution of around 150μm and 50μm respectively.
- All three new imaging modalities are disadvantaged by image degradation from ocular media opacities such as significant cataract (particularly posterior subcapsular or cortical cataracts, the types seen in diabetes) or vitreous haemorrhage, and by difficulties with small pupils and the relatively high cost of the currently available equipment. To date, all have been assessed only in case series.
- The electroretinogram (ERG) may possibly detect abnormalities at the retinal level before overt DR is evident. As with other imaging instruments, severe media opacities can also interfere with some standard ERG measures, although bright-flash ERG techniques can overcome this to some extent.

Laser Treatment (Photocoagulation) for Diabetic Retinopathy

- Multiple RCT, including the DRS and ETDRS, have shown that panretinal photocoagulation (PRP) significantly reduces the risk of severe vision loss (best corrected visual acuity <5/200) from PDR by at least 50%, and that focal or grid laser photocoagulation reduces the risk of moderate vision loss (doubling of the visual angle) from CSME by at least 50%.
- Recommendations of the type and pattern of laser photocoagulation have not changed since the ETDRS reported guidelines in 1987:
  - Apply PRP using 200- to 500-micron burns placed approximately one-half burn width apart, from the posterior fundus to the equator.
  - Apply focal laser photocoagulation using 100-micron laser burns to areas of focal leakage (i.e. leaking microaneurysms) and areas of capillary non-perfusion in the peri-macular region.
  - Apply grid laser photocoagulation using 50-100 micron burns in a grid pattern to areas of diffuse leakage and non-perfusion at the macula.
  - Although treatment is ideally guided by fluorescein angiography, this may not be needed to treat many cases with focal DME. Treatment is unlikely to be beneficial in the presence of significant macular ischaemia.
- ETDRS results were achieved by rigorous application of laser recommendations and close follow-up with re-treatment, as needed.
- Mild, diffuse macular grid laser was shown to have no benefit over routine focal/grid laser, reducing DME and OCT macular thickness less than standard treatment, so is not recommended.
- The following timing of laser treatment is recommended:
  - Patients should be seen at follow-up visits every 1-4 weeks during the course of PRP and then every 2-4 months thereafter until stable.
  - Follow-up of patients with DME should also occur every 2-4 months until stable.

Role of Vitrectomy in Managing Diabetic Retinopathy

- The Diabetic Retinopathy Vitrectomy Study (DRVS) was a multi-centre RCT that evaluated indications and timing of pars plana vitrectomy for management of advanced DR.
- The indications and rationale for vitrectomy established by the DRVS still guide therapy, but the thresholds for performing surgery are lower as a consequence of improved surgical results, improvements in vitreoretinal instrumentation and technique, and the introduction of ancillary modalities or modified techniques.
- Early vitrectomy for treatment of vitreous haemorrhage secondary to DR was found highly cost-effective in a cost-utility analysis using DRVS results.
- The benefits of early vitrectomy for non-resolving severe vitreous haemorrhage were less for type 2 diabetes.
- Vitrectomy was found in small RCT to benefit chronic or diffuse DME.
- OCT is valuable to confirm and quantify DME, and to confirm traction and its response to surgery.
- Vitrectomy, possibly combined with inner limiting membrane peeling, in selected eyes with thickened or taut posterior hyaloid has been found to facilitate more rapid resolution of DME and improvement in visual acuity.
- Combined cataract surgery (phacoemulsification and insertion of a posterior chamber intraocular lens) with vitrectomy has been shown to result in earlier visual rehabilitation by avoiding need for later cataract surgery.
- Complications from vitrectomy include recurrent vitreous haemorrhage, endophthalmitis, glaucoma, retinal tear or detachment, rubeosis iridis, and premature development of cataract.

Medical Therapies for Diabetic Retinopathy

- Trials of blood-pressure-lowering therapy in diabetes suggest the importance of hypertension/ blood pressure as a major modifiable risk factor for DR. It is unclear from the trials whether a threshold exists beyond which further lowering of blood pressure no longer influences DR progression.
- Benefits on DR may also be seen from the use of anti-hypertensive agents in people with diabetes and normal blood pressure levels.
- The renin-angiotensin system and angiotensin converting enzyme (ACE) are expressed in the eye, may independently affect VEGF expression, and are involved in the pathogenesis of DR. ACE inhibitors, used in managing blood pressure, have been evaluated for effects on DR.
- Lisinopril was shown to reduce DR progression in a 2-year RCT (Level II evidence). Other larger trials are ongoing. The UKPDS, however, did not find an ACE inhibitor superior to a beta blocker in its effect on DR. Blood pressure reduction alone may be the important parameter in determining progression of DR.
- Disordered blood lipids may increase the risk of macular hard exudate deposition and CSME. Fenofibrate reduced the need for laser treatment in a large diabetes cardiovascular trial. Studies to date suggest a potential role for fibrates or statins in managing DR, particularly in patients with extensive hard exudate deposition.
- ETDRS data showed that aspirin did not increase the risk of vitreous haemorrhage or exacerbate the severity or duration of vitreous or preretinal haemorrhage.
- Protein kinase C (PKC) plays a major role in hyperglycaemia-induced microvascular dysfunction in diabetes and DR. One PKC inhibitor, ruboxistaurin, has been the subject of 3 large RCT. Two trials showed benefit in reducing risk of moderate visual loss, but not on progression of DR or progression to DME. The third trial failed to demonstrate a reduced need for laser with this drug. Further trials are ongoing. Overall, there is insufficient evidence to recommend use of ruboxistaurin.
- A pathogenic role for aldose reductase in DR is likely. However, trials of aldose reductase inhibitors (ARIs) to reduce severity or progression of retinopathy have not shown benefit and have been limited by toxicity of the agents tested.

- Elevated growth hormone levels have been associated with accelerated DR. A small trial of a somatostatin analogue (Octreotide) compared to conventional therapy showed a reduced need for PRP laser and progression. Use of this therapy may be limited by its high maintenance cost.
- A pathogenic role for advanced glycation end-products (AGEs) in DR is likely. AGE inhibitors such as aminoguanidine are currently being evaluated in trials.
- Human trials have shown benefits from use of steroid agents in treating DME. Because of the transience of most steroid agents (e.g. cortisone), depot steroid agents such as triamcinolone, have been used.
- Intravitreal triamcinolone (IVTA) is widely used in managing DME that persists despite focal/ grid laser treatment. A small 2-year Australian RCT demonstrated benefit from IVTA on OCT macular thickness and visual acuity . Repeated injections are frequently needed, at around 6-monthly intervals.
- IVTA may also be used in treating patients with massive hard exudates deposition or as an adjunct to PRP for PDR.
- Frequent adverse ocular effects from IVTA include elevated intraocular pressure and glaucoma and development of posterior subcapsular cataract, often needing surgery.
- Unresolved issues include the ideal triamcinolone dosage, need for additional post-IVTA focal/grid laser, duration of repeat therapy, and concerns regarding the formulation in current use.
- Anti-Vascular Endothelial Growth Factor (VEGF) drugs, administered by repeat intravitreal injection, offer great promise in managing both PDR (including iris new vessels) and DME. Their use is accompanied by acceptably low rates of serious adverse ocular effects (less than from IVTA). Repeated applications are needed, and their long-term safety is not known.
- For PDR, anti-VEGF agents (particularly bevacizumab) are currently widely used as an adjunct to laser treatment and prior to vitrectomy surgery. For these two indications, RCT evidence is lacking. For DME, there is accumulating RCT evidence of benefit.
  - Pegaptanib (Macugen) has been shown to reduce OCT macular thickness and visual loss due to DME.
  - Bevacizumab (Avastin) is currently the most widely used anti-VEGF agent for DR; it reduces OCT macular thickness, and PDR activity and severity, and improves visual acuity. There are unresolved concerns regarding its systemic safety.
  - Ranibizumab (Lucentis) may have similar effects
- Ovine hyaluronidase (Vitrase) has been shown to accelerate the clearing of vitreous haemorrhage in PDR.

Management of Cataract

- Diabetes is associated with an increased risk of both cataract (particularly cortical and posterior subcapsular cataract) and cataract surgery.
- Vitrectomy in diabetic patients is associated with earlier onset of cataract and need for cataract surgery.
- Cataract surgery may be needed to adequately assess need for laser and to permit laser treatment to be completed.
- Cataract surgery may also lead to substantial visual improvements in diabetic patients.
- The visual outcome after cataract surgery in people with diabetes depends on the severity of pre-operative DR and presence of DME. Asymmetric retinopathy progression can occur in the operated eye, and the risk of rubeosis iridis or neovascular glaucoma increases after cataract surgery.
- Pre-operative DME and active PDR are strong predictors of a poor visual result.
- Although modern cataract surgical techniques show consistently improved visual outcomes in diabetic patients, a systematic review of case series and clinical trials consistently demonstrated worse visual results from cataract surgery in persons with than without DR.