Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation

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This report

Abstract

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Background: Diabetic retinopathy is an important cause of visual loss. Laser photocoagulation preserves vision in diabetic retinopathy but is currently used at the stage of proliferative diabetic retinopathy (PDR).

Objectives: The primary aim was to assess the clinical effectiveness and cost-effectiveness of pan-retinal photocoagulation (PRP) given at the non-proliferative stage of diabetic retinopathy (NPDR) compared with waiting until the high-risk PDR (HR-PDR) stage was reached. There have been recent advances in laser photocoagulation techniques, and in the use of laser treatments combined with anti-vascular endothelial growth factor (VEGF) drugs or injected steroids. Our secondary questions were: (1) If PRP were to be used in NPDR, which form of laser treatment should be used? and (2) Is adjuvant therapy with intravitreal drugs clinically effective and cost-effective in PRP?

Eligibility criteria: Randomised controlled trials (RCTs) for efficacy but other designs also used.

Data sources: MEDLINE and EMBASE to February 2014, Web of Science.

Review methods: Systematic review and economic modelling.

Results: The Early Treatment Diabetic Retinopathy Study (ETDRS), published in 1991, was the only trial designed to determine the best time to initiate PRP. It randomised one eye of 3711 patients with mild-to-severe NPDR or early PDR to early photocoagulation, and the other to deferral of PRP until HR-PDR developed. The risk of severe visual loss after 5 years for eyes assigned to PRP for NPDR or early PDR compared with deferral of PRP was reduced by 23% (relative risk 0.77, 99% confidence interval 0.56 to 1.06). However, the ETDRS did not provide results separately for NPDR and early PDR. In economic modelling, the base case found that early PRP could be more effective and less costly than deferred PRP. Sensitivity analyses gave similar results, with early PRP continuing to dominate or having low incremental cost-effectiveness ratio. However, there are substantial uncertainties. For our secondary aims we found 12 trials of lasers in DR, with 982 patients in total, ranging from 40 to 150. Most were in PDR but five included some patients with severe NPDR. Three compared multi-spot pattern lasers against argon laser. RCTs comparing laser applied in a lighter manner (less-intensive burns) with conventional methods (more intense burns) reported little difference in efficacy but fewer adverse effects. One RCT suggested that selective laser treatment targeting only ischaemic areas was effective. Observational studies showed that the most important adverse effect of PRP was macular oedema (MO), which can cause visual impairment, usually temporary. Ten trials of laser and anti-VEGF or steroid drug combinations were consistent in reporting a reduction in risk of PRP-induced MO.

Limitation: The current evidence is insufficient to recommend PRP for severe NPDR.

Conclusions: There is, as yet, no convincing evidence that modern laser systems are more effective than the argon laser used in ETDRS, but they appear to have fewer adverse effects. We recommend a trial of PRP for severe NPDR and early PDR compared with deferring PRP till the HR-PDR stage. The trial would use modern laser technologies, and investigate the value adjuvant prophylactic anti-VEGF or steroid drugs.

Study registration: This study is registered as PROSPERO CRD42013005408.

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List of abbreviations

AAO	American Academy of Ophthalmology	DRS	Diabetic Retinopathy Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes	DTSQ	Diabetes Treatment Satisfaction Questionnaire
AMD	age-related macular degeneration	DVLA	Driver and Vehicle Licensing Agency
ARVO	Association for Research in Vision and Ophthalmology	EDIC	Epidemiology of Diabetes Interventions and Complications
BCVA	best corrected visual acuity	EME	Efficacy and Mechanism Evaluation
BP	blood pressure	EQ-5D	European Quality of Life-5 Dimensions
BSE	better-seeing eye		
CARDS	Collaborative Atorvastatin Diabetes Study	ETDRS	Early Treatment Diabetic Retinopathy Study
CD	choroidal detachment	FA	fluorescein angiography
CEAC	cost-effectiveness acceptability curve	FA-LTE	Family Apgar-List of Threatening Experiences
CHEERS	Consolidated Health Economic Evaluation Reporting Standards	FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
CI	confidence interval	FLA	fluorescein leakage
CMT	central macular thickness	GLX	solid-state green laser
COS	Canadian Ophthalmological Society	HADS	Hospital Anxiety and Depression Scale
CPRP	central classical pan-retinal photocoagulation	HbA_{1c}	glycated haemoglobin
CRVO	central retinal vein occlusion	HR-PDR	high-risk proliferative diabetic retinopathy
CSII	continuous subcutaneous insulin infusion	HRC	high-risk characteristic
CSMO	clinically significant macular oedema	HRC-PDR	high-risk characteristics proliferative diabetic retinopathy
DCCT	Diabetes Control and Complications Trial	HRQoL	health-related quality of life
DCE	discrete choice experiment	HTA	Health Technology Assessment
DD	disc diameter	HTN	hypertension
DMO	diabetic macular oedema	HUI	Health Utilities Index
DPSS	diode-pumped solid state	ICER	incremental cost-effectiveness ratio
DR	diabetic retinopathy	IOP	intraocular pressure
DRCRN	Diabetic Retinopathy Clinical Research Network	IOVS	*Investigative Ophthalmology & Visual Science*

IRMA	intraretinal microvascular abnormality
IVB	intravitreal bevacizumab
IVR	intravitreal ranibizumab
IVTA	intravitreal triamcinolone acetonide
MAPASS	MAnchester PSC Study
mETDRS	modified ETDRS
MO	macular oedema
MPC	macular photocoagulation
MS-PRP	multiple-session pan-retinal photocoagulation
MT-PRP	minimally traumatic pan-retinal photocoagulation
NDRLTA	National Diabetic Retinopathy Laser Treatment Audit
Nd:YAG	neodymium-doped yttrium aluminium garnet
NEI	National Eye Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnnaire-25
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NPA	non-perfused area
NPDR	non-proliferative diabetic retinopathy
NPS	numerical pain score
NSC	National Screening Committee
NV	neovascular
NVD	neovascularisation of the disc
NVE	neovascularisation of the retina elsewhere (outside the disc)
NVG	neovascular glaucoma
NVI	neovascularisation of the iris
OCT	optical coherence tomography

ONS	Office for National Statistics
PASCAL	PAtterned SCAnning Laser
PDR	proliferative diabetic retinopathy
PPDR	pre-proliferative diabetic retinopathy
PPV	pars plana vitrectomy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	pan-retinal photocoagulation (also sometimes called 'scatter photocoagulation')
PSC	pattern scan
PSS	Personal Social Services
PSTA	posterior sub-Tenon's triamcinolone injection
QALY	quality-adjusted life-year
QoL	quality of life
QWB	quality of well-being
RCOphth	Royal College of Ophthalmologists
RCT	randomised controlled trial
RR	relative risk
S-PC	selective photocoagulation
SAH10A	Standard Airlie House photograph 10A
SBP	systolic blood pressure
SD	standard deviation
SDM	sub-threshold diode micropulse laser photocoagulation
SDRGS	Scottish Diabetic Retinopathy Grading Scheme
SEM	standard error of mean
SF	short form
SF-6D	Short Form questionnaire-6 Dimensions
SG	standard gamble
SI-PRP	standard intensity pan-retinal photocoagulation

SIGN	Scottish Intercollegiate Guidelines Network	VA	visual acuity
SS-PRP	single-session pan-retinal photocoagulation	VAS	visual analogue scale
		VEGF	vascular endothelial growth factor
STAI	State–Trait Anxiety Inventory	VF	visual field
STDR	sight-threatening diabetic retinopathy	VFQ	Visual Function Questionnaire
		VisQoL	Vision and Quality of Life
SVL	severe visual loss	WDRS	Wisconsin Diabetes Registry Study
SVLV	severe visual loss or vitrectomy	WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
TA	triamcinolone acetonide		
TMV	total macular volume	WF-FA	wide-field Optos FA
TRP	targeted retinal photocoagulation	WHO	World Health Organization
TTO	time trade-off	WSE	worse-seeing eye
UKPDS	United Kingdom Prospective Diabetes Study	WTP	willingness to pay

Plain English summary

Diabetes is the leading cause of blindness in adults of working age.

Diabetic eye disease is called retinopathy. It can go through different stages to the sight-threatening stage known as proliferative diabetic retinopathy (PDR).

Proliferative diabetic retinopathy is treated by laser to preserve vision, once the retinopathy reaches an advanced PDR stage.

The question for this review is whether laser treatment at an earlier stage of retinopathy would be better than waiting until high-risk PDR develops. There are side events associated with laser treatment. These must be balanced against any benefits of treating earlier stages where the risks of blindness are lower.

Most of the evidence on treating at earlier stages comes from trials done in the 1980s using older lasers and does not provide enough evidence to recommend earlier treatment.

Treatment with newer laser machines may be as effective but safer and cause less discomfort. Side effects may be reduced by drugs injected into the eye. There are now better methods of monitoring treatment. These factors may support laser treatment at an earlier stage. That could be cost-effective compared to delaying treatment, but considerable uncertainties remain. We think that there should be a high-quality trial of laser treatment at an earlier stage, before high-risk PDR develops. The trial would include the use of modern lasers and drug treatment in the eye to reduce harm from pan-retinal photocoagulation.

Scientific summary

Background

The commissioning brief asked:

What is the clinical effectiveness and cost-effectiveness of pan-retinal laser treatment in the management of non-proliferative (pre-proliferative) diabetic retinopathy (NPDR)?

A review of clinical guidelines showed that treatment at the NPDR stage is currently either not recommended or recommended only in certain circumstances.

Decision problem

With the agreement of the Health Technology Assessment (HTA) programme, we extended the question in the commissioning brief in two ways. Firstly, there have been developments in methods of laser photocoagulation. So if the evidence supported pan-retinal photocoagulation (PRP) at the NPDR stage, one question would be which form of laser treatment would be used. Secondly, there have been advances in drug treatment with the arrival of the anti-vascular endothelial growth factor (VEGF) drugs. Our scoping searches showed that they were being used in combination with laser treatment to reduce adverse effects, and so we include a review of such combinations.

So the decision problem becomes:

- Would it be worthwhile to intervene with PRP earlier in diabetic retinopathy (DR), at the severe NPDR stage, rather than wait till the high-risk proliferative diabetic retinopathy (HR-PDR) stage? Treating at early PDR stage would be another option.
- If so, what form of laser treatment should be used?
- Are drug–PRP combinations clinically effective and cost-effective?

Note that the review is not concerned with the effectiveness of laser treatment of diabetic macular oedema (DMO), which is done with focal or grid laser.

Methods

Systematic reviews of the trial evidence on:

- treatment at NPDR stage versus waiting till PDR develops
- the relative effectiveness and safety of newer versus conventional laser methods
- the effectiveness of anti-VEGF drugs and injected steroid in combination with PRP.

This was supplemented by evidence on adverse effects from other types of study.

Review of previous economic studies. Construction of an economic model and cost-effectiveness analysis.

Results

Evidence on the timing of PRP came almost entirely from the Early Treatment Diabetic Retinopathy Study (ETDRS). This was a large high-quality study that recruited patients with moderate to severe NPDR or early PDR, with or without macular oedema (MO), in the years 1980 to 1985. Patients were randomised to immediate PRP ('early photocoagulation') or to observation and PRP at the HR-PDR stage ('deferred photocoagulation'). Those with no MO were further randomised to different intensities of PRP, known as full or mild scatter. Those with MO randomised to early photocoagulation were further randomised to either full or mild scatter, and to early or delayed focal laser treatment for the DMO.

There were three groups of eyes in ETDRS:

- Category 1 Moderate to severe NPDR or early PDR but no MO.
- Category 2 Mild to moderate NPDR ('less severe retinopathy') and MO.
- Category 3 Severe NPDR or early PDR ('more severe retinopathy') and MO.

The primary end point of the ETDRS was the development of severe visual loss (SVL). The absolute risks of SVL in the trial were low: 2.6% with early laser and 3.7% with deferred PRP. The 5-year relative risk (RR) of SVL for eyes assigned to early photocoagulation compared with deferral was 0.77 [99% confidence interval (CI) 0.56 to 1.06]. So early photocoagulation reduces the risk of SVL by about 23%, though the 99% CI levels overlapped with no difference.

The RRs for the three categories differed:

- Category 1 = 1.37 (99% CI 0.67 to 2.77).
- Category 2 = 0.59 (99% CI 0.32 to 1.09).
- Category 3 = 0.70 (99% CI 0.44 to 1.11).

Compared with deferral of photocoagulation, early photocoagulation reduced progression to HR-PDR in each baseline category. Full scatter reduced progression to HR-PDR by 50% and mild scatter by 25% compared with the deferred group.

By 5 years, 3.9% in the deferred group and 2.2% in the early group had undergone vitrectomy. The indications for vitrectomy were either vitreous haemorrhage (53.9%) or retinal detachment with or without vitreous haemorrhage (46.1%).

The RR of the combined end point of SVL or vitrectomy for eyes assigned to early photocoagulation compared with eyes assigned to deferred photocoagulation was statistically significant at 0.67 (99% CI 0.52 to 0.87).

One harm associated with early PRP was early moderate visual loss, shown more frequently at 6 weeks and 4 months than with eyes assigned to deferral; however, there was no difference at 3-year follow-up.

The ETDRS found that the benefits of early PRP were greater in patients with type 2 diabetes than in those with type 1, though this may have been a chance finding.

The conclusions of the authors of the study were cautious, leaving some uncertainty regarding PRP at the severe NPDR stage:

> *Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate non-proliferative retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage.*
>
> *Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology 1991;**98**:766–85.*[9]

The evidence from ETDRS suggests that treatment of severe NPDR and early PDR was more effective – though the 99% CIs were wide – in reducing future visual loss, than waiting to treat at HR-PDR stage, but ETDRS did not provide results separately for severe NPDR and early PDR. The primary end point, SVL [defined as visual acuity (VA) < 5/200 at two consecutive follow-up visits 4 months apart], was very severe. The observed reduction in HR-PDR might have been expected to lead to further reductions in visual loss with longer follow-up.

Types of laser

We included only studies published since 2000, in order to reflect current practice, and we included studies at any stage of retinopathy because of a dearth of laser studies at NPDR stage. For effectiveness in terms of visual state, we preferred a minimum duration of 6 months, but we included trials with shorter follow-up, because regression of neovascularisation can be seen 2–3 months after PRP. We also included non-trial studies of shorter duration for data on adverse effects.

We found 12 randomised controlled trials (RCTs), generally of good quality, but often with small numbers of patients. The majority of the patients had PDR, with a few with very severe NPDR.

The types of laser, and method of use, varied considerably amongst studies. Newer lasers can do a number of burns at the same time, known as pattern or multi-spot, which reduces the time required for PRP. However, other variations include the type of laser and wave length used (for instance argon vs. diode; 810-nm vs. 532-nm wave length; whether micropulse technology is used), and the parameters than can be changed when actually applying the laser (power, which can be decreased to 'sub-threshold' levels or increased to achieve 'light' or more 'marked' burns; spot size; duration of the laser burn).

There were three trials of multi-spot or pattern photocoagulation against single-spot argon PRP, with a total of 280 eyes treated. Pattern photocoagulation appeared to be as effective but with fewer adverse effects.

Other studies examined different ways of giving standard PRP, some suggesting that lighter burns PRP with conventional lasers gave similar effectiveness but fewer adverse effects than more intense burns. None of the studies showed a significant difference amongst the lasers in terms of change in VA.

The Japanese approach of selective PRP aimed at ischaemic areas only in pre-proliferative diabetic retinopathy (PPDR) (their term, presumably severe NPDR) delayed progression to PDR, with only 15% of the selective group developing PDR compared with 52% of those receiving no photocoagulation ($p = 0.03$). The rationale is that it is the ischaemic areas that produce VEGF, and treating only those saves some peripheral vision.

In summary, recent evidence has shown a trend towards 'lighter' photocoagulation, with reduced intensity of laser burns, but, in most studies, without loss of effectiveness. It is worth noticing that lighter photocoagulation can be given with argon machines.

Data on adverse events come from both RCTs and non-randomised studies, with a mixture of different types of lasers and different methods of photocoagulation, different levels of severity of DR, different follow-up times, and different methods of measuring outcomes.

Pan-retinal photocoagulation destroys retinal tissue and this can lead to symptoms due to the loss of function of the burned areas, including peripheral visual field defects, reduced night vision, reduced colour vision and decreased contrast sensitivity. Visual field defects can occur in up to 50% of treated patients, depending on intensity of PRP and level of testing. However, it does help preserve the more important central vision.

The most important adverse effect associated with PRP is MO, which can lead to a reduction in VA, mostly in the short term, though in one of the older trials, persistent VA losses were attributed to treatment, of one line in 11% and two or more lines in an additional 3%, on the Snellen chart.

In older studies such as ETDRS, which were carried out before optical coherence tomography (OCT) became available, some patients may have had undiagnosed MO at baseline, which was exacerbated rather than caused by PRP. With better detection of MO, focal laser treatment or anti-VEGF therapy can be given before PRP to reduce the risk, with choice of treatment being based on retinal thickness, as per National Institute for Health and Care Excellence guidelines. Because of the risk of precipitating MO, conventional argon laser photocoagulation is usually given over several sessions. There is some evidence that the risk is less with modern laser technologies.

It appears that pattern scan lasers are now standard for PRP, with single-spot argon lasers being replaced.

The conclusion from the review of recent laser studies is that there have been advances in laser technologies but no convincing evidence as yet that modern lasers are more effective than the argon laser used in ETDRS.

Drug and laser combinations

We reviewed studies of the efficacy of drug and laser combination in patients with NPDR or PDR. The main interest was reduction in adverse effects, and in particular PRP-associated MO.

Eleven trials compared the efficacy of anti-VEGFs or steroids used in conjunction with PRP. Seven studies used the anti-VEGFs ranibizumab or bevacizumab, and six were of triamcinolone (two trials included both an anti-VEGF drug and a steroid). Five studies included some patients with NPDR. Most trials had small numbers of patients and were short term but that should not be a problem because the MO provoked by PRP occurs soon after PRP.

For the anti-VEGF drugs the evidence is fairly consistent – a single injection appears to reduce the risk of PRP-induced MO.

In three trials, intravitreal triamcinolone (IVTA) reduced the risk of MO after PRP and improved best corrected visual acuity (BCVA) in patients with clinically significant macular oedema (CSMO), but in another it did not. However, IVTA increased intraocular pressure (IOP), a well-known side effect of steroids. One trial of a single sub-Tenon's capsule injection of triamcinolone before PRP showed benefit in preventing visual loss at 6 months, without increasing IOP. Given the higher risk of adverse effects, anti-VEGF treatment might be preferable to steroids, though cost would need to be considered. Triamcinolone is not licensed for use in the eye.

Overall, adjuvant anti-VEGF or triamcinolone treatment reduced the adverse effects of PRP. The strength of the evidence base is that we have a set of RCTs. The limitations are their small size, and, for our purposes, that most patients had HR-PDR rather than severe NPDR. We also need more data on the value of anti-VEGF treatment for different patterns of MO, such as foveal and extra-foveal.

One implication of modern laser methods and the use of anti-VEGF or steroid drugs may be a reduction in the risk of DMO when PRP is given in one session.

Cost-effectiveness

We carried out a systematic review of previous economic evaluations on the use of PRP, with or without adjuvant anti-VEGF drugs or steroid. A broad search was done in MEDLINE, EMBASE and Web of Science, and included meetings abstracts.

Studies were considered relevant to this review if they met the following inclusion criteria:

- full economic analysis on the treatment (laser and/or medication) for DR, *or*
- partial economic analysis (costs or effects) on the treatment (laser and/or medication) for DR (e.g. costing studies or quality-of-life studies).

We checked 1896 abstracts. Five studies provided partial economics analyses. No studies provided a full economic evaluation. However, many abstracts provide useful data on adverse events, disutilities and patient preferences.

We constructed a Markov model, starting with a cohort of people with moderate NPDR who could progress through all the stages of retinopathy to SVL. The model had two treatment arms:

1. *Current practice*. Patients are observed until they progress to the HR-PDR health state (or later) when they receive PRP.
2. *Early PRP (intervention)*. Patients receive PRP once they progress to the severe NPDR health state, or at the early PDR stage.

For the base case, we used the data from the ETDRS trial, which is the only one that addresses the timing question. The results indicate that early PRP could be more effective and less costly than delayed PRP.

There have been developments since the landmark ETDRS trial, including those mentioned above: advanced laser technologies', more accurate diagnosis of MO using OCT, and reduction in the risk of PRP-associated MO by adjuvant drug treatment. We therefore carried out sensitivity analyses to take account of these but the results were similar.

Limitations in the economics analysis include the wide CIs in the ETDRS, differences in results by type of diabetes, and uncertainties with progression rates, but the main one is the lack of a trial of early versus deferred PRP with modern laser techniques and adjuvant drug treatment.

Not everyone with severe NPDR would progress to HR-PDR, so treatment of severe NPDR might mean treating some people who might not benefit.

Research needs

For the key question of timing of PRP, we are dependent on the ETDRS, which did not provide results separately for severe NPDR and early PDR, and in which the reduction in SVL did not quite reach statistical significance, albeit using 99% CIs. Our view is that the current evidence base is insufficient to recommend a policy of PRP at the severe NPDR stage, and that a trial is necessary.

Since the ETDRS, the balance of benefits and harms may have changed. The side effects of PRP may be less than those observed at the time of the ETDRS, given newer laser technologies and modes of treatment, better identification of subclinical DMO using new imaging technologies such as OCT, and new treatment options for preventing or treatment PRP-induced DMO.

The use of adjuvant anti-VEGF or short-acting steroid drugs may further reduce the harms, perhaps allowing lighter laser and fewer burns.

The trial would compare 'best' PRP at severe and very severe NPDR stage versus the same PRP regimen delayed till HR-PDR develops. It would use pattern laser systems. There might be three arms: severe and very severe NPDR, early PDR, and HR-PDR. A further randomisation could examine the value of anti-VEGF drugs in reducing adverse effects.

Outcomes would include preservation of central vision, and also peripheral vision and driving standards. Loss of ability to drive is important to patients.

Conclusions

The current evidence is insufficient to recommend that PRP be used at the non-proliferative stage of DR.

Chapter 1 Background

The commissioning brief notes that diabetic retinopathy (DR) is the major cause of sight loss in the working age population in the UK, and that people with diabetes are 25 times more likely than the general population to go blind. Pan-retinal photocoagulation (PRP) by laser treatment is the standard intervention for patients with proliferative diabetic retinopathy (PDR), and it has been shown to reduce the risk of severe vision loss by 50%.

In some areas, such as Newcastle District, diabetes may no longer be the leading cause of blindness in the population of working age, because of the success of the screening and treatment programmes.[1] A review by Wong et al. (2009)[2] concluded that rates of progression to PDR have fallen over recent times because of earlier identification and treatment of retinopathy, and improved control of blood glucose and blood pressure (BP). This is supported by a recent paper from Wisconsin.[3]

Nevertheless, DR remains common. A Liverpool study by Younis et al. (2003)[4] reported prevalences of any DR and PDR to be 46% and 4%, respectively in type 1 diabetes, and 25% and 0.5% in type 2 diabetes, although the prevalence will vary with mean duration of diabetes, with higher proportions of those with longer duration having DR. Conversely, an increasing incidence of type 2 diabetes would reduce the overall proportion with DR because more people with short duration would be entering the pool.

Introduction to diabetic retinopathy

The Royal College of Ophthalmologists (RCOphth) guidelines define DR as:[5]

> Diabetic retinopathy is a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with the prolonged hyperglycaemia and other conditions linked to diabetes mellitus such as hypertension.

And continues:

> Diabetic retinopathy is a potentially blinding disease in which the threat to sight comes through two main routes: growth of new vessels leading to intraocular haemorrhage and possible retinal detachment with profound global sight loss, and localised damage to the macula/fovea of the eye with loss of central visual acuity.
>
> Reproduced with permission from The Royal College of Ophthalmologists. Guidelines for Diabetic Retinopathy. 2012. URL: www.rcophth.ac.uk/page.asp?section= 451&sectionTitle=Clinical+Guidelines (accessed 24 September 2013).[5]

Diabetic retinopathy is due to damage to the retina, particularly to its blood vessels, caused by raised blood glucose levels. The earliest changes tend to affect the capillaries, starting with dilatation.

The next stage is closure of some capillaries leading to loss of blood flow (non-perfusion) to part of the retina. If large areas of the retina are deprived of their blood supply they may be seen as paler areas. Smaller areas of ischaemia may be detected only by fluorescein angiography (FA). In this investigation, a dye is injected into a vein and passes through the blood vessels which can then be seen, thereby revealing areas without blood flow.

Non-perfusion due to capillary occlusions is the most important feature of DR, as it leads to other changes.

Capillary closure is associated with two other features: cotton wool spots and blot haemorrhages.

Cotton wool spots are so called because they appear as greyish white patches in the retina instead of the usual red colour. They are areas where blood flow has ceased. There are usually only a few, but if many (more than 6–10 in one eye) develop, it may be a sign of rapidly developing serious retinopathy.

Haemorrhages come in different sizes and shapes, referred to as 'dot and blot'. Multiple large haemorrhages are a bad sign and indicate large areas of non-perfusion. They may herald proliferative retinopathy.

Microaneurysms appear as small red dots in the retina. These are due to dilated capillaries. Small ones may not be visible with the ophthalmoscope but are revealed by FA. With ophthalmoscopy, it may not be possible to distinguish microaneurysms from small haemorrhages.

Damage to arteries also occurs, with thickening of the walls of the artery and narrowing of the lumen, and sometimes blockage (occlusion) of the artery, thereby reducing blood flow to parts of the retina.

There are also changes in the retinal veins, such as dilatation, and sometimes looping. Loops are usually related to areas of capillary non-perfusion. Venous beading can occur and is one of the signs of severe non-proliferative diabetic retinopathy (NPDR). The walls of the veins may be thickened. Retinal vein thrombosis may follow – this is known as retinal vein occlusion.

Abnormal new retinal blood vessels may develop and are the most serious manifestation of DR. This is called 'neovascularisation'. Because these vessels are new, their presence is referred to as indicating 'proliferative' retinopathy. The new abnormal vessels are fragile and are more liable to bleed, causing haemorrhages. If they bleed into the vitreous, a gel-like structure that fills the eye, the result is called vitreous haemorrhage. They may also lead to the formation of fibrous scar tissue that can put traction on the retina, leading to tractional retinal detachments. Rarely, they may regress spontaneously.

Exudates are yellowish white patches, initially small specks but may later form larger plaques. They are usually near the macula, the most sensitive part of the eye, and are associated with areas of oedema. They contain lipid deposits.

Retinopathy takes years to develop. It is not seen at diagnosis of type 1 diabetes. If seen at diagnosis of type 2 diabetes, it is an indication that the patient had undiagnosed diabetes for years.

Retinopathy may go through several stages. The first stage is called non-proliferative diabetic retinopathy (NPDR), previously known as background DR. It is very common and most people with long-standing diabetes will have it. The features include microaneurysms, haemorrhages, hard exudates and occasional cotton wool spots. Progression is variable and the changes may regress. The prognosis for mild NPDR is good, but some patients will progress to the more serious forms of NPDR, macular oedema (MO) (maculopathy) and proliferative retinopathy. The presence of multiple cotton wool spots and widespread retinal haemorrhages may indicate that proliferative retinopathy is developing. Large blot haemorrhages are usually followed by new vessels within a few months.

Maculopathy refers to visual loss due to MO (fluid leaking out of blood vessels into the macula, making it swell). It can occur in the absence of proliferative retinopathy, especially in type 2 diabetes. Maculopathy can lead to gradual visual deterioration from increasing oedema, although it can also resolve spontaneously.

About half of the people with proliferative retinopathy also have MO, but it can occur at earlier stages without PDR.

For a useful description, see www.nei.nih.gov/health/diabetic/retinopathy.asp.

Classification of diabetic retinopathy

Classification and severity grading of DR have historically been based on ophthalmoscopically visible signs of increasing severity, ranked into a stepwise scale from no retinopathy through various stages of non-proliferative or pre-proliferative disease to advanced proliferative disease.

Two different approaches to classification have emerged: (1) those used in ophthalmology, covering the full range of retinopathy, based on the Airlie House/Early Treatment Diabetic Retinopathy Study (ETDRS) classification and (2) those used in population screening.

There are various methods of classifying DR. As one protocol referee noted, no grading system is ideal for all purposes. Older studies used the ETDRS modification of the Airlie House classification and this is said to be the gold standard for classifying DR.[6]

The commissioning brief refers to R2, which comes from the classification used by the English National Diabetic Retinal Screening Programme:[7]

- R0 No retinopathy.
- R1 Background – microaneurysms, retinal haemorrhages, with/without any exudate. This is broadly equivalent to the ETDRS mild NPDR stage.
- R2 Pre-proliferative – multiple blot haemorrhages, intraretinal microvascular abnormalities (IRMAs). Moderate NPDR, referable to Ophthalmology.
- R3 PDR.

The Scottish Diabetic Retinopathy Screening Service classification is shown in *Table 1*, and is slightly more detailed.[8]

TABLE 1 The Scottish Diabetic Retinopathy Screening Service classification

Stage	Description	Action required
Retinopathy		
R0	No retinopathy anywhere	Routine rescreening at 12 months
R1	Mild background retinopathy	Rescreen at 12 months
R2	Background retinopathy requiring monitoring for progression	Rescreen at 6 months
R3	Background retinopathy sufficient to require referral	Refer to Ophthalmology, probably for surveillance rather than laser treatment
R4	Proliferative retinopathy	Refer to Ophthalmology, probably for laser treatment
Maculopathy		
M0	No features predictive of maculopathy	Rescreen 12 months
M1	Any hard exudates within one to two DDs of the centre of the macula	Rescreen in 6 months
M2	Any hard exudates or blot haemorrhages within one disc radius of the centre of the macula	Refer to Ophthalmology, probably for surveillance rather than laser treatment

DD, disc diameter.

One problem with these classifications is that, for our purposes, the key category (R2 England or R3 Scotland), is too broad, as we are interested in the groups with severe NPDR or very severe NPDR. Another problem is that the term 'pre-proliferative' is sometimes used as synonymous with non-proliferative, but this usage implies that all NPDR progress to PDR, which is not the case.

There are problems with published studies because some authors talk simply of 'moderate' or 'mild' DR and do not provide sufficient data to determine the more detailed grading – as used by ETDRS. In this review, when studies have not used an accepted classification such as ETDRS, we have tried to extract enough details to allocate patients or studies to a classification as below, so that results can be expressed in terms of defined risk and features.

- *Mild to moderate NPDR:*

  - intraretinal haemorrhage in fewer than four quadrants
  - microaneurysms
  - hard exudation
  - MO
  - abnormalities in the foveal avascular zone

- *moderate to severe NPDR:*

  - mild/moderate intraretinal haemorrhage in four quadrants
  - cotton wool spots
  - venous beading
  - IRMAs

- *severe NPDR (4–2–1 rule)* (one of the following):

  - severe intraretinal haemorrhage in four quadrants
  - venous beading in two quadrants
  - IRMA in one quadrant

- *very severe NPDR* (two of the above)
- *proliferative diabetic retinopathy with or without high-risk characteristics (HRCs)* (any three of the following):

  - presence of neovessels
  - location of the neovessels (at the optic nerve)
  - size of the neovessels: if at the optic nerve [neovascularisation of the disc (NVD)] ≥ ¼–⅓ disc area if elsewhere in the retina [neovascularisation of the retina elsewhere (outside the disc) (NVE) ≥ ½ of the disc area (if both NVD and NVE present, classified based on neovessels at the disc)
  - presence of pre-retinal haemorrhage or vitreous haemorrhage.

About half of patients with severe or very severe NPDR will progress to PDR within a year.

The descriptions used in the ETDRS[9] are attached as *Appendix 1*.

Treatment of diabetic retinopathy

Laser treatment is not usually administered to people with NPDR. However, the commissioning brief from the Health Technology Assessment (HTA) programme poses the question whether:

> intervention with pan-retinal laser treatment earlier in the disease, during the pre-proliferative stage (Level R2), may be more beneficial in terms of preventing loss of vision, given the detrimental and potentially irreversible effects of PDR if treatment is not obtained or is delayed.

Pan-retinal photocoagulation is sometimes referred to as scatter photocoagulation.

In considering treatment for retinopathy, three issues need to be considered:

- The risk of visual loss without treatment.
- The risk of visual loss with treatment.
- The adverse effects of treatment. Laser treatment is a destructive process that can cause loss of peripheral vision in order to preserve the more important central vision.

Laser photocoagulation has been of great benefit to many people with PDR but in most cases has been better for preserving vision than restoring it, though it can improve vision, for example in eyes that have vitreous haemorrhages.

Two key studies of PRP were published in the 1980s: the ETDRS[9] and the Diabetic Retinopathy Study (DRS).[10] The ETDRS[9] recruited people with NPDR and people with PDR but without HRCs, and one aim was to determine when PRP should be used. In the EDTRS,[9] laser treatment reduced the risk of moderate visual loss (a loss of three ETDRS lines) by 50%, but visual acuity (VA) improved in only 3% of patients. These studies[9,10] are described in *Chapter 2*.

Laser has adverse side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported. Ability to drive can be affected. Hence laser treatment is not undertaken lightly, and to extend it to people with NPDR would require careful consideration.

Treatment of DR has been based largely on the results of the ETDRS[9] and DRS.[10] A small non-randomised study reported that laser treatment in people with type 1 diabetes at the severe NPDR stage reduced visual loss, compared with waiting to treat at the PDR stage, but this difference did not reach statistical significance.[11] A Swedish study by Stenkula (using xenon arc photocoagulation) also reported benefit from treating severe NPDR in a trial of PRP with one eye randomised to treatment.[12]

One consideration is that if PDR is being detected earlier and treated more effectively than at the time of the landmark trials, notably ETDRS[9] in the early 1980s, then any marginal benefit of treating at the NPDR stage may now be less.

We are aware that PRP is usually used when people reach the proliferative stage, but also that there is some variation in how it is applied. Some ophthalmologists may start with sparse very scattered PRP, with further lasering if the retinopathy progresses. Others may start with full mid-peripheral PRP. A third approach might be to laser only areas of mid-peripheral ischaemia as seen on FA.

It may be used when patients have high-risk features, such as new vessels, or earlier, at severe NPDR stage. There are also different stages of PDR, with some patients being classified as 'high-risk PDR' (HR-PDR), and one protocol referee argued that laser was mainly of benefit in PDR with high-risk characteristics (HRC-PDR) and not all PDR.

Figure 1 (reproduced with permission) from a review by Neubauer and Ulbig (2007)[13] outlines current practice. Since the landmark studies DRS[10] and ETDRS,[9] new laser devices have been introduced.

Argon and krypton lasers use ionised gas as the lasing medium, while the tunable dye laser uses a liquid solution. Neodynium-doped yttrium aluminium garnet (Nd:YAG) and diode lasers are both solid-state lasers that utilise crystals and semiconductors, respectively. The solid-state lasers are becoming the preferred option owing to their portability and ability to deliver laser in continuous and pulse mode.

Most people now use the pattern scan (PSC) or multi-spot lasers, rather than the argon laser, because they are faster and less painful. Some centres still use argon. With the traditional single-spot laser, treatment of large areas of the retina is time-consuming, can be uncomfortable for patients because of the length of time required, and there is a risk that, if the patient moves, laser may be mis-directed. With the pattern lasers, a number of spots can be applied simultaneously with one press of the foot pedal. In theory, this could be up to 56 with the PAtterned SCAnner Laser (PASCAL) system (developed by OptiMedica Corp, Santa Clara, CA, but now marketed by Topcon Corporation – Topcon UK, Newbury, Berkshire) but in practice smaller numbers are often used.

Other multi-spot lasers include the Valon TT (Valon Lasers, Vantaa, Finland), the Array LaserLink (Lumenis, Yokneam, Israel), the Navilas (OD-OS GmbH, Teltow, Germany) and the Quantel Supraspot (Quantel Medical, Cedex, France). However, most studies published used the PASCAL system.[14]

The multi-spot system is much more comfortable for patients, and may reduce the number of sessions required.

The sub-threshold diode laser has been introduced though mainly for diabetic macular oedema (DMO)[15,16] but has not spread much into use in PDR, possibly because for PRP it requires more sessions and more burns. It allows very short [millisecond (ms)] pulses of laser, shorter than conventional laser, sometimes called 'micro-pulsed'.
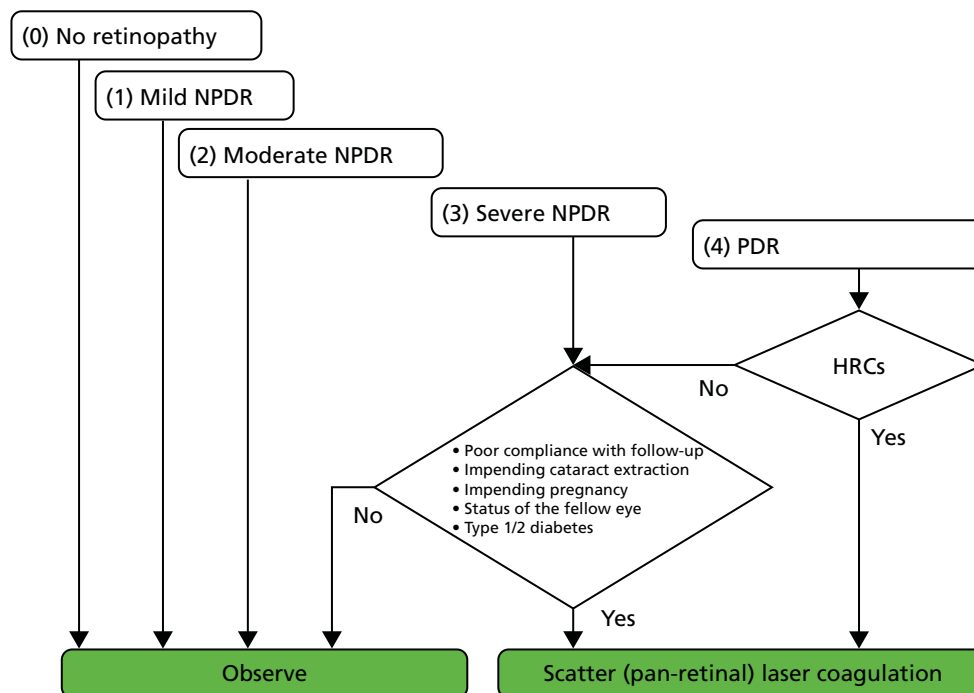
FIGURE 1 Algorithm for pan-retinal scatter coagulation of the retina. Reproduced from Neubauer and Ulbig[13] with permission from S. Karger AG, Basel.

The sub-threshold refers to the visibility of burn spots. Photocoagulation is started with very low parameters, increased till a laser spot is seen, after which the power is reduced until the spot is just not seen – sub-threshold – and then the whole treatment is done at that level. But it is important to note that this is for treating the macula where the power used is much lower than that used in PRP.

We also note that in Japan a more selective approach to laser therapy is used, with targeting based on FA, so that only ischaemic areas are lasered.[17] This is a more restrictive approach than traditional PRP. Hence this review will need to classify methods of laser treatment.

Guidelines

Current guidelines from the RCOphth[5] state that:

> *Mild and moderate DR does not require treatment, but patients should be monitored annually and advised to maintain as good diabetes control as possible.*

> *Severe NPDR requires closer monitoring, usually every 6 months, in ophthalmology clinics, by clinical examination and digital photography. The aim is to detect progression to PDR.*

> *In patients with very severe NPDR, PRP is considered in order to reduce progression in the following groups:*

> - *in older patients with type 2 diabetes*
> - *where monitoring of DR is difficult because of poor attendance or obscured retinal view*
> - *before cataract surgery, because that may be associated with progression*
> - *if vision has been lost in the other eye.*

> *Reproduced with permission from The Royal College of Ophthalmologists. Guidelines for Diabetic Retinopathy. 2012. URL: www.rcophth.ac.uk/page.asp?section= 451&sectionTitle=Clinical+Guidelines (accessed 24 September 2013).[5]*

In patients with PDR, urgent PRP is recommended.

The guidelines note that some ophthalmologists treat at NPDR stages:

> *10.3.1 Earlier treatment: Recognition that earlier laser prevents progression to high risk retinopathy, and that PDR has higher risk of blindness was reported in both DRS and ETDRS (LEVEL 1). However the balance of risks with laser modalities available at that time meant that laser intervention was recommended only when retinopathy approached high risk PDR. With modern laser techniques, PRP is often done before the development of PDR.*

The RCOphth include, in the guidelines, a useful table (*Table 2*) comparing the different classifications.

The SIGN diabetes guideline[18] recommends that 'Patients with severe or very severe NPDR should receive close follow-up or laser photocoagulation'.

Neither the National Institute for Health and Care Excellence (NICE) diabetes guideline on type 1 diabetes[19] nor on type 2 diabetes[20] covers laser therapy.

TABLE 2 Approximate equivalence of currently used alternative classification systems for DR (from table 1.1 RCOphth guidelines[5])

ETDRS	NSC	SDRGS	AAO International	RCOphth
10 none	R0 none	R0 none	No apparent retinopathy	None
20 microaneurysms only	R1 background	R1 mild background	Mild NPDR	Low risk
35 mild NPDR			Moderate NPDR	
43 moderate NPDR	R2 pre-proliferative	R2 moderate BDR		High risk
47 moderately severe NPDR				
53A–D severe NPDR		R3 severe BDR	Severe NPDR	
61 mild PDR	R3 proliferative	R4 PDR	PDR	PDR
65 moderate PDR				
71, 75 HR-PDR				
81, 85 advanced PDR				

AAO, American Academy of Ophthalmology; BDR, background diabetic retinopathy; NSC, National Screening Committee; SDRGS, Scottish Diabetic Retinopathy Grading Scheme.

Other treatment options

Control of blood glucose and blood pressure

Good control of blood glucose [aiming at glycated haemoglobin (HbA_{1c}) no greater than 7% (53 mmol/mol)], BP (aiming at 130/80 mmHg) and blood triglycerides reduces the risk of retinopathy, though in those who have some retinopathy and poor glycaemic control, too rapid restoration of good control may worsen retinopathy, usually temporarily.

Intravitreal drugs

In recent years, two groups of drugs for intravitreal use have become available. These are:

- Steroids, including triamcinolone, the long-acting dexamethasone implant (Ozurdex, Allergan) and the longer-acting fluocinolone implant (Iluvien, Alimera).
- The 'anti-vascular endothelial growth factor (VEGF)' drugs, bevacizumab, pegaptanib, ranibizumab and aflibercept. These inhibit the action of VEGF or bind it. Aflibercept also blocks placental growth factor. VEGF increases vascular permeability and promote the growth of abnormal new vessels (neovascularisation).

The long-acting steroids have significant adverse effects, notably causation or acceleration of cataracts in the eye, and also raised intraocular pressure (IOP) that can lead to glaucoma. They are unlikely to be much used at such an early stage as NPDR because of the risk of cataract formation, but may have a role in pseudophakic patients, or in patients with DMO that does not respond to anti-VEGF treatment. The short-acting steroid, triamcinolone, is not licensed for use in the eye, but has been widely used.

The rationale for using the anti-VEGF drugs in PDR and NPDR has been summarised by the Diabetic Retinopathy Clinical Research Network (DRCRN).[21] First, they note reports of raised VEGF in ocular fluid from patients with active new vessel formation compared with no rise in patients with NPDR or inactive PDR, suggesting that VEGF stimulates neovascularisation.[22] Second, they report a number of observational studies which report that anti-VEGF drugs cause regression of PDR, albeit temporarily because the effects last only a few weeks, making repeat injection necessary, as has been shown in the treatment of DMO.

The anti-VEGF drugs have fewer adverse effects, and would probably be more acceptable at early stages than the steroids. They do have to be given by injection into the eye. In DMO, these injections are given monthly initially, but reducing in frequency thereafter. Nevertheless, anti-VEGF treatment places a significant burden on both patients and the NHS. In addition, it is, at least in DMO, only successful in about 30–50% of patients (defining success as a gain of 10 or more letters in VA).[23] Lastly, as experience is gained on the use of anti-VEGF in DR it is possible that initially unrecognised side effects may be apparent, as it was the case in age-related macular degeneration (AMD), where accumulating evidence suggests a possible effect of anti-VEGF on the development of retinal pigment epithelial atrophy.[24]

The anti-VEGF drugs are now being used in combination with PRP, and we review the evidence on that in *Chapter 4*.

Fenofibrate

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate could reduce macrovascular and microvascular events in type 2 diabetes.[25] However, a sub-study within FIELD[25] recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate vs. 4.9% on placebo) but the sub-study used retinal photography to assess progression of retinopathy or development of MO. The hazard ratio at 6 years for MO was 0.69 [95% confidence interval (CI) 0.54 to 0.87] in the fenofibrate group compared with placebo. The effect of fenofibrate did not seem related to changes in blood lipid levels.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Eye Study reported a reduction of 40% in the risk of progression of retinopathy over a 4-year follow-up in patients on fenofibrate and a statin compared with those on a statin alone.[26] This was associated with a decrease in serum triglycerides. Lowering cholesterol does not appear to affect progression, as shown in the CARDS (Collaborative Atorvastatin Diabetes Study) trial of atorvastatin.[27]

Preliminary searches have identified some evidence on the use of fenofibrate eye drops but such use appears to be at an early stage. The drops seem to have been patented and piloted, but not yet trialled in humans, though some work in rats suggests efficacy in arresting neovascularisation.[28] In Australia, oral fenofibrate has been approved for slowing the progression of retinopathy in type 2 diabetes.[29]

Fenofibrate seems to be little used in the UK for retinopathy.

This review includes only drugs that are administered directly into the eye.

What do clinical guidelines say?

This section outlines the recommendations from five clinical guidelines, from England, Scotland, Canada, Australia and the USA, on laser photocoagulation on the treatment of NPDR and PDR.

England, Canada, USA and Australia produced separate guidelines for DR, whereas Scotland devoted one section in the Management of Diabetes guideline to the management of DR. *Table 3* summarises the recommendations.

As recommended in the ETDRS, laser treatment is not considered in any of the guidelines for patients with DR at stages up to and including moderate NPDR. However, only the RCOphth UK and the American Academy of Ophthalmology (AAO) guidelines actually state this in their guidelines.

Consideration of early PRP in conjunction with close follow-up at the severe stage of NPDR is recommended in England, Scotland, America and Australia but not in Canada, where the guidelines consider only the treatment of PDR. While the Scottish Intercollegiate Guidelines Network (SIGN) guidelines[18] very generally

TABLE 3 Summary of recommendations from five guidelines on laser treatment for DR

Guideline	Mild to moderate NPDR	Severe/very severe NPDR	Non-HR-PDR	High-risk/proliferative PDR	Advanced/severe PDR
RCOphth [RCOphth UK (England)][5]	No treatment indicated	Early PRP if retinopathy approaches the proliferative stage in specific patient groups (see text above)	Not covered in guidelines	Full scatter PRP	Vitrectomy with intravitreal anti-VEGF injection is recommended if PRP seems ineffective
SIGN (Scotland)[18]	Not covered in guidelines	Close follow-up or PRP	Not covered in guidelines	PRP	With VH too severe for PRP consider vitrectomy
COS (Canada)[30]	Not covered in guidelines	Not covered in guidelines	Not covered in guidelines	PRP	With VH consider vitrectomy and anti-VEGF
AAO (USA)[31]	No treatment indicated	Early PRP in specific patient groups (see text above)	Early PRP in specific patient groups (see text above)	PRP	Consider vitrectomy
NHMRC Australia[32]	Not covered in guidelines	Early PRP in specific patient groups (see text above)	Not covered in guidelines	PRP	Consider vitrectomy if unresponsive to PRP

AAO, American Academy of Ophthalmology; COS, Canadian Ophthalmological Society; NHMRC, National Health and Medical Research Council; SIGN, Scottish Intercollegiate Guidelines Network; VH, visual haemorrhage.

recommend the consideration of PRP in patients with severe or very severe NPDR, the RCOphth UK reserved the treatment to patients approaching the proliferative stage and only in certain patient groups, i.e. older patients with type 2 diabetes, in patients in whom retinal view is difficult or examination is difficult, in patients who cannot be followed up closely, in patients in whom one eye has already been lost to PDR, and, generally, before cataract surgery. The AAO[31] and the National Health and Medical Research Council (NHMRC) Australia[32] do not seem to subcategorise the severe NPDR stage but list the same patient groups for consideration. They further include pregnancy (AAO[31]) and renal disease (NHMRC[32]) under the medical conditions for consideration. The AAO[31] states further that partial PRP is not recommended and that, consequently, if PRP is indicated, full PRP should be performed. The AAO[31] also includes the non-HR-PDR stage into this recommendation.

Pan-retinal photocoagulation is recommended for PDR with HRCs (AAO,[31] NHMRC,[32] COS[30]) and PDR with any new vessels (RCOphth UK and SIGN). The AAO,[31] RCOphth UK[5] and the Australian NHMRC[32] stress the urgency of such treatment in their guidelines.

Anti-vascular endothelial growth factor and steroids

None of the guidelines includes anti-VEGF as a treatment option for NPDR/PDR either alone or in combination with laser photocoagulation. However, three out of the five guidelines recommend anti-VEGF for the treatment of DMO. The RCOphth UK and the AAO recommend consideration of anti-VEGF either with or without combination laser therapy, and the RCOphth classes it as 'the new gold standard of therapy . . .' for DMO. The Canadian guidelines, however, recommend anti-VEGF prior to PRP only for PDR with DMO. They further recommend anti-VEGF treatment before vitrectomy. The Australian guidelines recognise that anti-VEGF treatment for the management of PDR with DMO is already widely in use but say that anti-VEGF for PDR prior to laser treatment or vitrectomy lacks evidence from randomised controlled trials (RCTs).

Although anti-VEGF drugs need to be administered frequently, slow-release steroid implants have the advantage of lasting longer. The American guidelines state that intravitreal steroids might be considered in combination with PRP in patients with combined moderate NPDR and DMO. Similarly, the Australian guidelines suggest consideration of steroids in PDR with DMO in certain patient groups. Overall, recommendations to use steroids are very cautious and the Canadian Ophthalmological Society (COS), which does not include intravitreal steroids in their guidelines, reports that studies investigating the use of steroids produced conflicting results. The SIGN guidelines do not recommend any pharmacological treatment for the management of any form of PDR owing to lack of convincing evidence.

Decision problem

The commissioning brief gave the background to the topic as follows:

> Diabetic retinopathy (DR) is the major cause of sight loss in the working age population in the UK and people with diabetes are 25 times more likely than the general population to go blind. Panretinal photocoagulation (PRP) by laser treatment is the standard intervention for patients with high risk progressive* diabetic retinopathy (PDR) and it has been shown to reduce the risk of severe vision loss for eyes at risk by 50%. However, an intervention with pan-retinal laser treatment earlier in the disease, during the preproliferative stage, may be more beneficial in terms of preventing loss of vision, given the detrimental and potentially irreversible effects of PDR if treatment is not obtained or is delayed.

*The term used in the brief, but presumed to mean proliferative.

The key question for this review is about the timing of PRP – would there be advantages in PRP at the severe NPDR stage, rather than waiting till PDR develops?

Population: people with NPDR.

Interventions: PRP at the NPDR stage. All variants of PRP will be included. Drug–laser combinations using an anti-VEGF drug or an injected steroid will be included.

Comparator: PRP delayed till PDR develops. This may be at the HR-PDR stage but may be used in early PDR.

Outcomes: the primary outcome is visual loss with central and peripheral loss described separately when data permit.

Secondary outcomes include the need for further treatment, and adverse effects such as the development of DMO after PRP, peripheral visual loss, quality of life (QoL), ability to drive, colour vision.

Chapter 2 The landmark trials: Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study

Methods

Literature searches and study selection

The search question posed in the commissioning brief was:

> What is the clinical and cost-effectiveness of pan-retinal laser treatment in the management of non-proliferative (pre-proliferative) diabetic retinopathy (NPDR)?

The patient groups specified were those with early stages of NPDR (Level R2) versus the control or comparator treatment of PRP at PDR (Level R3), in any appropriate setting.

Our scoping searches gave a very low retrieval of studies that would be relevant to this search question, but did show that there were recent developments in types of laser and in the use of laser and drug combinations. Therefore, in the draft protocol we proposed a wider scope for this Technology Assessment Report than had been envisaged in the commissioning brief. This was approved by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) after being supported by the external referees. The decision problem was subsequently expanded to become:

> Treatment of non-proliferative diabetic retinopathy: a review of pan-retinal photocoagulation, other forms of laser treatment, and combinations of photocoagulation and anti-VEGF drugs or inject steroids.

However, the broader searches revealed that there were no RCTs that compared patients at the NPDR level to those at later stages of PRP. Indeed, the most relevant and largest study done addressing the timing of PRP laser in the treatment of DR, the ETDRS, grouped together patients with moderate to severe NPDR and early PDR, and did not report outcomes on these groups separately.

Therefore, it seemed likely that a trial to address the original research question was needed, and, in order to inform a future study on PRP treatment of patients at the NPDR stage, we decided to further broaden the searches to capture all forms of current laser and topical drug treatment of DR at any stage, and explore if these newer treatments could be applied to patients at the NPDR stage.

The databases MEDLINE, EMBASE and The Cochrane Library were searched for previous systematic reviews or meta-analyses relevant to our search question (see *Appendix 2* for search strategies). There were 94 potentially relevant records downloaded and the full text of five articles was examined by two reviewers (PR, NW). The most relevant review was one by Mohamed *et al.* (2007).[33] Although this was a useful review, its objective was to review the best evidence for primary and secondary intervention in the management of DR, including DMO, which was a lot broader than our review, so did not address our specific research question. Also, the searches were performed in May 2007, so it was several years out of date.

We searched for RCTs for the treatment of DR. We separated the results into three categories in order to provide evidence for each of the different aspects of our decision problem (*Appendix 2* shows the details of the search strategies and *Figure 2* shows the flow diagram for RCTs searches).

- Trials of:

  - laser alone at the NPDR or early PDR stage versus later stages (reviewed in this chapter)
  - laser studies at any PDR stage (reviewed in *Chapter 3*)
  - combined laser and anti-VEGFs or injected steroids at any PDR stage (reviewed in *Chapter 4*).

From the 102 full-text papers assessed, independently checked against the inclusion criteria by two reviewers (PR/NW), 22 references relevant to category 1 above were identified. Upon reading the full text of these references, it became evident that all were papers arising from two large RCTs, the DRS and the ETDRS, each producing many papers. Further searches were done to search specifically for publications arising from the DRS and ETDRS, and reference lists were checked, in order to obtain all the relevant papers from these two trials; this resulted in an additional 18 articles.

The excluded papers were retained and were assessed for inclusion criteria relevant to category 2 and 3 searches above, and are reviewed in *Chapters 3* and *4*.
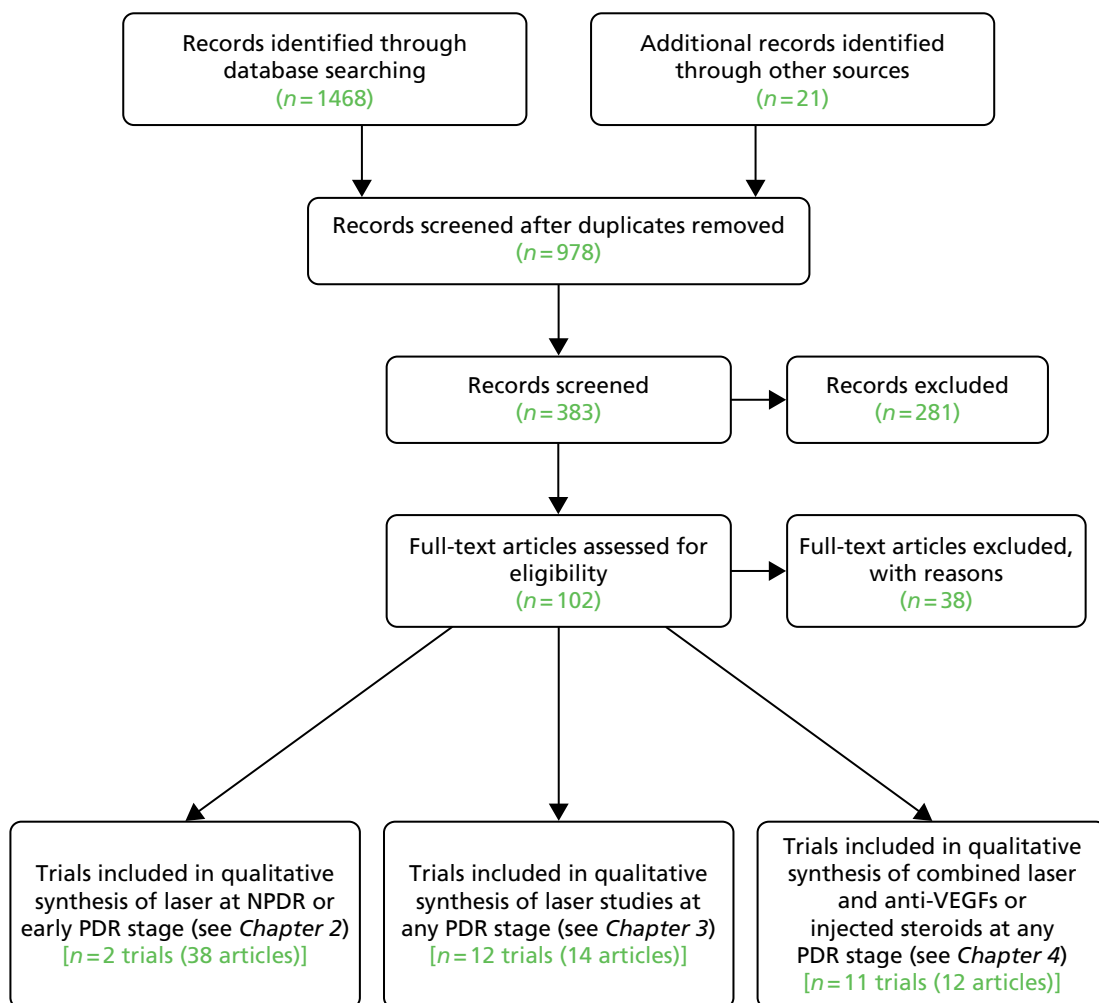
FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for identifying RCTs included in *Chapters 2–4*.

Data extraction and quality assessment

The data extractions, and quality assessments (based on the Cochrane Collaboration's risk of bias tool[34]), of the two trials were carried out by one reviewer (PR) and checked by a second (NW). The final number of papers reviewed was 14 from the DRS and 24 from the ETDRS.

The flow of studies is shown in *Figure 2*.

The Diabetic Retinopathy Study

Background

Laser photocoagulation had become widely used in the management of DR by the early 1970s in the USA. However, there was a lack of good-quality evidence supporting the risk and benefits of this procedure. Therefore, in 1971, the National Eye Institute (NEI) funded the DRS[35] to evaluate photocoagulation treatment for PDR.

Study design

The DRS was a randomised, controlled clinical trial involving 15 clinical centres. A total of 1758 patients were enrolled between 1972 and 1975. Patient follow-up was completed in 1979.

The main aim of the DRS was to determine whether photocoagulation helps prevent severe visual loss (SVL) from PDR, and whether a difference exists in the efficacy and safety of argon versus xenon photocoagulation for PDR. Another objective was to obtain information on the natural history and clinical course of proliferative retinopathy.

Patients were eligible if they had best corrected visual acuity (BCVA) of 20/100 or better in each eye, and the presence of PDR in at least one eye or severe non-proliferative retinopathy in both eyes. Both eyes had to be suitable for photocoagulation. The eye to be treated was chosen randomly.

The baseline VA of the enrolled patients was equal to or better than 20/20 in approximately half of the eyes. Patients were predominantly white and had a mean age of 42.6 years; approximately 45% were classified as juvenile-onset diabetics, and there were slightly more men than women.

The principal end point was SVL, which was considered to have occurred if VA was less than 5/200 at two or more consecutively completed 4-month follow-up visits.

Quality assessment

The DRS was a high-quality trial with a low risk of bias, as shown in *Table 4*. The details of the design, methods and baseline results of the DRS were extensively reported in DRS report no. 6 (DRS #6).[36]

Treatment

One eye of each patient was randomly assigned to immediate photocoagulation and the other to follow-up without treatment, regardless of the course followed by either eye. The eye chosen for photocoagulation was randomly assigned to argon laser or to xenon arc photocoagulation. Treatment was usually completed in one or two sittings. Both treatment techniques included extensive scatter photocoagulation (PRP) and focal treatment of new vessels on the surface of the retina.

The argon treatment technique specified 800–1600 scatter burns, 500 μm in size, 0.1-second duration and direct treatment of new vessels whether on or within one disc diameter (DD) of the optic disc (NVD) or outside this area (NVE). The xenon technique was similar, but scatter burns were fewer in number, generally of longer duration, and stronger, and direct treatment was applied only to NVE on the surface of the retina. Focal treatment was also applied to microaneurysms or NVE lesions thought to be causing MO. Those treated with argon could have flat or elevated NVE treated.

TABLE 4 Quality assessment and risk of bias of DRS

Adequate sequence generation	Adequate allocation concealment	Adequate masking	Incomplete outcome data assessed	Free of selective outcome reporting	Free of other biases (e.g. similarity at baseline, power assessment)
Yes (randomisation schedules were created by the co-ordinating centre by the co-ordinating centre for each clinical centre and were designed to balance both the number of right and left eyes assigned to treatment and the number assigned to argon and xenon)	Yes (the co-ordinating centre sent the treatment allocation form to each clinic in a sealed envelopes)	Yes [the protocol specified that the individual who measured VA should be unaware of ('masked' with regard to) the identity of the eye assigned to treatment and VA at previous visits]	Yes (the number of patients who completed specified visits up to 5 years was reported in table 3 of DRS #8[10])	Yes (all prespecified outcomes reported)	Yes (percentage of patients with specified baseline characteristics for 14 different variables, and yielded no significant difference at 5% level. Sample size calculations set recruitment goal at 800 patients in each treatment group)

Follow-up visits were planned at 4-month intervals for a minimum follow-up of 5 years, where follow-up treatment was applied as needed. BCVA was measured in both eyes by masked techniques before treatment and at 4-month intervals after treatment.

The DRS data were reviewed every 3 months by the Data Monitoring Committee for evidence of adverse and beneficial treatment effects.

Results (before protocol change)

In 1975 after an average of only 15 months of follow-up (range 0–38 months), the 2-year incidence of blindness was 16.3% in untreated eyes but only 6.4% in treated eyes.[37] Therefore, photocoagulation had reduced the 2-year risk of blindness by about 60%. This finding was unexpected and highly statistically significant. These beneficial effects were noted to some degree in all stages of DR included in the study.

Protocol change

On the basis of these results a decision was made in 1976 (more than 3 years before the planned termination of the study) to consider photocoagulation treatment for the initially untreated eyes, which now, or in the future, would fulfil any one of the following criteria, referred to as eyes with HRCs:

- Moderate or severe new vessels on or within one DD of the optic disc.
- Mild new vessels on or within one DD of the optic disc if fresh vitreous or pre-retinal haemorrhage is present.
- Moderate or severe new vessels elsewhere (NVE), if fresh vitreous or pre-retinal haemorrhage is present, and if the area of new vessels was half the disc area or more.

Photocoagulation techniques were modified when treatment was carried out in eyes initially assigned to the untreated control groups after the 1976 protocol change. Argon treatment was preferred, and to decrease the risk of VA loss, many DRS investigators divided scatter treatment into two or more episodes, days or weeks apart.

Evidence of recovery before protocol change

Although the principal goal of photocoagulation treatment is to prevent visual loss, not to improve vision, there were eyes with some evidence of recovery, defined as VA ≥ 5/200 at any subsequent visit at 1, 2 or 3 consecutively completed follow-up visits. The percentage of eyes with some evidence of recovery at each visit were 28.6%, 12.2% and 7.7% in untreated eyes compared with 48.8%, 28.6% and 20.8% in treated eyes, respectively. Therefore, it appeared that recovery of VA was more frequent in treated than untreated eyes.

Harms

Some harmful effects of treatment were also found, including moderate losses of VA and constriction of peripheral visual field, which were greater in the xenon treated group than the argon group. The loss in sharp, central vision was temporary in some patients but persisted in others. However, DRS physicians believed that these harmful effects of photocoagulation in eyes with moderate or severe retinopathy were outweighed by the reduced risk of SVL without treatment at these stages.

Results after the protocol change

Additional follow-up after the DRS protocol change confirmed previous reports that, by 24 months, photocoagulation reduces the risk of SVL by 50% or more.

Cumulative rates of SVL for argon and xenon groups combined up to 72 months' follow-up are shown in *Table 5* (adapted from table 2, DRS #8[10]). Although the risk of SVL in untreated eyes increases from 14% at 24 months to 36.7% at 72 months, it can be seen that over this time period the treatment effect was consistent (ranging between 56% and 59%).

TABLE 5 Cumulative event rates of SVL: cumulative event rates per 100 eyes at risk (adapted from table 2, DRS #8[10])

Follow-up (months)	Treated	Untreated	Reduction of SVL (%)
8	0.7	1.2	41.7
24	6.2	14.0	55.7
36	9.0	21.7	58.5
48	11.6	27.8	58.3
60	13.9	33.0	57.9
72	16.6	36.7	54.8

The 24-month data in *Table 5* differ slightly from that presented earlier (prior to the protocol change), as 43% of the 2-year visits and all of the 4-year visits included were carried out after the 1976 protocol change. All eyes are classified in the group to which they were originally randomly assigned, ignoring treatment of control eyes.

The treatment effect was somewhat greater in the xenon group than in the argon group (data not shown), but its statistical significance was borderline, and its clinical importance was outweighed by the greater harmful treatment effects observed with the xenon technique used in the DRS.

Occurrence of severe visual loss in eyes classified according to baseline severity

As patients enrolled in DRS had a broad range of severity of DR, it was important to evaluate results for different stages. *Table 6* (taken from table 2, DRS #14[38]) shows the cumulative 2- and 4-year rates of SVL by eyes grouped by their severity of retinopathy at baseline and treatment assignment.

It can be seen that the treatment effect in *Table 6* is substantial (except for the group without PDR at 2 years) and fairly uniform across all subgroups at both 2 and 4 years, with reductions of SVL by from 54% to 65%.

TABLE 6 Cumulative 2- and 4-year rates of SVL by eyes grouped by baseline severity of retinopathy and treatment assigned (from table 2 DRS #14[38])

Severity of retinopathy	Rate	Treated SVL (%)	No. at risk	Untreated SVL (%)	No. at risk	Reduction of SVL (%)
NPDR	2 year	2.8	303	3.2	297	12.5
	4 year	4.3	188	12.8	183	66.4
Proliferative without HRCs	2 year	3.2	615	7.0	603	54.3
	4 year	7.4	390	20.9	332	64.6
Proliferative with HRCs	2 year	10.9	570	26.2	473	58.4
	4 year	20.4	324	44.0	238	53.6
All eyes	2 year	6.2	1489	14.0	1378	55.7
	4 year	12.0	903	28.5	754	57.9

The rate of SVL for untreated eyes with proliferative retinopathy with HRCs after 24 months of follow-up is about 26% and is reduced to 11% in treated eyes. However, in eyes with proliferative retinopathy without HRCs, the untreated rate at 2 years is much lower (7.0%), and although the beneficial treatment effects are substantial (a 54% reduction in SVL), the risks without treatment are smaller, and so the harmful effects of treatment need to be given more weight than for eyes with a higher risk.

In eyes with severe NPDR the risk of SVL without photocoagulation treatment at 2 years is low (3.2%) and reduces to 2.8% (a reduction of 12.5%) only with treatment, so the risks of treatment become even more important.

Harms: argon and xenon

Decreases of VA of one or more lines and constriction of peripheral visual field due to treatment were also observed in some eyes. These changes were sometimes due to an increase in MO, and sometimes the reduction in VA was temporary. In others, the changes persisted. The changes in visual field are important because they may mean that patients can no longer meet the requirements for driving.

Visual fields were measured using the Goldman method, wherein normal fields range from 50° (superiorly) to 90° (temporally). The DRS group defined modest visual field loss as a reduction from over 30° up to 45°, and 30° or less as severe.

The UK legal requirement is VA of 6/12 (measured in metres) or better (this is equivalent to 20/40 using measurements in feet) and with regards to visual field, to have a binocular visual field of 120° horizontally (in the horizontal axis) and no significant defect within the central 20°, horizontally or vertically (above or below the horizontal meridian).

These harmful effects were more frequent and more severe following the DRS xenon technique; 50% of xenon-treated eyes suffered some loss of visual field compared with 5% of the argon-treated eyes. It was also estimated that a persistent VA decrease of one line was attributable to treatment in 19% of xenon-treated eyes and a persistent decrease of two or more lines in an additional 11%. Comparable estimates for the argon group were 11% and 3%, respectively.

Xenon photocoagulation has been discontinued.

Macular oedema in the Diabetic Retinopathy Study patients (DRS #12)

The DRS[39] was not designed to evaluate the effect of photocoagulation in eyes with MO. Although focal treatment was carried out in those eyes with MO assessment, its direct effect cannot be determined because it was always combined with scatter treatment.

The loss of VA associated with scatter photocoagulation observed soon after treatment was especially prominent in eyes with pre-existing MO. It was also associated with the intensity of treatment. It was suggested that reducing MO by focal photocoagulation before initiating scatter treatment and dividing scatter treatment into multiple sessions with less-intense burns may decrease the risk of the visual loss associated with photocoagulation.[39]

Summary

Results of the DRS showed that photocoagulation reduced the 2-year incidence of SVL by more than half in eyes with PDR, both with and without HRCs. However, in eyes with NPDR, where the 2-year risk of SVL in the untreated control group was low at 3.2%, photocoagulation only reduced the risk to 2.8%. Therefore, in patients with NPDR the harmful effects of photocoagulation assume more importance. Some of the harmful effects of treatment for some patients included a moderate loss of VA and a narrowing of the visual field.

Implications of Diabetic Retinopathy Study findings for treatment of early proliferative or severe non-proliferative retinopathy

The DRS concluded that in the eyes with PDR and HRCs the risk of SVL without treatment substantially outweighs the risks of photocoagulation, and prompt treatment is usually advisable. However, as the DRS findings result from a comparison between prompt treatment versus no treatment, they did not provide evidence on the relative value of prompt treatment versus deferral of treatment in the earlier stages of DR. They recommended careful follow-up for changes with DR and when non-proliferative changes are present, the follow-up visits should be at frequent intervals.[37]

Finally, their conclusions stated:

> Demonstration that prompt treatment of eyes with early proliferative or severe nonproliferative retinopathy is better than no treatment does not mean that prompt treatment is superior to deferral of treatment until progression occurs.[37]

They called for a randomised trial to examine when best to apply PRP.

Early Treatment Diabetic Retinopathy Study

Background

The ETDRS was a multicentre, randomised clinical trial designed to evaluate argon laser photocoagulation in the management of patients with non-proliferative or early PDR. It was supported by the NEI and arose from results of the DRS, which had shown that laser photocoagulation was effective in reducing the rate of SVL from an advanced stage of DR.[9,40]

Purpose and aims

The three principal clinical questions of ETDRS were:

1. When in the course of DR is it most effective to initiate photocoagulation therapy?
2. Is photocoagulation effective in the treatment of MO?
3. Is aspirin effective in altering the course of DR?

This summary will focus on the first of these questions. Our main interest is between early scatter treatment of eyes with moderate to severe NPDR or PDR without HRCs and deferral of scatter treatment unless PDR with HRCs develops.

Initially, patients were also assigned randomly to aspirin (650 mg per day) or placebo. However, aspirin was not found to have an effect on retinopathy progression, so patients assigned to aspirin were pooled with those assigned to placebo.

Quality assessment

The ETDRS was a high-quality trial with a low risk of bias as shown in *Table 7*.

Patient recruitment

Recruitment of eligible patients began in December 1979 and was completed in July 1985. The 3711 patients accepted for the study, from 22 clinical centres in the USA, were followed through to 1989. Recruitment ended with 98% of the goal of 4000 patients enrolled. By study end, 706 patients had died, and, of the 2971 patients known to be alive, 164 did not have a final eye examination but all but 11 had some sort of final check.

TABLE 7 Quality assessment and risk of bias of ETDRS

Adequate sequence generation	Adequate allocation concealment	Masking[a]	Incomplete outcome data assessed	Free of selective outcome reporting	Free of other biases (e.g. similarity at baseline, power assessment)
Yes (co-ordinating centre staff assigned patients randomly)	Yes (sealed mailer from the central co-ordinating centre)	Partial/unclear? (masking of outcome assessors 'Fundus Photograph Reading Center Staff did not have knowledge of the assigned photo-coagulation strategy', 'Visual acuity examiners were masked from treatment assignment')	Yes (90–95% of expected follow-up visits were completed for first 3 years; 80–90% completed for follow-up longer than 3 years Of the 130,908 expected VA scores, all but 1.5% were available)	Yes (all prespecified outcomes reported)	Yes (groups were well balanced for all characteristics, except a significantly greater proportion in the full scatter group had higher diastolic BP; power calculations performed)

a Details of the methods of the ETDRS were contained in the 894-page ETDRS *Manual of Operations*, (published by the National Technical Information Service, USA) to which we did not have access. Therefore, it was not possible to determine whether patients were aware of the baseline category or the specific type of scatter photocoagulation (full or mild) to which they were assigned.

Patient eligibility

To be eligible for the ETDRS, patients had to be aged between 18 and 70 years and to have DR in both eyes. Each eye had to meet either of the following eligibility criteria:

1. No MO, VA of 20/40 or better and moderate or severe non-proliferative or early proliferative retinopathy, *or*
2. MO, VA of 20/200 or better and mild, moderate or severe non-proliferative retinopathy or early proliferative retinopathy.

Methods for assessing outcome variables

Best corrected visual acuity was measured with logarithmic VA charts at baseline and each subsequent follow-up visit, scheduled at 4-month intervals. A standardised protocol for the collection of VA measurements was used in all clinical centres.

Stereoscopic 30° colour photographs were taken of seven standard fields at baseline, 4 months, 1 year after entry and yearly thereafter. All fundus photographs were graded according to a standardised procedure by the Fundus Photograph Reading Center staff, who had no knowledge of treatment assignments and clinical data.

Definitions of diabetic retinopathy

The ETDRS adopted the DRS definitions of severe NPDR and HR-PDR and defined moderate NPDR (see table in *Appendix 1*). Subsequently, the ETDRS developed a more detailed scale, which provided further subdivisions within both the NPDR and the PDR categories.[6]

Assessment of severity of retinopathy and macular oedema

Fundus Photograph Reading Center staff, without knowledge of treatment assignments and clinical data, followed a standardised procedure to grade fundus photographs and fluorescein angiographs for individual lesions and DR.

Randomisation procedure

To obtain information on the appropriate timing of scatter photocoagulation, one eye of each patient in the ETDRS was assigned randomly to early photocoagulation (either mild or full scatter) and the other to deferral of photocoagulation, with follow-up scheduled every 4 months and photocoagulation to be performed promptly if HR-PDR developed.

All eyes chosen for early photocoagulation were further randomised to one of two scatter photocoagulation techniques (full or mild). Full scatter involved 1200–1600 burns in two sessions, mild scatter 400–650 burns in one session. Eyes also with MO were assigned randomly to one of two timing strategies for focal photocoagulation (immediate or delayed), so that for these eyes there were four strategies of early photocoagulation.

Three categories were defined on the basis of retinopathy severity and the presence or absence of MO at baseline, and the type of photocoagulation differed for each category.

Less severe retinopathy was defined as eyes with mild to moderate non-proliferative retinopathy, and more severe retinopathy as eyes with severe non-proliferative or early PDR.

- **Category 1: eyes without MO** Eyes in this category had moderate to severe non-proliferative or early proliferative retinopathy.

Eyes randomised to immediate photocoagulation were further randomised to full or mild scatter.

In the deferred arm, eyes were followed up at 4-monthly intervals and received photocoagulation if PDR with HRC-PDR developed.

In both arms, delayed focal photocoagulation was initiated during follow-up if clinically significant macular oedema (CSMO) developed (i.e. MO that involved or threatened the centre of the macula).

Ideally, the trial would have separated NPDR from PDR, but this was not done.

- **Category 2: eyes with MO and less severe retinopathy** Eyes in this category had MO and mild to moderate NPDR.

Early photocoagulation for these eyes consisted of (1) immediate focal photocoagulation to treat the MO, which was seen as a greater threat to vision than the retinopathy, with scatter photocoagulation (with further randomisation to mild or full) added if severe non-proliferative or early proliferative retinopathy developed during follow-up and (2) immediate scatter photocoagulation (with further randomisation to mild or full), with focal photocoagulation delayed for at least 4 months.

Eyes assigned to delayed focal photocoagulation received treatment at the 4-month visit if the oedema had not improved clinically and the VA score had not increased by five or more letters by that time. Focal photocoagulation was initiated at the 8-month visit if the oedema was not substantially improved, as demonstrated by either a return of an initially thickened macular centre to normal thickness or improvement in VA score by 10 or more letters. At and after the 12-month visit, initiation of focal photocoagulation was required for all eyes assigned to early PRP if they had CSMO and had not yet received focal photocoagulation. So focal was not given if the MO improved.

In the deferred arm, eyes were followed up at 4-monthly intervals and received scatter photocoagulation if HRC-PDR developed. They could receive focal photocoagulation if CSMO developed. Note that this group could only receive scatter PRP if HRC-PDR developed, whereas the early treatment arm could have PRP if they progressed to severe NPDR, early PDR or HRC-PDR.

- **Category 3: eyes with MO and more severe retinopathy** Eyes in this category had MO and severe non-proliferative or early PDR.

Early photocoagulation for these eyes consisted of (1) immediate focal and scatter photocoagulation (with random allocation to mild or full) or (2) immediate scatter photocoagulation (randomisation to mild or full), with focal photocoagulation delayed for at least 4 months. The same procedure as described above for initiating focal photocoagulation at or after 4 months was used.

In the deferred arm, eyes were followed up at 4-monthly intervals and received photocoagulation if HRC-PDR developed.

Thus, in each of the three categories there are four different randomly allocated strategies for the timing and extent of early photocoagulation. All eyes received scatter (mild or full) originally, and if the retinopathy progressed to HRC-PDR, the mild scatter group received full scatter. Eyes that had MO, or developed it, received full focal photocoagulation treatment. (Approximately 85% of eyes with MO at baseline eventually received focal photocoagulation compared with only 40% of eyes without MO at baseline.)

In the deferred arms, the initial protocol specified that full scatter be given if HRC-PDR developed. The protocol was modified in 1985 to allow focal photocoagulation if CSMO was present. This was because the data had by then shown that focal photocoagulation reduced visual loss in eyes with CSMO.

Early Treatment Diabetic Retinopathy Study photocoagulation technique

Argon laser was chosen for photocoagulation in the ETDRS. The photocoagulation treatment techniques used were based on those used in the DRS and on the clinical experience of the ETDRS investigators.

Major features of the scatter and focal photocoagulation techniques used in the ETDRS are shown in the table in *Appendix 3*.

Full scatter Full scatter treatment consisted of a spot size of 500 μm and exposure time of 0.1 second, used with power adjusted to obtain moderately intense white burns that do not spread to become appreciably larger than 500 μm. It was estimated that a total of 1200–1600 burns were required to complete the full scatter treatment. The protocol specified that division of scatter treatment be applied in two or more episodes, in the hope of reducing the incidence of adverse treatment effects. If applied in two episodes, these were to be no less than 2 weeks apart; if in three or more episodes, these must be at least 4 days apart. No more than 900 scatter burns were to be applied in a single episode, and the initial treatment session was to be completed within 5 weeks.

Mild scatter Mild scatter treatment involved a spot size, exposure time and intensity the same as for full scatter treatment, in order to produce burns of the same strength. Burns were placed at least one burn diameter apart and scattered uniformly across the same zone of retina as specified or full scatter, using 400–650 burns, usually applied at a single episode.

Focal photocoagulation Focal photocoagulation for MO consisted of the application of argon laser burns to focal lesions (such as leaking microaneurysms as determined by FA or areas of retinal ischaemia) located between 500 and 3000 μm from the centre of the macula.

Definition of terms used in the Early Treatment Diabetic Retinopathy Study

A definition of the terms as used in the ETDRS studies is given in *Table 8.*

TABLE 8 Early Treatment Diabetic Retinopathy Study: definition of terms

SVL	VA < 5/200 at two consecutive follow-up visits (scheduled at 4-month intervals)
Moderate visual loss	Loss of 15 or more letters between baseline and follow-up visit, equivalent to a doubling of the visual angle (i.e. 20/20 to 20/40 or 20/50 to 20/100)
MO	Thickening of the retina within one DD of the centre of the macula: and/or hard exudates ≥ standard photograph 3 in a standard 30-degree photographic field centred on the macula (field 2), with some hard exudates within one DD of the centre of the macula
CSMO	Retinal thickening at or within 500 μm of the centre of the macula; and/or hard exudates at or within 500 μm of the centre of the macula, if associated with thickening of the adjacent retina. A zone or zones of retinal thickening one disc area or larger, any part of which is within one DD of the centre of the macula
NVD	New vessels on the disc or retina within one DD of the disc margin, or located in the vitreous any distance anterior to this area, determined by grading fundus photographs
NVE	New vessels 'elsewhere' (outside the area defined for NVD), determined by grading fundus photographs

End points

The primary end point for assessment of early photocoagulation was the development of SVL. This was defined as VA < 5/200 at two consecutive follow-up visits (scheduled at 4-month intervals). BCVA was measured at 6 weeks and 4 months after randomisation. The procedure was repeated every 4 months thereafter.

Other end points evaluated included either severe visual loss or vitrectomy (SVLV), and change between baseline and follow-up visits in visual field, colour vision or retinopathy. Visual fields were assessed by Goldman perimetry and identification of scotomas.

Study power

Power calculations for the primary end point of SVL assumed that 10% of eyes assigned to deferral would develop SVL within 5 years. With 2000 eyes assigned to the deferral group and their 2000 fellow eyes assigned to early photocoagulation, a 40% reduction in the rate of SVL could be detected with 98% power.

Statistical methods

Comparisons of end points expressed as proportions of events were made with two-sample tests of equality of proportions. Comparisons of continuous variables were based on the two-sample z-test of equality of means.

Because multiple end points in the different groups were compared several times for the Data Monitoring Committee, a 0.01 level of probability was used for the primary end points rather than 0.05. Observed z-values of ± 2.58 or more extreme (corresponding to a 0.01 level for a single test of significance) were considered statistically significant.[9]

Baseline characteristics

The baseline characteristics of the ETDRS patients, by assignment of scatter photocoagulation are shown in *Table 9*.

Of the 3711 patients randomised, 56% were male, 52% were between 50 and 70 years of age, 57% had a duration of diabetes between 10 and 19 years, and 30% were classified as having type 1 diabetes.

By today's standards, control of blood glucose, BP and cholesterol would not be considered satisfactory; 19% had systolic blood pressure (SBP) of 160 mmHg or more, and 42% had HbA_{1c} of 10% or more; 36% had total cholesterol level over 6.2 mmol/l. The mean HbA_{1c} was over 12%.

Groups were well balanced for all characteristics, except that a significantly greater proportion in the full scatter group had higher diastolic BP.

In 75% of ETDRS patients both eyes belonged to the same baseline category. Within each baseline category there were no large differences in mean VA scores between groups of eyes assigned to various strategies for early photocoagulation and eyes assigned to deferral of photocoagulation. Randomised treatment groups were comparable. Adherence to the assigned strategy for photocoagulation at the initial treatment session was reviewed and found to be over 98% for application of the assigned scatter and/or focal photocoagulation.

TABLE 9 Baseline characteristics of the ETDRS patients (from table 6, ETDRS #7[40])

Characteristics		Mild scatter (n = 1868)		Full scatter (n = 1843)	
		n	%	n	%
Age at entry (years)	< 30	300	16	326	18
	30–49	611	33	557	30
	≥ 50	957	51	960	52
Sex (male)		1063	57	1033	56
Race (white)		1440	77	1394	76
Type 1 diabetes		558	30	572	31
Duration of diabetes (years)	< 10	312	17	298	16
	10–19	1085	58	1034	56
	≥ 20	471	25	511	28
Per cent desirable weight	≥ 120	768	41	773	42
SBP (mmHg)	≥ 130	1215	65	1233	67
	≥ 160	357	19	392	21
Diastolic BP (mmHg)	≥ 85	691	37	760	41[a]
	≥ 90	478	26	583	32[b]
History of cardiovascular disease		884	47	928	50
Cigarettes/day ≥ 6		842	45	799	43
Severity of retinopathy	Level ≤ 35 (mild NPDR)	316	17	288	16
	Level 43 (moderate NPDR)	452	24	459	25
	Level 47 (moderately severe NPDR)	477	26	482	26
	Level 53a–d (severe NPDR)	245	13	231	13
	Level 53e (very severe NPDR)	50	3	53	3
	Level 61 (mild PDR)	169	9	169	9
	Level 65 (moderate PDR)	153	8	155	8
	Level 71 (HR-PDR)	6	< 1	6	< 1
For patients enrolled before September 1983	HbA$_{1c}$ ≥ 10%	566	42	556	42
Serum cholesterol	≥ 240 mg/100 ml (6.2 mmol/l)	495	36	470	35
Low-density lipoprotein	Cholesterol ≥ 160 mg/100 ml (4.1 mmol/l)	318	25	346	27

a $p < 0.01$ (using a z-test for equality of portions).
b $p < 0.001$ (using a z-test for equality of portions).

Results

Severe visual loss

All eyes in ETDRS had low rates of SVL, whether they received early photocoagulation (2.6%) or were in the deferral group (3.7%) at 5 years.

The relative risk (RR) of SVL for the entire period of follow-up in eyes assigned to early photocoagulation (including all strategies) compared with eyes assigned to deferral photocoagulation was 0.77 (99% CI 0.56 to 1.06), calculated using a Cox proportional hazards model with retinopathy severity and presence or absence of MO at baseline as covariates.

The RRs of SVL with photocoagulation compared with deferral for all baseline retinopathy categories when all photocoagulation strategies are compared are summarised in *Table 10*. It can be seen from the CIs that in none of the categories was the RR statistically significant.

Data for the development of SVL for all baseline categories are shown in *Table 11*, which gives estimates of RR in each of the categories. Analyses for the 5-year follow-up period demonstrated no statistically significant differences between any of the strategies for early photocoagulation and deferral within each category.

The eyes assigned to full scatter showed a trend towards a greater treatment effect than eyes assigned to mild scatter in the first two categories. The RR of SVL for the entire period of follow-up for all categories combined in eyes assigned to early full scatter compared with eyes assigned to deferral was 0.69 (99% CI 0.45 to 1.05); in eyes assigned to mild scatter the RR was 0.84 (99% CI 0.57 to 1.25); so neither early or full scatter showed a significant decrease in RR, but full was slightly better than mild at preventing SVL.

Both the severity of retinopathy and the presence of MO at baseline were both significantly associated with the development of SVL. The RR (adjusting for the presence of MO) for the development of SVL for eyes with more severe retinopathy compared with eyes with less severe retinopathy was 2.41 (99% CI 1.73 to 3.37). Similarly, the RR (adjusting for severity of retinopathy) for the development of SVL for eyes with MO compared with eyes without MO was 1.73 (99% CI 1.17 to 2.57).

Causes of severe visual loss in the Early Treatment Diabetic Retinopathy Study

Severe visual loss developed in 257 eyes (219 persons); however, 17 of these 257 eyes with SVL had insufficient follow-up and were not included in the analysis. Of the 240 eyes left for analysis, 149 eyes (127 persons) did not recover to 5/200 or better at any visit (persistent SVL) and VA improved in 91 eyes.[41]

The most common cause of SVL was vitreous or pre-retinal haemorrhage, occurring in 125 (52.1%) of the 240 eyes included in the analysis. The second and third most common causes were MO (13.8%), and macular or retinal detachment (7.1%).

TABLE 10 Relative risk of SVL for eyes assigned to early photocoagulation (combining all strategies for photocoagulation) compared with deferral

Baseline retinopathy category	RR
1. Eyes without MO	1.37 (99% CI 0.67 to 2.77)
2. Eyes with MO and less severe retinopathy	0.59 (99% CI 0.32 to 1.09)
3. Eyes with MO and more severe retinopathy	0.70 (99% CI 0.44 to 1.11)
All baseline categories combined	0.77 (99% CI 0.56 to 1.06)

TABLE 11 Development of SVL (taken from table 7, ETDRS #9[9])

| Baseline retinopathy category | Photocoagulation treatment strategy | | | | |
| | Early full scatter | | Early mild scatter | | |
	Immediate focal	Delayed focal	Immediate focal	Delayed focal	Deferral
1. No MO					
1-year rate (%)		0.2		0.3	0.2
3-year rate (%)		1.8		1.8	0.9
5-year rate (%)		2.7		2.6	2.2
No. of eyes		583		590	1179
RR (99% CI)		1.24 (0.52 to 2.98)		1.49 (0.65 to 3.39)	
2. MO and less severe retinopathy					
1-year rate (%)	–	0.3			0.1
3-year rate (%)	0.3	0.9	0.3	0.9	1
5-year rate (%)	1	0.9	2.2	1.2	2.9
No. of eyes	362	356	365	365	1429
RR (99% CI)	0.43 (0.13 to 1.44)	0.43 (0.13 to 1.44)	0.75 (0.29 to 1.91)	0.74 (0.29 to 1.88)	
3. MO and more severe retinopathy					
1-year rate (%)	1.5	1.2	0.7	0.4	1.1
3-year rate (%)	2.6	2.8	3.5	2.4	3.8
5-year rate (%)	4.7	3.8	4	4.1	6.5
No. of eyes	272	270	276	272	1103
RR (99% CI)	0.78 (0.68 to 1.62)	0.59 (0.26 to 1.34)	0.74 (0.35 to 1.57)	0.68 (0.31 to 1.46)	

When patients with persistent SVL were compared with patients without persistent SVL, they were found to have higher mean levels of HbA_{1c} (10.4% vs. 9.7%; $p = 0.001$) and higher levels of cholesterol (244.1 vs. 228.5 mg/dl; $p = 0.0081$) at baseline.[41]

The low frequency of SVL in ETDRS is probably due to the use of PRP as soon as HR-PDR developed, and to vitrectomy when required.

Severe visual loss: subgroup analysis of type 1 versus type 2 diabetes

Patients were categorised into type 1 and type 2 diabetes in order to conduct a subgroup analysis of the ETDRS data to determine whether the effects of photocoagulation on SVL in patients differed by type of diabetes.[42]

The benefit of early photocoagulation for SVL was statistically significantly greater in patients with type 2 diabetes than in those with type 1 diabetes. (Cox regression for SVL: interaction of early photocoagulation and type of diabetes; $p = 0.0003$). However, the reduction was small and the risk was low in the deferral group in which only 3.7% developed SVL. (Note that the definition used was truly severe – very low levels of vision). Also, because of the high correlation between age and type of diabetes, a subgroup analysis by age showed similar results. The results varied amongst the categories, and according to outcome. In patients with mild to moderate NPDR at baseline, a small benefit of laser in reducing SVLV was seen in both types of diabetes with no interaction between laser treatment and type of diabetes. In patients with more severe retinopathy (severe NPDR or early PDR) there was no difference in SVLV in type 1 diabetes between early and deferred laser, but a large difference in type 2, partly because they had much poorer outcomes than those with type 1.[42]

If we use progression to HRC-PDR as the outcome, statistically significant benefit is seen in both types of diabetes. If we use reduction in VA, there is a large difference between early and deferred laser in patients with type 2 diabetes and clinically significant MO who had severe NPDR or early PDR at baseline but little in patients with type 1. If we look only at those who did not have CSMO at baseline, there is no difference in type 2 between early and deferred groups.

If we use legal blindness (defined in ETDRS as VA worse than 20/100), patients with type 2 diabetes again show a significant difference between early and deferred groups, whereas no difference is seen in type 1, but the frequency of this outcome was much higher in type 2.

The difference between the types of diabetes may be due to chance. As the ETDRS authors stated, many analyses were done and chance could lead to 'statistically significant' results. They show this quite neatly by doing a subgroup analysis on date of birth, which showed a statistically significant interaction.[42]

Vitrectomy

The initial ETDRS protocol said that vitrectomy should be done after SVL had occurred, but this was changed after the results of the Diabetic Retinopathy Vitrectomy Study appeared in 1985, and earlier vitrectomy was performed, either 1 month after detection or as soon as progressive retinal detachment occurred.[43] This meant that vitrectomy was performed in many ETDRS patients who had not developed SVL.

Vitrectomy was performed at least once in 208 (243 eyes) of the 3711 patients (the overall vitrectomy numbers suggest that about 18% of eyes had more than one vitrectomy.) At baseline, eyes undergoing vitrectomy were more likely to have severe non-proliferative or worse retinopathy. Also, there were no differences in the mean VA scores or percentages with clinically significant MO. It appears that all patients who had vitrectomy, did so after developing HRC-PDR, on average 21 months before vitrectomy. About 20% had SVL before vitrectomy.[44]

The majority of patients undergoing vitrectomy had type 1 diabetes. The indications for vitrectomy were either vitreous haemorrhage (53.9%) or retinal detachment with or without vitreous haemorrhage (46.1%).

The cumulative rates of vitrectomy were 3.9% and 2.2% in the deferred and early groups, respectively, so this outcome was about as common as SVL.

The 5-year vitrectomy rates for eyes grouped by their initial photocoagulation assignment were 2.1% of eyes assigned to early full scatter photocoagulation group, 2.5% of eyes assigned to the early mild scatter group, and 4.0% of eyes assigned to the deferral group (based on ETDRS #17[44] – ETDRS #9[9] gives a figure of 3.9% for the deferred group).

Comparison of eyes assigned to deferral of photocoagulation with eyes assigned to early photocoagulation showed no statistically significant difference in post-vitrectomy VA results; however, it should be noted that because they all developed HR-PDR before vitrectomy, most (88%) had had PRP, most with full scatter. After vitrectomy, results in immediate and deferred groups were similar – the outcome of surgery was not affected by delaying PRP. Also, there was no statistically significant difference between eyes that received either less than full scatter or no photocoagulation compared with eyes that received full scatter photocoagulation.[44]

Severe visual loss or vitrectomy

The ETDRS #7[40] (the design paper) does not mention vitrectomy as an outcome. However, the final analysis used as one outcome, the combination of SVL and vitrectomy (SVLV), based on the reasoning that vitrectomy had saved an unknown number of eyes from SVL, and because vitrectomy could be considered an indicator of vitreous haemorrhage that had failed to clear.

The RR of SVLV at end of follow-up for eyes assigned to early photocoagulation compared with eyes assigned to deferred photocoagulation was statistically significant at 0.67 (99% CI 0.52 to 0.87).[9]

The RRs of SVLV by baseline categories were:

- no MO = 0.78 (99% CI 0.47 to 1.29)
- MO and less severe retinopathy = 0.55 (99% CI 0.33 to 0.94)
- MO and more severe retinopathy = 0.68 (99% CI 0.47 to 0.99).

So, once again, eyes in category 1 had a lower reduction in RR than eyes in the MO groups.

The VA immediately before vitrectomy was 5/200 or worse in 67%, but afterwards only about 28% were left with such poor vision. About 20% had VA better than 20/40 at 3 years, so vitrectomy was highly beneficial in most.

Development of high-risk characteristics proliferative diabetic retinopathy

Results for the development of HRC-PDR by baseline retinopathy category and photocoagulation strategy are shown in *Table 12*.

Compared with deferral of photocoagulation, early photocoagulation reduced the rate of progression to HR-PDR in each baseline category (Mantel–Cox test: $p < 0.001$ for each strategy of early photocoagulation compared with deferral, except for immediate focal and mild scatter photocoagulation in eyes with MO and less severe retinopathy; $p = 0.09$). The reduction was greater in eyes with full scatter than mild scatter, essentially similar for all categories.

The RRs are adjusted for retinopathy severity and the presence or absence of MO.

TABLE 12 Development of HRC-PDR by photocoagulation strategy (taken from table 5, ETDRS #9[9])

Baseline retinopathy category	Early full scatter		Early mild scatter		
	Immediate focal	Delayed focal	Immediate focal	Delayed focal	Deferral
No MO					
5-year rate (%)		18.8		26.9	38.5
RR (99% CI)		0.41 (0.31 to 0.55)		0.64 (0.51 to 0.61)	
No. of eyes		583		590	1179
MO and less severe retinopathy					
5-year rate (%)	13.7	8.5	21.4	16.6	26.7
RR (99% CI)	0.52 (0.36 to 0.75)	0.27 (0.16 to 0.44)	0.81 (0.59 to 1.11)	0.56 (0.39 to 0.80)	
No. of eyes	362	356	365	365	
MO and more severe retinopathy					
5-year rate (%)	28.8	26.3	40.3	46.7	61.3
RR (99% CI)	0.36 (0.26 to 0.49)	0.34 (0.25 to 0.47)	0.59 (0.46 to 0.77)	0.67 (0.53 to 0.87)	
No. of eyes	272	270	276	272	

The deferral arms afforded the possibility to determine the natural history of retinopathy by examining the 5-year rate of progression to the HR-PDR stage. The risks of progression in the deferral arms were 38.5% in the eyes with no MO and more severe retinopathy, 26.7% in eyes with MO and less severe retinopathy and 61.3% in eyes with MO and more severe retinopathy.

Table 13 shows the development of HRC-PDR in eyes assigned to deferral by baseline retinopathy severity level. It can been seen that the risk of progression increases steadily with severity of retinopathy at baseline, with 5-year rates increasing from 15.5% in eyes with mild NPDR, to 56% in eyes with severe NPDR, up to 74.5% in eyes with moderate proliferative retinopathy.

In all categories, the 5-year risk of HRC-PDR was lowest in eyes that had full scatter PRP and highest in the deferred group. Full scatter reduced HRC-PDR by 50% and mild scatter by 25% compared with the deferred group.

Results after lens extraction

Lens surgery was performed on 205 patients (270 eyes) of the 3711 patients in the ETDRS, during follow-up that ranged from 4 to 9 years. Those having surgery were more likely to be white, older and have type 1 diabetes. Most of the lens surgery was done because of cataract; however, some may have been performed because of lens opacity that developed during or after vitrectomy.[45]

Eyes assigned to early photocoagulation were more likely than eyes assigned to deferral of photocoagulation to have received scatter and/or focal photocoagulation before lens surgery. However, 64.8% of eyes assigned to deferral of photocoagulation also had scatter and/or focal photocoagulation before lens surgery.

A large proportion of all operated-on eyes had improved VA postoperatively. Eyes assigned to early photocoagulation had a trend towards a better VA outcome after lens surgery than eyes assigned to deferral, but this was not statistically significant ($p = 0.04$).

TABLE 13 Development of HRC-PDR in all eyes assigned to deferral by baseline retinopathy severity level (based on table 6, ETDRS #9[9])

Baseline retinopathy severity (level)	No. of eyes	Cumulative rate (%) of high-risk proliferative retinopathy: 5 years
Level ≤ 35 (mild NPDR)	609	15.5
Level 43 (moderate NPDR)	906	26.5
Level 47 (moderately severe NPDR)	938	39.4
Level 53a–d (severe NPDR)	500	56.0
Level 53e (very severe NPDR)	92	71.3
Level 61 (mild PDR)	339	63.8
Level ≥ 65 (moderate PDR)	327	74.7
Total	**3711**	**40.7**

Moderate visual loss

Percentages of eyes in which moderate visual loss occurred are shown for each baseline category in
Table 14 for up to 5 years of follow-up. Moderate visual loss in the deferred groups was commoner at
5 years in the two MO groups (prevalence 30.2% and 32.1%) than in category 1 with no MO (17.6%).

It can been seen that for all baseline categories full scatter photocoagulation appeared to have an adverse
effect on moderate visual loss at both the 6-week and 4-month follow-up visits. This effect was also seen
to a lesser extent with mild scatter. For eyes without MO there was a statistically significant effect of higher
moderate visual loss in eyes for full scatter up to 2 years. At 3 and 5 years there was a no significant
difference in eyes with photocoagulation compared with deferral.

TABLE 14 Occurrence of moderate visual loss (taken from table 9, ETDRS #9[9])

Baseline retinopathy category	Early full scatter		Early mild scatter		
	Immediate focal	Delayed focal	Immediate focal	Delayed focal	Deferral
No MO					
6-week rate (%)		3.1[a]		0.8	0.4
4-month rate (%)		3.8[a]		1.0	0.6
1-year rate (%)		7.5[b]		4.3	3.6
2-year rate (%)		10.8[a]		8.3	5.9
3-year rate (%)		13.6		12.1	9.8
5-year rate (%)		15.5		13.3	17.6
No. of eyes		583		590	1179
MO and less severe retinopathy					
6-week rate (%)	1.4	4.5	1.6	3.0	1.6
4-month rate (%)	2.5	9.7[a]	2.2	6.4	3.8
1-year rate (%)	5.3	15.9[a]	3.7[a]	10.5	8.6
2-year rate (%)	7.6[a]	19.1	8.9[a]	15.1	16.6
3-year rate (%)	11.2[a]	23.1	12.2[a]	19.0	21.1
5-year rate (%)	22.4	29.8	19.5[a]	21.8[b]	30.2
No. of eyes	362	356	365	365	1429
MO and more severe retinopathy					
6-week rate (%)	7.7[a]	7.8[a]	7.6[a]	5.9[b]	1.7
4-month rate (%)	12.2[b]	11.2	4.8	10.1	6.5
1-year rate (%)	16.2	16.9	12.7	13.6	15.5
2-year rate (%)	21.1	20.0	15.3[b]	21.5	22.2
3-year rate (%)	23.6	20.9	20.7	23.3	27.1
5-year rate (%)	26.2	24.1	24.1	25.7	32.1
No. of eyes	272	270	276	272	1103

a *p* < 0.001 (using a *z*-test for equality of portions).
b *p* < 0.01 (using a *z*-test for equality of portions).

In eyes with MO and less severe retinopathy the increase in moderate visual loss was statistically significant at 4 months, and 1 year for eyes with full scatter, but at 2, 3 and 5 years there were no significant differences. At the 5-year follow-up there was a statistically significant decrease in moderate visual loss in eyes with mild scatter and a non-significant decrease in eyes with full scatter. Eyes with immediate focal photocoagulation appeared to show a statistically significant beneficial effect of early photocoagulation for all follow-up points, beginning with the first year.

In eyes with MO and more severe retinopathy, there was a significant increase in moderate visual loss at 6 weeks for all strategies of photocoagulation. At 4 months this was seen only for eyes with immediate focal and full scatter. The only other significant difference was a lower rate at 2 years for eyes with immediate focal and mild scatter.

The summary of ETDRS #9[9] notes that scatter photocoagulation was not effective in reducing moderate visual loss in patients with MO.

Visual field

The cumulate distribution of visual field scores obtained using the Goldman 1/4e test object at baseline, 4- and 48-month visits showed no difference in distributions of visual field between categories of assigned strategies at baseline.[9] The Goldman method is less sensitive than methods used today.

By the 4-month visit, eyes assigned to deferral of photocoagulation showed no significant change in scores compared with baseline. By contrast, at 4 months all three baseline categories of eyes assigned to immediate full scatter photocoagulation had significantly greater loss of visual field than eyes assigned to deferral ($p < 0.001$). Eyes with mild scatter also showed a lower loss of visual field. There was a statistically significant difference ($p < 0.001$) between the loss of visual field between eyes assigned to immediate full and immediate mild scatter. So mild scatter may be less effective, but has fewer adverse effects.

The visual field worsened in all groups from baseline to 4 years. The scores for eyes assigned to immediate full scatter remained significantly ($p < 0.001$) worse than for eyes assigned to deferral. This reflects the harm done by PRP.

Colour vision

Colour vision was measured using the Farnsworth–Munsell 100 hue test at baseline, and at 8-month and 4-year follow-up visits. There was significant impairment of colour vision at baseline, with 50% of the ETDRS population having colour vision scores worse than 95% of the normal population. Colour vision is a macular function so should not be affected by PRP to the peripheral retina, but might be affected by focal or grid laser for MO.

Eyes with more severe retinopathy, both without and with MO, showed no significant difference at any visit between eyes assigned to any strategy of early photocoagulation and eyes assigned to deferral. All of the eyes with MO and more severe retinopathy assigned to early photocoagulation had scatter photocoagulation as part of their initial treatment.

However, for eyes with less severe retinopathy and MO assigned to immediate focal and delayed scatter photocoagulation, there was less loss of colour vision at the 4-year visit ($p < 0.001$) comparing the combination of both groups of eyes assigned to immediate focal with eyes assigned to deferral.

Summary and conclusions

Severe visual loss

The primary end point of the ETDRS was the development of SVL. The 5-year RR of SVL for eyes assigned to early photocoagulation (combining all strategies for photocoagulation) compared with deferral for all baseline categories combined was 0.77 (99% CI 0.56 to 1.06). Thus, it was shown that early photocoagulation reduces the risk of SVL by about 23%, but the 99% CI overlapped with no difference.

When analysed by baseline retinopathy category it was shown that eyes with MO and less severe retinopathy had a lower RR of 0.59 (99% CI 0.32 to 1.09) and eyes with MO and more severe retinopathy showed a RR 0.70 (99% CI 0.44 to 1.11), respectively. Eyes with no MO and more severe retinopathy had a higher RR of 1.37 (99% CI 0.67 to 2.77) but the CIs were wide.

Severe visual loss or vitrectomy

The combined end point of SVLV showed a 33% reduction with early photocoagulation compared with deferral, with a RR of 0.67 (99% CI 0.52 to 0.97). As noted above, about 20% of eyes that had vitrectomy had SVL before vitrectomy but the rest did not, and many improved thereafter.

High-risk proliferative retinopathy

Early photocoagulation resulted in a significant reduction in the rate of developing high-risk proliferative retinopathy compared with deferral of photocoagulation. Strategies for photocoagulation that included immediate full scatter reduced the rate of developing high-risk proliferative retinopathy by approximately 50%, whereas strategies that included immediate mild scatter reduced that rate by approximately 25%.

When eyes assigned to deferral were stratified according to baseline retinopathy, the rate of progression to the high-risk stage generally increased as the retinopathy increased.

Harms

There were some harmful effects associated with early scatter photocoagulation. Adverse effects of moderate visual loss were shown more frequently at 6 weeks and 4 months compared with eyes assigned to deferral, but this loss was not shown in any group by the 3-year follow-up.

There was evidence of a significant loss of visual field in all groups at 4 years and this was worse for eyes assigned to full scatter. Also, colour vision showed some reduction at 4 years in the category of eyes with less severe retinopathy and MO assigned to immediate focal and delayed scatter photocoagulation.

The Early Treatment Diabetic Retinopathy Study conclusions and recommendations

Data from the ETDRS demonstrated that early photocoagulation reduced the risk of developing SVL, and the risk of progression of retinopathy. However, the rates of SVL were low in both the early photocoagulation and deferral groups, and statistical significance using 99% CIs was obtained for SVLV but not for DVL alone.

When making the decision whether to initiate scatter photocoagulation, the side effects must be carefully considered. For most eyes that have not yet reached the high-risk proliferative stage, these side effects of scatter photocoagulation must be balanced with the possible small benefit of early photocoagulation in reducing the risk of SVL.[9]

The ETDRS recommended that:

> Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate non-proliferative retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage.

Discussion

Rates of progression to SVL in ETDRS were low. They might be even lower now, with tighter control of blood glucose, BP and lipids. Tighter control of metabolic factors especially glycaemia can also slow progression. There was a fear that if HbA$_{1c}$ is reduced too quickly, retinopathy may temporarily worsen, usually, but not always, temporarily – the 'glycaemic re-entry' phenomenon.[46] This phenomenon may date from the days when patients were left poorly controlled on oral agents for years and then started on insulin, and is less common now. However, it is still seen in pregnancy if that stimulates a rapid improvement in control – a dramatic drop in HbA$_{1c}$ may be associated with a deterioration in retinopathy.

The diagnosis of sight-threatening retinopathy may be a powerful motivating factor.

The differences were more marked in progression to HR-PDR, so perhaps with longer follow-up the SVL differences would have increased, though not if they were carefully monitored and PRP given once HRC appeared. However, it should be borne in mind that in category 2 (MO and less severe retinopathy) the deferred group could receive PRP only once they reached HR-PDR, whereas the early photocoagulation groups could have 'rescue' PRP from the severe NPDR stage onwards. So there was some imbalance in application of rescue laser.

As reported in *Table 10*, the RR for progression to SVL in category 1 eyes (i.e. eyes without MO) was 1.37 (99% CI 0.67 to 2.77), i.e. the early PRP group did worse, though not statistically significantly, than in categories 2 and 3, which all had MO at baseline. It is likely that if this group was removed from the combined analysis, the overall RR would have been less than the 0.77 (99% CI 0.56 to 1.06) and the primary end point result would have been statistically significant. This might suggest that treating MO avoided SVL more than treating retinopathy. However, as reported above, the main cause of SVL was vitreous or pre-retinal haemorrhage (52%), with MO well behind at 14%, followed by macular or retinal detachment (7.0%).

The reason for the MO groups doing better than category 1 may simply be that they had a higher risk of visual loss and so more to gain.

The level of vision used for the primary outcome (less than 5/200) was very low – any trial nowadays would try to preserve vision at better levels, for example at 20/200. The ETDRS definition of moderate visual loss was defined in ETDRS #9[9] as loss of 15 letters or more between baseline and follow-up, which would apply today.

Pautler (2010)[47] noted the clear recommendation from the ETDRS group against PRP in eyes with mild or moderate NPDR, but commented that the recommendations for severe NPDR and early PDR were much less clear – only that PRP should be considered. He suggests that 'This cautious wording may have led physicians away from treating this group of eyes'.

Pautler (2010)[47] suggests that PRP might be used in severe NPDR and early PDR in the following situations:

- bilateral DR approaching HR-PDR
- poor compliance with follow-up
- poor glycaemic control
- type 1 diabetes (despite the ETDRS result showing greater effect in type 2 diabetes)
- DMO (but treating the DMO first)
- previous SVL in the other eye
- pregnancy
- rubeosis (new vessels in the iris)
- large area of new vessels outside the macula.

He also suggests factors that might lead to postponement of PRP in eyes with severe NPDR or early PDR such as past laser harm in the other eye, good glycaemic control, no DMO, low-risk of visual loss in the fellow eye and patient preference.

In the ETDRS, PRP was applied to all midperipheral retina, whether ischaemic or not. Currently, using wide-angle FA, areas of retinal ischaemia can be adequately identified. Laser photocoagulation could be applied selectively to areas of retinal ischaemia, potentially reducing side effects of this treatment, such as visual field defects, as in the Japanese trial[17] described in *Chapter 3*.

The risk of progressing to HRC-PDR was reduced more than that of SVL. The reduction in the risk of progression to HRC-PDR is not unexpected. PRP treatment ablates much of the retina. As it appears that retinal ischaemia drives the VEGF response required for the development and support of neovascularisation, following laser treatment there would be little chance for PDR to occur. In the ETDRS, patients were followed at 4-monthly intervals (unless a problem such as vitreous haemorrhage occurred). It is unknown whether similar results would still be observed if the trial would have allowed closer follow-up so that HR-PDR could have been treated more promptly.

One of the possible side effects of PRP that could have a negative impact in the QoL of patients undergoing this treatment is the development of peripheral visual field defects. Depending on their severity, peripheral visual field defects may prevent individuals from driving. Delaying PRP until it is clearly needed – for instance, until neovessels develop – may give individuals extra years of maintaining driving standards and better QoL. About 20% of people may not meet Driver and Vehicle Licensing Agency (DVLA) driving standards after bilateral PRP.[48]

The ETDRS established two groups, based on fundus examination, for the evaluation of treatment effects: (1) severe NPDR and early PDR and (2) HR-PDR. However, the presence or absence of neovascularisation clearly determines a different stage of disease, as visual loss occurs as a direct result of the neovascularisation process in most cases. This is illustrated by the fact that over half of people in the ETDRS who experienced SVL did so as a result of vitreous or pre-retinal haemorrhage. Thus, it might have been more appropriate to evaluate the effectiveness of treating with PRP at early PDR (less than HRCs) stage when compared with treating when HR-PDR characteristics had developed. A third group with severe NPDR could have also been included. Having severe NPDR and early PDR together made this group somewhat heterogeneous.

Decision problem revisited

The ETDRS was a very good quality and detailed study. However, it was conducted several decades ago, and one question is whether new developments since the time of the ETDRS have changed the balance of benefits and harms.

These developments include:

- Improvements in diabetes care, with better control of blood glucose, BP and lipids.
- Changes in laser treatment, arising from advances in laser technologies, different regimens and better targeting of laser therapy. There has been a trend to 'lighter' laser treatment with the aim of causing fewer adverse effects but retaining the same effectiveness.
- The advent of new drugs for DMO, which may also affect retinopathy, and, more importantly for our purposes, are being used in combination with laser photocoagulation in DMO, partly to reduce the adverse effects. Patients with both DMO and PDR will be expected to receive both PRP and anti-VEGFs, and the latter may affect the PDR.
- Advances in imaging, such as optical coherence tomography (OCT), which may make detection of DMO more reliable.

Given these changes, the next questions are:

1. If it was decided to start PRP at the NPDR stage, based on the results of ETDRS, what sort of laser treatment would be used? Pattern lasers?
2. If PRP was given earlier, should it be targeted at areas of retinal ischaemia, as detected by wide-angle FA, or given by conventional PRP that ablates the whole mid/peripheral retina, both perfused and non-perfused areas (NPAs)? (The same question could apply to PRP for PDR.)
3. Should drug treatment, mainly with the anti-VEGF drugs, or perhaps with intravitreal steroids, also be used in combination with PRP?

These questions are addressed in the *Chapters 3* and *4*.

Another issue is whether modern techniques of measuring DR and MO might also affect staging of retinopathy, and aid selection of people for PRP. This might be done both by determining who is at most risk of progression to HR-PDR, and who is at most risk from damage by PRP. This might ensure that PRP is given to the people who will most benefit. It is known that eyes with MO before PRP are more likely to have a reduction in VA after PRP,[9,49] and, as has been pointed out by Browning (2005)[50]/Browning *et al.* (2004)[51] and Massin *et al.* (2006),[52] ophthalmologists often have difficulty detecting MO. Browning *et al.* (2008)[53] also reported that the probability of MO being detected by OCT, but not by clinical examination (stereoscopic slit-lamp examination), increased as the retinopathy became more severe. The advent of OCT with its very good sensitivity for detecting retinal thickening should lead to better detection of MO and consequent tailoring of laser treatment to the needs of the individual eye.

Chapter 3 Laser studies: efficacy and safety

Aim of the chapter

The evidence from ETDRS suggests that treatment of severe NPDR and early PDR was more effective in reducing future visual loss than waiting to treat at HR-PDR stage, but there are weaknesses in the evidence. Only SVLV reached statistical significance. ETDRS did not provide results separately for severe NPDR and early PDR. The primary end point was SVL which was uncommon in all groups, and as defined was very severe. The reduction in the development of HRC-PDR in eyes treated with PRP earlier might have been expected to lead to further reductions in visual loss with longer follow-up.

So one question for policy-makers is whether the evidence is deemed sufficient to recommend PRP at NPDR and early PDR stage, or whether further research is necessary, which might include separating NPDR and early PDR.

However, the balance of risk and harm, and costs, may have changed since the advent of new laser technologies and treatment regimes. These may be as effective but have fewer adverse effects. So recommendation for treatment or for further research would need to take account of changes in:

- laser machines
- more modern regimens. It is necessary to consider both type of laser and the ways in which they are used – number of burns, number of sessions, selective versus PRP
- more accurate diagnosis aided by imaging devices such as OCT and wide-angle cameras, that were not available at the time of the DRS and ETDRS
- metabolic control.

In this chapter we review some laser studies from more recent times. The main aim is to identify which machines and regimens would be used now, either in treatment or research. Preliminary searches showed that none of the newer trials addressed our primary question of the optimum timing of PRP, and we therefore decided to use studies of laser photocoagulation at later stages and see what could be extrapolated from these.

A feature of trends in laser photocoagulation is that it tended to use less intense laser burns, and may be more targeted, for example treating only areas of peripheral ischaemia detected using wide-angle FA, with fewer adverse effects. One question which then arises is whether it has become less effective.

Modified ETDRS (mETDRS) direct/grid photocoagulation as used for DMO was described by the DRCRN (DRCRnet) as being targeted only at areas of thickened retina, areas of retinal non-perfusion and leaking microaneurysms using a smaller laser spot (50 μm) and less intense burn end point (grey) in order to balance therapeutic effect and adverse effects.[54]

Most people now use pattern lasers for PRP, rather than the argon laser, because they are faster and less painful, but there is still sparse use of argon.

The sub-threshold diode laser is less destructive than the argon laser, depending on how it is applied. If at sub-threshold level then it would be expected to cause less damage than argon applied at threshold levels. If the diode was applied with a micropulse mode (reducing the temperature of the tissue – less thermal effect so less damage. Photocoagulation with the diode laser is reported to damage only the outer retinal layers and the choroid, whereas the argon laser damages both inner and outer retina and choroid.[55]

The sub-threshold diode laser has been introduced in the treatment of DMO, but has not spread much into use, possibly because for PRP, it requires more sessions and more burns.[15]

We also note that in Japan, a more selective approach to laser therapy is used, with targeting based on FA, so that only ischaemic areas are lasered.[17] This is a more restrictive approach than traditional PRP.

Methods

Inclusion and exclusion criteria for Chapters 3 and 4
We used the same approach for laser trials (this chapter) and drug–laser combinations (see *Chapter 4*).

Inclusion criteria

Type of studies

- For comparing effectiveness of different types of laser treatment and of the combination of lasers and anti-VEGF and steroid injections, we looked for RCTs.
- For assessing adverse events, we also included observational studies.
- Publication year 2000 or later, in order to reflect current practice.
- We included studies at any stage of retinopathy because of a dearth of laser studies at NPDR stage. For effectiveness in terms of visual state, we preferred a minimum duration of 6 months, but we included trials with follow-up of 3 months or more, because regression of neovascularisation can be seen 2–3 months after PRP. We also included non-trial studies of shorter duration for data on adverse effects.

Types of participants

- Patient groups – type 1 and type 2 diabetes, with NPDR or PDR, being treated with laser photocoagulation.

Follow-up

- For effectiveness, studies with a minimum follow-up period of 6 months were included.
- For safety, shorter duration trials were also included.

Outcomes

- Visual acuity; progression and regression of retinopathy; contrast sensitivity.
- Adverse effects in eye – pain, cataract, raised IOP, vitreous bleeds, need for vitrectomy.
- Number of treatments and hence visits required.
- We were not interested in outcomes not evident to patients such as retinal or central macular thickness (CMT), or angiogram results, which are more guides to treatment than outcomes.

Exclusion criteria

- Studies of treatment of DMO were excluded for assessing laser efficacy, as PRP is not used for DMO. However, they could be included for assessing the efficacy of drugs if they reported effects on DR (NPDR or PDR). Studies with fewer than 20 eyes were excluded.

Search strategy

The databases MEDLINE, EMBASE and The Cochrane Library were searched using the search strategies detailed in *Chapter 2* and *Appendix 2*. The databases were searched from their inception until August 2013 and then auto-alerts were run until February 2014. However, for this section, only studies published since 2000 were included, as we were interested in recent laser methods and drug developments. In practice, this applied only to laser trials, as there were no drug-plus-laser studies before 2000.

Identification of studies

Titles and abstracts of the records retrieved were checked against the inclusion criteria by two independent reviewers (NW/PR). Any studies definitely or possibly fulfilling the inclusion criteria were retrieved in full and checked for final inclusion by two reviewers independently (NW/PR). There was no need for discussions with a third reviewer.

Data extraction strategy

Data were extracted into a predesigned data extraction form. Data were extracted by one reviewer (PR/DS/KF) and checked by a second reviewer (KF/DS/PA).

Quality assessment strategy

The risk of bias or quality of RCTs was assessed using the Cochrane risk of bias tool, including the following items:

- adequacy of sequence generation
- allocation concealment
- masking (patients, doctors, outcome assessors)
- adequacy of handling of incomplete outcome data
- selective reporting
- presence of other bias (e.g. lack of similarity at baseline, inadequate power)
- funding source and authors conflict of interest.

The quality assessment was done by one reviewer (DS/KF) and checked by a second reviewer (KF/DS/PA).

Results

Results of the searches

A total of 978 records were retrieved by the searches. The titles and abstracts were screened for inclusion and exclusion. Based on titles and abstracts, 102 were considered possible inclusions and full texts of these were obtained. Out of these, 38 were included in *Chapter 2*, and 38 were excluded because of not meeting the inclusion criteria outlined above. Seventeen were excluded as they were published pre-2000; the reasons for exclusion of the remaining 21 studies are given in *Table 15*. For the sake of brevity the trials will simply be referred to by the name of the first author and publication year.

We included 12 RCTs (in 14 articles) published after 2000 to assess the efficacy and safety of new laser technologies in patients with DR, though most had PDR. These are reviewed in this chapter.

Also included were 11 RCTs (published in 12 articles) that used anti-VEGFs or injectable steroids on their own or in combination with laser and compared it against laser. These are reviewed in *Chapter 4*.

TABLE 15 Reasons for exclusions of studies

Study ID	Reason for exclusion
Bandello 2005[56]	Patients have DMO only
Bressler 2013[57]	Patients received focal/grid laser only
Brown 2003[58]	Not a RCT
Cardillo 2008[59]	Patients have DMO only
Chappelow 2012[60]	Not a RCT
Cho 2009[61]	Superseded by later report
DRCRN 2009[62]	Not a RCT
Gurelik 2004[63]	Not a RCT
Lee 2000[64]	Not a RCT
Lee 2010[65]	Not a RCT
Luttrull 2008[66]	Not a RCT
Mason 2008[67]	Not a RCT
Muqit 2013[68]	Not a RCT
Neubauer 2007[13]	Not a RCT
Shimura 2005[49]	Not a RCT
Sivaprasad 2012[15]	Not a RCT
Summanen 2012[69]	Not a RCT
Venkatesh 2011[70]	Patients have DMO only
Vujosevic 2010[71]	Patients have DMO only
Writing committee for DRCRN 2007[54]	Patients have DMO only
Zucchiatti 2009[72]	Not a RCT

Trials of laser photocoagulation (published after 2000)

Diabetic retinopathy

The studies included groups at different stages:

- PDR: this included five studies (Bandello 2001;[73] Muqit 2010/11;[74–76] Muqit 2013;[77] Muraly 2011;[78] Tewari 2000[55]). Of these, Muqit 2010/11,[74–76] Muqit 2013[77] and Muraly 2011[78] included newly diagnosed PDR.
- One study (Bandello 2001[73]) included HR-PDR patients, in which HR-PDR was defined as PDR with two to four HRCs, i.e. new vessels at disc greater than ¼ to ⅓ of disc area or vitreous or pre-retinal haemorrhage associated with less extensive new vessels at disc, or with new vessels elsewhere of half of the disc area or more in size.
- One study (Al-Hussainy 2008[79]) included patients with PDR ($n = 17$), central retinal vein occlusion (CRVO; $n = 2$) and ocular ischaemic syndrome (definition not given; $n = 1$) who were undergoing PRP for the first time.
- Shimura (2003)[80] included patients with severe NPDR or early PDR without visual disturbances.
- Two studies (Mirshahi 2013;[81] Nagpal 2010[82]) included patients with bilaterally symmetrical very severe NPDR or PDR.

- One study (Japanese Society of Ophthalmic Diabetology 2012[17]) included patients with pre-proliferative diabetic retinopathy (PPDR) (the definition of PPDR was not clear – patients with no previous laser and multiple non-perfusion areas larger than one disc area on FA were included).
- One study (Salman 2011[83]) included patients with NPDR with CSMO, or PDR.
- One study (Suto 2008[84]) included patients with severe NPDR or early PDR of similar severity in both eyes and a similar cataract grade in both eyes.

Other patient characteristics

Table 16 provides details of number of patients and eyes treated in the included studies. In most of the studies, patients were receiving laser for the first time. The ages of participants ranged between 26 and 86 years.

Six trials included only patients with type 2 diabetes (Japanese Society of Ophthalmic Diabetology 2012;[17] Mirshahi 2013;[81] Salman 2011;[83] Shimura 2003;[80] Suto 2008;[84] Tewari 2000[55]) and one included only patients with type 1 diabetes (Bandello 2001[73]). Two studies included patients with either type of diabetes (Muqit 2010/11;[74–76] Muqit 2013[77]). Three studies (Al-Hussainy 2008;[79] Nagpal 2010;[82] Muraly 2011[78]) did not report the type of diabetes.

Baseline VA was reported in logMAR scale (Bandello 2001;[73] Japanese Society of Ophthalmic Diabetology 2012;[17] Mirshahi 2013;[81] Muqit 2011;[76] Salman 2011[83]) or in letters (ETDRS) (Muqit 2010[74]) or in Snellen scale (Muraly 2011;[78] Nagpal 2010;[82] Tewari 2000[55]). Four studies did not report baseline VA (Al-Hussainy 2008;[79] Muqit 2013;[77] Shimura 2003;[80] Suto 2008[84]). VA ranged from 0.02 to 1.0 logMAR in seven studies; 77–79 letters in one study and 6/6 (20/20) to 6/60 (20/200) in three studies. Details of previous treatments were not reported in two studies (Shimura 2003;[80] Tewari 2000[55]). In the remaining studies, patients with previous histories of treatment with laser, drugs or surgery were excluded. In some, patients were receiving laser for the first time (see *Table 16*).

Co-morbidities were not reported consistently. In Bandello 2001,[73] 26–35% of patients had CSMO. In the Japanese Society study,[17] there were 70–84% with cataract, 64–71% with hypertension (HTN) and 31–42% with nephropathy. The remaining studies did not report comorbidities.

TABLE 16 Details of number eyes/patients recruited in the trial

Study (author and year)	No. of patients	No. of eyes	Details of previous treatment
Al-Hussainy 2008[79]	20	20	PRP for first time
Bandello 2001[73]	50	65	Patients with previous history of treatment excluded
Japanese Society of Ophthalmic Diabetology 2012[17]	69	69	Patients with no previous photocoagulation were included
Mirshahi 2013[81]	33	66	Patients with previous history of laser excluded
Muqit 2010/11[74–76]	22	36	Treatment-naive patients
Muqit 2013[77]	24	30	Treatment-naive patients
Muraly 2011[78]	50	100	PRP for first time
Nagpal 2010[82]	60	60	Patients with previous history of laser and anti-VEGFs excluded
Salman 2011[83]	120	120	Patients with previous history of laser and anti-VEGFs excluded
Shimura 2003[80]	36	72	Not clear
Suto 2008[84]	29	58	Not clear
Tewari 2000[55]	25	50	Patients with previous history of laser excluded

Follow-up

Four studies (Muqit 2010;[74] Muqit 2013;[77] Salman 2011;[83] Shimura 2003[80]) had less than 6 months of follow-up (*Table 17*). In four studies, (Mirshahi 2013;[81] Muraly 2011;[78] Nagpal 2010;[82] Tewari 2000[55]), patients were followed up for 6 months. One study (Suto 2008[84]) followed patients for 12 months. Patients were followed up for 18 months in Muqit 2011.[76] The follow-up period ranged from 6 to 45 months in Al-Hussainy 2008.[79] In one study (Japanese study of Ophthalmology 2012[17]) the follow-up period ranged between 6 and 60 months. In Bandello 2001,[73] the average follow-up period was around 22 months.

Intervention (details of laser)

Table 18 gives details of types of lasers used in the included RCTs.

Five studies (Muqit 2010/11;[74,76] Muqit 2013;[77] Muraly 2011;[78] Nagpal 2010;[82] Salman 2011[83]) studied the efficacy of pattern photocoagulation (PSC) used in different ways, i.e. in duration or form or sittings.

Quality assessment/risk of bias

Not all studies gave enough details to assess risk of bias. In that case, we categorised them as 'unclear'. See *Table 19* for details.

Allocation

In seven studies (Bandello 2001;[73] Japanese Society of Ophthalmic Diabetology 2012;[17] Mirshahi 2013;[81] Muqit 2010;[74] Muqit 2013;[77] Suto 2008;[84] Tewari 2000[55]), the method of randomisation was adequate, for example computer-generated random numbers (Bandello 2001),[73] random number tables (Japanese Society of Ophthalmic Diabetology 2012),[17] through hospital pharmacy's centralised service (Mirshahi 2013),[81] permuted blocks (Muqit 2010;[74] Muqit 2013;[77] Suto 2008[84]) and tossing a coin (Tewari 2000[55]). In the remaining studies (Al-Hussainy 2008;[79] Muraly 2011;[78] Nagpal 2010;[82] Salman 2011;[83] Shimura 2003 [80]), the randomisation procedure was either not reported or reported inadequately. In three studies (Muqit 2010;[74] Muqit 2013;[77] Suto 2008[84]) the allocation concealment was adequate. None of the other studies reported on allocation concealment.

TABLE 17 Follow-up period in the included studies

Studies	Follow-up
Al-Hussainy 2008[79]	6–45 months
Bandello 2001[73]	22.4 ± 9.7 months in the light PRP group; 21.6 ± 9.3 months in the classic PRP group
Japanese Society of Ophthalmic Diabetology 2012[17]	6–60 months
Mirshahi 2013[81]	6 months
Muqit 2010/11[74–76]	12 weeks – Muqit 2010;[74] 18 months – Muqit 2011[76]
Muqit 2013[77]	12 weeks
Muraly 2010–11[78]	6 months
Nagpal 2010[82]	6 months
Salman 2011[83]	Average 9–10.8 weeks
Shimura 2003[80]	12 weeks
Suto 2008[84]	12 months
Tewari 2000[55]	6 months

TABLE 18 Details of types of laser used in the included studies

Pattern laser trials			
Author and year	**PSC experimental arm(s)**	**Comparator regimen**	**Notes**
Muqit 2010/11[74–76]	20-ms multi-spot single session	100-ms multi-session single-spot PRP	Patients with active PDR underwent top-up PRP treatment with 20-ms pulse PSC photocoagulation using ETDRS guidelines. Laser used was frequency-doubled Nd:YAG solid-state laser, 532 nm, both arms
Muqit 2013[77]	1. TRP – single session, 20 ms, 1500–2500 grey-white burns 2. MT-PRP, light grey barely visible burns	SI-PRP, 2500 grey-white burns	Frequency-doubled 532-nm Nd:YAG solid-state laser consisting of a modified slit lamp and optical system All arms used the PASCAL laser (Topcon Medical Laser Systems, Santa Clara, CA)
Muraly 2011[78]	PSC (OptiMedica, Santa Clara, CA): single sitting of PRP. Usually 30 ms, 2100–3900 burns	Conventional laser using 532-nm frequency-doubled Nd:YAG (Carl Zeiss Meditec, Dublin, California): two to three sittings of PRP	Both methods adjusted to achieve mild to moderate (grey to grey-white) retinal burn
Nagpal 2010[82]	20-ms PSC (OptiMedica Corp, Santa Clara, CA) 950–1100 spots	GLX (532 nm) (Iridex Corp, Mountain View, CA) single-spot slit-lamp delivery PRP, 500–700 burns	Both lasers performed in two sittings
Salman 2011[83]	PASCAL (OptiMedica, Silicon Valley, CA) 20 ms, 200 µm, 1000 burns	Conventional laser, 700 burns; 532 nm green-light diode-pumped solid state (Novus Spectra, Lumenis, USA)	Two groups, one having PRP, the other having focal or grid for CMSO

Other trials			
Author and year	**Experimental/intervention**	**Standard/experimental/ no treatment**	**Notes**
Al-Hussainy 2008[79]	Short exposure (0.02 seconds or 20 ms) high-energy scatter PRP	Conventional exposure (100 ms or 0.1 seconds) PRP, power sufficient to produce a visible grey-white burn	532-nm, frequency-doubled Nd:YAG laser (manufacturer not given)
Bandello 2001[73]	Light PRP on non-perfused peripheral and midperipheral areas	Conventional PRP on non-perfused peripheral and midperipheral areas	All eyes treated with 920 argon lasers (Argon Coherent Medical, Palo Alto, CA or Argon Ophtalas, Biophysic Médical, Clermont Ferrand, France) monochromatic green light using three types of contact lenses. Fluorescein angiograms were done to show perfusion
Japanese Society of Ophthalmic Diabetology 2012[17]	Selective PRP to NPA in PPDR	No photocoagulation till PDR develops	Details of type of laser not given

TABLE 18 Details of types of laser used in the included studies (*continued*)

Other trials			
Author and year	**Experimental/intervention**	**Standard/experimental/ no treatment**	**Notes**
Mirshahi 2013[81]	Single-spot short duration (20 ms) PRP	Conventional (100 ms) PRP	In both, conventional continuous-wave, frequency-doubled Nd:YAG 532-nm photocoagulation used (Novus Varia, Lumenis, USA)
Shimura 2003[80]	Weekly PRP	Biweekly PRP	PRP scatter laser in four sessions. Krypton red laser (Nidek, Gamagori, Japan)
Suto 2008[84]	PRP then cataract surgery (PRP-first group)	Cataract surgery then PRP (surgery-first group)	Multicolour laser (Coherent Inc., Palo Alto, CA) and a quadraspheric fundus laser lens used. All treatment done using a yellow mainly or red krypton if cataract present
Tewari 2000[55]	Diode laser (810 nm, Microlase, Keeler Inc., UK)	Argon laser (514 nm, Novus 2000, Coherent)	Scatter photocoagulation performed in two to four sittings

GLX, solid-state green laser; MT-PRP, minimally traumatic pan-retinal photocoagulation; SI-PRP, standard intensity pan-retinal photocoagulation; TRP, targeted retinal photocoagulation.

TABLE 19 Quality assessment/risk of bias of included post-2000 laser studies

Study (author and year)	Adequate sequence generation	Adequate allocation concealment	Masking	Incomplete outcome data assessed	Free of selective outcome reporting	Free of other biases (e.g. similarity at baseline, power assessment)
Al-Hussainy 2008[79]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Bandello 2001[73]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Japanese Society of Ophthalmology 2012[17]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Mirshahi 2013[81]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Muqit 2010/11[74–76]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Muqit 2013[77]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Muraly 2011[78]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Nagpal 2010[82]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk
Salman 2011[83]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk
Shimura 2003[80]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Suto 2008[84]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Tewari 2000[55]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk

Masking

The included studies were checked to see whether both assessors and patients were masked to study treatment. The masking of the former is more important than the latter. Only five studies (Al-Hussainy 2008;[79] Bandello 2001;[73] Muqit 2010;[74,75] Muqit 2013;[77] Suto 2008[84]) gave sufficient description of masking while the remaining studies had no information regarding this. In Al-Hussainy (2008),[79] patients were masked to the order and the initial site of the treatment (superior or inferior, which was chosen at random). However, it was not clear whether assessors were masked to the treatment.

In Bandello (2001),[73] all the post-treatment controls were performed in each centre by an investigator unaware of the treatment group of patients. The post-treatment controls involved complete examination, a series of retinal photographs, and fluorescein angiograph, and this was done on 6 and 12 weeks and every 3 months in the first year and, after 12 months, done every 6 monthly. In Muqit 2010,[74] two graders masked to the treatment assessed fundus photographs and fundus FA at baseline at the final visit to grade PDR activity.

In Muqit (2013),[77] participants were masked to single-session treatment allocation but the investigator was not masked. After laser treatment, a masked assessor used a questionnaire to assess pain responses. In addition, two masked retina specialists independently assessed PDR grade.

In Suto (2008),[84] masked ophthalmologists assessed the disease stage using the ETDRS classification.

Power

Only two studies, Muqit (2010)[74] and Suto (2008),[84] reported power calculations.

Incomplete outcome data

There was adequate description about incomplete data except in two studies (Salman 2011;[83] Shimura 2003[80]).

Free of selective reporting

All studies except Salman (2011)[83] reported all prespecified and predefined outcomes. In Salman (2011),[83] only narrative information was provided on complications and pain. In addition, there was no information on intra- and post-procedure pain.

Free of other biases

In most studies, the baseline characteristics were comparable between treatment groups. In Salman (2011),[83] baseline VA was slightly different in the two treatment groups (0.31 vs. 0.6 logMAR). In Shimura (2003),[80] baseline characteristics of patients were not given.

Funder/conflict of interest

Funding was not clear in some studies (Al-Hussainy 2008;[79] Bandello 2001;[73] Mirshahi 2013;[81] Muraly 2011;[78] Tewari 2000[55]). However, it appears these studies were funded by the affiliated academic's institution. One study (Muqit 2010/11[74–76]) was funded by the manufacturer of the PSC laser (OptiMedica Corporation, Santa Clara, CA, USA). One study (Muraly 2011[78]) reported that the authors had no conflict of interest. In Muqit 2010/11,[74–76] one author was an employee of OptiMedica Corporation and one author had received financial support from the same company. In the remaining studies, this information was not available.

Details of studies

The studies are each described narratively below and summarised in table format in *Table 20*.

Al-Hussainy 2008

This trial compared short and standard exposures.[79] Al-Hussainy (2008)[79] used a scatter PRP frequency-doubled Nd:YAG laser with a wavelength of 532 nm with oxybuprocaine 0.4% analgesia. The laser was given either as short (0.02 seconds) exposure, high-energy laser or longer (0.1 seconds) laser with approximately 500 burns of spot size 300 µm to get similar effects. The conventional laser was performed in the superior or inferior retina while the remaining hemi-retina was treated with the short exposure laser. It was not clear whether the two lasers were given in the same eye of the same patient. In 18 out of 20 patients with follow-up ranging between 6 and 45 months, there was resolution of neovascularisation on and around the optic disc (NVD) and new vessels elsewhere (NVE). In the remaining two cases (one with CRVO and the other with PPDR), there was no resolution. Vitreous haemorrhage developed in the patient with CRVO, which meant no further treatment could be given. The patient with PPDR had no NVD/NVE at baseline and did not develop it during follow-up. Visual analogue scale (VAS) was used to measure the pain response. Pain response was significantly lower in the group receiving a short exposure high-energy laser than for those receiving conventional laser (1.4 cm vs. 5.11 cm on VAS; $p < 0.001$). On retinal photographs, no obvious differences were seen in photocoagulation reactions between the two lasers.

Bandello 2001

In Bandello (2001),[73] a low-energy power (light PRP) laser application was compared against the conventional classic PRP in a trial in 65 eyes. The aim was ablation of non-perfused peripheral and mid-peripheral NPAs. Light was argon laser aiming at a very light grey effect, using the lowest energy possible with the target burnt areas corresponded to the grade 1 of L'Esperance scale (barely visible, blanching of pigment epithelium), whereas in the latter the target resembled the classic burn, i.e. grade 3 of L'Esperance scale (opaque, dusky, grey-white, off-white). Both lasers were delivered using monochromatic green light through contact lenses. The authors found no difference between the two treatments in terms of mean change in BCVA (0.06 vs. 0.13 logMAR). (LogMAR is on scale of 0–1, with lower better.) LogMAR increased from 0.12 to 0.18 in light and 0.14 to 0.27 in standard.

(Note that the visibility of burns varies amongst different people. A whitish scar may appear in a very pigmented person with the same power that would give only a very faint scar in a blond individual.)

Slightly more patients in the classic PRP group showed regression of HRCs than in the light PRP group (97% vs. 91%); however, the difference was not statistically significant ($p = 0.615$). Improvement in PDR was considered if there was a reduction of one or more HRCs. One eye in each group showed worsening of retinopathy. In the light PRP group, at the 12-months follow-up one eye had an increase in HRCs therefore was given additional classic PRP group. Median power in the classic PRP group was significantly greater than in the light PRP (420 mW, range 200–950 mW vs. 235 mW, range 100–540 mW; $p < 0.001$). In both forms of laser, spots were 500 µm in size. The spot numbers were significantly greater in the light PRP group {2748 [standard deviation (SD) 468] vs. 2080 (SD 320); $p < 0.001$}. The mean number of sessions and total sessions was significantly higher in the classic PRP group than in the light PRP group [8.7 (SD 2.1) vs. 3.5 (SD 1.3); $p < 0.001$; total: 9.9 (SD 2.2) vs. 7.4 (SD 2.4); $p < 0.001$]. More patients in the classic PRP group than in the light PRP group complained of troublesome pain (13% vs. 3%, $p = 0.184$). Significantly more of patients in the classic PRP group developed vitreous haemorrhage (19% vs. 0%; $p = 0.009$) and appearance or worsening of CSMO (23% vs. 3%; $p = 0.023$) than in the light PRP group. Furthermore, slightly more patients in the classic PRP group than in the light PRP group developed other complications including choroidal detachment (CD) (10% vs. 0%; $p = 0.103$) and neurotrophic keratopathy (6% vs. 0%; $p = 0.224$).

So the lighter laser technique appeared almost as effective but with fewer adverse effects. The authors attribute the lower rates of complications, such as vitreous haemorrhage in the lighter group, to the lower energy used, resulting in reduced heat absorption.

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		

Study ID: Al-Hussainy 2008[79]

Aim: To compare short exposure, high-energy laser settings with conventional settings, using a 532-nm, frequency-doubled, Nd:YAG laser and assess the patients in terms of pain experienced and effectiveness of treatment

Design: Prospective, masked, randomised study

Follow-up: 6–45 months

Proportions completing the study: 100%

Reasons for withdrawal (brief): n/a

Participants and baseline values:

n: 20 PDR = 17; CRVO = 2; ocular ischaemia = 1

Inclusion criteria: Patients undergoing PRP for first time

Exclusion criteria: NR

Age (years): Mean 62 (range 26–76)

Sex: NR

Diabetes type: NR

HbA$_{1c}$: NR

Baseline VA: NR

Baseline CMT: NR

Baseline DR stage: PDR = 17 (not clear which grade of PDR)

Previous laser or intravitreal drug treatment: All patients undergoing PRP for first time

Ocular comorbidities: NR

Intervention:

Group 1: Treatment A, the superior or inferior retina was treated with approximately 500 shots of scatter laser photocoagulation using 'conventional' laser parameters: spot size 300 μm, exposure 0.1 seconds, power sufficient to cause blanching of retina

Group 2: The remaining hemi-retina was treated with treatment B with approximately 500 burns of spot size 300 μm and parameters of higher power but shorter duration (0.02 seconds) to give a similar visible laser end point

Description of type of laser and delivery: Scatter PRP, frequency-doubled, Nd:YAG laser, with a wavelength of 532 nm

Outcomes and ocular safety:

Pain:

	Treatment A (0.1 seconds)	Treatment B (0.02 seconds)	p-value
Pain response (cm on the VAS)	5.11	1.405	< 0.001
SD	2.861	0.951	

Resolution of neovascularisation on and around the optic disc (NVD) and new vessels elsewhere (NVE):

18/20 patients with follow-up ranging from 6 to 45 months

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Bandello 2001[73] **Aim:** To verify whether a PRP performed using low levels of argon green laser energy (light PRP) has the same efficacy as conventional PRP using argon green wavelengths (classic PRP) in eyes with HR-PDR **Design:** RCT **Follow-up:** Light 22.4 months (±9.7); classic 21.6 (±9.3) **Proportions completing the study:** 100% **Reasons for withdrawal:** None	**n:** 65 eyes with HR-PDR of 50 consecutive patients **Inclusion criteria:** Age at least 18 years, BCVA of 0.4 or more, PDR with two to four HRCs (new vessels at disc greater than ¼ to ⅓ DA or vitreous or pre-retinal haemorrhage associated with less extensive new vessels at disc, or with new vessels elsewhere ½ DA or more in size) **Exclusion criteria:** VH obscuring more than 20% of the fundus, maculopathy reducing the BCVA to below 0.4, tractional retinal detachment, media clarity inadequate to permit completion of laser PRP, and previous laser treatment **Age (years):** 48–57 (SD 11–13) **Sex:** 37–38% female **Diabetes type:** Insulin dependent **HbA$_{1c}$:** NR	**Group 1:** In eyes selected for light PRP, the operator tried to obtain a very light grey biomicroscopic effect on the retina. The energy used was the lowest capable of producing a result on the retinal tissue. The target corresponded to the grade 1 of L'Esperance scale (barely visible, blanching of pigment epithelium), median power 235 mW, spot size 500 µm, spot number 2748±468, mean session number 3.5±1.3 **Group 2:** In eyes selected for classic PRP, the treatment target was the classic burn (figure 2) corresponding to grade 3 of L'Esperance scale (opaque, dusky, grey-white, off-white). Median power 420 mW, spot size 500 µm, spot number 2080±320, mean session number 8.7±2.1 **Description of type of laser and delivery:** Classic and light PRP using monochromatic green light	*(see tables below)*

Mean logMAR BCVA

	Light PRP	Classic PRP	*p*-value
Baseline	0.12±0.13	0.14±0.15	0.493
Final	0.18±0.25	0.27±0.30	0.231

Regression of HR-PDR (end of follow-up)

	Light PRP	Classic PRP	*p*-value
No HRCs	31/34 eyes (91%)	30/31 eyes (97%)	0.615
Unchanged	Two eyes (6%)	–	
Worsening	One eye (3%)	One eye (3%)	

	Light PRP	Classic PRP	*p*-value
Median power (mW) (range)	235 (100–540)	420 (200–950)	<0.001
Spot size (µm)	500	500	
Spot number	2748±468	2080±320	<0.001
Mean session number	3.5±1.3	8.7±2.1	<0.001
Total mean session no.	7.4±2.4	9.9±2.2	<0.001

Twenty-six eyes (76%) in the light PRP and 14 (45%) in the classic PRP group, whose retinal photographs and fluorescein angiographies at the 3-month control showed no new vessels regression, underwent further treatment ($p = 0.012$)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		Light PRP	Classic PRP	*p*-value (Fisher's exact test)
	Baseline VA: BCVA (logMAR) 0.12 to 0.14 (SD 0.13 to 0.15)		**Side effects**				
	Baseline CMT: NR			VH	0	6 (19%)	0.009
	Baseline DR stage: PDR			CD	0	3 (10%)	0.103
	Previous laser or intravitreal drug treatment: No			Troublesome pain	1 (3%)	4 (13%)	0.184
	Ocular comorbidities: 26.5–35.5% CSMO			Neurotrophic keratopathy	0	2 (6%)	0.224
				Appearance or worsening of CSMO	1 (3%)	7 (23%)	0.023

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
Study ID: Japanese Society of Ophthalmic Diabetology 2012[17]	**n:** 69 patients	**Group 1:** Non-PC group (no photocoagulation)	***Development of PDR in 69 patients***			
	Inclusion criteria: Patients with PPDR treatment in 2004–8 in the participating institution with no previous photocoagulation and multiple NPA larger than one DA on FA images	**Group 2:** S-PC group (PC group)	Overall 18/69 (26%)			
Aim: To determine whether the S-PC of NPAs in PPDR is effective at preventing the development of PDR. The VA course in patients who received the S-PC was also evaluated		**Description of type of laser and how delivered:** S-PC of NPAs		**Non-PC group**	**PC group**	***p*-value**
				15/37 (41%)	3/32 (95)	0.003
	Exclusion criteria: Clear FA images not obtainable due to opaque media; unable to perform FA due to conditions like allergy; history of intraocular surgery (but those with ≥3 years after cataract surgery included); those with severe PPDR requiring PRP		***Development of PDR in 36 patients***			
Design: RCT – multicentre				**Non-PC group**	**PC group**	***p*-value**
				12/23 (52%)	2/13 (15%)	0.03
Follow-up: Ranged from 6 to 60 (average 34.4, SD 18.00) months			***Photocoagulation in 36 patients***			
			No. of coagulation spots for the initial coagulation		92–365 (mean 233)	
Of the 69 patients, 36 patients (23 in non-photocoagulation; 13 in photocoagulation) completed the 36-months' follow-up	**Age (years):** 59.3–60.8 (SD 8.1 to 10.9)		Additional coagulation performed		17 patients (54%) either once or twice (mean 1.1 times)	
	Sex (female): 19–31% female		No. of additional coagulation spots		128 to 372/session (mean 224) performed 6–30 months after initial coagulation (mean 14.6 months)	
			VA in 36 patients after 36 months (logMAR)			
Proportions completing the study: 77% (53/69)	**Diabetes type:** Type 2			**Non-PC group**	**PC group**	***p*-value**
				0.12, SD 0.43	0.14, SD 0.33	0.86
	HbA$_{1c}$ (%): 7.5–7.7 (SD 1.5 to 1.7)		***VA change in 36 patients (logMAR)***			
				Non-PC group	**PC group**	***p*-value**
				0.11, SD 0.47	0.11, SD 0.27	0.97

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
Reasons for withdrawal: 10 stopped coming to the hospital, three switched hospitals, one developed SVL due to central retinal artery occlusion, one died, and one developed an allergy to fluorescein	**Baseline VA (logMAR):** 0.02–0.03 (SD 0.12 to 0.22) **Baseline CMT:** NR **Baseline DR stage:** PPDR **Previous laser or intravitreal drug treatment:** No PC **Ocular comorbidities:** Cataract: 70–84%; HTN: 64–71%; nephropathy: 31–42%; posterior vitreous detachment: 3–14%		**A decrease of ≥ 0.2**		
			Non-PC group	**PC group**	***p*-value**
			2/23 (9%)	3/13 (23%)	0.24
			Reason for decrease of VA in non-photocoagulation – cataract progression (*n* = 1), VH (*n* = 1); reason in photocoagulation – cataract progression (n = 1), MO (*n* = 2)		
			Severe VA loss (defined by the ETDRS as corrected VA of < 0.025)		
			n = 1 with VH in the non-photocoagulation group		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety	Conventional group	Short-time group	*p*-value
Study ID: Mirshahi 2013[81]	**n:** 66 eyes from 33 patients	**Group 1:** Single-spot short duration time (20 ms) PRP	**Outcomes:**			
Aim: To compare pain score of single-spot short duration time (20 ms) PRP with conventional (100 ms) PRP in DR	**Inclusion criteria:** Patients with bilaterally symmetrical very severe non-PDR or PDR	**Group 2:** Conventional (100 ms) PRP	Pain score (VAS)	7.5 ± 1.14	1.75 ± 0.87	0.000
	Exclusion criteria: Any type of glaucoma, rubeosis iridis, significant media opacity, any history of intraocular surgery except cataract surgery, CSMO, CMT > 300 µm by OCT and marked leakage in FA, previous retinal laser therapy, and patients with combined retinal detachment, uncontrolled HTN (BP ≥ 180/110 mmHg), and poor glycaemic control (HbA$_{1c}$ ≥ 10 mg/dl)	**Description of type of laser and delivery:** A conventional continuous-wave, frequency-doubled Nd:YAG (532 nm) retinal photocoagulator (Novus Varia, Lumenis, USA) with spot size of 200 µm was used in both laser types. Pulse duration of 20 ms was used for the short time PRP and 100 ms for the conventional PRP. Laser energy was adjusted to achieve moderate whitening on the retina. Laser was done in a single session, but five patients in the conventional group did not tolerate the SS-PRP, and the PRP was completed in the next week	Mean pre-laser BCVA (logMAR)	0.40 ± 0.24	0.37 ± 0.27	0.718
Design: Randomised double-masked, placebo-controlled, single-centre trial			Mean post-laser BCVA (logMAR)	0.44 ± 0.28	0.32 ± 0.22	0.144
			Additional PRP (patients)	4	3	0.68
Follow-up: 6 months			Efficacy of treatment (%)	87.9	90.9	0.66
Proportions completing the study: Recruited 76 eyes from 38 patients. Five patients did not complete the follow-up period, and were excluded			PRP sessions (single/two)	28/5	33/none	0.02
			Complications	None	None	
Reasons for withdrawal: Five patients did not complete the follow-up period	**Age (years):** 58.9 (SD 7.8) **Sex (female):** 48%					

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Diabetes type: Type 2 (all)		
	HbA$_{1c}$ (mg/dl): 8.23 (SD 1.18)		
	Baseline VA:		
	Conventional group: 0.40 ± 0.24		
	Short-time group: 0.37 ± 0.27		
	$p = 0.718$		
	Baseline CMT:		
	Conventional: 255 ± 33.7 µm		
	Short-time: 266 ± 33.8 µm; $p = 0.334$		
	Baseline DR stage: Non-PDR ($n = 18$); PDR ($n = 15$)		
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*		
	Ocular comorbidities: See *Exclusion criteria*		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Muqit 2010/11[74–76] **Aim:** To compare a single-spot, 100-ms PRP across three sessions and multi-spot PSC 20-ms PRP in a single session (aimed to test the non-inferiority of SS-PRP compared with MS-PRP) **Design:** Randomised trial **Follow-up:** 12 weeks (but follow-up data for 18 months in Muqit 2011 Manchester PSC Study Report 4[76]) **Completion rate:** 100% **Reasons for withdrawal:** n/a	**n:** 40 eyes of 24 patients (one eye from each group discarded so 38 eyes) **Inclusion criteria:** Patients aged > 18 years, newly diagnosed PDR; either type 1 or type 2 diabetes; ETDR VA 35–85 letters; mean CRT < 300 μm with absence of intraretinal and/or subretinal fluid; adequate pupil dilatation and clear media to perform laser photocoagulation, digital photography and OCT; ability to perform accurate Humphrey visual field test **Exclusion criteria:** Recent (last 6 months) or ongoing poor glycaemic control; HbA_{1c} > 10 mg/dl; uncontrolled HTN (BP ≥ 180/100 mmHg); history of CRF or renal transplant for DN; lens opacity/cataract; any previous surgical or laser treatment to the study or fellow eye; planned YAG peripheral iridotomy; previous laser photocoagulation or macular laser treatment to the study or fellow eye; history of DMO in study or fellow eye; any previous ocular condition that may be associated with a risk of MO,	**Group 1:** 20 eyes underwent multi-spot, 20-ms SS-PRP using 5.5 and 4.4 multi-spot arrays **Group 2:** 20 eyes underwent single-spot, 100-ms MS-PRP in three sessions across a period of 4 weeks **Description of type of laser and delivery:** The PSC laser is a frequency-doubled, Nd: YAG, solid-state laser with a wavelength of 532 nm. Photocoagulation is applied in a rapid pattern array with a pulse duration of 10–20 ms. In both groups, threshold laser photocoagulation treatment was titrated to, and designated by, a mild grey-white burn (between grade 2+ and 3+) according to ETDRS guidelines. All eyes received 1500 burns performed under topical anaesthesia. The mean power used for SS-PRP was significantly higher at 277 mW (range, 200–456 mW; *p* < 0.001) than MS-PRP (143 mW; range, 104–188 mW). The mean fluence for SS-PRP was 4.2 J/cm² (range, 3–7 J/cm²), significantly lower than that for MS-PRP (11.2 J/cm²; range, 8–15 J/cm²;	**Outcomes:** ● VA increased by four letters (SD six letters) in SS-PRP vs. MS-PRP ● PDR grade at 12 weeks: no difference ● At end follow-up, no differences in VA ● Complete regression 6/8 group 1. 14/21 group 2. 3/7 group 3 ● Pain score higher in conventional than short exposure group

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	active eyelid or adnexal infection; previous retinal treatment – laser, drug or surgery; planned intraocular surgery within 1 year	$p < 0.001$). The total PRP treatment time for 1500 burns was significantly shorter using multi-spot SS-PRP than with single-spot MS-PRP [SS-PRP, mean, 5.04 minutes (SD 1.5 minutes); vs. MS-PRP, mean, 59.3 minutes (SD 12.7 minutes); $p < 0.001$]	
	Age (years): Mean 56; range 29–60		
	Sex (female): 34% (13 eyes)		
	Diabetes type: Type 1 and type 2		
	HbA$_{1c}$ (%): Mean 8.2; range 5.5–10.0		
	Baseline VA: SS-PRP group – 77 letters (SD 9.9); MS-PRP group – 79 letters (SD 7.9)		
	Baseline CMT: 240 µm in SS-PRP group; 242 µm in MS-PRP group; range 182–297 µm		
	Baseline DR stage: Mild (8 eyes); moderate (23 eyes); severe (7 eyes)		
	Previous laser or intravitreal drug treatment: None		
	Ocular comorbidities: HTN (19 eyes)		

continued

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety	Outcomes:			
				Group 1 (*n* = 8)	Group 2 (*n* = 21)	Group 3 (*n* = 7)	*p*-value
Study ID: Muqit 2010/11 (Manchester PSC Study Report 4)[74–76] **Aim:** To quantify the 20-ms PSC PRP ablation dosage required for regression of PDR, and to explore factors related to long-term regression **Design:** Retrospectively studied a cohort of patients who participated in a RCT, the Manchester PSC Study **Follow-up:** 18 months **Completion rate:** 36 patients included for analysis **Reasons for withdrawal:** No one withdrew; however, some patients failed to comply with follow-up appointments since completion of MAPASS *(Please note this study includes patients from Muqit 2010[74])*	***n:*** 36 eyes of 22 patients **Inclusion criteria:** Newly diagnosed PDR; aged more than 18 years; type 1 or type 2 diabetes; ETDRS VA between 35 and 85 letters; mean CRT of less than 300 μm; adequate pupil dilatation and clear media to perform laser photocoagulation, digital photography and OCT scans; ability to perform accurate Humphrey visual field test; if both eyes eligible then both eyes randomised as per protocol and treated independently **Exclusion criteria:** Last 6 months or ongoing poor glycaemic control. HbA_{1c} > 10 mg/dl; uncontrolled HTN; history of chronic renal failure or renal transplant for DR; lens opacity/cataract that could influence vision and results; any previous surgical or laser treatment in study or fellow eye; planned YAG peripheral iridotomy; previous laser photocoagulation or macular laser treatment to study eye or fellow eye; history of DMO in study or fellow eye; any previous ocular	Please see above for details of two different interventions After this, all patients with active PDR underwent top-up PRP treatment using 20-ms pulse PSC photocoagulation using ETDRS guidelines. Threshold top-up PRP treatment was titrated to and designated by a mild grey-white burn (between grade 2+ and 3+) according to ETDRS guidelines at MREH. All treatments performed in a single session under topical 0.4% oxybuprocaine hydrochloride, using 20-ms PSC 5 × 5, 4 × 4, 3 × 3 or 2 × 2 multi-spot arrays. Burn distribution for top-up PRP treatment involved one burn width apart, greater than two DDs temporal to the fovea, no closer than one row within the arcades, and burn placement as close to the ora serrata as possible Patients categorised into three groups according to baseline grade of PDR: Group 1 (grade 1), Group 2 (grade 2) and Group 3 (grade 3)	VA (logMAR)	No change	No change	No change	NR
			Mean power of PRP	213 mW (range 104–350, SD 96)	220 mW (range 116–482, SD 101)	291 mW (range 140–398, SD 59)	NR
			Complete disease regression	6/8 (75%) eyes	14/21 (67%) eyes	3/7 (43%) eyes	NR
			Mean time to regression	5.8 months (range 3–10)	11 months (range 3–19)	17 months	NR
			Total no. of laser spots, mean (range)	2187 (1500–3450)	3998 (1500–8364)	6924 (4097–9234)	Group 2 vs. 1: *p* = 0.012; Group 3 vs. 1: *p* = 0.012
			Average sessions	1–3	4	6	NR
			Laser dosimetry required to produce complete PDR disease regression	2416 burns (*n* = 6)	3902 (*n* = 14)	5446	
			Laser ablation required to achieve complete regression	Mean 264 mm², SD 95 (181–416 mm²)	471 mm², SD 264 (181–698 mm²)	657 mm², SD 258 (494–954 mm²)	Group 2 vs. 1: *p* = 0.036; Group 3 vs. 1: *p* = 0.0091
			Fitness to drive – patients who had undergone bilateral PRP treatment	*N* = 14; questioned about the status of fitness to drive according to DVLA UK requirements. All patients underwent independent VA and binocular VF testing within 6 months of the final study visit. 13/14 patients reported passing the DVLA standard driving standards. One patient failed because of suboptimal VA level, despite a satisfactory binocular VF test			

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	condition that may be associated with a risk of MO; active lid or adnexal infection; previous retinal treatment: laser, drug or surgery; planned intraocular surgery within 1 year		**Ocular safety:**
			● No unexpected adverse or serious adverse events
			● No signs of intraretinal/subretinal haemorrhage or blood vessel damage from 20-ms PRP burns, and no indirect laser-related ocular complications
	Age (average): Group 1, 42 years; group 2, 42 years; group 3, 47 years; (range 29–70)		● VH ($n = 7$) and tractional retinal detachment ($n = 1$) associated with elevated/forward NVD greater than SAH10A
			● Uncomplicated VH ($n = 3$)
	Sex: Nine eyes female		● Over 6 months after completion of MAPASS, DMO developed ($n = 3$). Unrelated to top-up PRP treatments, one patient developing pregnancy-related DMO
	Diabetes type: Type 1 (24 eyes) and type 2 (12 eyes)		
	HbA$_{1c}$ (%): Range 5.5–10		
	Baseline VA (logMAR): Group 1, 0.04 (SD 0.04); Group 2, 0.17 (SD 0.17); Group 3, 0.14 (SD 0.12)		
	Baseline CMT: NR		
	Baseline DR stage: Grade 1 (7 eyes); grade 2 (21 eyes); grade 3 (7 eyes)		
	Previous laser or intravitreal drug treatment: Treatment-naive patients		
	Ocular comorbidities: NR		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Muqit 2013 BJO (PETER PAN Study)[77] **Aim:** To evaluate the short-term effects on macular thickness of a standard intensity PSC TRP and reduced fluence/MT-PRP compared with SI-PRP **Design:** Prospective randomised clinical trial **Follow-up:** 12 weeks (4 and 12 weeks) **Proportions completing the study:** 100% **Reasons for withdrawal:** n/a *(Short-duration trial – therefore useful for adverse effects but, no effectiveness)*	**n:** 30 eyes of 24 patients (10 eyes/arm) **Inclusion criteria:** Patients aged > 18 years of age with newly diagnosed treatment-naive PDR; type 1 or 2 diabetes; ETDRS VA between 35 and 85 letters; mean CRT of < 300 μm; adequate pupil dilatation and clear media to perform laser photocoagulation, digital photography and OCT scans; ability to perform accurate Humphrey visual field test **Exclusion criteria:** Poor glycaemic control (HbA$_{1c}$ > 10 mg/dl); uncontrolled HTN (BP ≥ 180/100 mmHg); chronic renal failure or renal transplant for diabetic nephropathy; lens opacity/cataract; planned yttrium aluminium garnet peripheral iridotomy; treatment (medical, surgical, pan-retinal or macular laser) within the last 12 months; history of MO in study eye; any previous condition associated with a risk of MO; systemic treatment toxic to the retina or risk of MO; active lid or adnexal	**Group 1:** TRP (single session, multi-spot 20-ms TRP) **Group 2:** Minimally traumatic PRP **Group 3:** Standard intensity PRP **Description of type of laser and delivery:** The PSC photocoagulation system is a frequency-doubled 532-nm Nd:YAG solid-state laser (Topcon Medical Laser Systems, Santa Clara, CA) that consists of a modified slit lamp and optical system, which telecentrically images the surface of a multimode step index optical fibre through a two-axis scanner	See below

PDR activity (12 weeks)

	TRP	MT-PRP	SI-PRP	p-value
Partial regression	60%	50%	70%	No difference between groups
Complete regression	10%	20%	20%	
No change	30%	20%		
Worsening			10%	

One eye in each group (n = 3) required additional 1500 burns of their respective laser at 4 weeks

VA (at 12 weeks)

Comparison	Difference	p-value
TRP vs. SI-PRP	1.3 letters, SD 11; 95% CI –6.55 to 9.15	0.717
TRP vs. MT-PRP	0.7 letters, SD 8.4, 95% CI –5.33 to 6.73	0.799
MT-PRP vs. SI-PRP	0.6 letters, SD 7.2 95% CI –4.53 to 5.73	0.797

Pain response (12 weeks):

	TRP	SI-PRP	MT-PRP
Description of pain:			
Sharp	n = 2	n = 3	n = 1
Shooting		n = 2	

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
			TRP	**SI-PRP**	**MT-PRP**
	infection; planned intraocular surgery within 6 months; vitreomacular traction on FD-OCT scan; ≥ grade 2 epiretinal membrane on FD-OCT scan	Stabbing	$n = 1$		
		Burning	$n = 1$		
		Throbbing		$n = 1$	$n = 1$
	Age (years): 42–45 (SD 8.8–15.9)	Electric shock-like		$n = 1$	$n = 1$
	Sex (female): 20–40%	Mean NPS score	1.7 SD 2.3	3.1 SD 2.7	0.5 SD 1.3
			(All categorised as mild pain; no pain in 80% of patients in the MT-PRP group)		
	Diabetes type: Type 1 (70–90%); type 2 (10–30%)	Mean VAS score immediately post laser	15.7 SD 23.7	32.4 SD 24.2	3.5 SD 7.8
	HbA$_{1c}$ (%): 8.4–8.6 (SD 1.1 to 1.5)		(All categorised as mild)		
	Baseline VA: NR	NPS, numerical pain score. No significant differences for pain responses between TRP vs. MT-RP (NPS, $p = 0.05$; VAS, $p = 0.19$) and TRP vs. SI-RP (NPS, $p = 0.12$; VAS, $p = 0.07$). MT-RP had significantly less pain than SI-RP (NPS, $p = 0.001$; VAS, $p = 0.005$).			
	Baseline CMT: NR				
	Baseline DR stage: Mild PDR ($n = 14$; moderate PDR ($n = 8$); severe PDR ($n = 8$)	● No ocular complications or adverse events during the immediate or short-term, following after treatment			
	Previous laser or intravitreal drug treatment: None	● No signs of intraretinal haemorrhage or blood vessel compromise at the locations of TRP, MT-PRP or SI-PRP burns			
	Comorbidities: No patients with HTN, cardiovascular disease or nephropathy				

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		PSC laser	Conventional laser	p-value
Study ID: Muraly 2011[78] **Aim:** To describe the results of a single session of PSC vs. multiple sessions of conventional laser in cases of PDR **Design:** Prospective study. Two eyes of an individual patient were randomly assigned: one for a single session of PRP using PSC and the other for multiple sessions of conventional laser **Follow-up:** 6 months (days 1, 7 and 30 and then every month for the next 6 months) **Completion rate:** All patients were followed up **Reason for withdrawals:** None **Retreatment criteria:** (1) if new vessels appear active; (2) appearance of new vessel; and (3) increase in frequency and extent of VH since the last visit	**n:** 100 eyes of 50 patients with PDR on whom PRP was done for the first time **Inclusion criteria:** PDR with two to four high-risk characters (new vessel at the disc of at least ⅓ to ¼ DA or vitreous or pre-retinal haemorrhages associated with less extensive new vessel at the disc, or with new vessels elsewhere ½ DA or more in size). Only patients with early PDR and HR-PDR in both eyes were included in the study; age at least 18 years or more; BCVA of 6/60 or better **Exclusion criteria:** DMO excluded; VH obscuring view; patients with vision in only one eye or those in whom only one eye had PDR/high-risk PDSR; maculopathy; tractional retinal detachment; media clarity inadequate to perform a complete laser; previous laser; poor follow-up; and uncontrolled high BP, blood sugar or nephropathy	**Group 1:** PSC: single sitting of PRP via PSC, power and describe the results of a single session of PSC vs. multiple sessions of conventional laser in cases of PDR **Group 2:** Conventional laser: two to three sittings of PRP via conventional laser, power and duration were adjusted to obtain mild to moderate (grey to grey-white) retinal burn. The laser spot diameter in air was 200 mm **Description of type of laser and delivery:** The following instruments were used: 1. Mainster 165 lens (Mainster standard contact) 2. PSC (OptiMedica, Santa Clara, CA) 3. Conventional laser using a 532-nm frequency-doubled Nd:YAG (Carl Zeiss Meditec, Dublin, CA)	**Outcomes:**			
			Mean power (mW)		439 (275–950)	192.8 (125–300)	NR
			Duration (ms)		20–30	200	NR
			Mean total no. of spots		2795 (2100–3892)	1414 (1200–1672)	NR
			Mean time taken (minutes)		10.4 (6–16)	29 (20–29)	0.0001
			Pain, *n* (%):				
				Mild	40 (80)	0 (0)	–
				Moderate	10 (20)	11 (22)	0.291
				Severe	0	25 (50)	–
				Very severe	0	14 (28)	–
			Retreatment:				
				Yes	5 (10)	14 (28)	0.006
				No	45 (90)	36 (72)	–
			1 month:				
				Regressed NVE and NVD	45 (90)	32 (64)	–
				Persisting NVE and NVD	5 (10)	12 (24)	0.841
				VH fresh	0(0)	6 (12)	–
			6 months:				
				Regressed NVE and NVD	49 (98)	44 (88)	–
				Persisting NVE and NVD	0(0)	3 (6)	0.933
				VH old	1 (2)	3 (6)	–

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Pain determined based on the patients response: mild (no facial expression during laser and no complain of pain during the procedure); moderate (facial expression and complained of pain during the procedure); severe (patients not able to tolerate pain during the procedure, requiring a break of few minutes before continuing or requiring peribulbar or retrobulbar injection) All patients with moderate or severe pain received oral analgesic after the procedure	**Age (years):** Mean 58.24 (range 32–78 for men; 33–70 for women) **Sex:** 32% female **Diabetes type:** NR; only reported that '39 were diabetic and 11 had both diabetes and HTN' **HbA$_{1c}$:** NR **Baseline VA:** Right eye 20/20 to 20/300; left eye 20/20 to 20/1200 **Baseline CMT:** NR **Baseline DR stage:** Early PDR (10 eyes) and HR-PDR (40 eyes) **Previous laser or intravitreal drug treatment:** Patients with previous laser were excluded **Ocular comorbidities:** NR		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Nagpal 2010[82] **Aim:** To compare the efficacy, collateral damage, and convenience of PRP for PDR or severe NPDR using a 532-nm GLX vs. a multi-spot 532-nm PSC **Design:** Prospective RCT. One eye of each patient was randomised to undergo PRP with the GLX and other eye with the PSC **Follow-up:** At months 1, 3 and 6 **Completion rate:** 100% **Reasons for withdrawal:** n/a	**n:** 60 patients with bilaterally symmetrical PDR or severe NPDR **Inclusion criteria:** Bilaterally symmetrical PDR or severe non-proliferative DR **Exclusion criteria:** Patients with a history of previous laser treatments and/or intravitreal injections in either eye, eyes with a pre-treatment BCVA of <6/24, patients with media opacities such as significant cataract, corneal opacity, or VH obscuring fundus details in either eye, eyes with diabetic maculopathy, other coincidental ocular disorders, such as glaucoma, uveitis, retinitis pigmentosa, myopia >–6 D, retinal degenerations and dystrophies, optic disc pathologies, present or past	**Group 1:** GLX single-spot slit-lamp delivery PRP, two sittings: total of 500–700 laser spots in each sitting, spot size of 200 μm, pulse duration of 200 ms, power was adjusted to achieve grade 3 burns, spots placed at one spot distance with a Mainster 165 PRP lens **Group 2:** PSC two sittings: 950–1100 laser spots in each sitting, spot size of 200 μm, pulse duration of 20 ms, power was adjusted to achieve grade 3 burns, spots placed at one spot distance with a Mainster 165 PRP lens, used 5 × 5 square grid, thereby applying 25 spots simultaneously	(see tables below)

Length per sitting:

	PSC	GLX	*p*-value
Average	1.43 minutes per sitting	4.53 minutes per sitting	0.008

Pain:

	PSC	GLX	*p*-value
VAS	Range 0–1, average 0.33	Range 3–9, average 4.6	0.007

VA:

Laser	6/6–6/12	6/18–6/24	*p*-value
GLX (no. of subjects):			Difference between post-treatment visual acuities between the two groups was not statistically significant. The change in VA was not statistically significant (*p* = 0.508)
Pre laser	27	33	
Post laser	31	29	
PSC (no. of subjects):			
Pre laser	28	32	
Post laser	34	26	

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Age (years): Age range 45–61 (mean age 52)		**Macular thickness:**
			No evidence of change in macular thickness was seen in any of the eyes
	Sex: 26 female; 34 male		
	Diabetes type: NR		**Regression:**
			Comparable regression in eyes treated with either modality
	HbA$_{1c}$: NR		
	Baseline VA: (Best corrected) 6/6–6/12: 27 patients (GLX) and 28 (PSC); 6/18–6/24: 33 patients (GLX) and 32 (PSC)		**Complications:**
			None of the eyes developed any complication
			Six patients required laser augmentation because of fresh neovascularisation (NVE) fronds: GLX group = 4; PSC group = 2
	Baseline CMT: NR		**Retinal sensitivity:**

	PSC	GLX	*p*-value
Central 15°	25.08 dB (range, 20.56–27.62 dB)	23.16 dB (range, 19.31–27.37 dB)	Difference was not statistically significant (zone A; *p* = 0.26; zone B; *p* = 0.09)
15–30°	22.08 dB (range, 8.25–23.88 dB)	17.14 dB (range, 6.93–23.25 dB)	

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Baseline DR stage: 31 patients proliferative DR, 29 severe NPDR		
	Previous laser or intravitreal drug treatment: Excluded		
	Ocular comorbidities: MO, CSMO; other, e.g. cataract, glaucoma – excluded		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Salman 2011[83] **Aim:** To compare the safety and efficacy of PSC laser photocoagulation in comparison with the conventional laser photocoagulation in the treatment of DR **Design:** Prospective randomised case series (120 patients divided into four groups. Operator chose whether or not to do PSC, based on the random distribution by computer system) **Follow-up:** B1, mean 10.8 weeks (SD = 5.6); B2, mean 9.0 weeks (SD = 4.5)	**n:** 120 procedures of 120 patients (60 with PDR) **Inclusion criteria:** Patients with type 2 DR with need for laser for (NPDR) with (CSMO), focal or diffuse maculopathy or for PDR **Exclusion criteria:** Patients with ischaemic maculopathy, previous laser or intravitreal injection, vitrectomy or associated retinal diseases as retinal vein occlusion **Age (years):** Mean age 48.9 (SD 9.3, range 41–86) **Sex:** 72 (60%) male; 48 (40%) female	**Group A1:** Patients undergoing focal or modified grid macular laser photocoagulation for NPDR (with MO) using conventional laser (The Novus Spectra, which is a 532 nm green-light diode-pumped solid-state (DPSS) photocoagulator (Lumenis) with treatment durations: 10–3000 ms, spot size from 50 μm up to 500 μm and power from 50 mW up to 2500 mW **Group A2:** Patients undergoing focal or modified grid macular laser photocoagulation for NPDR (with MO) using PSC laser photocoagulation	**For treatment of PDR:** Success rate (regression of neovascularisation, and no further treatment planned): B2 = 28/30 vs. B1 = 20/30 ($p < 0.05$) Nine out of ten procedures with additional PSC were successful with regression of neovascularisation at their latest follow-up visit. One eye needed further laser. Three patients had needed a sub-Tenon's anaesthetic for their conventional laser session, but none of them required it for their PSC procedure B2: 14 (46%) performed in single session, 16 (54%) in two sessions None of the eyes with SS-PRP developed any complications, regression noted in all, with no further treatment planned at their last follow-up visit No complications related to laser treatment were noted in any patient **Post-laser VA logMAR:** B1 = 0.3 (SD = 0.27) Snellen equivalent: 6/12 B2 = 0.53 (SD = 0.61) Snellen equivalent: 6/18

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Completion rate: 100%	**Diabetes type:** Type 2	**Group B1:** Patients undergoing pan laser photocoagulation (PRP) for PDR using conventional (DPSS) laser photocoagulation	
Reasons for withdrawal: n/a	**HbA₁c:** NR		
(Follow-up less than 6 months; group A is DMO only)	**Baseline VA:**	PSC was used for additional fill-in PRP in 10/30 procedures of group B1 in which conventional laser photocoagulation was not successful in controlling the neovascularisation	
	Group B1: mean VA logMAR (minimal angle resolution): 0.31 (SD = 0.23), Snellen equivalent: 6/12		
	Group B2: mean VA logMAR (minimal angle resolution): 0.6 (SD = 0.61), Snellen equivalent: 6/24	**Group B2:** Patients undergoing PRP for PDR using PSC laser photocoagulation	
	Baseline CMT: NR		
	Baseline DR stage:		
	Groups B1 and B2: PDR		
	Previous laser or intravitreal drug treatment: Excluded		
	Ocular comorbidities: Not mentioned for PDR group		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Shimura 2003[80]	**n:** 36 diabetic patients with severe non-proliferative or early PDR without visual disturbances	**Group 1:** Weekly PRP treatment	**Additional focal laser treatment for retinal neovascularisation at 16 weeks:**
Aim: To investigate the alterations of macular thickness during and after PRP in patients with severe DR and good vision, and to compare the outcomes of weekly and biweekly treatments	**Inclusion criteria:** Diabetic patients with symmetrical, severe non-proliferative or early PDR without visual disturbances, VA of 20/20 or better	**Group 2:** Biweekly PRP treatment	Weekly group: 15 eyes
			Biweekly: 13
		Description of type of laser and delivery: PRP scatter treatment completed in four sessions. The size of the spots on the retina was 200–500 μm, and the duration of the application was 0.15–0.2 seconds. The initial burns were non-confluent and placed > 2 DDs from the fovea out to the equator. A krypton red laser was used, resulting in a grey retina. Each spot was produced by a 120- to 180-mW exposure. The number of spots in each session was around 500	There was a significant difference of the initial HbA_{1c} levels between patients who did not need additional treatments ($p = 0.0031$)
Design: Prospective, comparative interventional case series	**Exclusion criteria:** Clinically significant MO		**VA:**
Follow-up: 12 weeks	**Age (years):** 55.6 ± 7.8 (range 35–68)		After the completion of PRP, the VA was maintained in 89% (32 of 36 eyes) of eyes treated weekly and in 92% (33 of 36 eyes) treated biweekly
Completion rate: Unclear	**Sex (% female):** 42 (15/36)		
	Diabetes type: Type 2		
	HbA_{1c}: 8.7 ± 1.4 mg/dl		

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Reasons for withdrawal: Seven eyes of four patients (four eyes in the weekly treated group and three eyes in the biweekly) who developed MO and reduced VA were excluded because the time course of macular thickening in those eyes was monotonically increasing and different from that in the remaining patients *(Follow-up less than 6 months)*	**Baseline VA:** NR **Baseline CMT:** Weekly group: 191 ± 9.9 μm Biweekly: 191 ± 10.7 μm $p = 0.814$ **Baseline DR stage:** Severe non-proliferative or early PDR **Previous laser or intravitreal drug treatment:** NR **Ocular comorbidities:** No history of any other ocular disease except refractive errors was reported		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
Study ID: Suto 2008[84]	**n:** 29 patients	**Group 1:** PRP was performed before cataract surgery in one eye (PRP-first group). Cataract surgery was performed 1 to 3 months after the final preoperative PRP session in the PRP-first eye	**Outcomes:**			
			Parameter	**PRP first**	**Surgery first**	**p-value**
Aim: To evaluate the outcomes in patients with DR and cataract who had PRP first and cataract surgery second in one eye, and cataract surgery followed by PRP in the fellow eye	**Inclusion criteria:** Untreated severe non-proliferative or early PDR of similar severity in both eyes and a similar cataract grade in both eyes and who were at least 50 years old		BCVA 20/40 or better, n (%)	20 (69.0)	28 (96.6)	0.012
			MO severity, n			
		Group 2: PRP was performed after cataract surgery in the contralateral eye (surgery-first group). Cataract surgery was performed within 4 days	Absent	6	6	
	Exclusion criteria: Age <50 years, high lens opacity, loss of zonular fibres, pupillary anomalies synechias, history of serious coexistent ocular disease (e.g. glaucoma, optic atrophy, ocular tumour), pseudoexfoliation syndrome, use of topical or systemic steroids or non-steroidal anti-inflammatory drug during previous months, corneal opacities, history of uveitis or retinal vein occlusion, previous ocular trauma or intraocular surgery, severe refractive error, decrease in HbA$_{1c}$ by ≥3% from 3 months, serious renal, hepatic, endocrine, pulmonary, cardiac neurological, rheumatic, psychiatric, or cerebral dysfunction, alcohol		1	4	6	
Design: RCT			2	10	12	
			3	9	5	
Follow-up: 12 months			Rate of progression of MO, n (%):	16 (51.7)	8 (27.6)	0.033
Proportions completing the study: 100%		**Description of type of laser and delivery:** A multicolour laser and a quadraspheric fundus laser lens were used. The laser parameters conditions were 200 μm, 0.12 to 0.16 W, and 0.2–0.4 seconds in the PRP-first group and 200 μm, 0.08 to 0.12 W, and 0.2–0.4 seconds in the surgery-first group. All treatment was done using a yellow mainly or red krypton if cataract was higher	Focal treatment			0.527
			Before surgery	3	0	
Reasons for withdrawal (brief): n/a			After surgery	14	8	
			DR severity, based on ETDRS scale:			
			Level 53	16	13	
			Level 61	10	10	
		When macular lesions were observed, they were treated before PRP	Level 65	3	6	
			Rate of progression or retinopathy, n (%)	8 (27.6)	12 (41.4)	0.270

Risk of progression of MO higher in the PRP-first group than in the surgery-first group (RR = 2.0; 95% CI 1.49 to 2.51)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	or drug abuse problems, allergy to fluorescein, posterior capsule rupture during surgery, Nd:YAG laser capsulotomy for posterior capsule opacification during observation period		
	Age (mean ± SD), years: 66.0 ± 7.5		
	Sex (female): 69 (20/29)		
	Diabetes type: Type 2		
	HbA$_{1c}$ (mean%): 7.4 ± 1.0		
	Baseline VA: NR		
	Baseline DR stage: Severe non-proliferative or early proliferative diabetic based on ETDRS scale:		
	Cataract first: Level 53: $n=22$; level 61: $n=7$		
	PRP first: Level 53: $n=21$; level 61: $n=8$		
	Previous laser or intravitreal drug treatment: None		

TABLE 20 Summary of RCTs of laser vs. other lasers post 2000 (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
Study ID: Tewari 2000[55]	**n:** 50 eyes of 25 patients	**Group 1:** Argon laser: spot size: 200–500 µm, duration 0.1–0.2 seconds, mean no. of spots 1694 ± 234	**Outcomes:**		
Aim: To compare treatment with diode infrared and argon green scatter photocoagulation for PDR	**Inclusion criteria:** Patients with bilateral PDR			**Argon laser**	**Diode laser**
	Exclusion criteria: Patients who had previously received photocoagulation; who had hypertensive retinopathy, vascular block, or hazy media; and those in whom laser delivery was difficult	**Group 2:** Diode laser: spot size: 200–500 µm, duration 0.2–0.3 seconds, mean no. of spots 1439 ± 206	Regression of neovascularisation	18/25 eyes (72%)	16/25 eyes (64%)
			VH	2/25 eyes (8%)	2/25 eyes (8%)
Design: Prospective randomised trial			Lager augmentation requirement	8/25 eyes (32%)	12/25 eyes (48%)
Follow-up: 6 months		**Description of type of laser and delivery:** Diode infrared (810 nm) and argon green (514 nm) scatter photocoagulation done in two to four sittings; laser power varied between 0.2 and 0.4 W	**Mean VA:**		
Completion rate: Unclear	**Age:** Mean 56.25 (SD 8.2) years			**Argon laser**	**Diode laser**
Reasons of withdrawal: n/a			Before laser treatment	4.16 ± 2.77	3.22 ± 2.05
	Sex: NR		Six weeks after laser photocoagulation	5.04 ± 3.03	4.56 ± 2.56
			Final after 6 months	4.76 ± 2.83	3.62 ± 2.12
	Diabetes type: Type 2				
	HbA$_{1c}$: NR		Constriction of the peripheral visual field (I-4-e) in both groups		

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Baseline VA: 6/9 to 6/60 (better than 20/30 to 20/200) in argon group and 6/6 to 6/60 (20/20 to 20/200) in diode group **Baseline CMT:** NR **Baseline DR stage:** Bilateral PDR **Previous laser or intravitreal drug treatment:** NR **Ocular comorbidities:** NR		**Contrast sensitivity:** Diode vs. argon ($p = 0.06$; Student's t-test) **Pain:**

	Argon laser	Diode laser	*p*-value
	7 (28%)	23 (92%)	< 0.001 χ^2

BJO, *British Journal of Opthalmology*; CD, choroidal detachment; CRT, central retinal thickness; D, dioptre; DA, disc area; dB, decibel; DPSS, diode-pumped solid state; GLX, solid-state green laser; MAPASS, MAnchester PSC Study; MREH, Manchester Royal Eye Hospital; MS-PRP, multiple-session pan-retinal photocoagulation; MT-PRP, minimally traumatic PSC pan-retinal photocoagulation; n/a, not available; NPA, non-perfusion areas; NR, not reported; PC, photocoagulation; S-PC, selective photocoagulation; SI-PRP, standard intensity PSC pan-retinal photocoagulation; SS-PRP, single-session pan-retinal photocoagulation; SAH10A, Standard Airlie House photograph 10A; SD, standard deviation; TRP, targeted retinal photocoagulation; VAS, visual analogue scale; VF, visual field; VH, visual haemorrhage; YAG, yttrium aluminium garnet.

Japanese Society of Ophthalmic Diabetology 2012

Targeted retinal photocoagulation (TRP) treats only areas of retinal non-perfusion.

The aim of this RCT was to compare selective photocoagulation (S-PC) with no photocoagulation in patients with NPDR.[17] In Japan, most ophthalmologists use S-PC in which NPAs are identified by FA and treated at the NPDR stage. (The paper uses the term PPDR. Those with PPDR severe enough to be deemed to require PRP were excluded.)

This study[17] compared S-PC (S-PC group) of NPAs only in PPDR, with no photocoagulation till PDR developed (non-photocoagulation group). In the S-PC group, the photocoagulation spots on the retina were of 400–500 μm with a space of approximately one photocoagulation spot between the two. In the non-photocoagulation group, patients were followed up and no interventions were given until they developed PDR, when PRP was performed. It is not clear how many were so treated. PDR was defined as any so includes early PDR as defined by ETDRS. If MO developed, patients could have laser if the ophthalmologist decided it was needed.

Only 69 patients were recruited, all with type 2 diabetes. PPDR is not defined.

The study[17] was stopped early because more PDR developed in the non-photocoagulation arm. About one-third of the patients had not reached the 3-year follow-up, and 16 dropped out (more in the photocoagulation arm).

Change in VA after 36 months was not different between the two groups (0.11, SD 0.47, logMAR in non-photocoagulation group vs. 0.11, SD 0.27, in photocoagulation group; $p = 0.97$). Slightly more patients in the S-PC group [3/13 (23%)] than in the non-photocoagulation group [2/23 (9%)] lost VA of ≥ 0.2 logMAR; however, the difference was not statistically significant ($p = 0.24$). Reasons for decreases in VA in the non-photocoagulation group were cataract progression ($n = 1$) and vitreous haemorrhage ($n = 1$), and in the S-PC group cataract progression ($n = 1$) and MO ($n = 2$). One patient in the non-photocoagulation group had SVL (defined by the ETDRS as corrected VA of < 0.25) due to vitreous haemorrhage. Significantly more patients in the non-photocoagulation group developed PDR, defined as new vessels on FA, than those in the S-PC group. If only those with 3-year follow-up are included, the incidence of PDR was 52% (12/23) in the no-photocoagulation group and 15% (2/13) in the photocoagulation group ($p = 0.03$).

The mean number of spots during the initial photocoagulation in 36 patients was 233 (range 92–365). In 54% patients ($n = 17$) additional coagulation was performed either once or twice (mean 1.1 times). The mean number of additional coagulation spots was 224 (range 128–372 per session), which was performed between 6 and 30 months (mean 14.6 months) after initial photocoagulation.

In summary, early PRP at the PPDR stage reduced progression to PDR but was not associated with any difference in mean VA at 36 months. The effects on visual fields or driving vision were not reported. This was a small study[17] but might be worth repeating with larger numbers. However, it might be argued that might be unethical because of the results.

Literature searches by the authors found little evidence on the use of this method. They reported another study from Japan (in Japanese) by Shimizu et al. (1989),[85] which was a non-randomised comparison in eyes with PPDR but only 20% had S-PC – the rest had PRP.

They concluded that this method was used only in Japan.

Mirshahi 2013

This study compared different exposures.[81] A continuous-wave, frequency-doubled Nd:YAG (532 nm) retinal photocoagulation with spot size of 200 μm was used. The difference between the two arms was only in the duration of the exposure: single-spot short duration (20 ms) PRP and conventional (100 ms) PRP. The energy of the laser was adjusted to achieve moderate whitening on the retina. The conventional laser required a mean power of 273 ± 107 mW, while the short-duration laser required 721 ± 406 mW to achieve moderate whitening on the retina. In the former, an average of 1218 ± 441 spots was performed and an average of 2125 ± 503 spots in the latter. Photocoagulation was usually performed in a single sitting, but in five patients in the conventional group the treatment had to be completed in the following week. There was no difference in change in VA between the two treatments: single-spot short duration (20 ms) PRP against conventional (100 ms) PRP ($p > 0.05$). All short PRP was performed in single sessions, whereas five of the conventional laser was performed in two sessions and remainder (28) in single sessions. The difference between the two in terms of sessions was significant ($p = 0.02$). Three patients in the short PRP group and four patients in the conventional group required additional PRP ($p = 0.68$). The pain score was significantly lower in patients receiving single-spot short duration (20 ms) PRP than in those receiving conventional (100 ms) PRP [1.75 (SD 0.87) vs. 7.5 (SD 1.14) on VAS; $p < 0.001$]. No complications were seen with single-spot short duration PRP.

In summary, the short exposure laser performed in single sitting was found to be significantly less painful and as effective as the conventional laser.

Muqit 2010/11

The MAnchester PSC study (MAPASS) (Muqit 2010;[74,75] Muqit 2011[76]) compared multi-spot 20-ms single-session PRP (SS-PRP) using 5.5 and 4.4 multi-spot arrays, given in a single session, with single-spot 100-ms multiple-session PRP (MS-PRP) given in three sessions over 4 weeks.[74–76] Patients (40 eyes of 24 patients; in analysis 38 eyes included) had newly diagnosed PDR, described as being in three grades:

- *Mild PDR* Less than Standard Airlie House photograph 10A (SAH10A) mean logMAR 0.04.
- *Moderate PDR* Neovascularisation away from disc (NVE) greater than half DD and/or NVD greater than Airlie House 10A, mean logMAR 0.17.
- *Severe PDR* Multiple NVE and or NVD, mean logMAR 0.14.

The laser used was PSC a frequency-doubled Nd:YAG solid-state laser with a wavelength of 532 nm. In both groups, the threshold laser photocoagulation treatment was titrated to, and designated by, a mild grey-white burn (between grades 2 and 3) according to ETDRS guidelines. All eyes received 1500 burns performed under topical anaesthesia.

Outcomes in Muqit (2010)[74,75] included:

- Central subfield retinal thickness.
- *Mean change in VA* At 12 weeks, VA increased by four letters (SD six letters) from baseline in the SS-PRP compared with the MS-PRP group.
- *PDR grade at 12 weeks* No significant difference between the treatment groups in terms of effect on PDR activity.
- *Adverse events* Numerical pain score (NPS) within 1 hour and mean numerical headache score 1 month after treatment. The mean NPS immediately after laser was higher in the conventional exposure group than in the short exposure group [2.4 (SD 2.3) vs. 4.9 (SD 3.3)]. Patients in the former group categorised pain as moderately severe in intensity, and those in the latter group as mild. At 1 month, the mean numerical headache score was significantly lower in the short exposure group than in the conventional group [1.5 (SD 2.7) vs. 3.2 (SD 3.5); diff. 95% CI 3.7 to 0.3; $p = 0.045$]. The median duration of photophobia was significantly lower in the short exposure group (3 hours vs. 72 hours; $p < 0.001$). The effect of the laser on driving and other activities was similar in both treatment groups. No other immediate or short-term ocular complications were reported.

Initial follow-up was only 12 weeks, but follow-up after the initial trial was in routine care, for 1–2 years, range 15–19 months according to grade.

In Muqit (2011),[76] data from a cohort of patients from Muqit (2010)[74,75] were used to quantify the 20-ms PSC ablation required for regression of PDR.

Patients were grouped according to their baseline PDR (Group 1 – grade 1, Group 2 – grade 2, Group 3 – grade 3). Numbers in groups were quite small (8–14).

Twenty eyes received multi-spot, 20-ms single-session PRP, while the remaining 20 eyes underwent single-spot, 100-ms multiple sessions PRP (three sessions across a period of 4 weeks). Only 36 eyes of 22 patients were included in the analysis because one patient died shortly after completing the MAPASS trial and another patient was lost to follow-up. The mean power of the laser ranged from 104 to 482 mW across groups. Patients with grade 1 PDR (Group 1) received the lowest mean power laser (213 mW, range 104–350 mW), followed by those with grade 2 PDR (Group 2) (220 mW, range 116–482 mW) and patients with grade 3 PDR (Group 3) (291 mW, range 140–398 mW). Similarly, Group 1 had the lowest mean total number of spots (2187, range 1500–3450 mW), followed by Group 2 (3988, range 1500–8364 mW) and finally Group 3 (6924, range 4097–9234 mW). The difference was significant in comparisons of Group 2 versus Group 1 ($p = 0.012$) and Group 3 versus Group 1 ($p = 0.012$). The average number of sessions ranged from one to three in Group 1, four in Group 2 and six in Group 3.

Outcomes in Muqit (2011)[76] included:

- complete PDR regression – no leakage on WF-FA (wide-field Optos FA) and/or disappearance of neovascular (NV) complexes
- VA – no significant changes at final follow-up.

Safety end points were:

- DMO
- vitreous haemorrhage
- tractional retinal detachment.

At the end of follow-up, there was no significant change in VA within and between the groups (only SD reported, no p-value reported). The study[76] also reported that cataract surgery ($n = 1$), vitrectomy ($n = 1$) and top-up PRP did not affect VA. Patients who underwent bilateral PRP treatment ($n = 14$) with mean burns of over 4000, were questioned about the status of fitness to drive according to DVLA UK requirement. All patients underwent testing within 6 months of the final study visit. Out of 14 patients, 13 passed the DVLA standard driving standards, and one failed because of suboptimal VA level, despite having a satisfactory binocular visual field test.

Complete regression was seen in 75% (6/8 eyes) in Group 1; 67% (14/21) in Group 2; and 3/7 eyes in Group 3. In Group 1 complete disease regression occurred at a mean time of 5.8 months (range 3-10 months). In Groups 2 and 3, the mean times to regression were 11 months (range 3-19 months) and 17 months, respectively. The mean laser ablation required to achieve complete PDR regression in Groups 1, 2 and 3 were 264 mm^2 (SD 95 mm^2; range 181–416 mm^2); 471 mm^2 (SD 264 mm^2; range 181–698 mm^2); and 657 mm^2 (SD 258 mm^2; range 494–954 mm^2), respectively.

No complications were seen with a 20-ms PSC laser. There were also no reports of unexpected adverse or serious adverse events in the study.[76] None of the patients showed signs of intraretinal/subretinal haemorrhage or blood vessel damage from 20-ms PRP burns and no indirect laser-related ocular complications. However, there were reports of seven vitreous haemorrhage and one tractional retinal detachment associated with elevated/forward NVD greater than the SAH10A. Three eyes developed

uncomplicated, complete posterior vitreous detachment. Within 6 months after completing the study, DMO developed in three eyes but was unrelated to top-up PRP treatments, and in one patient it was related to pregnancy.

Muqit et al. (2011)[76] concluded that SS-PRP was as safe and effective as MS-PRP. PDR was improved in 74% of eyes in the SS-PRP group and 53% of eyes in the MS-PRP group (difference not statistically significant).

Muqit 2013

Muqit et al. (2013)[77] is a pilot study (PETER PAN study) of 30 eyes of 24 patients with newly diagnosed treatment-naive PDR, 35–85 letters (6/60 or better), excluding DMO or any other cause MO, compared three arms:

- *Standard intensity PSC PRP* Grey-white burn, single session, 2500 burns, 20 ms. SI-PRP.
- *A minimally traumatic or reduced fluence PSC PRP (MT-PRP)* Single-session, titrated to produce grey-white burn then power reduced to produce light grey barely visible burn. 2500 burns, 20 ms. Lower power used – compared with TRP and SI-PRP.
- *SI-TRP* Standard intensity PSC targeted laser to treat areas of retinal capillary non-perfusion. 1500–2500 burns, 20 ms covering area of capillary non-perfusion (Optos wide-angle directed). The aim of targeting is to avoid damage (scarring) to well-perfused areas. See earlier study from same group for details of targeted approach.[68]

One aim was to avoid causing MO.

At the end of 12 weeks, the changes in VA were not significantly different (but note that they had only eight patients in each group) between the treatment groups [TRP vs. SI-PRP 1.3 letters (SD 11 letters), 95% CI 6.55 to 9.15 letters; $p = 0.717$; TRP vs. MT-PRP 0.7 letters (SD 8.4 letters), 95% CI 5.33 to 6.73 letters; $p = 0.799$; MT-PRP vs. SI-PRP 0.6 letters (SD 7.2 letters) 95% CI 4.53 to 5.73 letters; $p = 0.797$]. At 12 weeks there was no significant difference amongst the three treatment groups (TRP; MT-PRP; SI-PRP) in terms of PDR activity. Seventy per cent of patients in the SI-PRP group, 60% in the TRP group and 50% in the MT-PRP group had partial regression of PDR activity. Similar proportions of patients (20%) in the MT-PRP and SI-PRP groups had complete regression of their PDR activity, whereas only 10% of patients in the TRP group had complete regression. PDR worsened in about 10% of patients in the SI-PRP but in none in the other groups. In 30% in the TRP group and 20% in the MT-TRP there was no change in their retinopathy. Measures like description of pain, mean NPS and VAS were used to report the effect of lasers on pain. During 12 weeks' follow-up, mean NPS was greater in the SI-PRP group [3.1 (SD 2.7)] than in the other two groups [1.7 (SD 2.3) in TRP; 0.5 (SD 1.3) in MT-PRP]. NPS was significantly lower in the MT-PRP group than the SI-PRP group ($p = 0.001$) but not against the TRP group ($p = 0.05$). Pain was categorised as mild in all of the groups. In the MT-PRP group, 80% of patients had no pain. Similarly, mean VAS score was significantly lower in the MT-PRP group than in the SI-PRP group [3.5 (SD 7.8) vs. 32.4 (SD 24.2); $p = 0.005$] but not against the TRP group [3.5 (SD 7.8) vs. 15.7 (SD 23.7); $p = 0.19$]. Again pain was categorised as mild in all groups.

There were no ocular complications or adverse events during the immediate or short-term follow-up after treatment. Wide-angle imaging was done using the Optos device. There were also no signs of intraretinal haemorrhage or blood vessel compromise at the locations of TRP, MT-PRP or SI-PRP burns. Both MT-PRP and SI-PRP produced less retinal thickening than SI-PRP.

In summary, the three methods PSC were not significantly different from each other in terms of change in VA and regression of PDR activity. Pain appeared to be significantly lower with MT-PRP and TRP than with SI-PRP.

Muraly 2011

This study compared the efficacy of single-session PSC against two to three sessions of conventional laser in 100 eyes of 50 patients with PDR or HR-PDR in both eyes.[78] One eye was randomised to PSC laser, whereas the other eye of the same patient received conventional laser (a 532-nm frequency-doubled Nd:YAG) in two to three sittings. The intervals between sessions were not reported.

At 1- and 6-month follow-up, more patients in the PSC laser group had regression of NVE and NVD than in the conventional laser group (90% vs. 64% 1 month; 98% vs. 88% 6 months). Fluorescein angiograms were performed. Fewer patients in the PSC group had persisting NVE and NVD at 1 month and none at 6 months (10% vs. 24% 1 month; 0% vs. 6% 6 months). At 1 month, six patients in the conventional laser group developed fresh vitreous haemorrhage but none in the PSC group did so. One patient in the PSC group and three patients in the other group had old vitreous haemorrhage at 6 months' follow-up. The mean power of the laser was greater for pattern laser PSC than that of the conventional laser (439 mW, range 275–950 mW vs. 192.8 mW, range 125–300 mW; *p*-value not reported). The duration of the PSC laser was usually 30 ms, but ranged from 20 to 200 ms, whereas that of the conventional laser was 200 ms. The mean time taken to perform the laser was significantly greater for the conventional photocoagulation than for the PSC treatment (29 minutes vs. 10.4 minutes; $p < 0.0001$). More patients receiving PSC photocoagulation had only mild pain compared with those receiving conventional laser (mild – 80% vs. 0%). Many of those receiving the latter had severe to very severe pain, whereas no one in the PSC laser group complained of severe to very severe pain (severe – 50% vs. 0%; very severe – 28% vs. 0%). BCVA was not reported.

Muraly *et al.* (2011)[78] concluded that photocoagulation with a single PSC session was as effective as conventional laser.

The Muraly study (2011)[78] was criticised by Jojo and Mohamed (2012)[86] (who thought that the PSC group had had more extensive treatment than the conventional arm), but Muraly *et al.* (2012)[87] noted that expansion after conventional laser treatment equalised the affected area.

Nagpal 2010

Nagpal *et al.* (2010)[82] compared the efficacy of single-spot 532-nm solid-state green laser (GLX) against a multi-spot 532-nm PSC in patients with bilaterally symmetrical PDR or severe NPDR. One eye was randomised to receive PSC photocoagulation, whereas the other eye of the same patient received GLX. Both lasers were completed in two sittings in each eye with an interval of 7 days between the two sittings. The durations were 20 ms for PSC and 200 ms for GLX, with spot size of 250 µm in both. PSC photocoagulation involved 950–1100 spots and GLX 500–700 laser spots. There was no significant difference in the post-laser VA between the GLX and the PSC group. In addition, the difference in the change in VA between the two groups was not statistically significant ($p = 0.0508$). The average length per sitting for PSC was 1.43 minutes and for GLX was 4.53 minutes. The difference between the two was statistically significant ($p = 0.008$). Regression in retinopathy was comparable between the two groups but no data were reported. The effect of GLX and PSC on retinal sensitivity was not statistically significant different between the two groups [central 15° (Zone A): 25.08 dB, range 20.56–27.26 dB with PSC vs. 23.16 dB, range 19.31–27.37 dB with GLX; $p = 0.26$] [15–30° (Zone B): 22.08 dB, range 8.25–23.88 dB with PSC vs. 17.14 dB, range 6.93–23.25 dB with GLX; $p = 0.09$]. Mean VAS score was significantly lower in the PSC than with the GLX (average 0.33, range 0–1 vs. average 4.6, range 3–9; $p = 0.007$).

In summary, PSC photocoagulation was quicker and caused significantly less pain than GLX while giving similar results in regression in retinopathy and change in VA.

Salman 2011

Salman *et al.* (2011)[83] compared the safety and efficacy of PSC against conventional laser photocoagulation (Novus Spectra 532-nm green light; treatment duration of 10–3000 ms, spot size from 50 to 500 µm, power from 50 to 2500 mW) in 120 patients either with NPDR and CSMO or, PDR.

There were four groups of 30 patients (A1, A2, B1 and B2) in the study.[83] Groups A1 and A2 included patients with NPDR and CSMO, whereas those in groups B1 and B2 had PDR. Patients in Group A1 and A2 underwent focal or modified grid macular laser photocoagulation for NPDR (as stated by the authors but presumably it was for the MO). Group A1 patients received conventional laser, whereas patients in Group A2 received PSC laser photocoagulation. Patients in group B1 and B2 underwent PRP, the former with conventional diode-pumped sold-state (DPSS) laser and the latter with the PSC laser.

In Group A1, the mean power of the conventional laser used was 100 mW (SD 20.5 mW) and an average of 85 (SD 76.6) burns were performed. The mean power of the conventional laser was 215 mW (SD 51.3 mW), with an average of 700 (SD 201.1) burns performed in Group 2. Patients in Group A2 received PSC photocoagulation, the mean power of which was 332 mW (SD 105.5 mW) and an average of 145 (SD 92.2) burns were performed. Those in Group B2 also received PSC photocoagulation, mean of 1090 (SD 410.4) burns with a mean power of 410 mW (SD 115.2 mW). The power of the laser used was significantly higher with the PSC than the conventional laser ($p < 0.001$) because the former is given for a relatively shorter duration.

Follow-up at 12 months included BCVA, photography and FA.

Visual acuity did not change significantly following laser in any groups. More patients receiving PSC achieved success, i.e. regression of neovascularisation and no further treatment planned, than those patients receiving the conventional laser (28/30 vs. 20/30; $p < 0.05$).

In Group B2 (PSC), 46% (14) had a single session and 54% (16) had two sessions. None of the patients in the single-session PRP group developed any complications and all had regression of their retinopathy. Also none of the patients needed further treatment plan at his/her last follow-up visit. There were also no reports of complications related to laser treatment. When asked to rate the pain following laser on a scale between 0 and 5, with '5' being very severe pain, patients rated PSC as 0.61 and standard laser as 2.72.

The authors concluded that PSC was safe, rapid and effective but required higher power because of shorter exposure time.

Shimura 2003

In this study, the efficacy of pan-retinal scatter photocoagulation used either as weekly or biweekly treatment was compared in 36 patients with severe NPDR or non-HR-PDR but good vision (baseline VA of 20/20 or better) before laser therapy.[80] A krypton red laser was used. One eye of the patient was treated weekly, whereas the other eye of the same patient was treated biweekly. All had four sessions. In each session, around 500 spots were performed, with each spot of 200–500 µm in diameter and the duration of the exposure ranging from 0.15 to 0.2 seconds. The order of the treatments was nasal followed by inferior, superior and, finally, temporal. Slightly more patients in the biweekly PRP group maintained their VA at 16 weeks than the eyes treated with the weekly PRP (92% vs. 89%). At 16 weeks, 15 eyes in the weekly group and 13 eyes in the biweekly group received additional focal laser treatment for retinal neovascularisation.

Suto 2008

Suto *et al.* (2008)[84] compared PRP before cataract surgery (PRP-first group) and after cataract surgery (surgery first group) in patients with bilateral cataract and severe NPDR or early PDR.[84] One eye had PRP first, and the other eye of the same patient had PRP after cataract surgery. In the PRP-first group, cataract surgery was done 1–3 months after the final PRP session. In the surgery-first group, cataract surgery was performed within 4 days. The laser treatment involved making spot size of 200 µm, 0.12–0.16 W, and 0.2–0.4 seconds in the PRP-first group and 200 µm, 0.08–0.12 W, and 0.2–0.4 seconds in the surgery-first group. At 12 months' follow-up, significantly more eyes in the surgery-first group had a BCVA of 20/40 or better than in the PRP-first group (96.6% vs. 69%; $p = 0.012$). There was no significant difference in the rate of progression of DR (27.6% in PRP-first vs. 41.4% in surgery-first group; $p = 0.270$). Worsening of

MO (assessed by FA, not by OCT) was twice as likely in the PRP-first group as in the surgery-first group (RR = 2.0; 95% CI 1.49 to 2.51). In summary, the authors found that patients in the surgery-first group had better VA than those in the PRP-first group. There was no difference in the rate of progression of DR in the two groups, but progression of MO was commoner in the PRP-first group. This was presumably related to the higher power required.

Tewari 2000

Tewari *et al.* (2000)[55] compared diode (810 nm) and argon laser (514 nm) PRP in 25 patients with bilateral PDR. One eye received diode laser (810 nm) treatment and the other eye received argon laser (514 nm) treatment, each done in two to four sittings.[55] Around 200–500-μm spots were applied, with exposure ranging from 0.1 to 0.2 seconds with the argon laser, and 0.2–0.3 seconds with the diode laser. The power of the laser varied between 0.2 and 0.4 W to give 'moderate intensity' burns. At 6 months' follow-up, VA (as measured by reciprocals of Snellen) in the argon group reduced from 4.16 (SD 2.77) to 4.76 (SD 2.83), and from 3.22 (SD 2.05) to 3.62 (SD 2.12) in the diode laser group. The difference in change in VA between the two groups was not significant. There was no statistical difference between the two groups in regression of neovascularisation (72% vs. 64%; p = not reported; only states not statistically significant). There was reduction in contrast sensitivity (Cambridge low-contrast gratings) in both groups (diode, from 169.2 ± 59.3 to 142.2 ± 49.2; argon, from 164.6 ± 56.2 to 142.2 ± 49.2). Vitreous haemorrhage developed in two eyes (8%) in each group. Slightly more eyes in the diode laser group required laser augmentation than those in the argon laser group (48% vs. 32%). Significantly more patients receiving diode laser complained of pain than those receiving argon laser (92% vs. 28%; $p < 0.001$). In summary, there is no difference in efficacy between argon and diode laser. Pain appeared to be significantly lower with the argon laser. The authors of the study[55] concluded that diode laser is an appropriate alternative to the argon laser to perform scatter laser in DR, though they recommend a study with longer follow-up than their 6 months.

Summary

All of the studies included above are RCTs, most of them with low risk of bias. Findings include:

- Some had only small numbers of patients, and follow-up was often short.
- The majority of the patients included in these studies had PDR, with a few with very severe NPDR.
- There were five trials of PSC photocoagulation against conventional PRP. One study compared the efficacy of PSC laser given in three different ways – TRP, MT-PRP or SI-PRP.[77] The efficacy of PSC photocoagulation was also compared if given as multi-spot 20-ms single session against single-spot 100 multi-session in one study.[75,78]
- One study compared threshold diode and argon laser.[55] No study compared PSC with sub-threshold diode laser. One study compared light (grade 1 of L'Esperance scale) with standard PRP (grade 3).[73] Other studies examined different ways of giving standard PRP.
- In most studies, patients were followed for at least 6 months. We included four trials with follow-up period of less than 6 months, mainly to look at adverse events.
- It appeared that most of the studies were funded by academic institutions. One trial was funded by a PSC laser manufacturer.
- VA – At the end of follow-up, in all studies there was no significant difference amongst laser types in terms of change in VA.
- Retinopathy – Scatter PRP was found to cause resolution of neovascularisation on and around the optic disc (NVD) and new vessels elsewhere (NVE). Trials of modern methods of PRP, light, PSC and diode either showed no difference in improvement in retinopathy (three trials) or reported better results with PSC (two trials).

The Japanese approach of selective PRP aimed at ischaemic areas only, in PPDR delayed progression to PDR, with only 15% of the selective PRP group developing PDR compared with 52% of those receiving no photocoagulation ($p = 0.03$).

There are also no differences between PRP performed before or after cataract surgery in progression of DR. However, patients in the surgery-first group had better VA than those in the PRP-first group. Progression of MO was significantly higher in the PRP-first group.

Adverse events

Pain was more common with conventional photocoagulation than with PSC. Pain was significantly less in patients receiving short exposure laser, less in those receiving light PRP, and in those receiving PSC compared with GLX. In a study comparing different types of PSC photocoagulation, pain was higher in SI-PRP followed by TRP and MT-PRP (Muqit 2013[77]). However, pain was mild in nature. Pain was more common with diode laser than argon laser.

Discussion of randomised controlled trial evidence

The general conclusion from the trials reviewed above is that modern methods of laser photocoagulation are as effective as conventional lasers, but it is not possible to say that they are more effective. Multi-spot photocoagulation has advantages, such as reduced pain and faster treatment, making treatment less onerous for patients. Pain relates mainly to the power and duration of the laser used and as modern laser technologies use shorter-duration laser pulses and are probably given with less intensity (not looking for a white laser mark but more for grey mark) then they are less painful. Less intense and confluent PRP may be slightly less effective but has fewer side effects. Shorter pulses are as effective but cause less pain.

The published evidence base is somewhat limited because of the small size and short duration of some studies.

Bandello *et al.* (1993)[88] suggest that the advantages of the diode laser include compact size, no need for a cooling system, low price, high transmission of laser through cataract and vitreous haemorrhages.

Diode laser treatment was reviewed by Neubauer and Ulbig (2007),[13] who report that its advantages include small size and lower cost. They report no difference in progression of PDR, but more pain.

In another narrative review, mainly of use in DMO, Sivaprasad and Dorin (2012)[15] argue that sub-threshold diode laser micropulse photocoagulation (SDM) is as effective as, but less destructive than, standard focal/grid photocoagulation. Standard is taken to be the mETDRS approach, which is aimed only at areas of thickened retina and non-perfusion, and leaking microaneurysms, using burns with smaller areas and less-intense heat (grey). In micropulse lasering, the laser is used in a series of short pulses, with the theory being that this allows the retinal tissue to recover a bit between pulses, thereby causing less thermal damage and subsequent scarring.

The authors found little evidence for the use of SDM for PRP, but the main one being a retrospective case series (see Luttrull *et al.* 2008[66] reviewed later). In DMO, Sivaprasad and Dorin (2012)[15] report five RCTs of:

- SDM versus conventional continuous-wave 514-nm argon laser threshold photocoagulation (two trials)[89,90]
- three trials of SDM versus mETDRS: two with 514-nm argon laser, the other unspecified.

These trials and the observational studies are reported as confirming the advantages of SDM, but more when the high-density version of SDM is used, rather than the normal density one. In the trial by Lavinsky *et al.* (2011),[91] twice as many eyes gained 15 or more letters with HD-SDM than with mETDRS.

Sivaprasad and Dorin (2012)[15] ponder on why there has been little uptake of SDM, and suggest the following reasons:

- SDM has been undergoing a slow evolution.
- Micropulse lasering has been being refined.
- The arrival of the anti-VEGF drugs has taken attention away from laser treatments.
- Lasers with micropulse emission were not available.
- The optimum dosing remains to be determined.
- The laser used is the 810-nm infrared diode, which has not been as popular as the 514-/532-nm green lasers.

Subthreshold diode micropulse laser photocoagulation is said by Muqit *et al.* (2013)[77] to produce clinically undetectable laser lesions requiring a high number of laser treatments. The source cited is Luttrull (2008),[66] already mentioned.

Data on adverse effects from observational studies

It is important to review the evidence on the adverse effects of laser photocoagulation for three reasons. The first is the usual one, in that we need to balance the benefits of photocoagulation against the harms, especially when considering administering PRP at earlier stages of retinopathy. The second is that the types of laser treatment have been changing, with a trend towards lighter laser treatment, and the harms seen in the landmark trials such as ETDRS, may not be a good guide to the harms seen in modern laser therapy. Lighter may mean many things, such as a less-white burn but also a laser applied in a different manner than before (for instance, with shorter duration pulses compared with longer ones).

Third, modern imaging methods such as OCT make it easier to detect MO, allowing that to be treated first, so preventing worsening of MO after PRP.

Although it could be argued that the most useful data on harms might come from RCTs, a counter argument may be that RCTs may not reflect routine care. A systematic review in 2001 found evidence that being in a trial improves care (a 'trial effect'),[92] though a later Cochrane review in 2008 did not confirm this finding.[93]

We decided to review non-RCT evidence on adverse effects. Although, in what follows, we are primarily concerned with adverse effects, we also provide some data on efficacy. This is partly because adverse effects might be reduced by much lighter laser treatment, but at the cost of reduced effectiveness. Lack of efficacy could be considered as an adverse event. However, for efficacy we rely mainly on the RCT evidence presented above.

Searches for evidence of adverse effects of lasers from non-randomised controlled trial studies

Searches additional to those for RCTs were done to find any non-RCT studies concerning laser photocoagulation in DR at any stage. Searches of MEDLINE and EMBASE (as shown in *Appendix 2, Search strategies, section f*) were run and downloaded into EndNote version 7 (Thomson Reuters, CA, USA).

In addition, the EndNote database created from previous searches for PRP and lasers (see *Appendix 2, Search strategies, sections a–e*) was searched using the following keywords: *(adverse or risk* or harm* or side effect* or safety or pain or visual loss or complication*) and (laser or photocoagulation or panretinal or pan-retinal or scatter or PRP).*

A systematic review, by Fong *et al.* (2007),[94] which covered the earlier literature on safety of lasers was found. Given that and our focus on the safety of currently used lasers, we limited our selection of articles to those published from the year 2000 onwards.

The searches described above resulted in 137 unique references, of which 84 were excluded on the basis of title and abstract or publication date. The full papers for the remaining 53 references were obtained and checked for inclusion by two authors (PR/NW). Articles that were letters to the editor or comments or editorials were excluded. Also, articles that were RCTs and had been already reviewed in this chapter were excluded.

As we were interested in studies with outcomes that were reported by patients, we excluded outcomes such as change in retinal thickness, as it is been shown that it is not well correlated with visual loss. (The DRCRN group noted only modest correlation between VA and retinal thickness after focal laser photocoagulation for DMO.[95])

This left 19 studies[49,60,62,65,66,68,72,96–107] remaining, of which six[68,96–100] were excluded for reasons shown in *Table 21*. Of the remaining 13 studies, 10[49,60,62,65,66,72,101–104] were data extracted and included in *Table 22*. Three studies were dealt with narratively.[105–107]

Description of non-randomised controlled evidence for safety of lasers

Three studies were concerned with multi-spot pattern photocoagulation,[60,72,104] which delivers a group of burns in a pattern, with one application (by depressing the foot control), rather than the standard one burn at a time. So patients are less likely to become fatigued and uncomfortable. However, the number of spots that can be delivered at the same time is limited by pain, increasing if more than four spots at a time are used. All used the PASCAL laser from Topcon.

Chappelow (2012)[60] compared the efficacy of the PASCAL laser PSC with standard argon laser PRP in 82 eyes (41 eyes in each group) of patients newly diagnosed with HR-PDR in a retrospective case series, with mean follow-up times of 313 and 410 days, respectively. There was a higher incidence of vitreous haemorrhage and pars plana vitrectomy (PPV) in the PSC group than in the argon group (37% vs. 24% and 24% vs. 12%, respectively) but both these differences were not statistically significant. Also, 10% of the PSC group had neovascularisation of the iris (NVI) and 5% neovascular glaucoma (NVG), whereas none in the argon group was reported. However, the study[60] was not adequately powered to detect a significant difference in these outcomes – it would have needed five times as many eyes for that. The incidence of vitreous haemorrhage was much higher than in other studies. This may reflect reduced efficacy of PSC but incidence was also high in the argon group. The authors also noted that the comparison was between a standard argon laser with which they were very experienced, and a PSC system that was newly introduced.

TABLE 21 Reasons for exclusion of non-RCT safety studies

Study ID	Reason for exclusion
Du 2011[96]	No patient-reported outcomes – reports very sensitive measures of retinal function that might not be detected by patients
Maeshima 2004[97]	No patient-reported outcomes
Muqit 2013[68]	No patient-reported outcomes
Raman 2010[98]	Patients did not have DR
Shimura 2009[99]	No patient-reported outcomes
Wang 2014[100]	No patient-reported outcomes – reports a method of measuring VFs

VF, visual field.

TABLE 22 Safety of lasers from non-RCT studies

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Chappelow 2012[60]	**n:** 82 eyes of 82 patients	• **Traditional argon green laser** (n = 41) (January 2007 or earlier). 514-nm (green) pulses approximately one burn width apart, pulse duration 200 ms; spot size 200–300 μm; power 200 mW, increased by 10–20 mW until a grey-white lesion was attained	• VH: 37% PSC; 24% argon
Aim: To evaluate the efficacy of PRP performed via the PSC vs. argon laser PRP	**Description of DR:** Newly diagnosed HR-PDR		• NVI: 10% PSC; 0% argon
			• NVG: 5% PSC; 0% argon
Design: Retrospective comparative case series	**Age (mean), years:** ≈56		• PPV: 24% PSC; 12% argon
		• **PSC laser** (n = 41) (after January 2007). Settings: 200-μm spot size, 20-ms pulse duration, power increased from 200 mW until a grey-white lesion was attained. Burns were placed one burn width apart. Operator preference whether burns delivered as a small or larger array. 44% patients completed in one session, remainder required one or two additional sessions	**Conclusion:** Differences in VH and PPV not statistically significant (study was not adequately powered to detect a significant difference in incidence of VH, NVI, NVG or need for vitrectomy)
Follow-up: PSC = 313 days; argon = 410 days	**Diabetes type:** Argon green laser: 33% NIDDM, 67% IDDM; PSC: 20% NIDDM, 80% IDDM		
		Group 1: Argon green laser = 41	
		Group 2: PSC = 41	

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: DRCRN 2009[62]	**n:** 155 eyes of 155 people	**One-sitting regimen:** 1200–1600 burns	**VA**
Aim: To compare the effects of single-sitting vs. four-sitting PRP with argon laser on MO in subjects with severe non-proliferative or early proliferative DR with relatively good VA and no or mild centre-involved MO	**Description of DR:** 144 of the 155 subjects had fundus photographs that could be graded by the Reading Center; 73 eyes (51%) were classified as having non-proliferative retinopathy, 50 eyes (35%) had non-high-risk retinopathy	**Four-sitting regimen:** Spread over 12 weeks, with each sitting separated by 4 weeks (±4 days), ≈300 burns in each of the first two sittings and investigator judgement for number of burns for the third and fourth sittings, as long as the total for the four sittings was between 1200 and 1600 burns. The burn characteristics were argon laser using 200-µm spot size; exposure 0.1 second recommended, 0.05–0.20 second allowed; intensity, standard mild white retinal burns; distribution, edges at least one burn width apart, no closer than one row within the arcades, no closer than two DDs temporal to the fovea; extent, arcades ≈3000 µm from the macular centre to at least the equator; wavelength, green or yellow (red could be used if VH was present precluding use of green or yellow)	*3 day visit:* VA was slightly worse in the one-sitting group than in the four-sitting group; median change from baseline in letter score of −3 and −1, respectively ($p = 0.005$)
Design: Non-randomised, prospective, multicentred clinical trial	PDR and 21 eyes (15%) had HR-PDR (but not considered to have HR-PDR by the enrolling ophthalmologist). MO considered to be present on baseline photographs in 27 eyes (18%)		*Weeks 4 and 17:* Median VA changes from baseline in letter score of −1 in each group at both visits ($p = 0.37$ and 0.66, respectively)
Follow-up: 34 weeks	**Age (median), years:** 55		*Week 34,* VA was slightly worse in the four-sitting group, with a median change from baseline in letter score of 0 vs. −2 ($p = 0.006$)
Proportions completing the study: At 34 weeks visit completion was 88% in the one-sitting group and 82%, in the four-sitting group	**Sex:** 49% female		7% in the one-sitting group and 9% in the four-sitting group had VA of 10 or more letters worse than baseline ($p = 0.75$)
	Diabetes type: 22% type 1, 78% type 2		**VH:** A VH reducing acuity by 10 or more letters from baseline occurred in two eyes in each group between the 17- and 34-week visits
	HbA$_{1c}$ (median): Group 1 = 7.7%; Group 2 = 8.2%	**Group 1:** One-sitting PRP ($n = 84$)	**MO** was commoner in the four-sitting group
	Baseline VA: 20/25 (mean letter score 83)	**Group 2:** Four sittings of PRP ($n = 71$)	**Conclusion:** Results suggest that clinically meaningful differences in VA are unlikely following application of PRP in one sitting compared with four sittings in subjects in this cohort

continued

TABLE 22 Safety of lasers from non-RCT studies (*continued*)

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Kaiser 2000[101] **Aim:** To describe the clinical features and complications of DR 1 year after PRP for PDR in a tertiary care centre between 1985 and 1995 **Design:** Retrospective cohort study – data collection from medical records **Follow-up:** 1 year (treated between 1985 and 1995)	**n:** 297 eyes of 186 patients **Description of DR:** PDR not previously treated with PRP **Age (median), years:** 55 **Sex:** 43% male **Diabetes type:** 25% using insulin, 75% NIDDM	In general, eyes were treated according to guidelines summarised in the ETDRS. Patients diagnosed with CSMO at the time of initial PRP were either first treated with the appropriate focal or grid macular laser therapy, after which PRP was initiated, or PRP and focal treatment were instituted simultaneously. PRP was completed with an argon laser placing 500-mm spots. The average number of burns placed during the PRP sessions was 1806 spots per treated eye	**VH** was present in 44% of eyes at baseline. New VH developed in 37% of eyes during the first year after PRP **Vitrectomy** was performed in 10% of eyes from baseline through the 1-year follow-up visit **Traction retinal detachment** was present in 4% of eyes at baseline and newly developed in 6% of eyes during follow-up **Repeat PRP treatment** was performed in 107 (39%) of eyes after initial treatment. Most of these eyes (75 eyes) had just one additional treatment within the first year after initiation of the first PRP treatment **Conclusion:** The data from this study are applicable to many patients treated in a tertiary treatment centre and hence useful for counselling patients on the possible complications of PRP, e.g. to prepare them for the possibility of needing at least one additional laser treatment during the first year after completion of their initial PRP

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Kovacic 2012[102]	**n:** 180 eyes	**Blue–green argon laser.** Pan-retinal (mild scatter) photocoagulation was performed in two different ways:	**MO**
Aim: To compare two PRP techniques for effectiveness of treatment of PDR and to determine which has fewer complications of MO and VA	**Description of DR:** Type 1 diabetic patients with PDR and incipient papillary neovascularisation (papillary neovasculates or within one papillary diameter from papillae), which is a high-risk indicator for serious sight loss	**Group 1:** n = 87 eyes. CPRP was performed with 'mild-scatter' technique number 650 spots with 500 μm, exposition 0.5 second, two optic DD from macula to pre-equatorial (15° to 80°)	*Before therapy* MO in 48.4% eyes with CPRP and 52.9% eyes PPRP (p = 0.54)
Design: Comparative case series – patients were divided into two groups according to the types of laser treatment	**Age (mean years):** Group 1 = 41.6; Group 2 = 37.7	**Group 2:** n = 93 eyes. PPRP technique, 650 spots, 500 μm in diameter, exposition 0.5 second, five optic DD from the centre of the macula (40°–105°)	*After 1 week* The CPRP group has 1.6 times more MO than in the PPRP group (p = 0.010)
Follow-up: 6 months	**Sex:** 50.8% male		*After 3 and 6 months* No statistically significant difference between treatment with CPRP and PPRP (p = 0.389 and p = 0.166). MO at 6 months = 18.3% in CPRP and 10.3% in PPRP
	Diabetes type: All type 1		**VA**
	HbA$_{1c}$: NR		*Before therapy* Mean VA (SD) in CPRP group = 0.75 ± 0.22, PPRP group = 0.72 ± 0.22, (p = 0.025 for difference)
			After 1 week Mean VA in CPRP group = 0.60 ± 0.29, PPRP group = 0.67 ± 0.21 (p = 0.081)
			After 3 months Mean VA for CPRP group = 0.69 ± 0.27, PPRP group = 0.73 ± 0.22 (p = 0.749)
			After 6 months Mean VA CPRP group = 0.7 ± 0.26, PPRP group = 0.71 ± 0.26 (p = 0.71)
			Conclusion: VA deteriorated 1 week after treatment with CPRP and PPRP as a result of pre-existing or worsening MO. After 3–6 months of beginning of treatment, MO and VA were not changed significantly. VA was slightly better in patients treated with PPRP

continued

TABLE 22 Safety of lasers from non-RCT studies (*continued*)

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Lee 2010[65] **Aim:** To investigate changes in macular thickness after PRP in patients with severe DR without MO and to compare the VA outcomes **Design:** Prospective cohort study **Follow-up:** 12 months	***n:*** 60 eyes in 30 patients **Description of DR:** Severe non-proliferative or early proliferative DR. VA in each eye was ≥ 0.8 with no MO as determined by clinical examination and OCT **Age (mean), years:** 60 **HbA$_{1c}$ (mean):** 7.6 mg/dl	An argon green laser was used, with a retinal spot size of 500 m and an intensity of 200–500 mW until a grey burn spot was evident. The duration of the application was 0.1 second and the total number of spots was 1200–1600 During the 12-month follow-up period, additional PRP was required in 6/60 eyes (10%) because of residual retinal neovascularisation. PRP treatment was designed to be completed in four sessions	**VA:** The mean ± SD of the VA measurements, converted to logarithm of the minimal angle of resolution, was 0.02 ± 0.11 before PRP and 0.04 ± 0.11, 0.04 ± 0.07, 0.02 ± 0.07, and 0.04 ± 0.08 at 1, 3, 6 and 12 months after PRP, respectively. None of the follow-up measurements differed significantly from the baseline VA before PRP (> 0.05 for each) **Conclusion:** Biweekly PRP (1200–1600 spots) had no effect on VA in patients with severe DR without MO, determined by clinical and OCT examination, although mild macular thickening frequently persists. PRP was performed safely and without visual loss for patients in whom MO was not detected by OCT examination before PRP

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Luttrull 2008[66] **Aim:** To report the VA and clinical outcomes of a pilot study of SDM PRP for treatment of DR **Design:** Retrospective chart review of all patients undergoing PRP for DR between April 2000 and February 2003 **Follow-up:** Median of 1 year	**n:** 99 eyes of 63 patients **Description of DR:** Severe non-proliferative retinopathy or any degree of PDR **Age (mean), years:** 60.5 **Sex:** 62% male **Diabetes type:** 41% type 1, 59% type 2 **HbA$_{1c}$:** NR	**SDM PRP:** An 810-nm diode laser photo-coagulator was used in its MicroPulse operating mode. All patients were treated with a 500-µm aerial spot size, 0.20-second pulse envelope duration, with an initial 2.0 W power setting. Within the laser pulse envelope, a 15% duty cycle, each delivering a train of 100 sequential laser pulses of 300 ms 'on' time separated by 1700 ms 'off' time, was employed for each patient. Treatment sessions per eye ranged from one to six (with a median of two sessions per eye). All SDM PRP was performed by a single surgeon	**VH:** Probability of VH at 1 year following initial SDM PRP for PDR was 12.5% (Kaplan–Meier survival analysis) **Vitrectomy:** Probability of undergoing vitrectomy following SDM PRP for PDR was 14.6% at 12 months (Kaplan–Meier survival analysis) **Complications of SDM PRP:** No complications were observed i.e. no visible laser lesions, laser-induced chorioretinal scarring, no patient complained of postoperative pain or loss of VA, accommodation, night vision, or VF; postoperative inflammation was not observed in any eye; no eye demonstrated worsening of MO following SDM PRP, and no eye without MO developed MO postoperatively **Conclusion:** SDM PRP minimised retinal damage and treatment complications in the management of high-risk non-proliferative and PDR. Visual loss was prevented with a low rate of VH and vitrectomy postoperatively

TABLE 22 Safety of lasers from non-RCT studies (*continued*)

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Shimura 2005[49]	**n:** 64 eyes	PRP performed four times at 2-week intervals. Size of the spots on the retina was 200–500 µm, duration of the application was 0.15–0.2 seconds, using the Volk Super Quad 160 fundus laser lens and a krypton red laser mounted on a slit lamp	**VA**
Aim: To compare macular thickness and BCVA before and after PRP in patients with severe DR and good VA to identify factors that predict postoperative visual function	**Description of DR:** Severe non-proliferative or early PDR. VA of each eye was 20/20 or better with no CSMO. The absence of CSMO was diagnosed by at least three independent clinicians		Patients divided into three groups based on changes in VA over 24-week observation period
		No. of spots in each session ≈500; total no. of burns after the four sessions was ≈2000	• Group A: 54 eyes (84.4%). VA remained at the preoperative level
Design: Prospective, non-comparative, interventional case series	**Age (mean), years:** 58.8		• Group B: 3 eyes (4.7%). VA decreased <2 lines but returned to preoperative VA
			• Group C: 7 eyes (10.9%). VA decreased slightly (<2 lines) at 2 weeks but then continued to decrease to <20/60 at 24 weeks' examination
Follow-up: 24 weeks	**Sex:** 36 male; 28 female		
	Diabetes type: All patients		In both groups B and C, VH and cataract progression were not observed, so cause of the decreased vision was probably from MO
	HbA$_{1c}$: 8.4% (mean)		**Conclusion:** For eyes with severe DR and good VA, PRP did not affect postoperative VA in more than 80% of patients at 24 weeks

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Tinley 2009[103] **Aim:** To evaluate the outcomes of routine, single-session, indirect PRP for PDR, to examine adverse events related to indirect laser within the first 8 weeks of treatment, and to compare results with the UK NDRLTA **Design:** Retrospective study – review of case notes of patients treated from 2000 and 2006 **Follow-up:** 8 weeks (and 9 months' final follow-up)	**n:** 107 eyes of 107 patients **Description of DR:** Patients with PDR undergoing indirect PRP in theatre. For patients undergoing bilateral simultaneous treatment, the eye with the worse VA was included. Patients who had received prior PRP treatment were excluded **Age (mean), years:** 54.5 **Sex:** 29% female **Diabetes type:** 35.5% type 1, 64.5% type 2	**Single-session indirect PRP.** Indirect laser was performed using the Lumenis Novus 2000 machine and a 20- or 30-D lens. Typical laser settings were 200–300 mW power on continuous mode, with burn duration adjusted to produce moderately intense burns, spaced approximately one burn width apart, and extending to the far retinal periphery. No. of burns not given	15 patients (14.0%) returned with adverse events within the first 8 weeks of indirect PRP 10 events were mild or transient, resolving within a further 2 months but five were persistent and visually significant, with three requiring vitrectomy during the study period **Conclusion:** The incidence of significant PRP-induced adverse events was low after indirect PRP and the outcomes were not inferior to the outpatient-based UK NDRLTA. Therefore, for patients with PDR, routine, single-session, indirect PRP in an operating theatre setting is an acceptable and well-tolerated alternative to slit lamp-based treatment. (However it is presumably higher cost.)

TABLE 22 Safety of lasers from non-RCT studies (*continued*)

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Velez-Montoya 2010[104]	**n:** 1301 cases	All sessions were conducted by two surgeons with a PSC photo-coagulator, a 532-nm double-frequency Nd:YAG laser. For PRP, the 2 × 2, 3 × 3, 4 × 4 and 5 × 5 arrays were most commonly used, but changes were made during treatment between these different patterns according to experience and patient characteristics	**Retinal bleeding** in 17 cases (1.3%)
Aim: To analyse the safety profile of the PSC photocoagulator laser	**Description of DR:** 80% of treatments in patients with severe non-proliferative or PDR, most with some type of media opacities (cataract or VH grade I or 2)		All cases had a clinical diagnosis of PDR. 12 patients had a previous history of photocoagulation. The mean follow-up time was 42 days, during which complete resolution of the bleeding was observed without further consequences and without need for additional treatment
Design: Retrospective case series (review of the clinical records of all laser sessions that were performed using the PSC system from November 2007 to July 2008)	**Exclusions:** All incomplete records and those involving MPC treatments	All burns were applied one burn width apart	**CD** in two cases (0.15%)
			Both cases had a clinical diagnosis of PDR with poor metabolic control
Follow-up: 8 months			The detachments occurred 5 and 7 days after laser application. The follow-up times were 56 and 44 days, after which the cases resolved satisfactorily after treatment
			Exudative retinal detachment in one case (0.07%)
			Patient had poor metabolic control and a history of multiple previous laser treatments. The follow-up time was 45 days, during which the patient received periocular steroids and topical NSAIDs. The retinal detachment resolved without further complications and the final BCVA was 20/40
			Conclusion: The PSC photocoagulation system has a low incidence of complications

Study	Participants and baseline values	Description of intervention and laser	Ocular safety outcomes
Study ID: Zucchiatti 2009[72] (meeting abstract) **Aim:** To evaluate the safety and efficacy of the PSC photocoagulator system in the treatment of PDR **Design:** A retrospective review of cases between December 2006 and May 2008 **Follow-up:** 11.5 months average (6–19 months range)	**n:** 26 eyes of 21 patients **Description of DR:** Naive severe NPDR or PDR; 7 eyes (27%) had severe NPDR, 16 eyes (62%) had early PDR, 3 eyes (11%) had HR-PDR	Full PRP was performed using the PSC system. On average, 3.9 sessions were required for a complete PRP. Parameters: mean power was 822 mW, exposure time of 20 ms, spot size was 200–400 μm. In 21 eyes the 5 × 5 pattern was used (81%), and the 3 × 3 pattern was applied in five eyes (19%). An average of 880 spots were delivered in each session	No major side effects were registered in most eyes. One eye only developed a choroidal detachment after receiving 2600 spots at higher power a single session, which resolved spontaneously in 1 week **Conclusion:** Retinal photocoagulation using PSC system has comparable efficacy to published results with conventional photocoagulation

CPRP, central classical pan-retinal photocoagulation; IDDM, insulin-dependent diabetes mellitus; MPC, macular photocoagulation; NDRLTA, National Diabetic Retinopathy Laser Treatment Audit; NIDDM, non-insulin-dependent diabetes mellitus; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; NVG, neovascular glaucoma; NVI, neovascularisation of the iris; PPRP, peripheral pan-retinal performed with photocoagulation; PPV, pars plana vitrectomy; VF, visual field; VH, visual haemorrhage.

Velez-Montoya (2010)[104] analysed the safety profile of PSC laser in a retrospective review of 1301 cases with a follow-up of 8 months. Approximately 80% of patients had severe NPDR or PDR, most with some type of media opacities. The most common complication reported was retinal bleeding in 17 cases (1.3%), followed by choroidal detachment in two cases (0.15%) and exudative retinal detachment in one case. They concluded that the PSC photocoagulation system has a low incidence of complications.

Zucchiatti (2009)[72] (meeting abstract only) in a retrospective cases series of 26 eyes of 21 patients evaluated the safety and efficacy of the PSC photocoagulator system in the treatment of PDR in patients with severe NPDR or PDR. Seven eyes (27%) had severe NPDR, 16 eyes (62%) had early PDR, three eyes (11%) had HR-PDR in an average follow-up of 11.5 months. They found no major side effects.

The latter two studies[72,104] find that PSC has few adverse effects.

The variation in adverse effects amongst the different studies may be due to differences in study designs, differing severity of PDR and differing methods of photocoagulation.

As noted earlier, the most common problem after PRP is MO.

The two following studies,[49,65] along with the DRCRN study[62] in the next section, looked at changes in VA in patients with severe NPDR or early PDR without MO.

Lee *et al.* (2010)[65] conducted a prospective cohort study to investigate VA and changes in macular thickness after biweekly PRP with argon green laser, designed to be completed in four sessions. The cohort included 60 eyes in 30 patients with severe NPDR or early PDR without MO, as determined by clinical examination and OCT. None of the VA measurements at 1-, 3-, 6- and 12-month follow-up differed significantly from baseline. Therefore, for patients in whom MO was not detected by an OCT examination before PRP, PRP was performed safely and without visual loss.

A prospective case series was conducted by Shimura *et al.* (2005)[49] in 64 eyes of 64 consecutive patients with severe non-proliferative or early PDR and good VA, and with no CSMO detected by ophthalmoscopy. PRP was performed four times at 2-week intervals using a krypton red laser. The patients were divided into three groups based on changes in VA after the 24 weeks' observation period. In Group A, 54 eyes (84%) had VA that remained at the preoperative level; in Group B (three eyes), VA decreased < 2 lines, but returned to preoperative VA, and in the remaining seven eyes in Group C the VA decreased slightly (< 2 lines) at 2 weeks but then continued to decrease to < 20/60 at the 24 weeks' examination. As no vitreous haemorrhage and cataract progression were observed in Groups B and C, it was assumed that the cause of the visual loss was probably from MO. As MO was assessed by ophthalmoscopy, it is possible that some may have been missed.

One-sitting photocoagulation versus four sittings pan-retinal photocoagulation

A prospective, non-randomised observational study sponsored by the DRCRN compared a single-sitting of PRP (*n* = 84 eyes) versus PRP delivered over four sittings (*n* = 71) on the development of MO.[62] The study[62] was not randomised because many members of the Network did not consider delivering PRP in one session to be safe, because of the risk of MO. So some operators gave all PRP in a single session, and the others in four sessions. The 155 eyes (of 155 patients) had severe NPDR or early PDR with relatively good VA and no or mild centre-involved MO. The completion rate at the 34 weeks' follow-up was 88% in the one-sitting group and 82% in the four-sitting group. A green or yellow argon laser was used, unless vitreous haemorrhage was present – when red could be used.

At the three-day visit VA was slightly worse in the one-sitting group than the four-sitting group, but, by week 34, VA was slightly worse in the four-sitting group, with a median change from baseline in letter score of 0 versus –2, respectively ($p = 0.006$). A vitreous haemorrhage reducing acuity by 10 or more letters from baseline occurred in two eyes in each group between the 17- and 34-week visits. The results of this study[62] indicated no clinically meaningful differences in VA between the application of PRP in one sitting compared with four sittings. This would be more convenient for patients and reduce costs, though some might prefer several shorter sessions to one long one. However, it would need a large randomised trial to confirm the results.

Real-world clinical setting

A retrospective cohort study by Kaiser *et al.* (2000)[101] looked at complications after 1 year in eyes treated with PRP for PDR. The study[101] was conducted in a tertiary care centre between 1985 and 1995, and included 297 eyes of 186 patients who had not been previously treated with PRP. Eyes were treated generally according to guidelines summarised in the ETDRS, and patients diagnosed with CSMO at the time of initial PRP were either first treated with the focal or grid macular laser therapy before PRP, or were simultaneously treated with PRP and focal laser.

During the first year after PRP, new vitreous haemorrhage developed in 37% of eyes, vitrectomy was performed in 10% of eyes, and traction retinal detachment was newly developed in 6% of eyes, and repeat PRP treatment was performed in 39% of eyes.

Such data, set in a large tertiary treatment centre, could be useful for preparing patients on likelihood of possible complications of PRP. However, the high vitreous haemorrhage and repeat treatment rates suggest a lack of efficacy. Although meeting our cut-off of publication after 2000, it does reflect practice as far back as 1985, so may be less useful as a guide to current methods.

Comparing two different techniques of delivering pan-retinal photocoagulation

Kovacic *et al.* (2012)[102] reported the results of a case series comparing two different PRP techniques in type 1 diabetic patients with PDR and incipient papillary neovascularisation. One group ($n = 87$ eyes) underwent central classical pan-retinal photocoagulation (CPRP) and the other group ($n = 93$ eyes) received PPRP. They were followed up for 6 months.

Before therapy, 48.4% eyes in CPRP group and 52.9% eyes in PPRP group had MO ($p = 0.54$ for difference). After 6 months there was no statistically significant difference between the groups ($p = 0.166$) for the percentage with MO after treatment, i.e. CPRP (18.3%) and PPRP (10.3%).

Visual acuity deteriorated 1 week after treatment with CPRP and PPRP owing to pre-existing or worsening MO, but after 6 months there was no statistically significant difference between groups ($p = 0.71$) in the mean VA.

Subthreshold diode micropulse pan-retinal photocoagulation for treatment of diabetic retinopathy

Luttrull *et al.* (2008)[66] studied the VA and clinical outcomes in a pilot study of SDM PRP for severe NPDR or any degree of PDR. The study[66] was a retrospective chart review of 99 eyes of 63 patients with severe NPDR or any degree of PDR diabetic undergoing SDM PRP between April 2000 and February 2003. Of the 99 eyes, 45 had severe NPDR or low-risk PDR. For severe NPDR, success was taken to be absence of progression to PDR. About 60% of patients had type 2 diabetes. Patients were offered SDM PRP on the grounds that it was less likely to cause retinal damage or scarring, but might need more treatments than conventional PRP.

The median follow-up period was 1 year. The number of treatment sessions per eye ranged from one to six (with a median of two sessions per eye). All were performed by a single surgeon.

The term 'burn' is not used, but an average of 1696 'laser applications' were delivered at the first session, and a mean total of 3003. Luttrull *et al.* (2008)[66] mention an absence of observable laser lesions and scarring at time of treatment or during follow-up. The implication is that no 'burns' were created, and that no retinal scarring was caused. Vitreous haemorrhage developed in 17 eyes (21%). Pain during the procedure was not reported, but the authors comment that SDM PRP was 'well tolerated'. The authors comment that the value of the study[66] is limited by small numbers, short follow-up, lack of controls, and lack of detailed tests of retinal function. They recommend a RCT.

The probability of vitreous haemorrhage at 1 year following initial SDM PRP for PDR was 12.5% (Kaplan–Meier survival analysis) and the probability of undergoing vitrectomy was 14.6% at 12 months. No complications were observed. The authors concluded that visual loss was prevented with a low rate of vitreous haemorrhage and vitrectomy postoperatively.

Single-session indirect pan-retinal photocoagulation

Tinley and Gray (2009)[103] evaluated the outcomes of routine, single session, indirect PRP for PDR. They explain that although indirect laser treatment is usually limited to patients with special needs, who may not tolerate slit-lamp treatment, in their centre they use it routinely for PDR, on the grounds that it provides easier access to the peripheral retina and is more comfortable for patients.

The aim was to examine adverse events related to indirect laser within the first 8 weeks of treatment, and to compare results with the UK National Diabetic Retinopathy Laser Treatment Audit (NDRLTA).[108]

Tinley and Gray (2009)[103] carried out a retrospective review of case notes of 107 eyes (of 107 patients) undergoing indirect PRP between 2000 and 2006. The initial follow-up period was 8 weeks, and then a 9 months' final follow-up. Fifteen patients (14.0%) returned with adverse events within the first 8 weeks of indirect PRP; five events were persistent and visually significant, with three requiring vitrectomy during the study period.

It was concluded that the incidence of significant PRP-induced adverse events was low after indirect PRP and the outcomes were not inferior to the outpatient-based UK NDRLTA. Hence single-session indirect PRP can be a suitable alternative to slit lamp-based treatment. They performed it in an operating theatre, which would be more expensive, but it can be done in an outpatient department.

Indirect PRP can be used in eyes where the view of the fundus is hazy.

Other studies reporting adverse events

Natesh *et al.* (2011)[105] performed 883 single-session PRPs over a 2-year period using the PSC photocoagulator, and reported one patient symptomatic of choroidal detachment (CD) and worsening MO (the laser parameters for the PRP were 2700 burns at 200 mW, a duration of 30 ms, and a spot size of 200 mm with a fluence of 19 joules (J)/cm^2. However, they acknowledge that that incidence of CD may have been a little higher owing to unreported, subclinical and self-limiting cases. They concluded that, although PSC PRP is superior to conventional PRP in terms of patient comfort, laser control, laser precision, and safety, there is still a risk of CD and worsening of MO, and patients should be counselled on these risks before undergoing PSC PRP. This study[105] provides further support for the single-session approach.

Kapoor *et al.* (2010)[106] reported an unusual case of acute angle closure glaucoma following argon laser PRP, which was initially mistaken for a viral illness (patients can present with ocular pain, nausea and vomiting).

Pain of photocoagulation

Pain is a common side effect of laser photocoagulation but was not reported in most of the studies in *Table 22*. Richardson and Waterman (2009)[107] undertook a national survey of all ophthalmic units within the UK in late 2006 to explore the effects of pain on the procedure within clinical practice.

They achieved a 77% response rate (111 questionnaires), and the vast majority of responses (96%) were from doctors. A large proportion (79%) of units saw up to 20 cases a week and most patients received up to five sessions of PRP.

Overall, 88% of the practitioners said that PRP could be painful, and 99% said that pain has a negative effect on the delivery of the therapy; however, 67% did not have a pain protocol and 80% said no analgesia was routinely given for PRP.

It was thought that once present, pain can significantly affect the number and strength of burns delivered and it can indirectly increase the number of sessions required to complete the therapy. Also it could delay treatment therefore extending patient stay. A small number of respondents thought it could potentially be a reason for a lack of compliance. Therefore, the effects of pain could lead to under-treatment and hence to accelerated sight loss in people with PDR.

The authors did comment that, as for all surveys, the results need to be viewed with caution, as, with all survey findings, they are what clinicians say they do, which may not be the same as what they actually do.

The RCOphth guideline recommends that when applying repeat laser therapy it is important to try to avoid the previously treated areas, as pain may be felt by patients who have had previous laser treatment if the new laser burns encroach on the previously treated areas, especially in the horizontal meridian.

Pain can be prevented by anaesthesia delivered through the sub-Tenon's capsule, but this blocks the eye for hours and it has to be patched because of the risk of dryness. There is also a risk of subconjunctival haemorrhage and infection, and some authorities have argued that with modern multi-spot PRP, anaesthesia is not required for most patients.[109]

Discussion

Data on the incidence of adverse events comes from a mixture of different types of lasers and different methods of delivering the lasers, different levels of severity of DR, RCTs and non-randomised study designs, different follow-up times, and different methods of measuring outcomes.

In some studies, such as Chappelow *et al.* (2012)[60] the higher incidence of adverse effects, such as vitreous haemorrhage, may reflect lower efficacy of the PSC photocoagulation.

Pan-retinal photocoagulation destroys retinal tissue, and this leads to symptoms due to the loss of function of the burned areas, including peripheral visual field defects, reduced night vision, reduced colour vision, and decreased contrast sensitivity. Fong *et al.* (2007)[94] noted that visual field defects could occur in up to 50% of treated patients, depending on intensity of PRP and level of testing.

Macular oedema
The most common complication of PRP is the exacerbation of MO. Bressler *et al.* (2011)[110] cites unpublished data from the ETDRS:

> . . . *in patients with such edema involving the center of the macula at baseline, an evaluation that was performed 4 months after baseline panretinal photocoagulation showed that 19% of the patients lost approximately two or more lines on a visual-acuity chart, including 11% who lost approximately three or more lines.*

The DRCRN (Protocol for NCT01489189) also reports that in the ETDRS, which was performed prior to the advent of OCT, 16% of eyes that underwent full PRP (1200–1600 spots) were noted to have MO on stereoscopic fundus photographs by 4 months compared with only 12% in eyes that did not have PRP (FL Ferris, MD, unpublished data, 17 June 2008 – cited in Protocol).[21]

Browning (2005)[50] reported that ophthalmologists without OCT support were liable to miss some cases of MO. Browning notes that after PRP for NPDR or PDR, eyes with MO are twice as likely (18% vs. 9%) to lose two or more lines of VA 6 weeks post treatment as eyes with no MO.

Yang et al. (2001)[111] also report that OCT is more sensitive than clinical examination (slit-lamp biomicroscopy) in detecting DMO.

The advent of OCT means that MO can be detected and treated with focal laser before administering PRP. Lee et al. (2010)[65] noted that in the past decade, OCT had become much more available, and that it is more sensitive than clinical examination for detecting DMO, especially when macular thickness was 201–300 μm. In past decades, PRP may have made undiagnosed MO worse, rather than causing MO de novo.

Fong et al. (2007)[54] concluded (from the ETDRS) that moderate visual loss occurs and appears to be more common in eyes with pre-existing MO. The RCOphth guidelines advise treating maculopathy either at the same time or prior to peripheral scatter retinal photocoagulation (PRP).[5]

The risk of MO is why PRP is usually given over two to four sessions, along with the problem of patients getting tired when spots had to be administered one at a time.

However, there is some evidence that the risk may be less with modern methods.

Lee et al. (2010)[65] reported a slight increase in macular thickness after PRP but no reduction in VA, which they attributed to exclusion of pre-PRP MO by OCT, giving PRP biweekly, and reducing the total number of spots from 2000 to 1200–1600.

Driving
The RCOphth guideline notes that, after full PRP, about 40–50% of patients have some reduction in visual fields, which may have implications for fitness to drive, but that the risk is lower with more modern regimens that have smaller and lighter burns.

Mackie 1995 applied the UK DVLA criteria to 100 consecutive patients who had had bilateral PRP with the argon laser, and found that 19% failed the driving criteria because of loss of visual field due to PRP.[112]

Vernon et al. (2009)[113] identified a group of patients who had had bilateral PRP, with small burn size, about 10 years before (in 1988–90) and obtained results from 25 of them. Of those (17) who drove, only two had stopped – neither because of failure to meet the DVLA rules – and nearly all of the rest confirmed having passed the driving vision test after PRP. Hulbert and Vernon (1996)[114] writing in 1992, argue that smaller burns [300 microns (μm) rather than 500 μm] gave a better chance of being able to retain a driving licence.

In a modelling exercise, Davies (1999)[115] concluded that the pattern of PRP could be adjusted in order to preserve driving vision, and that small burns (200 μm) would cause less loss of peripheral vision than large ones (500 μm). However, Quinn (1999)[116] was concerned that distributing burns in such a way as to preserve driving vision might leave untouched ischaemic areas, leading to neovascularisation, and suggested a randomised trial.

Driving at night may be a particular problem. Fong et al. (2007)[94] noted that after PRP, 38% of people reported worsened night driving and 60% worsened dark adaptation.

An excellent patient information leaflet notes that one in five people are aware of some loss of peripheral vision after PRP, and 3% have to stop driving because their peripheral vision has been reduced.[117]

People who have laser treatment to both eyes, or to one eye if they only have sight in one eye, are required in the UK to inform the DVLA.[118]

Other adverse events

The RCOphth guidelines list other adverse effects, though some are rare.[5] They include:

- some loss of contrast sensitivity
- loss of central vision due to inadvertent laser application to the foveal and parafoveal regions; the RCOphth guidelines recommend constant checking that the laser is not hitting the fovea
- reduction of VA
- a possible reduction in accommodative power
- some dimness of vision
- some loss of colour vision
- rare complications, such as corneal burns, raised IOP or angle closure, pre-retinal or subretinal fibrosis, and tractional retinal detachment.

Informing patients

Adverse events should be carefully considered before deciding when to give PRP and patients should be made aware of them. There is usually some hesitation in performing PRP on diabetic patients with less severe retinopathy, especially in eyes with good vision.[49,80] The RCOphth guideline notes that scatter PRP can cause transient worsening or development of MO and that patients should be warned of this and also of the possibility of vitreous and subhyaloid haemorrhages.[5]

Chapter 4 Combined laser and drug studies

Aims

Following laser therapy, MO may arise either de novo, or through exacerbation of prior MO. This can lead to temporary reduction in VA. It has been suggested that drugs like anti-VEGFs and steroids may have a place in reducing MO and vision loss when used in combination with PRP. If they do reduce the risk of DMO, they may make it safer to administer PRP in a single session.

Methods

The comprehensive search done for laser trials for *Chapter 3* also provided trials for this chapter. We selected studies that had investigated the efficacy of drug and laser combination in patients with NPDR or PDR. Because the main interest was reduction in adverse effects, we relaxed the minimum duration rule of 6 months.

Results

The details of the search strategies are given in *Chapter 3*. We included 11 trials (published in 12 papers[119–130]) that compared the efficacy of anti-VEGFs or injectable steroids used in conjunction with laser in patients with DR.

Seven studies (Cho 2010;[119] DRCRN 2011;[120] Ernst 2012;[121] Filho 2011[122,123] with Lucena 2013; Mirshahi 2008;[124] Preti 2013;[125] Tonello 2008[126]), as shown in *Table 23*, compared the efficacy of anti-VEGFs used in combination with laser in patients with DR. Cho *et al.* (2010)[119] and DRCRN (2011)[120] also used intravitreal triamcinolone acetonide (IVTA). Three trials (Cho 2010;[119] DRCRN 2011;[120] Preti 2013[125]) aimed to assess the effect of anti-VEGF in combination with laser in reducing adverse events such as DMO, and three trials (Tonello 2008;[126] Filho 2011;[122,123] Mirshahi 2008[124]) were more concerned with added therapeutic benefits of anti-VEGFs in combination with laser. One trial (Ernst 2012[121]) compared the efficacy of anti-VEGF alone with PRP alone in laser-naive patients.

Six studies (Cho 2010;[119] DRCN 2011;[120] Maia 2009;[127] Mirshahi 2010;[128] Shimura 2006;[129] Unoki 2009[130]), as shown in *Table 24*, compared the efficacy of triamcinolone as an adjunctive therapy to laser in patients with DR.

Baseline characteristics of included studies
Tables 23 and *24* give details of baseline characteristics of the participants in the included studies.

TABLE 23 Baseline characteristics of laser and anti-VEGF trials

Study (author and year)	No. of patients	No. of eyes	Follow-up	Comparisons	DR
Cho 2010[119]	76	46 eyes with CSMO, 45 eyes without CSMO	3 months	(i) PRP (ii) PRP + IVB (iii) PRP + IVTA	Very severe NPDR and HRC-PDR
DRCRN 2011[120]	319	345	14 weeks (primary outcome); 56 weeks for safety	(i) Sham injection + focal/grid laser + PRP (ii) 0.5 mg ranibizumab + focal/grid laser + PRP (iii) 4 mg TA + focal/grid laser + PRP	Severe NPDR or PDR and centre involving DMO
Ernst 2012[121]	10	20	12 months	(i) PRP (ii) IVB	Severe NPDR and PDR
Filho 2011[122,123]	40	29	48 weeks	(i) PRP (ii) PRP + IVR	HR-PDR
Mirshahi 2008[124]	40	80	16 weeks	(i) Laser + IVB (ii) Laser + sham	HR-PDR
Preti 2013[125]	35	70	6 months	(i) PRP (ii) PRP + IVB	HR-PDR
Tonello 2008[126]	22	30	16 weeks	(i) PRP (ii) PRP + IVB	HR-PDR

IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab.

TABLE 24 Baseline characteristics of laser and steroid trials

Study (author and year)	No. of patients	No. of eyes	Follow-up	Comparisons	DR
Cho 2010[119]	76	46 eyes with CSMO, 45 eyes without CSMO	3 months	(i) PRP (ii) PRP + IVB (iii) PRP + IVTA	Very severe NPDR and HR-PDR
DRCRN 2011[120]	319	345	14 weeks (primary outcome); 56 weeks for safety	(i) Sham injection + focal/grid laser + PRP (ii) 0.5 mg ranibizumab + focal/grid laser + PRP (iii) 4 mg TA + focal/grid laser + PRP	Severe NPDR or PDR and centre involving DMO
Maia 2009[127]	22	44	12 months	(i) PRP + macular laser (ii) PRP + macular laser + IVTA	PDR with CSMO
Mirshahi 2010[128]	18	36	6 months 18 months complications	(i) IVTA + PRP + MPC (injected eye) (ii) PRP + MPC (control eye)	HR-PDR with CSMO
Shimura 2006[129]	10	20	24 weeks	(i) Sub-Tenon's TA + PRP (ii) PRP only	Severe NPDR and early PDR
Unoki 2009[130]	41	82	6 months	(i) PRP only (ii) PSTA (posterior sub-Tenon's triamcinolone injection 20 mg) + PRP	Severe NPDR or PDR (plus could have CSMO but only if present in both eyes)

IVB, intravitreal bevacizumab; PSTA, posterior sub-Tenon's triamcinolone injection; TA, triamcinolone acetonide.

Study design
All the included studies were RCTs.

Diabetic retinopathy

- Anti-VEGFs:

    - four studies (Filho 2011;[122] Mirshahi 2008;[124] Preti 2013;[125] Tonello 2008[126]) – HR-PDR patients
    - one study (Cho 2010[119]) – very severe NPDR and HR-PDR
    - two studies (DRCRN 2011;[120] Ernst 2012[121]) – severe NPDR and PDR. Patients in DRCRN 2011 also had DMO.

- Steroids:

    - one study (Cho 2010[119]) – very severe NPDR and HR-PDR
    - one study (DRCRN 2011[120]) – severe NPDR or PDR and DMO
    - one study (Maia 2009[127]) – PDR and CSMO
    - one study (Mirshahi 2010[128]) – HR-PDR with CSMO
    - one study (Shimura 2006[129]) – severe NPDR and early PDR
    - one study (Unoki 2009[130]) – severe NPDR or PDR (plus could have CSMO but only if present in both eyes).

Quality assessment/risk of bias
Not all studies gave enough details to assess risk of bias. In that case, we categorised them as 'unclear'. See *Tables 25* and *26.*

Allocation
Four studies (Cho 2010;[119] Ernst 2012;[121] Preti 2013;[125] Mirshahi 2008[124]) only reported that patients were randomised. No details on allocation concealment were reported.

In two studies (Filho 2012;[122,123] Tonello 2008[126]), participants were allocated in groups of two and a technician was asked to pick one of the two identical opaque envelopes, which is a less secure method than central randomisation.

TABLE 25 Quality assessment/risk of bias of laser + anti-VEGF studies

Study (author and year)	Adequate sequence generation	Adequate allocation concealment	Masking	Incomplete outcome data assessed	Free of selective outcome reporting	Free of other biases (e.g. similarity at baseline, power assessment)
Cho 2010[119]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
DRCRN 2011[120]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ernst 2012[121]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk
Filho 2012 and Lucena 2013[122,123]	Unclear	Unclear – sealed envelopes	Low risk	Low risk	Low risk	Low risk
Mirshahi 2008[124]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Preti 2013[125]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Tonello 2008[126]	Low risk	Unclear – opaque envelopes	Low risk	Low risk	Low risk	Low risk

Study (author and year)	Adequate sequence generation	Adequate allocation concealment	Masking	Incomplete outcome data assessed	Free of selective outcome reporting	Free of other biases (e.g. similarity at baseline, power assessment)
Cho 2010[119]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
DRCRN 2011[120]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Maia 2009[127]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Mirshahi 2010[128]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Shimura 2006[129]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Unoki 2009[130]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk

Mirshahi (2010)[128] used block randomisation method to allocate participants into intervention and control group. However, there was no detail on allocation concealment.

The allocation method was not clear in Shimura (2006)[129] and Maia (2009).[127]

In DRCRN (2011),[120] central randomisation was provided via the DRCRN website. In Unoki (2009),[130] participants were randomised using a stratification method. The stratification was done according to BCVA.

Masking of outcome assessments

Five studies (Cho 2010;[119] Ernst 2012;[121] Mirshahi 2008;[124] Mirshahi 2010;[128] Preti 2013;[125] Shimura 2006[129]) had no details on masking. In three studies (Filho 2012;[122,123] Tonello 2008;[126] Maia 2009[127]) investigators were masked. In DRCRN (2011)[120] the staff measuring VA and the OCT technician were masked to allocation. Unoki (2009)[130] did not mask participants and investigators to study allocation. However, technicians measuring VA and OCT and statistician analysing the data were masked to study allocation.

Incomplete outcome data

Four studies (Cho 2010;[119] Shimura 2006;[129] Tonello 2008;[126] Maia 2009[127]) followed up all participants. One study (Ernst 2012[121]) reported that five patients were lost to follow-up but reasons were not given. However, all five patients were excluded from the analysis.

Four studies (DRCRN 2011;[120] Filho 2012;[122,123] Mirshahi 2010;[128] Preti 2013[125]) gave adequate description of withdrawals and lost to follow-up.

Free of selective reporting

All studies reported prespecified outcomes.

Free of other biases

In all studies, baseline characteristics between intervention and control groups were similar. Three studies (Maia 2009;[127] DRCRN 2011;[120] Unoki 2009[130]) gave information regarding power calculation. Unoki (2009)[130] reported that for 80% power, a total of 40 eyes in each treatment group was required. In Maia (2009),[127] it was reported that a total of 18 eyes of 18 patients was required for 80% power. However, after adjusting for a 20% lost to follow-up, the sample size required to reach the same study power increased to 22 eyes. In DRCRN (2011),[120] it was reported that for 90% power, a total of 364 eyes were needed to ascertain a difference in mean VA from baseline to 14 weeks between different interventions. For the primary outcome, an intention-to-treat analysis was done, which included all the randomised eyes. However, 19 eyes were excluded from one site, as the baseline imputed values of central subfield thickness was < 250 μm in 63% of eyes. For missing data, last observation carried forward method was used. For other outcomes (safety), missing data were not imputed.

Funder/conflict of interest

Three studies (Cho 2010;[119] Mirshahi 2010;[128] Shimura 2006[129]) appeared to be funded by an academic institution. DRCRN was funded by the US National Institutes of Health. In two studies (Ernst 2012;[121] Filho 2012[122,123]) the funding source was not clear. Shimura (2006)[129] gave no details on conflict of interest.

Four studies (Filho 2012;[122,123] Maia 2009;[127] Preti 2013;[125] Tonello 2008[126]) were part funded by research organisations and in three authors declared no conflict of interest. Tonello *et al.* (2008)[126] gave details (Filho – CNPq; Maia 2009 – part supported by CAPES; Preti 2013 – São Paulo Research Foundation; Tonello 2008 – supported partly by the Foundation to support Education, Research and Assistance, Clinics Hospital, Faculty of Medicine of Ribeirao Preto). Unoki (2009)[130] was supported by a grant from the Scientific Research from the Japanese Government.

The studies are described narratively below and a detailed summary given in *Table 27*.

Laser in combination with anti-vascular endothelial growth factors

Cho 2010

The aim of the study[119] was to assess and compare the efficacy and safety of IVTA and intravitreal bevacizumab (IVB) for reducing PRP-related short-term vision loss and MO, in patients ranging from having very severe NPDR to HR-PDR. One group of patients received only PRP (30 eyes), the second group received IVB plus PRP (31) and the third group received IVTA plus PRP (30). Scatter laser was given to all patients at three different time points, with 1-week intervals using a 532-nm argon green laser (Visulas 532s/LSL). Each patient received between 300 and 500 spots (500-μm spot) per episode at a power that caused blanching of the retina. If both eyes had HR-PDR, PRP was delivered in each eye on the same day. In eyes with CSMO, focal/grid photocoagulation was also performed at the time of initiation of PRP. In those receiving PRP and IVB, bevacizumab 1.25 mg/0.05 ml was injected about 1 week before the initiation of PRP. In the group receiving PRP and IVTA, triamcinolone 4 mg/0.1 ml was injected 1 day after the first session of PRP. All patients were followed up for 3 months.

The primary outcome measure was mean BCVA, which worsened significantly in the PRP group at both 1 (0.26 to 0.29 logMAR; $p = 0.031$) and 3 months (0.26–0.29; $p = 0.030$) follow-up. (The logMAR scale ranges from 0 to 1.0, with 0 best.) In contrast, there was no significant change in BCVA in the IVTA and IVB groups. In eyes with CSMO, there was significant improvement in BCVA during 3 months' follow-up only in the IVTA group. In eyes without CSMO, vision significantly worsened only in the PRP group.

The secondary outcome was gain in vision of ≥ 0.1 logMAR. In eyes with CSMO, significantly more eyes in the IVTA group (75%) than in the IVB (38%) and PRP (7%) groups achieved this. Similarly, more eyes in the IVTA group (38%) than in the PRP group (none) gained vision of ≥ 0.2 logMAR (< 0.05). More eyes in the PRP group lost vision of ≥ 0.1 (57%) or ≥ 0.2 logMAR (29%) than in the IVTA group (none). The corresponding figures for the bevacizumab group were 31% and 13% (all rounded to whole figures).

In eyes without CSMO, significantly higher proportions of eyes in the IVTA (43%) and IVB (35%) groups gained ≥ 0.1 logMAR than in the PRP group (6%). However, the proportion of eyes gaining vision of ≥ 0.2 logMAR was not statistically different between IVTA and IVB groups. The proportion of eyes losing vision of ≥ 0.2 logMAR was significantly higher in the PRP group (38%) than in the other two groups (none) ($p < 0.05$).

Patients in the IVTA and IVB groups had significant reduction in CMT in eyes with CSMO. In eyes without CSMO, CMT increased significantly only in the PRP group.

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Cho 2010[119] **Aim:** To compare and evaluate the efficacy and safety of IVTA and IVB as adjunctive treatments to PRP in reducing PRP-related short-term vision loss and MO **Design:** Prospective, comparative, interventional case series: the enrolled eye randomly received PRP with IVTA (IVTA group) or PRP with IVB (IVB group) or PRP only (PRP group); in patients with bilateral eyes eligible for the study, one eye of each patient was randomly chosen to receive PRP with IVTA or PRP with IVB or PRP only and the other eye received the other procedure **Follow-up:** 3 months **Proportions completing the study:** NR **Reasons for withdrawal:** NR	**n:** 46 eyes with CSMO and 45 eyes without CSMO of 76 patients **Inclusion criteria:** Patients age ≥ 18 years, very severe NPDR to HR-PDR, and Snellen BCVA of ≥ 0.3 **Exclusion criteria:** Systemic and diastolic BPs of ≥ 180 and 110 mmHg, HbA_{1c} levels exceeding 9.5%, chronic renal failure, major surgery within 1 month, previous systemic steroid or anti-VEGF treatment, patients with ocular conditions other than DR study (e.g. retinal vein occlusion, uveitis or other ocular inflammatory disease, NVG, etc.), patients with a history of treatment for DMO in the previous 3 months, previous PRP or focal/grid laser photocoagulation, previous intraocular surgery, uncontrolled glaucoma **Age:** IVTA group: Mean age was 50.8 ± 36.8 years IVB group: 50.9 ± 46.0 years PRP group: 51.0 ± 26.0 years	**Group 1:** PRP **Group 2:** IVB + PRP **Group 3:** IVTA + PRP **Description of type of laser and delivery:** Scatter laser treatment using a 532-nm argon green laser (Visulas 532s/LSL 532s Laser Slit Lamp; Carl Zeiss Meditec) at three time points (1-week intervals). Focal/grid laser photocoagulation was performed at the time of initiation PRP in patients with CSMO **Description of anti-VEGF treatment:** IVB (1.25 mg/0.05 ml) was given about 1 week prior to initial PRP with a 30-gauge needle with topical anaesthesia **Description of steroid treatment:** IVTA (4 mg/0.1 ml) was given 1 day after first session of PRP with a 30-gauge needle with topical anaesthesia	See outcomes table below

Mean BCVA (logMAR):

	PRP group	IVTA group	IVB group	p-value
Mean BCVA (logMAR)				
All eyes with PRP				
Baseline	0.26	–		
1 month	0.29	–		**PRP group** – vs. baseline: $p = 0.031$ **IVTA and IVB groups** – vs. baseline: not significant **Between group difference:** not significant
3 months	0.29		–	**IVTA and IVB groups** – vs. baseline: not significant **Between group difference:** not significant
Eyes with CSME				**IVTA group** – significant improvement of BCVA during 3 months; significant difference in mean BCVA between the IVTA and IVB groups
Eyes without CSMO				**PRP group** – significant worsening of BCVA

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
			CMT:			
				PRP group	IVTA group	IVB group	*p*-value
	Sex (female%):		**CMT**			
	With CSMO:		**All eyes with PRP**				Significant decreases in CMT during the follow-up period in both IVTA and IVB groups
	IVTA group: 31.25					
	IVB group: 37.5					
	PRP group: 35.71					
	Without CSMO:		**Eyes with CSMO**				Significant decreases in CMT in both IVTA and IVB groups
	IVTA group: 28.57					
	IVB group: 33.33		**Eyes without CSMO**	Baseline: 209.75 ± 27.47 μm			PRP group: 1 month *p* = 0.023; 3 months *p* = 0.011
	PRP group: 31.25			1 month: 259.00 ± 58.28 μm			IVTA and IVB groups: no significant changes
	Diabetes type: NR			3 months: 276.14 ± 47.38 μm			No significant difference in CMT at 1 month and 3 months between IVTA and IVB groups

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
	HbA$_{1c}$:		**Proportion of eyes with visual gain ≥ 0.1 logMAR:**			
			PRP group	**IVTA group**	**IVB group**	**p-value**
	With CSMO:		**Eyes with CSMO**	Proportion of eyes with visual gain ≥ 0.1 logMAR was significantly higher in IVTA than in IVB and PRP. Visual gain ≥ 0.2 logMAR was significantly higher in IVTA than in PRP		
	IVTA group: 6.91% (SD = 0.21)					
	IVB group: 7.81 (0.32)		**Eyes without CSMO**	Proportions of eyes with visual gain ≥ 0.1 logMAR was significantly higher in IVTA and IVB than in PRP. Proportions of eyes with visual gain ≥ 0.2 logMAR was not statistically different among three groups		
	PRP group: 7.31 (0.41)					
	Without CSMO:		**Proportion of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR:**			
	IVTA group: 7.12% (SD = 0.13)		**PRP group**	**IVTA group**	**IVB group**	**p-value**
	IVB group: 7.21 (0.23)		**Eyes with CSMO**	Proportion of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR was significantly higher in PRP than IVTA		
	PRP group: 7.18 (0.09)					
	Baseline VA:		**Eyes without CSMO**	Proportions of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR was significantly higher in PRP than in IVTA and IVB		
	IVTA group: mean BCVA (logMAR) 0.27 ± 0.25					
	IVB group: 0.28 ± 0.31					
	PRP group: 0.26 ± 0.28					

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
	Baseline CMT:		**Proportion of eyes with a decrease/increase in CMT:**			
	IVTA group: mean CMT 343.89 ± 330.79 μm			**PRP group**	**IVTA group**	**IVB group**	**p-value**
	IVB group: 328.02 ± 335.29 μm		**Eyes with CSMO**	Proportion of eyes with a decrease in CMT was significantly lower in PRP than in IVTA and IVB. Proportion of eyes with a decrease in CMT was significantly higher in IVTA than in IVB		
	PRP group: 326.27 ± 315.17 μm		**Eyes without CSMO**	Proportion of eyes with an increase in CMT was significantly higher in PRP than in IVTA and IVB		
	Baseline DR stage: Very severe NPDR to HR-PDR		PRP group: Four patients with increased proliferation and development of VH during follow-up			
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*		Injection-related complications:			
			• One eye with cataract progression, four eyes (three eyes with CSMO and one eye without) with increased IOP (15 ± 3 mmHg at 1 month) in the IVTA group			
	Ocular comorbidities: See *Exclusion criteria*		• No complications in the IVB group			

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: DRCRN 2011[120]	**n:** 345; 26 (8%) with two study eyes	**Group 1:** Sham injection + focal/grid laser + PRP (n = 123)	**Before the primary outcome (14-week visit):**
Aim: To assess the efficacy of intravitreal injection of ranibizumab or TA in patients with DR and DMO treated with focal/grid laser	**Inclusion criteria:** Patients aged 18 years or more with type 1 or type 2 diabetes and with severe NPDR or PDR and centre-involving DMO and BCVA ETDRS score of ≥ 24	**Group 2:** 0.5 mg ranibizumab + focal/grid laser + PRP (n = 113)	• All but one eye (triamcinolone) received their allocated treatments • At 4 weeks, 108/113 eyes received the second injection of ranibizumab • At 4 weeks, one eye in the triamcinolone arm received the drug instead of sham injection • Focal/grid laser performed in all eyes except two eyes in the ranibizumab and three eyes in the triamcinolone arm. Some eyes received focal/grid laser outcome the 3 and 10 days period – nine eyes in the sham, seven eyes in the ranibizumab and 10 eyes in the triamcinolone
Design: Phase 3, randomised, multicentre, clinical trial. 48 clinical sites in the USA	**Exclusion criteria:** Previous history of extensive and unnecessary treatment with PRP; treatment of DMO prior to 4 months of the study; treatment of steroid-induced increase IOP; glaucoma; IOP ≥ 25 mmHg	**Group 3:** 4 mg TA + focal/grid laser + PRP (n = 109) **Description of type of laser and delivery:** After baseline treatment with sham or ranibizumab or triamcinolone, patients received focal/grid laser between 3 and 10 days. Following focal/grid laser, all patients also received PRP immediately, or on the next	• No additional treatment were required for DMO • One eye in the sham, two eyes in the ranibizumab and two eyes in the triamcinolone arms did not complete their PRP sessions • 108 eyes in the sham, 97 eyes in the ranibizumab and 87 eyes in the triamcinolone completed their PRP session within 49 days from the day of baseline treatment • 49 eyes in the sham, 38 eyes in the ranibizumab and 41 eyes in the triamcinolone completed PRP in one session • Only one eye in the ranibizumab group required additional PRP before the 14-weeks study visit
Follow-up: Primary outcome (14 weeks); safety (56 weeks).		day, but no later than 14 days from the day of baseline treatment. PRP included giving 1200–1600 burns either in one session or in three sessions However, all PRP sessions should be completed within 49 days after allocation	**Change in BCVA from baseline to 14 weeks study visit:**
Proportions completing the study: 14 weeks – sham (n = 118 eyes, 96%), ranibizumab (n = 103, 91%), triamcinolone (n = 105, 96%);	**Age (years):** Mean 55, SD 12; median, 25th to 75th percentile [sham: 54, 45 to 61; ranibizumab: 57, 48 to 64); triamcinolone: 58, 49 to 64]		
56 weeks – sham (n = 111, 90%), ranibizumab (n = 95, 84%), triamcinolone (n = 93, 85%)	**Sex:** 40% female; [sham: 36%; ranibizumab: 42%; triamcinolone: 40%]	In the study, laser that could produce automated patterns, e.g. PSC laser could be used	
Reasons for withdrawal (brief): Death before 14 weeks = 4 (1%); death after 14 weeks = 4 (1%) – All deaths not related to study treatment			

Change in BCVA from baseline to 14 weeks study visit:

	Sham + laser (n = 123)	Ranibizumab + laser (n = 113)	Triamcinolone + laser (n = 109)	Difference compared against sham
Letter score				
Mean change from baseline	−4 SD 14	+ 1 SD 11	+ 2 SD 11	vs. ranibizumab: +5.6, 95% CI 2.2 to 9.0; p < 0.001 vs. triamcinolone: +6.7, 95% CI 3.2 to 10.1; p < 0.001
Median (25th to 75th percentile)	−2 (−8, +3)	+ 2 (−3, +7)	+ 1 (−3, +8)	

continued

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety	Sham + laser (*n* = 123)	Ranibizumab + laser (*n* = 113)	Triamcinolone + laser (*n* = 109)	Difference compared against sham
	Diabetes type: Type 1 (11 to 16%) or type 2 diabetes (82 to 87%) or uncertain (2 to 6%); [type 1 – sham: 16%; ranibizumab: 12%; triamcinolone: 11%]; [type 2 – sham: 82%; ranibizumab: 82%; triamcinolone: 87%]; [uncertain – sham: 2%; ranibizumab: 6%; triamcinolone: 2%]	**Description of anti-VEGF/steroid treatment:** All patients were prepared by applying povidone–iodine preparation on the conjunctiva	*Distribution of change*, **n (%)**				
			≥ 15-letter gain	5 (4)	8 (7)	11 (10)	NR
			14- to 10-letter gain	5 (4)	13 (12)	13 (12)	NR
		Treating investigators decided whether to give antibiotics before or after injection. One group of patients received intravitreal injection of 0.5 mg ranibizumab (Lucentis), while another group of patients received intravitreal injection of 4 mg TA (Trivaris)	9- to 5-letter gain	12 (10)	20 (18)	13 (12)	NR
			Same + 4 letters	54 (44)	53 (47)	50 (46)	NR
			5- to 9-letter loss	19 (15)	9 (8)	11 (10)	NR
	HbA₁c (%): Median 7.9 to 8.1; [sham: 7.9, 7 to 9.6; ranibizumab: 8.1, 7.1 to 9.9; triamcinolone: 8.1, 7 to 9.7		10- to 14-letter loss	10 (8)	2 (2)	8 (7)	NR
			≥ 15-letter loss	18 (15)	8 (7)	3 (3)	NR
	Baseline BCVA: Mean 64 ± 15 (approximately 20/50)		**Difference in proportion with ≥ 10-letter improvement from sham (95% CI)**	–	+10 (+1 to +20)	+14 (+4 to +25)	–
	Baseline CMT: Mean 392 ± 151 μm		RR for comparison with sham	1	2.79, 95% CI 1.33 to 5.87; *p* = 0.002	3.58, 95% CI 1.69 to 7.61; *p* < 0.001	
	Baseline DR stage: Based on investigator assessment – severe NPDR (18% of eyes); PDR (82% of eyes)		**Difference in proportion with ≥ 10 letter worsening from sham, 95% CI**	–	–13 (–24 to –3)	–13 (–23 to –3)	
	Based on reading centre assessment – moderately severe NPDR or less severe NPDR (20% of eyes); severe NPDR (5% of eyes); PDR (75% of eyes including 35% with HR-PDR or level 71–75)		RR for comparison with sham	1	0.4, 95% CI 0.19 to 0.87; *p* = 0.008	0.44, 95% CI 0.21 to 0.91; *p* = 0.01	

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
		Previous laser or intravitreal drug treatment: Scatter photocoagulation: 13–18%; no. of previous treatment for DMO: 65–66%; previous laser for DMO: 29–33%; previous IVTA for DMO: 1–8%; previous vitrectomy for DMO: 0–2%; previous peribulbar triamcinolone for DMO: 0–1%; previous anti-VEGF for DMO: 1–5% **Ocular comorbidities:** DMO – predominantly focal 17–30%, neither predominantly focal or diffuse 13–22%, predominantly diffuse 55–62%	**Change in VA from baseline to week 14 among subgroups:**			
			Sham, ranibizumab, triamcinolone (*n*)	Sham + laser	Ranibizumab + laser	Triamcinolone + laser
			Previous treatment			
			No 80, 75, 72	−4 ± 13	+2 ± 12	+2 ± 11
			Yes 43, 38, 37	−5 ± 14	+1 ± 9	+3 ± 11
			Baseline VA letter score			
			≥66 66, 64, 61	−5 ± 12	−1 ± 9	0 ± 7
			≤65 57, 49, 48	−2 ± 16	+4 ± 13	+5 ± 13
			Baseline central subfield thickness			
			<400 76, 68, 65	−3 ± 13	+1 ± 9	+2 ± 9
			≥400 46, 44, 42	−6 ± 15	+2 ± 14	+2 ± 12
			DR severity			
			NPDR 37, 26, 21	−2 ± 10	0 ± 10	−2 ± 8
			PDR 82, 83, 84	−5 ± 10	+2 ± 12	+3 ± 11

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Intervention	Participants and baseline values	Outcomes and ocular safety			
			Sham, ranibizumab, triamcinolone (*n*)	Sham + laser	Ranibizumab + laser	Triamcinolone + laser
			No. of PRP sittings			
			One sitting 49, 38, 41	−2 ± 12	+2 ± 7	+2 ± 12
			Multiple sittings 73, 73, 66	−5 ± 14	+1 ± 13	+2 ± 10
			PRP automated pattern used			
			Yes 36, 21, 21	−4 ± 12	+2 ± 13	0 ± 10
			No 86, 90, 86	−4 ± 14	+1 ± 11	+3 ± 11
			Baseline HbA$_{1c}$ (%)			
			<8 61, 46, 48	−3 ± 11	+3 ± 10	0 ± 11
			≥8 59, 57, 55	−6 ± 16	0 ± 12	+4 ± 10

After 14 weeks:

- Additional PRP was given in 21 eyes (19%) in the ranibizumab group, 24 eyes (23%) in the triamcinolone group and 29 eyes (24%) in the sham group. There was no difference when comparisons were made against sham (ranibizumab – $p = 0.39$; triamcinolone – $p = 0.77$)
- Standard care treatment for DMO was lower in the ranibizumab group (48 eyes, 44%) and triamcinolone group (45 eyes, 42%) than in the sham group (71 eyes, 59%) (vs. ranibizumab – $p = 0.04$; vs. triamcinolone – $p = 0.004$)

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Study	Participants and baseline values	Intervention	Outcomes and ocular safety	Sham + laser (n = 111)	Ranibizumab + laser (n = 95)	Triamcinolone + laser (n = 93)	Difference compared against sham
			Change in VA from baseline to week 56:				
			Letter score				
			Mean change from baseline	−6, SD 17	−4, SD 21	−5, SD 16	vs. ranibizumab: +1.9, 95% CI −3.7 to 7.5; p = 0.44 vs. triamcinolone: +1.2, 95% CI −4.4 to +6.8; p = 0.63
			Median (25th to 75th percentile)	−3 (−11, +4)	+1 (−12, +8)	−3 (−12, +3)	
			Distribution of change, n (%)				
			≥ 1-letter gain	6 (5)	12 (13)	7 (8)	NR
			14- to 10-letter gain	9 (8)	10 (11)	5 (5)	NR
			9- to 5-letter gain	9 (8)	12 (13)	8 (9)	NR
			Same + 4 letters	39 (35)	27 (28)	31 (33)	NR
			5- to 9-letter loss	16 (14)	8 (8)	14 (15)	NR
			10- to 14-letter loss	8 (7)	8 (8)	8 (9)	NR
			≥ 15-letter loss	24 (22)	18 (19)	20 (22)	NR

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
			Difference in proportion with ≥ 10 letter improvement from sham, 95% CI	–	+8 (–4 to +20)	+0.2 (–10 to +10)	–
			RR for comparison with sham	1	2.00, 95% CI 1.04 to 3.87; $p = 0.02$	1.22, 95% CI 10.57 to 2.63; $p = 0.55$
			Difference in proportion with ≥ 10 letter worsening from sham, 95% CI	–	–1 (–15 to +13)	+2 (–13 to +16)	–
			RR for comparison with sham	1	0.95, 95% CI 0.58 to 1.55; $p = 0.82$	1.04, 95% CI 0.64 to 1.69; $p = 0.85$

Major ocular adverse events:

Up to 14-week visit

	Sham + laser (*n* = 133)	Ranibizumab + laser (*n* = 116)	Triamcinolone + laser (*n* = 115)
Endophthalmitis	0	1 (0.9)	0
Ocular vascular event	0	0	0
Retinal detachment	4 (3)	1 (1)	1 (1)
Vitrectomy	1 (1)	0	1 (1)
VH	16 (12)	6 (5)	7 (6)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		Sham + laser (n = 133)	Ranibizumab + laser (n = 116)	Triamcinolone + laser (n = 115)
			Elevated IOP/glaucoma (mmHg)	Increase ≥ 10	3 (2)	0	20 (17)
				Increase ≥ 30	2 (2)	0	5 (4)
				Initiation of IOP-lowering medication	2 (2)	0	2 (2)
				No. of eyes meeting one or more of the above	3 (2)	0	20 (17)
			Glaucoma surgery		0	0	0
			Cataract surgery	Phakic at baseline	n = 120	n = 93	n = 105
				No. of eyes with cataract surgery	0	0	0

One case of endophthalmitis was related to ranibizumab injection

All had tractional detachment except in two eyes which had unspecified detachment (one before 14 weeks and one after 14 weeks)

All vitrectomies were done for PDR

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Intervention	Participants and baseline values	Outcomes and ocular safety		Sham + laser (*n* = 131)	Ranibizumab + laser (*n* = 111)	Triamcinolone + laser (*n* = 112)
			After 14–56 weeks visit				
			Endophthalmitis		0	0	0
			Ocular vascular event		0	0	0
			Retinal detachment		4 (3)	5 (5)	1 (1)
			Vitrectomy		17 (13)	8 (7)	7 (6)
			VH		28 (21)	25 (23)	20 (18)
			Elevated IOP/glaucoma (mmHg)	Increase ≥ 10 from baseline	6 (5)	6 (5)	10 (9)
				Increase ≥ 30	4 (3)	4 (4)	4 (4)
				Initiation of IOP-lowering medication at any visit after the 14-week visit	7 (5)	5 (5)	17 (15)
				No. of eyes meeting one or more of the above	11 (8)	7 (6)	20 (18)
				IOP-lowering medication at 56 week visit	3(2)	4 (4)	9 (9)
			Glaucoma surgery		0	1 (1)	1 (1)
			Cataract surgery	Phakic at 14 weeks	*n* = 119	*n* = 91	*n* = 102
				No. of eyes with cataract surgery	2 (2)	3 (3)	6 (6)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
				IVB	**PRP**	***p*-value**
Study ID: Ernst 2012[121] (note to editor)	**n:** 15 patients enrolled, 10 followed up (20 eyes)	**Group 1:** IVB	**BCVA (logMAR)**	−0.14 ± 0.19	−0.17 ± 0.10	Difference to baseline IVB: 0.52 PRP: 0.64
Aim: To investigate IVB injections alone without prior PRP	**Inclusion criteria:** Patients with type 2 diabetes and symmetric untreated severe NPDR or PDR	**Group 2:** PRP **Description of type of laser and delivery:** Treated in two sessions, with a third session only if there was angiographic evidence of NV activity at month 4	**Final CMT**	197 ± 17 μm	243 ± 49 μm	0.012
Design: Prospective, paired-eye, randomised pilot study. The right eye was randomly assigned to treatment with PRP or IVB, and the left eye received the other treatment	**Exclusion criteria:** MO or prior intraocular surgery		**NV leakage completely resolved**	4/5 eyes with PDR	1/5 eyes with PDR	0.11
	Age: Average 53 ± 9 years	**Description of anti-VEGF treatment:** 2.5 mg (0.1 ml) (Avastin, Genentech, San Francisco, CA, USA) were injected every 2 months during the study	**PDR development**	None of 10 eyes with severe NPDR		
Follow-up: 12 months	**Sex (% female):** 70 (7/10)		**Complications**	none	2/10 eyes VH, 3/10 MO	
	Diabetes type: Type 2					
Proportion completing the study: 10/15 (67%)	**HbA₁c:** NR					
	Baseline VA:					
Reasons for withdrawal: Unable to ascertain the reasons these patients left	IVB group: −0.12 ± 0.22					
	PRP group: −0.14 ± 0.23					
	Baseline CMT: NR					
	Baseline DR stage: Five patients had PDR and five had severe NPDR					
	Previous laser or intravitreal drug treatment: NR					
	Ocular comorbidities: MO – none					
	CSMO – other e.g. cataract, glaucoma					

TABLE 27 Laser vs. laser plus anti-EGF or anti-EGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety				
			Outcome	Week	PRP (difference to baseline)	PRPplus (difference to baseline)	Between-groups *p*-value (Wilcoxon)
Study ID: Filho 2011[122]	**n:** 40 patients enrolled (5 patients with one eye and 35 patients with PDR in both eyes), 29 followed up	**Group 1:** PRP	FLA	16	−2.4 ± 0.4 (0.0003)	−3.9 ± 0.4 (<0.0001)	0.0548
Aim: To evaluate the effects of PRP compared with PRP plus intravitreal injection of 0.5 mg of ranibizumab (IVR) in patients with HR-PDR		**Group 2:** PRP plus (PRP plus 0.5 mg IVR)		32	−3.1 ± 1.0 (0.0067)	−5.2 ± 0.6 (<0.0001)	0.0887
	Inclusion criteria: HR-PDR according to ETDRS definition (classification symptoms given in text)	**Description of type of laser and delivery:** Performed in two sessions (at week 0 and week 2) according to ETDRS guidelines. 600–800 500-µm spots were performed per session. CSMO treated with macular focal-grid laser at the time of the first PRP session. Patients could be retreated with focal laser or PRP at the 16- and 32-week study visits		48	−2.9 ± 1.3 (0.0083)	−5.8 ± 0.7 (<0.0001)	0.0291
Design: Prospective randomised trial			BCVA	16	0.06 ± 0.03 (0.0625)	0.00 ± 0.01 (0.5000)	0.1142
Follow-up: 48 weeks	**Exclusion criteria:** Prior laser treatment or vitrectomy, history of thromboembolic event including myocardial infarction or cerebral vascular accident; major surgery within the prior 6 months or planned within the next 28 days; uncontrolled HTN; known coagulation abnormalities or current use of anticoagulative medication other than aspirin; any condition affecting documentation			32	0.08 ± 0.03 (0.0078)	−0.01 ± 0.02 (0.5000)	0.0216
Proportions completing the study: 72.5% (29/40)		**Description of anti-VEGF treatment:** Intravitreal injection of 0.5 mg (0.05 ml) of ranibizumab was performed approximately 60 minutes after the completion of the first PRP session (at week 0) using 29-gauge needle inserted through the inferotemporal pars plana 3.0–3.5 mm posterior to the limbus using topical proparacaine drops under sterile conditions. Patients could be retreated with focal laser or ranibizumab at the 16- and 32-week study visits		48	0.08 ± 0.03 (0.0078)	0.00 ± 0.02 (0.5000)	0.0243
Reasons for withdrawal: PRPplus group: 2 patients died, lost to follow-up: 2 before week 16, 1 before week 32 (week 16: *n* = 17), (week 32: *n* = 16), (week 48: *n* = 15)			CSMT	16	34.4 ± 29.6 (0.0085)	−14.2 ± 36.9 (0.0188)	0.4706
	Age (mean):			32	54.7 ± 36.8 (0.0025)	−13.6 ± 41.8 (0.0820)	0.1897
PRP group: one patient excluded because of tractional retinal detachment, one patient excluded because of VH, two patients died, lost to follow-up: two patients before week 16 (week 16: *n* = 16), (week 32: *n* = 15), (week 48: *n* = 14)	PRP: 63.3 ± 2.5 PRPplus: 50.5 ± 3.0 (*p* = 0.0036)			48	18.1 ± 9.4 (0.0043)	−14.7 ± 39.1 (0.0698)	0.7106

All patients in the PRPplus group were retreated with IVR, and all patients in the PRP group received an additional 500-µm laser spots at weeks 16 and 32

No serious drug-related adverse events were observed in the 20 eyes (20 patients) treated with ranibizumab

Minor local transient adverse events:

Subconjunctival haemorrhage and foreign body sensation in 25% (5/20), 29.4% (5/17) and 31.25% (5/16) of patients at baseline, week 16 and week 32

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Sex (% female):		
	PRP: 36% (5/14)		
	PRPplus: 40% (6/15)		
	Diabetes type: NR		
	HbA$_{1c}$ (mean ± SD):		
	PRP: 9.3 ± 1.2		
	PRPplus: 9.4 ± 0.8		
	Baseline VA: NR		
	Baseline CMT: NR		
	Baseline DR stage: HR-PDR		
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*		
	Ocular comorbidities: See *Follow-up* and *Exclusion criteria*		

TABLE 27 Laser vs. laser plus anti-EGF or anti-EGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
				PRP plus	PRP	*p*-value
Study ID: Lucena 2013[123] (same study population as Filho 2011)	**n:** 40 patients enrolled (five patients with one eye and 35 patients with PDR in both eyes), 31 patients assessed	**Group 1:** PRP	Mean pain (±SEM)	4.7 ± 2.1 (12/17 patients pain score = 0)	60.8 ± 7.8 (minimal score for one patient = 10.5)	< 0.0001
Aim: To compare pain related to intravitreal injection and PRP in the management of patients with high-risk proliferative diabetic retinopathy	**Inclusion criteria:** Patients with HR-PDR, according to ETDRS (classification symptoms given in text)	**Group 2:** PRP plus IVR				
		Description of type of laser and delivery: PRP was performed in two sessions (at week 0 and week 2) according to ETDRS guidelines. 600–800 500-μm spots were performed per session, at the discretion of the treating investigator. If patients had CSMO) macular focal/grid laser was performed during first PRP session. Patients could be retreated with focal/grid laser at the 16- and 32-week study visits. If both eyes were eligible for the study, the eye with best VA was included				
Design: Randomised trial, open label	**Exclusion criteria:** Prior laser treatment or vitrectomy in the study eye; history of thromboembolic event; major surgery within the prior 6 months or planned within the next 28 days; uncontrolled HTN; known coagulation abnormalities or current use of anticoagulation medication other than aspirin; any condition affecting documentation or follow-up					
Follow-up: 16 weeks						
Proportions completing the study: 76% (31/40), 17 patients from PRPplus, 14 from PRP were evaluated for pain scores	**Age, mean ± SD (years):**					
Reasons for withdrawal: NR, see Filho 2011[122]	PRP: 63.5 ± 8.9					
	PRPplus: 51.1 ± 11.3 (*p* = 0.0018)					

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Sex (% female):	**Description of anti-VEGF treatment:** Intravitreal injection of 0.5 mg (0.05 ml) of ranibizumab was performed approximately 60 minutes after the completion of the first PRP session (at week 0) using 29-gauge needle inserted through the inferotemporal pars plana 3.0–3.5 mm posterior to the limbus using topical proparacaine drops under sterile conditions. Patients could be retreated with focal laser or ranibizumab at the 16- and 32-week study visits	
	PRP: 36% (5/14)		
	PRPplus: 41% (7/17)		
	Diabetes type: NR		
	HbA$_{1c}$ mean ± SD (%):		
	PRP: 9.3 ± 1.1		
	PRPplus: 9.1 ± 0.8 ($p = 0.5391$)		
	Baseline VA: NR		
	Baseline CMT: NR		
	Baseline DR stage: HR-PDR		
	Previous laser or intravitreal drug treatment: See *exclusion criteria*		
	Ocular comorbidities: See *exclusion criteria*		

TABLE 27 Laser vs. laser plus anti-EGF or anti-EGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety

Study ID: Mirshahi 2008[124]

Aim: To evaluate the additional therapeutic effect of a single intravitreal injection of bevacizumab (Avastin) on standard laser treatment in HRC. PDR patients in terms of regression of retinal neovascularisation

Design: A prospective, fellow-eye sham controlled clinical trial. Fellow eyes of each case were randomly assigned to receive Avastin or sham

Follow-up: 16 weeks

Proportions completing the study: 100%

Reasons for withdrawal: n/a

Participants and baseline values

n: 80 eyes – 40 bilateral HRC-PDR patients (Avastin: 40 eyes; sham: 40 eyes)

Inclusion criteria: Patients with bilateral HRC-PDR type 2 diabetes according to DRS criteria (criteria given in text) with or without MO

Exclusion criteria: Patients with uncontrolled HTN, recent (in the past 6 months) myocardial infarction or cerebrovascular accident, uncontrolled glaucoma, a history of any kind of retinal photocoagulation, or a diagnosis of tractional retinal detachment

Age (mean): 52 years (range: 39–68)

Sex (female%): 70 (28/40)

Intervention

Group 1: Standard laser treatment and focal or grid for CSMO + bevacizumab (Avastin) (single injection 1.25 mg)

Group 2: Standard laser treatment and focal or grid for CSMO + sham

Description of type of laser and delivery: Treatment according to ETDRS protocol, i.e. PRP (1200–1500 spots, 200-ms duration, ½ spot size apart) and focal or grid MPC for CSMO. PRP was completed in three sessions, 1 week apart

Outcomes and ocular safety

Regression:

Groups	Week 6 follow-up			Week 16 follow-up		
	Complete regression, n (%)	Partial regression, n (%)	None, n (%)	Complete regression, n (%)	Partial regression, n (%)	None, n (%)
Avastin (n = 40)	35 (87.5)	5 (12.5)	0	10 (25)	28 (70)	2 (5)
Sham (n = 40)	10 (25)	26 (65)	4 (10)	10 (25)	26 (65)	4 (10)

Difference between groups at 6 weeks ($p < 0.005$)

No clinical evidence of post injection uveitis, endophthalmitis, haemorrhage, and/or change in lens status was observed in follow-ups, no arterial embolic event

In the subgroup of Avastin-treated cases, recurrence of PDR in univariate analysis was associated with HTN, female gender, and higher HbA_{1c} levels, but in logistic regression analysis, only HbA_{1c} maintained a significant relationship

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Diabetes type: Type 2	**Description of anti-VEGF treatment:** 1.25 mg (0.05 cubic centimetres) bevacizumab (Genentech Inc.) on the first session of their laser treatment (following laser therapy). Under topical anaesthesia observing sterile conditions. First we did an anterior chamber paracentesis and then intravitreal injection was carried out through supratemporal pars plana	
	HbA$_{1c}$ (mean): 8.4%		
	Baseline VA: NR		
	Baseline CMT: NR		
	Baseline DR stage: HR-PDR		
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*	**Sham treatment:** Fellow eye injection was mimicked with a needleless syringe	
	Ocular comorbidities: 26 cases with CSMO that patients received MPC for		

TABLE 27 Laser vs. laser plus anti-EGF or anti-EGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		CG	SG	*p*-value
Study ID: Preti 2013[125] **Aim:** To compare the efficacy of therapy with PRP and IVB injections vs. PRP alone in patients with HR-PDR (HR-PDR) **Design:** RCT. Patients who met the inclusion criteria had the first eye randomised to the SG that received PRP with IVB injections and the second eye assigned to the CG, which received only PRP **Follow-up:** 6 months **Proportions completing the study:** 83% (35/42) **Reasons for withdrawal:** Development of VH	**n:** 84 eyes of 42 patients – 7 patients later removed from study owing to VH, 35 patients (70 eyes) assessed **Inclusion criteria:** ≥ 18 years, HR-PDR (HR-PDR) in both eyes with or without DMO and BCVA ≥20/200 **Exclusion criteria:** Pretreatment for DR (laser, intraocular medication, surgery), pre-retinal and VH, changes in the vitreous–retinal interface, external eye infection, prior thromboembolic events, SBPs and DBPs of ≥ 180 and 110 mmHg, A_{1c} levels exceeding 15%, chronic renal failure, major surgery within 1 month, previous treatment with antivascular agents **Age (mean):** 56 years (range 43–73) **Sex (% female):** 40 (14/35) **Diabetes type:** Type 2 **HbA$_{1c}$ (mean%):** 9.1	**Group 1:** PRP + IVB (SG) **Group 2:** PRP group (CG) **Description of type of laser and delivery:** Patients underwent 3 episodes (weekly for 3 weeks) of PRP in both eyes according to ETDRS methods using double-frequency Nd:YAG laser (523 nm Alcon, Opthalas 432 EyeLite Laser Photocoagulator, CA, USA) through the 160 Mainster OMRA-PRP lens (Volk Corp Mentor, OH, USA) 300–500 shots per episode, 500-μm-sized burns, exposure time 0.1–0.2 ms and moderate intensity (200–500 mW). If concomitant DMO existed it was treated at the time of PRP **Description of anti-VEGF treatment:** two IVB injections (1.25 mg/0.05 ml), PRP initiated 1 week after injection, second injection administered after third PRP session, plus 5% topical povidone	**Comparison between CG and SG:**			
			VA		–	–	No statistically significant difference between CG and SG
			Foveal thickness (μm)				
			1 month		335.86 ± 145.92	276.66 ± 81.30	0.013
			3 months		316.54 ± 137.70	296.49 ± 124.23	0.28
			6 months		364.83 ± 196.01	328.17 ± 150.58	0.45
			Macular volume (μm³)				
			1 month		9347.09 ±2095.60	8663.60 ± 1301.24	0.033
			3 months		9211.97 ±2030.17	8617.60 ± 1726.20	0.006
			6 months		9574 ±2751.88	9033.06 ±1991.39	0.11
			Patients with DMO in both eyes				
			VA				No statistically significant difference at any time point
			Foveal thickness (μm)				
			1 month		451.60 ± 145.38	341.33 ± 73.99	0.047
			3 months		400.67 ± 142.05	394.92 ± 133.48	0.60
			6 months		480.17 ±224.10	395.17 ± 160.54	0.32
			Macular volume (mm³)				No statistically significant difference in macular volume at any follow-up period

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
			Comparison of CG to baseline and SG to baseline:		
			CG	**SG**	***p*-value**
	Baseline VA (mean BCVA in logMAR):		*BCVA (reduction relative to baseline)*		
	SG group: 0.38 (range –0.01 to 1.00)		1 month	0.31 ± 0.25		vs. baseline – CG = 0.001; SG, no statistically significant difference
	CG group: 0.24 (range –0.02 to 0.88)		3 months	0.30 ± 0.24		vs. baseline – CG = 0.01; SG, no statistically significant difference
	Baseline CMT (mean foveal thickness):		6 months	0.34 ± 0.29		vs. baseline – CG = 0.02; SG, no statistically significant difference
	SG: 295 μm (range 179–600)		*Foveal thickness (μm) (increase relative to baseline)*		
	CG: 305.5 μm (range 171–578)		1 month	335.88 ± 145.92		vs. baseline – CG = 0.001; SG, no statistically significant difference
	p = 0.82		3 months	316.54 ± 137.71		vs. baseline – CG = 0.143; SG, no statistically significant difference
	Baseline macular volume (mm³):		6 months	364.83 ± 196.01		vs. baseline – CG = 0.042; SG, no statistically significant difference
	SG: 8582.49 (range 6016–13,880)		*Macular volume (increase relative to baseline)*		
	CG: 8730.11 (range 6470–14,189)		1 month	9347.10 ± 2095.60		vs. baseline – CG < 0.001; SG, no statistically significant difference
	p = 0.87		3 months	9211.97 ± 2030.17		vs. baseline – CG = 0.001; SG, no statistically significant difference
			6 months	9574.00 ± 2751.88		vs. baseline – CG = 0.003; SG, no statistically significant difference

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety		
			Patients with DMO in both eyes		
			BCVA		
				CG	SG	*p*-value
	Baseline DR stage: HR-PDR		Baseline	0.24 ± 017		
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*		6 months	0.42 ± 0.31		Difference in CG from baseline to 6 months; *p* = 0.033
	Ocular comorbidities: 37.2% (*n* = 13) had DMO in one eyes and 32.4% (*n* = 12) had DMO in both eyes					SG – no statistically significant differences

None of the patients experienced complications such as ocular HTN, lens opacity progression, anterior chamber reaction, arterial thromboembolic events

Study	Participants and baseline values	Intervention	Outcomes and ocular safety				
			Study period	PRPplus		PRP	
				BCVA (logMAR ± SEM)	Active NVs (mm² ± SEM)	BCVA (logMAR ± SEM)	Active NVs (mm² ± SEM)
Study ID: Tonello 2008[126] (same SG as Filho and Lucena) **Aim:** To evaluate the effects of PRP compared with PRP plus IVB on BCVA and total area of FLA from active new vessels (NVs) in patients with HR-PDR **Design:** RCT, patients randomly assigned to receive PRP (PRP group) or PRP plus **Follow-up:** 16 weeks **Proportions completing the study:** 100% **Reasons for withdrawal:** (Two patients presented with conditions that might have affected documentation or follow-up and were excluded)	**n:** 22 patients, 30 eyes, HR-PDR was identified in one eye of 14 patients and in both eyes of 8 patients (eye with worse VA was selected to receive PRP + IVB) **Inclusion criteria:** Patients were included if they had HR-PDR, which was defined according to the guidelines by the ETDRS (criteria given in text) **Exclusion criteria:** History of prior laser treatment or vitrectomy in the study eye; history of any thromboembolic event; major surgery within the prior 6 months or planned within the next 28 days; uncontrolled HTN; known coagulation abnormalities or current use of anticoagulative medication other than aspirin, any condition affecting documentation or follow-up **Age (mean):** PRPplus: 54.06 years ± 11.74 PRP: 51.4 years ± 10.65 **Sex (% female):** PRPplus: 26.7 (4/15) PRP: 46.6 (7/15)	**Group 1:** PRP **Group 2:** PRP plus IVB **Description of type of laser and delivery:** PRP performed at two time points – weeks 1 and 3 according to ETDRS guidelines), 600–800 500-μm spots per episode **Description of anti-VEGF treatment:** Intravitreal injection of 1.5 mg (0.06 ml) bevacizumab was administered about 60 minutes after the completion of the second PRP session (week 3) injected into the vitreous cavity via a 29.5-gauge needle inserted through the inferotemporal pars plana 3.0–3.5 mm posterior to the limbus using topical proparacaine drops under sterile conditions	Baseline	0.26 ± 0.07	11.15 ± 2.24	0.26 ± 0.05	15.31 ± 4.81
			Week 4	0.28 ± 0.05	0.62 ± 0.53	0.27 ± 0.07	14.73 ± 4.82
			Week 9	0.29 ± 0.04	0.67 ± 0.25	0.31 ± 0.06	14.26 ± 4.57
			Week 16	0.29 ± 0.04	4.46 ± 1.09	0.31 ± 0.06	13.58 ± 4.29

No serious drug-related adverse events were observed in the 15 eyes (15 patients) treated with bevacizumab

No significant changes in lens status or IOP were observed in any of the 15 injected eyes during the 16-week follow-up period

Minor local transient adverse events related to the treatment procedure, such as subconjunctival haemorrhage and foreign body sensation, were reported in seven (47%) and two (13.5%) patients, respectively

TABLE 27 Laser vs. laser plus anti-VEGF or anti-VEGF alone (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Diabetes type: NR		
	HbA$_{1c}$ (mean%):		
	PRPplus: 9.56 ± 1.50		
	PRP: 9.67 ± 1.49		
	Baseline VA (BCVA logMAR):		
	PRPplus: 0.26 (20/40)		
	PRP: 0.26 (20/40)		
	Baseline CMT: NR		
	Baseline DR stage: HR-PDR		
	Previous laser or intravitreal drug treatment: See *Exclusion criteria*		
	Ocular comorbidities: Nuclear sclerosis; three eyes in the PRP group, two eyes in the PRPplus group, some degree of macular non-perfusion (type 1–30) three eyes in the PRP group, four eyes in the PRPplus group		

CG, control group; FLA, fluorescein leakage; IVB, intravitreal bevacizumab; n/a, not available; NR, not reported; NV, new vessel; SEM, standard error of mean; SG, study group; TA, triamcinolone acetonide; VH, visual haemorrhage.

Four patients in the PRP group had progression of PDR, including vitreous haemorrhage, compared with none in the IVTA and IVB groups. In the IVTA group one eye had cataract progression and four eyes had increased IOP compared with none in the IVB group.

The authors conclude that both IVTA and IVB may be effective adjunctive treatments to PRP, minimising the risk of PRP-induced MO and visual loss. However, the study[119] was short term.

The Diabetic Retinopathy Clinical Research Network (2011)

This was a high-quality study.[120] The aim of the study[120] was to compare the efficacy of intravitreal injection of ranibizumab (Lucentis) or triamcinolone acetonide (TA) (Trivaris) in participants aged 18 years or more with severe NDPR (according to investigator assessment: severe NPDR in 18% of study eyes; according to the reading centre assessment: moderately severe NPDR or less severe NPDR in 20% of study eyes and severe NPDR in 5% of eyes) or PDR (according to investigator assessment, PDR in 82% of study eyes; according to the reading centre assessment: PDR in 75% of study eyes and out of this 35% had HR-PDR or level 71 or 75) and DMO treated with focal or grid laser. Those participants with previous history of extensive treatment with laser were excluded, as were participants with previous treatment for DMO, glaucoma, and increased IOP due to steroids and, lastly, those with IOP more than 25 mmHg. Patients were recruited from March 2007 to June 2009.

Initially, only one eye of each participant was included in the study.[120] Eyes were randomised to three different interventions. One group received sham injection (pressing a needleless syringe against the conjunctiva) at baseline and at 4 weeks, another group received intravitreal injection of 0.5 mg ranibizumab at baseline and 4 weeks and the third group received intravitreal injection of 4 mg TA at baseline and sham injection at 4 weeks. A later amendment to the protocol was made to include both eyes of the participant. During randomisation, patients could then receive one of three different treatment strategies. The first strategy involved injecting the better-seeing eye (BSE) with sham and injecting the worse-seeing eye (WSE) with ranibizumab or triamcinolone. The second strategy involved injection of ranibizumab or triamcinolone in the BSE and sham injection in the WSE. The third group included those patients with the same VA in both eyes. In this group, the right eye was categorised as the BSE and the other eye as the WSE.

Following randomisation, at baseline patients either received sham or intravitreal injection of ranibizumab or triamcinolone. All patients then received focal or grid laser for DMO between 3 and 10 days after baseline treatment. After this, patients could receive the first session of PRP immediately, or on the next day, but no later than 14 days after the baseline treatment. PRP included giving 1200–1600 burns in one session or in up to three sessions. All the sessions of PRP had to be completed within 49 days from the day of allocation. If patients lost vision by 10 or more letters following PRP due to worsening of MO then additional PRP treatment was postponed by 2 weeks or until the risk of MO reduced. The primary outcome measure was change in VA from baseline to 14 weeks. After this period, patients could receive additional treatment for their MO and retinopathy but only as part of their standard treatment. Hence, participants would not receive intravitreal injection of anti-VEGFs, steroids or focal/grid laser. Safety outcomes were measured at 56 weeks.

The 14-week visit was completed by 96% (118 eyes), 91% (103 eyes) and 96% (105 eyes) of eyes in the sham, ranibizumab and triamcinolone groups, respectively. The corresponding figures for 56 weeks completion rate were 90% (11 eyes), 84% (95 eyes) and 85% (93 eyes), respectively. Adherence to allocated therapies was very good.

During the 14 weeks' period, none of the eyes required additional treatment for their DMO. All eyes completed their PRP sessions except one eye in the sham, two eyes in the ranibizumab and two eyes in the triamcinolone arms. Slightly more eyes in the sham group completed PRP session in one sitting: 49 eyes (40%) in the sham, 38 eyes (34%) in the ranibizumab and 41 eyes (38%) in the triamcinolone.

There were no significant differences in the number of eyes requiring additional PRP: ranibizumab arm (21 eyes or 19%) than in the triamcinolone (24 eyes or 23%) and sham (29 eyes or 24%).

The number of eyes requiring additional treatment for DMO (part of standard care) was significantly lower in the ranibizumab (44%; $p = 0.004$) and triamcinolone (42%; $p = 0.004$) arms than in the sham arm (59%).

At 14 weeks, the mean change in VA from baseline was $+1 \pm 11$ in the ranibizumab arm, $+2 \pm 11$ in the triamcinolone arm and -4 ± 14 in the sham arm. The difference was statistically significant in both ranibizumab ($p < 0.001$) and triamcinolone arm ($p < 0.001$) compared with the sham arm. The proportion of patients gaining ≥ 15 letters was 10% in the triamcinolone arm, 7% in the ranibizumab arm and 7% in the sham arm. The proportion of patients gaining 10–14 letters was similar in the triamcinolone and the ranibizumab arm (12%) but only 4% in the sham arm. The proportion of patients losing letters was greater in the sham arm than in both ranibizumab and triamcinolone arms. The authors also reported changes in VA according to different subgroups – previous treatment for DMO, baseline VA (≥ 66 or ≤ 65), baseline central subfield thickness (< 400 or ≥ 400), DR (NPDR or PDR), diffuse vs. focal oedema, number of PRP sittings (one or multiple), PRP automated pattern use and baseline HbA$_{1c}$ levels (< 8 or $\geq 8\%$). In all subgroups, there was improvement (p-values not given) in vision in both triamcinolone and ranibizumab compared with the sham arm.

At 56 weeks, mean changes in VA letter score were similar: –6 (SD 17), –4 (SD 21) and –5 (SD 16) in the sham, ranibizumab and triamcinolone arms, respectively. During the follow-up period from baseline to week 14, there was one case of endophthalmitis, in the ranibizumab arm. There were no ocular vascular events. More eyes in the sham arm developed retinal detachment than in the other groups ($n = 4$, 3% vs. $n = 1$, 1% in ranibizumab and triamcinolone). Only one eye had vitrectomy in the sham arm. More eyes in the sham arm ($n = 16$ or 12%) had vitreous haemorrhage than in the ranibizumab ($n = 6$ or 5%) or triamcinolone ($n = 7$ or 6%) arm. More eyes ($n = 20$ or 17%) in the triamcinolone arm developed increased IOP of ≥ 10 mmHg from baseline than in the sham arm ($n = 3$ or 2%), and two developed IOP ≥ 30 mmHg. No eyes in the ranibizumab arm had increment of IOP ≥ 10 mmHg. No eyes had surgery for glaucoma or cataract.

Between 14 weeks and 56 weeks, there were slightly more cases of retinal detachment in the ranibizumab group ($n = 5$ or 5%) followed by sham ($n = 4$ or 3%) and triamcinolone ($n = 1$ or 1%). More eyes in the sham arm ($n = 17$ or 13%) had vitrectomy than in the ranibizumab ($n = 8$ or 7%) or triamcinolone arm ($n = 7$ or 6%). The number of eyes with vitreous haemorrhage was similar in the sham ($n = 28$ or 21%) and in the ranibizumab arm ($n = 25$ or 23%) but lower in the triamcinolone arm ($n = 20$ or 18%). Slightly more eyes in the triamcinolone arm had increments of IOP of ≥ 10 mmHg from baseline than the other two arms (9% vs. 5% rani vs. 5% sham). The number of eyes with an increment of IOP of ≥ 30 mmHg was similar in all groups ($\approx 4\%$). Significantly more eyes in the triamcinolone group (15%) received IOP-lowering medication at any visit after the 14-week visit than in the sham (5%) or ranibizumab group (5%). Similarly, more eyes in the triamcinolone arm received IOP lowering medication at 56 weeks visits than in other groups (9% vs. 2% sham vs. 4% ranibizumab). One eye each in the ranibizumab and triamcinolone groups had glaucoma surgery. Slightly more eyes receiving triamcinolone had cataract surgery (6% vs. 2% sham vs. 3% ranibizumab).

There was no significant difference amongst the groups in vascular events: 4 (4%) patients in the sham arm, 8 (7%) patients in the ranibizumab and 4 (3%) in the triamcinolone arm. No vascular events in the ranibizumab arm occurred at less than 3 weeks after the injection.

The authors concluded that both ranibizumab and triamcinolone are efficacious and safe in patients receiving focal/grid laser and PRP.

Ernst 2012

The aim of this paired-eye pilot study[121] was to investigate the efficacy of IVB alone in patients with type 2 diabetes with PDR (five patients) and severe NPDR (five patients), without MO, and naive to PRP. Patients were followed up every 2 months for 12 months. One eye of each patient had 2.5 mg (0.1 ml) of bevacizumab injected every 2 months while the other eye received PRP in two sessions. At month 4, if there was evidence of NV activity, then patients also received a third session of PRP.

In both groups, there was no significant change in mean BCVA (logMAR) from baseline [IVB –0.12 (SD 0.22) to –0.14 (SD 0.19); $p = 0.52$. PRP –0.14 (SD 0.23) to –0.17 (SD 0.10); $p = 0.64$]. Patients in the IVB group had significantly lower mean CMT than those in the PRP group [197 (SD 17 μm) vs. 243 (SD 49 μm); $p = 0.012$]. None of the eyes with severe NPDR developed PDR. NV leakage completely resolved in 4/5 eyes with PDR in the IVB group and 1/5 eyes with PDR in the PRP group. However, the difference between the two was not statistically significant ($p = 0.11$). No complications were reported in the IVB group but 2/10 eyes and 3/10 eyes in the PRP group developed vitreous haemorrhage and MO, respectively.

The authors concluded that IVB was effective in PDR and severe NPDR but that a larger study was needed to confirm this finding.

Filho 2011

The aim of the study[122,123] was to compare the effects of PRP against PRP plus intravitreal injection of 0.5 mg ranibizumab (IVR) in patients with HR-PDR. Of the initial 40 recruits, 29 were followed up for 48 weeks. The lasers were performed in two sessions, at week 0 and week 2. In each session, around 600–800 spots, of 500-μm size, were performed. In eyes with CSMO, focal/grid laser was given at the time of initiation of the first PRP session. During FA, if active new vessels were seen then patients were allowed to be retreated with 500 spots (500-μm size) per quadrant of active new vessels. At the 16 and 32 weeks study visits, if CSMO was present, patients were retreated with focal/grid laser if more spots were possible. Ranibizumab 0.5 mg (0.05 ml) was given approximately 60 minutes after the first PRP session. At the 16- and 32-weeks study visits, patients in the IVR groups could be re-treated with ranibizumab if active new vessels were seen.

The primary outcome was total area (mm³) of fluorescein leakage (FLA) from active NV but BCVA was also measured. At 48 weeks, the FLA reduction was significantly greater in the PRP group than in the PRP-plus-IVR group [–5.8 (SD 0.7) vs. –2.9 (SD 1.3); $p = 0.0291$] but the reduction was not statistically significant different at the 16 weeks (0.054) and 32 weeks (0.08) visits.

There was a reduction of BCVA of 0.6–0.08 logMAR compared with baseline in the PRP group at all three visits, but no change in the PRP plus group at any time points. The difference between the two groups was significant at 32 (0.021) and 48 weeks (0.024) study visits. CSMT increased by 20% from baseline in the PRP group but fell by 5% in the PRP-plus-IVR group. The difference between the two groups was not statistically significant.

There were no reports of serious drug-related adverse events (uveitis, endophthalmitis or change in lens or IOP) in the 20 eyes treated with IVR. There were reports of minor local transient (resolved within 1 week) adverse events related to procedures – subconjunctival haemorrhage and foreign body sensation in 5/20 (5%), 5/17 (29.4%) and 5/16 (31.25%) at week 0, 16 and 32, respectively.

A separate paper (Lucena 2013[123]) reported the results for pain. Pain score in each patient was measured using a 100-degree VAS. The mean pain score was significantly lower in the PRP plus group than in the PRP group [4.7 standard error of mean (SEM) 2.1 vs. 60.8 SEM 7.8; $p < 0.0001$]. The intensity of pain was also measured. In the PRP plus group, the intensity of pain score was 0 (meaning no pain at all during intravitreal injection) in 12/17 patients, whereas the pain intensity score in the PRP group was comparatively high. In the PRP group, only one patient had pain intensity score of 10.5, whereas in the remaining patients, the score was more than 30. The difference between the two groups was statistically significant ($p < 0.0001$).

The authors concluded that adding IVR after PRP appeared to protect against the modest VA loss and macular swelling observed in eyes treated with PRP alone.

Mirshahi 2008

The aim of the study[124] was to find out additional benefits of a single intravitreal injection of bevacizumab on standard laser treatment in 40 patients with bilateral HR-PDR. Patients were followed up for 16 weeks. The fellow eye of each patient was randomly assigned to receive IVB or a sham injection. All patients received standard PRP, with 1200–1500 spots performed about half-spot size apart, 200 ms in duration and completed in three sessions, 1 week apart. In eyes with CSMO, focal or grid macular photocoagulation (MPC) was performed (not clear when but presumably at the initiation of the first PRP session). The PRP-plus-IVB group received intravitreal injection of 1.25 mg (0.05 cc) of bevacizumab following the first PRP session. The PRP-plus-sham group had a needleless syringe pressed against the eye (also after the PRP session). If required, additional PRP was performed. The primary outcome was regression, defined as complete (no leakage at 2-minute image), partial (decrease of leakage at 2-minute image compared with baseline image) and none. At 6 weeks, a significantly higher proportion of patients in the IVB group than in the sham group (87.5% vs. 25%; $p < 0.005$) showed complete regression on angiography, and all showed some regression. However, at 16 weeks the proportion of patients achieving complete regression was similar in both groups (25%). The proportion of patients showing partial regression was slightly greater in the IVB group than in the sham group at 16 weeks (70% vs. 65%). Only about 5% of patients in the IVB group showed no regression, whereas the corresponding figure for sham group was 10%.

There were no reports of post-injection uveitis, endophthalmitis or haemorrhage, and no change in lens status or arterial embolic events. Univariate analysis of subgroup of IVB-treated patients showed that recurrence of PDR was associated with HTN and patient characteristics such as female gender and high HbA_{1c} levels. However, in logistic regression, only HbA_{1c} level was found to be a significant factor.

The authors concluded that a single injection of IVB considerably but temporarily improved the short-term response to scatter PRP in HR-PDR, but the effect was short-lived, as many of the eyes showed rapid recurrence.

Preti 2013

The aim of the study[125] was to compare the efficacy of PRP used on its own (control group) or in combination with IVB (study group) in 35 patients (70 eyes) with HR-PDR. Patients were followed up for 6 months. One eye was randomised to the study group and the fellow eye to the control group. All patients received three episodes (1 week apart) of PRP using double-frequency Nd:YAG laser with 300–500 shots per episode, a burn of 500 μm in size, exposure time of 0.1–0.2 seconds and in moderate intensity (200–500 mW). If patient had DMO, then it was treated at the time of initiation of PRP. The study group also received two intravitreal injection of 1.25 mg (0.05 ml) – one dose received 1 week before the first PRP session and the second injection received after the third PRP session.

There was no statistically significant difference in VA between the study and control group, in either the whole group or the bilateral DMO subgroup (12 patients). There were greater reductions in foveal thickness in the study group than in the control group, significantly at 1 month but not significantly different at 3 months ($p = 0.28$) and 6 months ($p = 0.45$). There were no reports of complications such as ocular HTN, lens opacity, progression, anterior chamber reaction or arterial thromboembolic events. The authors report a secondary outcome of change in VA from baseline as showing a significant decline in the control group but no change in the IVB group – it is not clear how this fits with the primary outcome showing no difference in VA between groups.

The authors concluded that in HRC-PDR, using IVB injections as adjuvant treatment to PRP reduces the VA deterioration compared with PRP alone. This was based only on secondary outcomes.

Tonello 2008

The aim of the study[126] was to compare the effects of PRP used on its own or in combination with IVB in 22 patients (30 eyes) with HR-PDR. None had CSMO. Patients were followed up for 16 weeks. Patients with HR-PDR in only one eye (14) were randomised but in eight patients with bilateral HR-PDR, the eye with worse VA was selected to receive PRP plus IVB and the other eye received PRP alone. So the study[126] was only partly a RCT. PRP was given in two sessions – week 1 and week 3 – performing 600–800 spots of 500-μm size per episode. Intravitreal injection of 1.5 mg (0.06 ml) bevacizumab was administered 60 minutes after completing the second PRP session (week 3).

At no time point was there significant change in BCVA from baseline in either groups (IVB – baseline 0.26 to week 16 0.29 logMAR; PRP – baseline 0.26 to week 16 0.31 logMAR) or between the groups.

In the IVB group, there was significant reduction in the total area of leakage from active NVs compared with the PRP group at all time points (weeks 4 and 9, ±1; week 16, ±2; $p < 0.001$).

There were no reports of serious drug-related complications in the 15 eyes (of 15 patients) treated with IVB, but only minor local transient adverse events that were related to the injection including subconjunctival haemorrhage (seven patients) and foreign body sensation (two patients).

The authors concluded that in the short-term, the adjunctive use of IVB with PRP was associated with a greater reduction in the area of active leaking NVs than PRP alone in patients with HR-PDR, but no difference in BCVA.

Adding intravitreal bevacizumab to laser: observational study

The efficacy of IVB in preventing PRP-induced macular thickening and visual dysfunction in eyes with HRC-PDR was investigated by Mason *et al.* (2008).[67]

They divided 60 eyes of 30 patients non-randomly into two groups. The patients had VA of 20/30 or better and no eye had CSMO. One group had 1.25 mg of IVB 1 week before initiation of PRP treatment and the control group had PRP treatment only. OCT was performed before all treatments and at each follow-up examination.

After 24 weeks the BCVA as measured by the mean (SD) LogMAR in the control group increased from 0.069 (0.076) at baseline to 0.149 (0.113) at 24 weeks; by contrast, the IVB group decreased from 0.073 (0.071) at baseline to 0.039 (0.054) at 24 weeks. The mean change in BCVA between each group from baseline to 24 weeks was statistically significant ($p \leq 0.0001$). Therefore, this study[67] indicates that a single IVB injection given before standard PRP may help prevent PRP-induced visual loss in eyes with HRC-PDR and good vision. However, this would need to be further tested in a larger randomised study with longer follow-up.

Laser in combination with steroids

These studies[119,120,127–130] are described narratively below and a detailed summary is given in *Table 28* [note that two studies, Cho *et al.* (2010)[119] and DRCRN (2011),[120] both of which have an anti-VEGF and a triamcinolone arm, have been summarised in *Table 27* so will not be repeated in *Table 28*].

TABLE 28 Laser vs. laser plus injectable steroids

Study	Participants and baseline values	Intervention	Outcomes and ocular safety	IVTA (mean ± SD)	Control (mean ± SD)	p-value
Study ID: Maia 2009[127]	**n:** 22 patients with bilateral treatment naive moderate PDR and CSMO	**Group 1:** PRP + macular laser	*logMAR BCVA (Snellen equivalent)*			
Aim: To evaluate the potential adjunctive effects of IVTA in combination with laser photocoagulation (pan-retinal and macular) treatment for the management of patients with both PDR and CSMO	**Inclusion criteria:** New vessels elsewhere ≥ 0.5 DA in one or more quadrants or new vessels on or within 1 DD of the optic disc < 0.25 to 0.33 DA, and CSMO by biomicroscopic evaluation in both eyes, 'symmetric' disease (defined for this study as the presence of the aforementioned characteristics [ETDRS severity level 65] in the absence of HR-PDR in each eye), and CMT greater than 250 μm on OCT evaluation	**Group 2:** PRP + macular laser + IVTA	Baseline	0.44 ± 0.17 (20/50⁻²)	0.38 ± 0.17 (20/50⁻¹)	0.019
		Description of type of laser and delivery: Bilateral laser photocoagulation consisting of full scatter PRP treatment performed in three episodes (at weeks 1, 2 and 3) according to ETDRS guidelines; 400–600 500-μm spots per session, at the discretion of the treating investigator. Macular (focal and/or grid) laser photocoagulation performed in each eye at the first laser treatment episode (at week 1)	Month 1	0.23 ± 0.13 (≈20/32⁻²)	0.44 ± 0.15 (20/50⁻²)	< 0.001
Design: Randomised trial, one eye (per patient) was randomly assigned to receive one IVTA (IVTA group), and fellow eyes received no additional treatment (CG)			Month 3	0.17 ± 0.09 (≈20/32⁻¹)	0.38 ± 0.13 (20/50⁻²)	< 0.001
			Month 6	0.14 ± 0.09 (20/25⁻²)	0.30 ± 0.14 (20/40)	< 0.001
Follow-up: 12 months			Month 9	0.14 ± 0.08 (20/25⁻²)	0.34 ± 0.17 (20/40⁻²)	< 0.001
			Month 12	0.12 ± 0.07 (20/25⁻¹)	0.32 ± 0.16 (20/40⁻¹)	< 0.001
Proportions completing the study: 86% (19/22)	**Exclusion criteria:** Aphakia, cataract surgery in the past 12 months or anticipated need for cataract surgery in the next 12 months, history of glaucoma, loss of vision as a result of other causes, systemic corticosteroid therapy, severe systemic disease other than diabetes, and any condition affecting follow-up or documentation (including pre-retinal or VH)		*CMT (μm)*			
		Description of steroid treatment: One intravitreal injection of 4.0 mg (0.1 ml) of TA performed approximately 60 minutes after the completion of the third session of PRP (week 3) using topical anaesthesia	Baseline	360.05 ± 84.85	331.68 ± 78.88	0.148
Reasons for withdrawal (brief): 3 patients (CG) developed vitreous and/or pre-retinal haemorrhage, and data were excluded from analyses of 6-, 9- and 12-month data for BCVA and OCT variables			Month 1	254.32 ± 27.06	351.64 ± 76.86	< 0.001
			Month 3	239.18 ± 27.62	308.05 ± 55.81	< 0.001
			Month 6	239.32 ± 26.48	290.16 ± 58.02	< 0.001
			Month 9	232.37 ± 22.89	301.26 ± 55.04	< 0.001
			Month 12	236.37 ± 16.14	265.74 ± 27.27	< 0.001
	Age (mean ± SD): 61.9 ± 5.3		*Total macular volume (mm³)*			
			Baseline	8.59 ± 1.68	8.44 ± 1.51	0.483
			Month 1	7.57 ± 0.89	8.30 ± 1.22	< 0.001
			Month 3	7.39 ± 0.77	8.01 ± 0.96	< 0.001
			Month 6	7.33 ± 0.69	7.83 ± 0.82	< 0.001
			Month 9	7.33 ± 0.68	8.01 ± 0.66	< 0.001
			Month 12	7.32 ± 0.60	7.78 ± 0.59	< 0.001

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Gender (female%): 54.5 (12/22)		IOP 1 month: significant increase in mean IOP in eyes in IVTA compared with eyes in control ($p = 0.012$)
	Diabetes type: type 2		IVTA group: mean increase in IOP = 3.2 mmHg (range 2–11)
	HbA$_{1c}$ (% ± SD): 9.6 ± 1.4		Cataract surgery after 12 months: 6 eyes in ITVA group (27.3% of eyes) ($p = 0.02$)
	Baseline VA [BCVA (logMAR)]		Additional macular laser photocoagulation:
	IVTA group: 0.44		IVTA: 2 of 22 (9.1%) eyes
	CG: 0.38		Control: 13 of 22 (59.1%) eyes
	$p = 0.019$		$p < 0.001$
	Baseline CMT:		No clinical evidence of uveitis, endophthalmitis, or ocular toxicity was observed. No serious drug-related adverse events in the IVTA group. Three patients (CG) developed vitreous and/or pre-retinal haemorrhage, and data were excluded from analyses
	IVTA: 360 μm		
	Control: 331 μm		
	$p = 0.148$		
	Baseline DR stage: Moderate PDR and CSMO		
	Previous laser or intravitreal drug treatment: NR		

TABLE 28 Laser vs. laser plus injectable steroids *(continued)*

Study	Participants and baseline values	Intervention
Study ID: Mirshahi 2010[128]	**n:** 23 patients	**Group 1:** IVTA injection 1 week before initial PRP and MPC (injected eye)
Aim: To compare the therapeutic effectiveness of combined IVTA plus PRP and MPC vs. PRP and MPC alone in patients with HR-PDR and CSMO	**Inclusion criteria:** HR-PDR, VA between 20/200 and 20/30, diffuse and subfoveal CSMO, CMT more than 230 μm measured by OCT	**Group 2:** PRP and MPC (control eye)
Design: Prospective, controlled trial, one eye of each patient was selected to undergo IVTA injection based on block randomisation (matched for age, duration of MO, and status of glycaemic control)	**Exclusion criteria:** History of prior laser treatment, existence of tractional retinal detachment, history of glaucoma, corticosteroid-responder patients, patients with active ocular surface disease and VH, hazy media that interferes with PRP, patients with one eye and a history of amblyopia, strabismus and anisometropia	**Description of type of laser and delivery:** PRP was performed in three sessions at weekly intervals. MPC was performed in the first session of PRP in both groups with grid photocoagulation
Follow-up: 6 months, 24 months for complications	**Age:** 55.6 ± 6.5 years	**Description of steroid treatment:** 4 mg triamcinolone was injected into the vitreous body 3.5 mm posteriorly from the inferotemporal of corneal limbus at 5 o'clock using a 27-gauge needle 1 week before PRP using topical anaesthesia
Proportions completing the study: 78% (18/23)	**Diabetes type:** Type 2	
Reasons for withdrawal (brief): Dense VH (two patients), tractional retinal detachment (one patient), loss of future follow-up (two patients)	**HbA$_{1c}$:** 9.93 ± 1.2%	
	Baseline VA [BCVA (logMAR)]:	
	IVTA: 0.46 ± 0.29	
	Control: 0.56 ± 0.27	

Outcomes and ocular safety

BCVA, CMT, IOP:

Variables	Follow-up intervals	IVTA eyes (n = 18)	Control eyes (n = 18)	*p*-value
LogMAR BCVA	Baseline	0.46 ± 0.29	0.56 ± 0.27	0.32
	1 month	0.50 ± 0.42	0.61 ± 0.25	0.04
	4 months	0.46 ± 0.34	0.56 ± 0.26	0.14
	6 months	0.39 ± 0.29	0.55 ± 0.33	0.08
CMT, μm	Baseline	319.2 ± 79.1	345.9 ± 100.6	0.65
	1 month	260.5 ± 78.5[a]	322.2 ± 90.3	0.01
	4 months	ND	ND	ND
	6 months	279.5 ± 76.9[b]	316.3 ± 105.7	0.36
IOP, mmHg	Baseline	15.72 ± 2.32	16.11 ± 2.16	0.48
	1 month	18.56 ± 2.09[c]	17.50 ± 1.50[d]	0.13
	4 months	17.18 ± 2.24[e]	16.41 ± 2.06	0.47
	6 months	16.71 ± 1.89[f]	16.35 ± 1.66	0.52

Mean ± SD

Remarkable difference within each group compared with baseline value: [a] $p = 0.024$, [b] $p = 0.06$, [c] $p = 0.001$, [d] $p = 0.001$, [e] $p = 0.026$, [f] $p = 0.045$

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Baseline CMT (μm):		**Standardised change in macular thickening (%):**

	SCMT in IVTA eyes		SCMT in control eyes	
	1 month	6 months	1 month	6 months
Mean	29.4	16.8	5.66	5.03
SD	52.2	55.8	31.5	47.4
Minimum	−61.3	−100.0	−45.9	−100.17
Maximum	97.7	95.7	45.8	81.5

IVTA: 319.2 ± 79.1

Control: 345.9 ± 100.6

p = 0.65

Baseline DR stage: HR-PDR

Three IVTA and four control eyes experienced recurrence of MO necessitating retreatment for five eyes

During the subsequent year after the regular visits, two IVTA eyes and one control eye had significant cataract progression in which surgical treatment was needed. Non-clearing VH (one eye control group) and tractional retinal detachment (two eyes control group)

continued

TABLE 28 Laser vs. laser plus injectable steroids (continued)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
Study ID: Shimura 2006[129] **Aim:** To evaluate prospectively the efficacy of a single sub-Tenon's capsule injection of TA against PRP-induced macular thickening and visual disturbance in patients with severe DR and good vision **Design:** Prospective controlled study, the eye injected with TA was determined randomly just before injection, and the uninjected eye served as the control **Follow-up:** 24 weeks **Proportions completing the study:** 100% **Reasons for withdrawal (brief):** n/a	**n:** 20 eyes of 10 patients **Inclusion criteria:** Symmetrical severe NPDR and early PDR, parafoveal thickness more than 300 μm; good VA in both eyes **Exclusion criteria:** IOP >16 mmHg after 1 month of treatment with topical 0.1% dexamethasone **Age (mean ± SD):** 63.0 ± 8.2 years **Gender (female%):** 50 (5/10) **Diabetes type:** Type 2 **HbA$_{1c}$:** 7.3 ± 0.76% **Baseline VA [BCVA (logMAR)]:** IVTA: 0.055 ± 0.07 Control: 0.065 ± 0.07 $p = 0.386$	**Group 1:** Sub-Tenon's capsule injection of 20 mg TA (triamcinolone) + PRP **Group 2:** PRP only **Description of type of laser and delivery:** PRP was performed four times at 2-week intervals in both eyes, size of the spots on the retina was 200–500 μm, and the duration was 0.15–0.2 seconds with a krypton red laser using topical anaesthesia. The number of spots in each session was approximately 500 **Description of steroid treatment:** 1 week before starting the first PRP session (−1 week), 0.5 ml (20 mg) TA was injected through the sub-Tenon's capsule space reaching the posterior pole in one eye	See outcomes table below

Foveal thickness, parafoveal thickness and BCVA (individual results for 10 patients also available):

	IVTA group				Control group				Difference at 24 weeks (p-value)
	−1 week	0 week	Difference to baseline	24 weeks	−1 week	0 week	Difference to baseline	24 weeks	
Alteration of foveal thickness									
Mean	235.5	204.4	$p = 0.029$	235.3	233.7	234.4	$p = 0.484$	312	0.0063
SD	37.5	21.9		38.6	39.8	40.2		68.2	
Alteration of parafoveal thickness									
Mean	388.4	290.5	$p < 0.0001$	302.2	388	387.6	$p = 0.499$	394.4	
SD	41.8	16.6		16.1	43.3	45.6		35.8	
Alteration of logMAR VA									
Mean	0.055	0.02	$p = 0.163$	0.085	0.065	0.07	$p = 0.455$	0.24	0.0063
SD	0.072	0.042		0.106	0.071	0.079		0.133	

−1 week: before laser and IVTA treatment

0 week: after IVTA but before laser treatment

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Baseline CMT:		
	IVTA: 235.5 ± 37.5 μm		
	Control: 233.7 ± 39.8 μm $p = 0.352$		
	Parafoveal thickness:		
	IVTA: 388.4 ± 41.8 μm		
	Control: 388.0 ± 43.3 μm		
	$p = 0.455$		
	Baseline DR stage: Severe non-proliferative and early PDR		
	Previous laser or intravitreal drug treatment: None of the patients had a history of retinal photocoagulation or ocular surgery		
	Ocular comorbidities: No clinically significant MO in either eye. No history of glaucoma, ocular HTN, or both. Cataract surgery, without complication in both eyes ($n = 3$), cataract in both eyes ($n = 7$)		

TABLE 28 Laser vs. laser plus injectable steroids (*continued*)

Study	Participants and baseline values	Intervention	Outcomes and ocular safety			
			LogMAR BCVA, retinal thickness, IOP:			
			Mean change at 6 months from baseline	**PSTA + PRP**	**PRP only**	***p*-value between groups**
Study ID: Unoki 2009[130]	***n:*** 82 eyes (41 patients)	**Group 1:** Single PSTA 20 mg before PRP	LogMAR BCVA (all patients)	Improvement of 0.072 (SD 0.028)	Worsening of 0.010 (SD 0.029)	0.04
Aim: To evaluate the efficacy of a single posterior sub-Tenon's capsule injection of TA (PSTA) before PRP	**Inclusion criteria:** 20 years or older of either gender with type 1 or type 2 diabetes; severe NPDR or PDR with clear ocular media and no other disease in either eye. The patients could have CSMO as defined by the ETDRS only if it was present in both eyes	**Group 2:** No injections before PRP **Description of type of laser and delivery:** The PRP was performed four times at 2-week intervals in both eyes. The spot size on the retina was 200–300 μm, the power of the laser was 150–200 mW, and the duration of the application was 0.2 seconds. The number of spots in each session was approximately 400, so the total number of burns after completion of the four sessions was approximately 1600. Topical anaesthesia was used in all cases, and all patients were treated as outpatients. If CSMO were present in both eyes at baseline, focal or grid laser therapy was performed at the first session of PRP	LogMAR BCVA in eyes without CSMO	Improvement of 0.04 (SD 0.13)	Worsening of 0.020 (SD 0.12)	
Design: Randomised, contralateral eye, controlled open-label trial			LogMAR BCVA in eyes with CSMO	Improvement of 0.12 (SD 0.22)	Worsening of 0.00 (SD 0.25)	
Follow-up: 6 months	**Exclusion criteria:** A history of pan-retinal or focal photocoagulation; a history of vitrectomy; presence of VH; signs of vitreomacular traction; periocular or intraocular steroid within the past 6 months; poorly controlled diabetes (HbA$_{1c}$ > 10%); a history of glaucoma or ocular HTN; BCVA that differed between eyes by more than two Snellen lines		Foveal thickness	Lessening of 9.7 (SD 85.6) μm	Increase of 32.8 (SD 82.8) μm	0.04
Proportions completing the study: 98%			IOP	There were no significant differences in IOP either between baseline and each follow-up point within the same group, or between the two groups at each follow-up point		
Reasons for withdrawal (brief): Lost to follow-up			Other complications	No other injection-related complications, including cataract progression, were observed		

Study	Participants and baseline values	Intervention	Outcomes and ocular safety
	Age (mean ± SD): 60.1 (11.5)	**Description of steroid treatment:** Posterior sub-Tenon's capsule injection under topical anaesthesia, 20 mg of TA (Kenacort: Bristol-Myers Squibb, New York) in a volume of 0.5 ml was injected in the inferotemporal quadrant; this was done 1 week before the first PRP session	
	Gender (female%): 44%		
	Diabetes type 2%: 98%		
	HbA$_{1c}$ %: 8.2 (SD 2.1)		
	Baseline VA [BCVA (logMAR)]: 0.13 (0.33)		
	Baseline foveal thickness (µm): 269.0 (114.9)		
	Baseline DR stage n (%): Severe NPDR = 29 (71%) PDR = 12 (29%)		
	Ocular comorbidities: CSMO in 17 (41%)		

CG, control group; DA, disc area; n/a, not available; NR, not reported; PSTA, posterior sub-Tenon's triamcinolone injection; VH, visual haemorrhage.

Cho 2010

Please see above for details of this study.

Diabetic Retinopathy Clinical Research Network 2011

Please see above for details of this study.

Maia 2009

The aim of the study[127] was to determine the adjunctive effects of IVTA in combination with PRP and MPC in 22 patients with PDR and CSMO. Patients were followed up for 12 months. One group of patients received PRP and macular laser, whereas the second group received PRP, macular laser and IVTA. All patients received bilateral full scatter laser (each eye sequentially on the same day) in three sessions – weeks 1, 2 and 3 – consisting of 400–500 500-μm-size spots performed per session. In addition, all patients received macular (focal/grid) laser photocoagulation in each eye at the time of the initiation of the first PRP session. At the end of the third PRP session, one eye per patient was randomly assigned to receive IVTA (IVTA group) and the fellow eye of the same patient to receive no additional treatment (control group). IVTA treatment was a single intravitreal injection of 4 mg/0.1 ml of triamcinolone (Kenalog 40) 60 minutes after the third PRP session. During follow-up visits, if patients still presented with CSMO and treatable lesions on FA, then additional macular (grid and/or focal) laser treatments were given. In patients with focal leaks of greater than 500 μm from the centre of the macula, treatment was given.

There was significant improvement in mean BCVA in the IVTA group at all time points ($p < 0.001$) compared with those in the control group. At 12 months' follow-up, mean BCVA in the IVTA group was 0.12 (SD 0.07) compared with 0.44 (SD 0.17) at baseline. The corresponding figures in the control group were 0.32 (SD 0.16) and 0.38 (SD 0.17), respectively. 12/19 (63.1%) eyes in the IVTA group and 2/19 (10.5%) eyes in the control group had improvements of two to three ETDRS lines. The difference between the two groups was statistically significant ($p < 0.001$). There was also significant reduction in mean CMT and total macular volume (TMV) in the IVTA group compared with the control group at all time points ($p < 0.001$). However, there was a significant increase in mean IOP in the IVTA group compared with the control group at 1 month ($p = 0.12$) but no difference at other time points. Mean IOP increase in the IVTA group was 3.2 mmHg, range 2–11 mmHg. Four eyes had to be treated with anti-glaucoma drops for 4–6 weeks as their IOP was greater than 24 mmHg.

All patients were phakic bilaterally, and, at 12 months' follow-up, cataract surgery was indicated in six eyes receiving IVTA and laser (27.3% of the IVTA group; $p = 0.02$). Significantly ($p < 0.001$) more eyes in the control group received additional macular laser due to persistent MO – 2/22 (9.1%) eyes in the IVTA group and 13/22 (59.1%)

There were no reports of uveitis or endophthalmitis. Three patients in the control group developed vitreous and/or pre-retinal haemorrhage.

The authors concluded that IVTA in combination with laser improved vision and reduced macular thickness in patients with moderate PDR with CSMO, but at the cost of some raised IOP and cataract development. In view of the small numbers in their study,[127] they advocated a large RCT.

Mirshahi 2010

The aim of the study[128] was to compare the benefits of IVTA in combination with PRP and MPC (injected eye) against the combination of PRP and MPC alone (control eye) in 18 patients with type 2 diabetes and bilateral HR-PDR and CSMO. One eye of each patient was randomised as the study eye and the fellow eye as control. The primary and secondary outcome measures were measured at 1, 4 and 6 months. Patients were then followed up for a maximum of 18 months for any possible complications or for any additional treatment. PRP was performed in three sessions at weekly intervals. MPC was performed at the time of initiation of the first PRP session. One week before the first PRP session, 4 mg TA was injected.

Mean HbA_{1c} was poor, at 9.93%.

At 1-month follow-up, mean VA was significantly greater in patients in the injected eye than in the control eye (20/50 vs. 20/66; $p = 0.04$). However, the difference was not significant at all other time points (4 months 20/58 vs. 20/73; $p = 0.14$; 6 months 20/50 vs. 20/70; $p = 0.08$). Similarly, mean change of VA was not statistically significant at 6 months follow-up (IVTA -0.05 ± 0.22 vs. control -0.008 ± 0.29; $p = 0.56$).

The reduction in CMT was significantly greater in the IVTA group than in the control group at 1 month ($p = 0.01$) but not significant at 6 months ($p = 0.36$). In the IVTA group, IOP was increased at 1 month [18.56 ± 2.09 mmHg; baseline: 15.72 (SD 2.32) mmHg], falling thereafter at 6 months, still high compared with the baseline value [16.71 (SD 1.89) mmHg]. In three eyes, IOP was treated.

Three eyes in the IVTA group and four eyes in the control group had persistent MO. Out of these, five eyes had to be re-treated. In the subsequent year after the regular visits, two eyes in the IVTA group and one eye in the control group had significant cataract progression requiring surgery. In the control group, one eye had non-clearing vitreous haemorrhage and two had tractional retinal detachment, respectively.

The authors concluded that their study[128] showed no benefit on vision from adding IVTA to laser photocoagulation.

Shimura 2006

The aim of the study[129] was to investigate the efficacy of a single sub-Tenon's capsule injection, rather than intravitreal, of IVTA for reducing PRP-induced macular thickening and visual disturbance. In 10 type 2 diabetes patients with severe DR and good vision, one eye of the eye received IVTA injection while the fellow eye of the same patient served as a control. The IVTA group received 0.5 ml (20 mg) TA injections 1 week before the first PRP session. All patients received PRP in both eyes for four sessions at 2 weeks' interval. Approximately 500 spots of 200- to 500-μm-size spots, exposure duration of 0.15–0.2 seconds was performed using a krypton red laser. Patients were followed up for 24 weeks.

Mean VA in the IVTA group improved initially [from 0.055 (SD 0.072) logMAR – week –1 to 0.02 (SD 0.04) at week 0] but remained unchanged after PRP. The final VA was 0.085 ± 0.11 logMAR, which was significantly ($p = 0.0063$) better than the control eye [0.24 (SD 0.13)]. In the control eye, VA reduced significantly following the PRP (week 0 to week 8) but stabilised after week 8.

In the IVTA group, foveal thickness reduced significantly following IVTA injection and before PRP ($p = 0.029$). However, foveal thickness increased following PRP therapy up to week 6 and gradually started to subside. In the control group, there was significant increment in foveal thickness, which never returned to the baseline level.

No IOP results are given, but the authors comment that no increases in IOP were seen – giving TA by the sub-Tenon's capsule route may be less likely to cause this, though the effect on MO may be less than with intravitreal injection.

The authors concluded that a single injection of TA prior to PRP has beneficial effects for preventing PRP-induced foveal thickness and visual loss in patients with severe DR and good vision. They recommend a larger trial, perhaps giving TA 5 weeks before PRP.

Unoki 2009

This is a 6-month RCT involving patients recruited from Kyoto University Hospital between July 2006 and October 2007.[130] It was designed to evaluate the efficacy of a single posterior sub-Tenon's capsule injection of triamcinolone acetonide (PSTA) before PRP versus PRP with no injection.

The primary end point of the trial, for which a sample size calculation was reported, was change in BCVA at 6 months compared with that at baseline using the logarithm of the minimum angle of resolution (logMAR). The secondary end points were changes in retinal thickness and IOP.

The trial included 82 eyes of 41 patients with bilateral severe NPDR (71%) or PDR (29%). The patients could have clinically significant MO as defined by the ETDRS, but only if it was present in both eyes. At baseline, 41% of patients recruited had CSMO. Nearly all (98%) had type 2 diabetes and the mean age was 60 years.

One eye of each patient was randomly allocated to one of two treatment arms (PTSA injection + PRP vs. PRP + no injection), which meant the fellow eye was automatically allocated to the other arm. The trial was open label to the patients and investigators, but the OCT technicians and statistical analysers were masked to the treatment assignment.

The PTSA injection consisted of 20 mg of TA (Kenacort) in a volume of 0.5 ml. It was injected 1 week before the first PRP session. Eyes in the control group received no injections.

The PRP treatment was performed four times at 2-week intervals in both eyes. The spot size on the retina was 200–300 μm, the power of the laser was 150–200 mW, and the duration of the application was 0.2 seconds. The total number of burns after completion of the four sessions was approximately 1600. If CSMO were present in both eyes at baseline, focal or grid laser therapy was performed at the first session of PRP.

The mean change in logMAR BCVA at 6 months from baseline in the PTSA + PRP group showed an improvement of 0.072 (SD 0.028) in the PSTA group and a worsening of 0.010 (SD 0.029) in the control group (PRP + no injection). This difference was statistically significant ($p = 0.04$).

The changes in foveal thickness between groups at 6 months were also statistically significant ($p = 0.04$), showing a lessening of 9.7 (SD 85.6) μm in the PTSA group and an increase of 32.8 (SD 82.8) μm in the control group.

There were no differences in IOP between groups at any of the time points (baseline, and 1, 3 and 6 months) measured. Also, there was no cataract progression observed, or any other injection-related complications.

The authors concluded that PSTA before PRP appears to be beneficial in preventing PRP-induced visual loss in eyes with DR by reducing the chance of macular thickening. The authors did point out a potential source of bias between the groups, in that focal/grid laser was performed in all with CSMO regardless of treatment assignment, and it was not possible to perform focal/grid laser in a standardised condition for each individual eye with CSMO.

Summary

For anti-VEGF the evidence from these mainly small trials is fairly consistent – the five bevacizumab and the two ranibizumab trials suggest that one or two injections can reduce the risk of PRP-induced MO. The trials are short term, but that is not a problem because the MO provoked by PRP is a short-term effect in the few months after PRP.

One question that cannot be answered by these trials is whether it would be as effective to treat with anti-VEGF drugs only if MO developed after PRP, given that many patients do not develop it. Treating prophylactically means that many would be treated unnecessarily, with cost implications. Indeed, even treating only those that do develop DMO might not be cost-effective if it is temporary with no long-term effects.

One study (DRCRN 2011[120]) found both ranibizumab and triamcinolone to be effective and safe up to 14 weeks. The same group of patients were followed up for up to 56 weeks but, without using study drugs, mainly to look at safety data, and found no difference between the two treatments. The authors, however, question whether there is a place for the use of anti-VEGFs and steroids long term.

Only one study (Cho 2010[119]) included patients with NPDR. The trial (Ernst 2012[121]) that compared bevacizumab alone with PRP alone concluded that the drug might be slightly better, but would need five to six injections over the first year compared with two laser sessions, and probably more in later years, as the effect of the anti-VEGFs is temporary.

The strength of the evidence base is that we have a set of RCTs. The limitations are their small size, and, for our purposes, that most patients had HR-PDR rather than severe NPDR.

In three trials, triamcinolone showed benefit in reducing the risk of MO after PRP and improving BCVA in patients with CSMO, but in another (Mirshahi 2008[124]) it did not. However, IVTA increased IOP, a well-known side effect of steroids. Triamcinolone given via the sub-Tenon's capsule did not (Unoki 2009[130]). However, in one RCT, sub-Tenon's capsule administration was reported to be less effective in reducing MO than the intravitreal route.[59]

Given the higher risk of adverse effects, anti-VEGF treatment might be preferable to steroids, though cost would need to be considered.

However, the question of whether anti-VEGF drugs should be used prophylactically remains open, as trials of the two (or three) strategies would be necessary, these being:

- no prophylaxis – treat only those people who develop MO after PRP
- routine prophylaxis – anti-VEGF before PRP
- no VEGF treatment – use focal laser if MO develops.

As will be reported in *Chapter 8*, a considerable amount of research is under way on the combination of PRP and anti-VEGF drugs.

Chapter 5 Systematic review of existing cost-effectiveness evidence

Introduction

This chapter reports a systematic review of existing economic evaluations (including model-based economic evaluations) of the use of PRP and/or anti-VEGF medication for patients with moderate and/or severe NPDR or early and/or severe PDR. The aim was to review the available literature including existing models and to identify any suitable data (e.g. costs, utilities and transition probabilities) to help inform our economic model.

Methods

The systematic search including searches of the following electronic databases: MEDLINE OVID (1946 to 12 September 2013), EMBASE (1974 to 12 September 2013), and the meeting abstracts database in the Web of Science (1900 to 24 October 2013). The search terms included economic and QoL terms cross referenced with DR terms. The search was limited to studies published in English Language and Humans. The search strategy was developed with input from an Information Specialist (PR). Details of the search strategies are provided in *Appendix 2*.

Citations and abstracts from each of the electronic online databases were exported into a citation software package (EndNote) and any duplicate citations were removed. Two reviewers (PA and HM) independently reviewed titles and abstracts to identify potentially relevant papers. There was no need for discussions with a third reviewer.

All abstracts were then read for relevance and were considered relevant to this review if they met the following inclusion criteria:

(a) The study is a full economic analysis on the treatment (laser and/or medication) for DR; or
(b) The study conducted a partial economic analysis (costs or effects) on the treatment (laser and/or medication) for DR (e.g. costing studies or QoL studies).

Abstracts that may provide useful information for the economic model (such as costs, utilities and transition probabilities) were further retained but not included in this review. These abstracts also included studies that specifically related to the treatment for DMO, treatment for AMD and of screening for DR. These studies were categorised as:

(a) The study contains useful information for DR on: adverse events/complications, disutilities, and/or natural history, incidence or prevalence (UK based).
(b) The study contains useful information on costs and/or effects for DR (the study does not have to be treatment related).
(c) The study discusses a model-based long-term economic analysis of screening for DR.

For the relevant abstracts, we obtained the relevant full-text articles. The reference lists of retrieved articles in category A or category B were checked for potentially relevant papers that met the inclusion criteria. A data extraction form was developed to capture the main characteristics associated with the relevant studies identified.

For any studies that were classed as full economic evaluations, we critically appraised them against the framework on quality assessment for economic evaluation studies developed by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) group.[131] The CHEERS framework sets out best practice for reporting economic evaluations under six main categories: title and abstract, introduction, methods, results, discussion and other. If the studies included any model-based economic evaluations, they were further critically appraised using the framework on quality assessment for economic modelling developed by Philips *et al.* (2004).[132] The framework developed by Philips *et al.* (2004)[132] sets out best practice for reporting on decision-analytic models used in economic evaluations under the dimensions of structure, data and consistency.

Results

The electronic database search identified 2556 potentially relevant citations. After removing duplicates, 1896 potential abstracts remained. After reviewing the published titles and abstracts of the remaining studies, no studies presented a full economic evaluation (including model-based evaluation) on the treatment (laser and/or medication treatment) for DR (category A). Six studies provided a partial economic analysis on the treatment (laser and/or medication) for DR (category B). One of the studies was excluded because it was a letter/reply to an article that was already included in category B.[133] In total, five articles[134–138] were retained for data extraction. *Figure 3* depicts a flow diagram of the abstracts identified and number of studies included in the cost-effectiveness review.
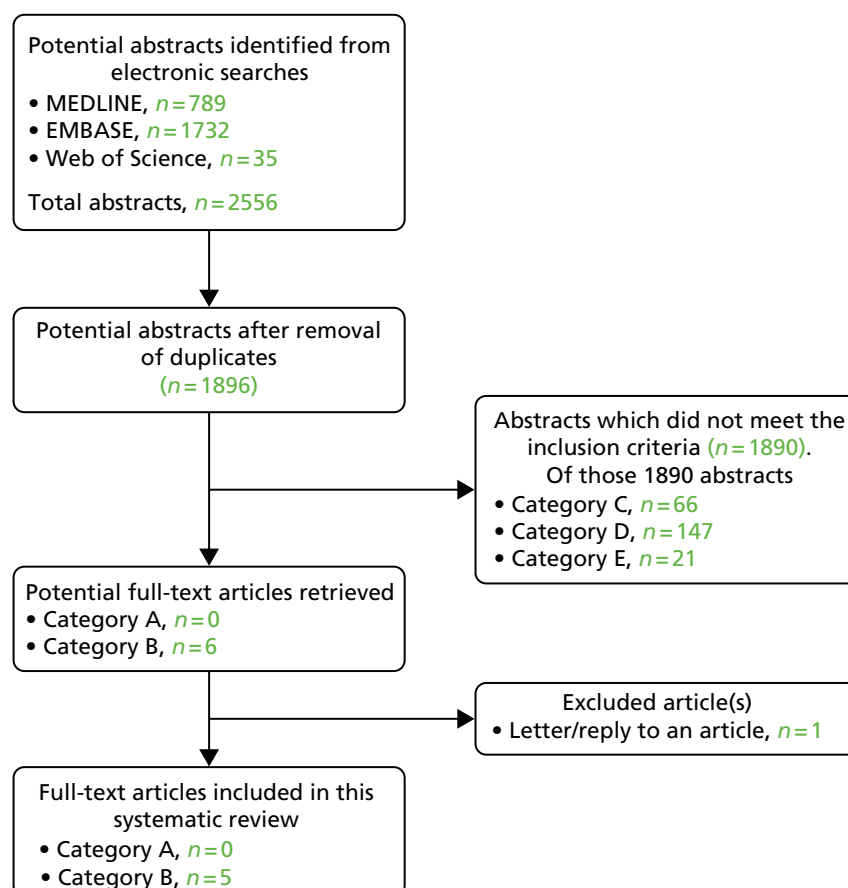
FIGURE 3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for cost-effectiveness studies.

Out of the 1890 abstracts that were excluded, 234 abstracts were retained as they appeared to contain some useful information for the model. Sixty-six abstracts contained useful information for DR with regards to adverse events, disutilities, incidence and prevalence (category C); 147 abstracts had useful information on the costs and/or effects for DR (category D); and 21 abstracts were model-based long-term economic analyses looking at screening for DR. Six of the included abstracts in category D related to cost-effectiveness studies which were treatment related (laser treatment/anti-VEGF medication) for other eye diseases (hence, they were not included in category A).

As no studies were found to be a full economic evaluation or model-based economic evaluations (category A), we did not assess the quality of these articles using either the CHEERS framework[131] or the Philips *et al.* (2004) checklist.[132]

None of the studies looked at the costs associated with DR and treatment (laser and/or medication). Five studies[134–138] focused on health outcomes associated with laser and/or medication treatment for patients with DR. Three papers were on QoL: Scanlon *et al.* (2006)[134] used qualitative interviews, Tsilimbaris *et al.* (2013)[135] used a vision-specific QoL measure, and Wirostko *et al.* (2011)[136] used conjoint analysis. We also found one study on patient satisfaction and the patient–provider relationship (Mozaffarieh 2005[137]) and one study on anxiety levels (Trento 2006[138]).

The five studies[134–138] were conducted in different countries: UK, Crete, Canada, Austria and Italy. The smallest sample size was 20 patients[135] and the largest sample size was 259 patients.[138] Three studies assessed patients who were undergoing laser treatment for the first time.[134,137,138]

The main limitations of the studies were the small sample sizes;[135] and the short durations of follow-up.[134,136] Most patients were generally satisfied with laser treatment.[134,137] The study by Tsilimbaris *et al.* (2013)[135] found that laser treatment did not have a significant impact on patients vision-related QoL; laser treatment was experienced by patients as an event that generates anxiety.[138] Finally, patients preferred the attributes which were associated with improving vision or preventing further vision loss.[136] The studies are described in more detail below.

Scanlon *et al.* (2006)[134] present data from 227 qualitative interviews with 156 patients. Interviews were conducted both pre-laser and post-laser treatment; 54% were PDR patients and 46% were MO patients. The interviews were conducted across four eye clinics in the UK. Our interest is mainly in the PDR patients. There were three groups of patients:

- *Group 1*　The first treatment group, of newly diagnosed patients coming for their first laser treatment. This included 27 PDR pre-treatment and 19 PDR post-treatment patient interviews.
- *Group 2*　The follow-up group were patients coming to a normally scheduled follow-up after their initial treatment. Six of the 11 interviews were in PDR patients.
- *Group 3*　The multiple treatment group consisted of patients already having had multiple treatments for their eye condition and who were returning for clinical follow-up visits or for additional treatment. There were 50 PDR pre-treatment and 21 PDR post-treatment interviews.

All of Group 1 and a subset of the Group 3 patients were interviewed before their treatment in the clinic and then by telephone again 2 weeks after their treatment. Both Group 2 and Group 3 patients were asked to recall symptoms before their first and after their laser treatment. The responses from all three groups were combined for the qualitative analysis.

Amongst Group 1 PDR patients, the most frequently reported symptoms prior to the first laser treatment were blurred vision (44%), short-sightedness (44%), and difficulty with poor lighting (41%). After photocoagulation their most frequently reported symptoms were short-sightedness (37%), blurred vision (21%) and flickering spots before their eyes (21%).

Responses in Group 2 were not reported separately for PDR and MO. For all of 11 Group 2 responders, blurred vision was both the most frequently reported symptom (55%) that they recalled having just prior to their first treatment, and the most frequent visual disturbance (50%) when they returned for their clinic follow-up visit. In Group 3 PDR patients, the most commonly reported symptoms were blurred vision, difficulty with poor lighting, difficulty with night vision and flickering spots before eyes.

Before and after photocoagulation differences varied amongst groups. Group 1 PDR patients had few comments about the pre–post differences, with the most common comments were 'Problem with reading/watching TV since treatment' and 'Not comfortable driving at night since treatment'. Group 3 PDR patients noted changes more often, mostly detrimental, after their laser treatment in their functional status or role limitations. The most common comments on pre–post differences in their functional status or role limitations were 'Problem with reading/watching TV since treatment', 'No change in limitations since treatment', 'Some improvement in limitations since treatment' and 'Not comfortable driving at all since treatment'.

In terms of comments about satisfaction with various aspects of laser treatment, there were a high number of expressions of the expectation that the treatment would arrest the progression of their eye disease even with those having had multiple treatments. Most participants indicated that they would elect to have the laser treatment again if their doctor felt it was necessary, even though the treatment had less of an impact than they hoped for, and expectations about the treatment were basically met for the majority of the participants. In Group 1 PDR patients the most frequent comment was 'Would have liked more information before treatment' followed by 'Felt treatment not as bad as expected'. Many patients going into their first treatments expected that the treatment would take care of their eye problem and they would not require repeated treatments.

Amongst Group 1 and 3 PDR patients under the theme of 'Feelings or satisfaction with treatment after laser' the most frequent comment was 'Would choose laser treatment again if needed'. When asked about the effect of treatment on QoL, the most frequent comment was 'My quality of life has not changed since treatment'. Therefore, it seems that the majority of patients registered no change in their QoL.

One of the main weaknesses of the study[134] was that follow-up interviews were conducted only 2 weeks post laser treatment, which was too soon to reflect the more beneficial long-term palliative effect from the laser treatment.

Tsilimbaris *et al.* (2013)[135] from Crete used the NEI 25-Item Visual Function Questionnaire (VFQ-25) tool at the beginning and at least 1 month after the completion of PRP, in patients with type 2 diabetes and bilateral PDR that was treated with PRP. Their study[135] was small consisting of 20 patients (12 men and 8 women) with a mean age of 65 years. They excluded patients who had had laser treatment before. PRP involved an average of 2140 laser spots, spot size of 200 μm, per eye, in multiple consecutive sessions. Mean energy of the spots was 252 mW and duration 200 ms. The NEI VFQ-25 consists of 25 vision-targeted questions representing 11 vision-related subscales, plus an additional single-item general health rating question. Each item is scored in a scale of 0–100; a higher score indicates greater vision-related QoL. The overall composite score is calculated by averaging across the subscale scores.

The mean composite score before laser treatment was 71.9 (SD 14.8) and after treatment it was 70.6 (SD 17.2) which was not significantly different ($p = 0.748$, paired *t*-test). The authors also found that none of the subscale scores had a statistically significant effect, before or after laser treatment. There was an increase in the composite score post-laser treatment in 11 patients, there was no difference in

one patient, and there was a decrease in eight patients. The treatment intensity, as indicated by the mean number of laser spots per eye each patient received, had no correlation with the pre-treatment to post-treatment change in the VFQ-25 composite score (Spearman's r = 0.104; p = 0.670). So PRP was well tolerated by the patients and did not seem to affect the patients' vision-related QoL.

One weakness of this study[135] was that any patients having complications such intravitreal haemorrhage were excluded from the final analysis. The authors do not report how many patients were excluded for this reason.

Wirostko et al. (2011)[136] assessed patient preferences for the different DR treatments (anti-VEGF, focal laser, pan-retinal laser or steroid treatment) using a technique called conjoint analysis in three centres in Canada. Preferences were sought from 161 patients: PDR – 25%; DMO – 31%; both PDR and DMO – 26%; no PDR or DMO – 18%. Of these patients, 49% (n = 79) were treated with laser only; 3% (n = 5) with injection (either steroid and/or anti-VEGF); 22% (n = 36) with both laser and injection; and 25% (n = 41) were treatment naive. The conjoint analysis survey involved patients making trade-offs among 11 DR attributes. The 11 attributes assessed were derived from a literature review and in consultation with three DR specialists, which included mode of administration, required number of office visits, treatment-related pain, the chance of improving central vision, and the risk of adverse events. Each attribute was described using two to three levels that represented the full range of possibilities across the four treatments. Utilities were generated for every level of each attribute and then ordinary least squares regression was used to calculate the final set of utilities for the attribute levels. The utilities were summed for different treatment profiles (based on the respective combinations of attribute levels) to determine which treatment would be preferred.

Of the 11 attributes, those affecting visual functioning were considered the most important such as improving VA and reducing adverse events (i.e. chance of cataracts) and those attributes not directly affecting vision such as administration or treatment-related pain were considered to be less important. Fifty-two per cent patients would prefer treatment by anti-VEGF compared with 20%, 17% and 11% with steroid, focal laser and pan-retinal laser, respectively. Patients who developed PDR, 46% preferred to be treated with anti-VEGF compared with 27%, 17% and 10% who would prefer to be treated with steroid, focal laser and pan-retinal laser, respectively. Preferences did not vary greatly by previous treatment experience, age or type of DR. Overall, the patient population were generally satisfied with the laser treatment that was provided.

In terms of limitations of the study,[136] the authors noted that the cost of treatment was not included as an attribute; a one-year time horizon was not long enough to capture all the effects of laser treatment and the sample did not represent the full range of patients with DR.

Mozaffarieh et al. (2005)[137] from Vienna assessed short-term treatment satisfaction after initial photocoagulation, and long-term satisfaction taking into account the patients' final expectations of their vision, in 105 patients undergoing first photocoagulation treatment for DMO (n = 49) or PDR (n = 56) between June 2002 and March 2004. Patients were informed of the benefits and adverse effects of laser photocoagulation, and were told that the main aim of treatment was to avoid further visual deterioration and blindness. The argon laser was used. To assess overall patient satisfaction with laser treatment, all patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ), scores ranged from 0 to 36; a higher score indicates greater satisfaction. Patients' degree of satisfaction in relation to VA results was assessed using a Likert scale.

Nine months after initial photocoagulation, 25% of patients reported improvement in VA, 71% reported no change in vision, and 4% reported deterioration in vision. Level of satisfaction as assessed by the DTSQ was high (mean score 29.6); 46.4% of patients with PDR scored 31 or higher on the DTSQ. Overall, using the Likert scale about 70% of the patients were completely satisfied, even though only 9% of these patients reported an improvement in VA. A further 21% were partially satisfied and 10% were dissatisfied with the results of treatment.

The authors emphasise the need to set realistic expectations by explaining, as they did, that the main aim of photocoagulation is to avoid further visual deterioration and that treatment may not necessarily improve their eyesight.

Trento *et al.* (2006)[138] from four centres in Northern Italy used four questionnaires – the Hospital Anxiety and Depression Scale (HADS), Family Apgar-List of Threatening Experiences (FA-LTE), State–Trait Anxiety Inventories 1 and 2 (STAI-1 and STAI-2) – to assess the anxiety associated with laser treatment in patients with sight-threatening diabetic retinopathy (STDR). They recruited two groups of patients: 131 waiting for laser treatment and 128 control subjects waiting for screening or other non-intervention visits. Scatter and/or focal-grid photocoagulation was performed by argon green laser. Most patients had type 2 diabetes and 80% of the laser group had previous photocoagulation, compared with only 1.5% of the comparison group.

High anxiety scores were detected by HADS, STAI-1 and STAI-2 among patients waiting for photocoagulation. Overall, scores for people waiting for laser treatment were higher than for control subjects, with the exception of FA-LTE. After adjusting for centre, gender, previous laser treatment and schooling, HADS and STAI-1 remained significantly lower among control subjects. Anxiety was not reduced by having had previous photocoagulation. However, there were differences amongst the centres. All four centres provided written material about DR and photocoagulation, but differed in facilities. Centre B provided further information about retinopathy and laser treatment in a relaxing setting, and had lower anxiety rates than Centre C, which had what the authors describe as an unpleasant setting and high patient throughput.

Discussion

The cost-effectiveness search highlighted only five studies[134–138] that were partial economic analyses looking at the treatment (laser and/or medication) for patients with DR. None of the studies looked at the cost of treatment and the cost of follow-up, and focused only on the health outcomes associated with treatment.

For the economic model, the two most useful studies found in the search in terms of the health outcomes are the studies by Tsilimbaris *et al.* (2013)[135] and Wirostko *et al.* (2011).[136]

The Tsilimbaris study[135] used a vision-related instrument (NEI VFQ-25) to measure vision-related QoL. The NEI VFQ-25 is a 25-item self-administered questionnaire, which assesses visual health and the impact this has on daily activities and QoL.[139] The questionnaire measures difficulty with near and distance vision activities, driving difficulties, limitations in social and role functioning, lack of independence due to vision, mental health symptoms caused by vision, peripheral and colour vision, and eye pain. The scoring is done in a two-stage process: (1) each item is scored on a scale of 0 (lowest score) to 100 (highest score), where a higher score represents better functioning; and (2) items within each subscale are averaged together (there are 11 subscales in total for the VFQ-25). To obtain the combined score for the questionnaire, the average of the subscales (excluding the general health rating question) is undertaken. Averaging across the subscales scores rather than individual items gives equal weight to each subscale.

The VFQ-25 has been used in various studies where they have used mapping methods to predict European Quality of Life-5 Dimensions (EQ-5D) utility scores (which are needed in order to estimate quality-adjusted life-years (QALYS), the recommended utility measure for NICE. For example, Browne *et al.* (2012)[140] predicted EQ-5D and Short Form questionnaire-6 Dimensions (SF-6D) utility values from the VFQ-25 for glaucoma patients using three types of models: ordinary least squares, Tobit regression and censored least absolute deviations, and the models were compared using the root-mean-square error and the mean absolute error, whereas, Payakachat *et al.* (2009)[141] also used the same three models to predict EQ-5D utility scores from VFQ-25 for patients with age-related macular degeneration. These models can be used for mapping questionnaires for any patient group.

The Wirostko study[136] used a technique called conjoint analysis or discrete choice experiments (DCEs). This technique is based on the premise that any intervention can be described by its characteristics (or attributes) and that the extent to which an individual values an intervention depends on the level of these attributes.[142] There are five main steps in conducting a DCE study: (1) identify the key attributes; (2) assigning levels to each of the key attributes; (3) developing the different choice scenarios; (4) establishing the preferences; and (5) data analysis. This method can help to elicit health-state utility values, which can be used to calculate QALYs as long as information on QoL and survival has been incorporated into the design of the DCEs.

The main limitations of the use of these two studies for our economic model are: the study by Tsilimbaris *et al.* (2013)[135] did not include a generic preference-based measure such as the EQ-5D or SF-12 or SF-6D; and in the study by Wirostko *et al.* (2011)[136] the cost of treatment was not included as an attribute. *Chapter 7* describes the economic model for patients with moderate/severe NPDR.

Chapter 6 Prevalence, progression and implications for modelling

Rationale for modelling

The main source of data for the effects of administering PRP at the severe NPDR stage, rather than waiting till PDR develops, is the ETDRS.[9] Much has changed in diabetes care over the decades since ETDRS, including improvements in diabetic control. As noted in the *Chapter 1*, the prevalence of serious retinopathy has declined in recent decades.

Mean HbA$_{1c}$ (the best measure of glycaemic control) has improved considerably since the 1980s. The recent Wisconsin paper comparing the Wisconsin Diabetes Registry Study (WDRS) and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[143] cohorts of people with type 1 diabetes, diagnosed in the periods 1987–92 and 1979–80,[3] reported that mean HbA$_{1c}$ in the WDRS cohort was 8.0% and in WESDR 9.3%. Interestingly, it should be noted that 48% of the WDRS cohort were on continuous subcutaneous insulin infusion (CSII) (insulin pumps) compared with less than 2% of the WESDR cohort. The 48% is far higher than the proportion of people with type 1 diabetes on CSII in the UK. A survey of Scottish Health Boards in March 2013 reported that only 3.5% of people over the age of 18 years with type 1, were on CSII.[144]

Nordwall *et al.* (2004)[144] reported that in Sweden, in patients with type 1 diabetes diagnosed under the age of 15 in the years 1961–85, the frequency of severe retinopathy (defined as need laser treatment) had declined from 47% after 25 years in the cohort diagnosed 1961–5, to 24% in the 1971–5 cohort. The peak age of diagnosis would be 10–12 years, so the 25-year follow-up would take them to 35–40 years of age. However, there was less reduction in background DR with 80% having that (presumably mild NPDR) at 25 years' duration.

The Wong *et al.* (2009)[2] meta-analysis divided studies of progression to PDR and SVL according to time period, before and after 1985 (when ETDRS results were published). They reported a big drop – 19.5% – with PDR at 4 years in former period, 2.6% in latter, and SVL at 4 years 9.7% in 1975–85 versus 3.2% in 1986–2008.

Ten-year rates for PDR were 11.5% versus 6.6%. For SVL, they were 6.0% versus 2.6%.

The mixes of types of diabetes in the two periods were different: 71% had type 1 in studies from latter period versus 48% in earlier one.

The people at highest risk of retinopathy are those with poor glycaemic control. Unfortunately, improvement in mean HbA$_{1c}$ may conceal the fact that a significant proportion is still poorly controlled. The Scottish Diabetes Survey 2011 (*Table 29*) reported that those with type 1 have a greater proportion with poor control – 37%.[143] Only 15% of people with type 2 had such poor control. However, because there are far more people with type 2 than type 1, most (77%) people with HbA$_{1c}$ over 9.0% had type 2 diabetes.

TABLE 29 Proportions in HbA$_{1c}$ bands by type of diabetes

HbA$_{1c}$	Type 1	Type 2	
< 7.5%	22%	62%	
7.5–9.0%	41%	23%	
> 9.0%	37%	15%	
Number with A1c > 9%	9000	30,000	% with T2 77%

Source: Scottish Diabetes Survey 2011.[143]

So overall, 17% of Scottish patients had HbA$_{1c}$ of over 9%. They are at highest risk of retinopathy, and the ETDRS results from a group with poor control (42% had HbA$_{1c}$ over 10%) should be applicable to them.

The National Diabetes Audit for England and Wales[145] reported that over 18.1% of people with type 1 diabetes and 7.2% of people with type 2 diabetes have poor glycaemic control (HbA$_{1c}$ > 10%) (*Table 30*).

Model run 1
So our first run uses ETDRS data,[9] applicable to those with poor glycaemic control. If early PRP at severe NPDR stage compared with delaying PRP till PDR develops is not cost-effective in this group, it is unlikely to be cost-effective in lower-risk groups.

Model run 2
The costing assumes that conventional argon laser is used, given over at least two sessions to reduce the risk of PRP-associated MO. In a sensitivity analysis, we test the effect in this cohort of replacing conventional argon laser with PSC laser given in one session, combined with a single injection of IVB to reduce the risk of DMO. In effect this run merely changes some costs, but also creates a more convenient scenario for patients.

Types of diabetes
One finding from ETDRS was that early PRP was more beneficial in patients with type 2 diabetes than those with type 1.[42] It was also noted that in the deferred group progression to HR-PDR was faster in type 1 than type 2, and that early PRP reduced the development of HR-PDR less in type 1: 3–40% versus 50% reduction in type 2.

One excellent source of data on progression of retinopathy in type 1 is the Diabetes Control and Complications Trial (DCCT) study, especially with the Epidemiology of Diabetes Interventions and Complications (EDIC) extension to give a further 18 years of follow-up. The DCCT data come from a cohort of type 1 diabetes only, mean age at end of DCCT/entry into EDIC 33 years.[145,147]

TABLE 30 Treatment target achievement rate for all patients in England and Wales for the audit year 2011–12

HbA$_{1c}$	Type 1 diabetes	Type 2 diabetes
< 48 mmol/mol (6.5%)	6.5%	26.2%
6.5–7.4%	20.5%	39.6%
7.5–10.0%	54.9%	27.0%
> 10.0%	18.1%	7.25%

Derived from *National Diabetes Audit 2011–2012 Report 1: Care Processes and Treatment Targets.*[146]

However, the figures for progression give insufficient detail. *Table 31* gives the prevalence of different levels of retinopathy for the conventional group. There was an increase in prevalence of severe NPDR of 22.9%, but we cannot say where the patients in that group came from.

Severe visual loss was rare in the DCCT and so we cannot model that.

Other studies of progression in type 1 diabetes include the Wisconsin (WESDR) study, which reported that, in those with no retinopathy or NPDR at baseline, 37% had developed PDR by 14 years of follow-up.[148]

In type 2 diabetes, the equivalent study to DCCT was the United Kingdom Prospective Diabetes Study (UKPDS). However, very few patients progressed to severe disease. Stratton *et al.* (2001)[149] reported that 37% had some retinopathy at diagnosis. Of these, 29% progressed by two ETDRS scale steps or more over 6 years, or laser photocoagulation or vitreous haemorrhage. HbA_{1c} predicted progression: 18% in lowest tertile of HbA_{1c} to 40% in top band (HbA_{1c} 7.5% and over). SBP was a weaker predictor: 26% lowest third, 36% highest. Smoking reduced the risk of progression by about half. So the UKPDS data is not suitable for our purposes.

Harris Nwanyanwu *et al.* (2013)[150] reported progression in people in a large managed care network in the USA (which sounds population based but may not be because many people do not have insurance). They followed 4617 people with NPDR (no details of stages given but said to be newly diagnosed) to see how many developed PDR for a mean on 1.7 years, during which time 6.7% progressed to PDR. An important finding was that for every 1% increase in HbA_{1c}, there was a 14% increase in the risk of progressing from NPDR to PDR.

Other studies reporting progression include the Blue Mountains Study,[151] wherein 4.1% of people with NPDR progressed to PDR over 5 years.

Jones *et al.* (2012)[152] from Norfolk provide data from a cohort of over 20,000 screened up to 14 times (Norwich was one of the pilot screening sites). Amongst those with background (mild and moderate NPDR?) 23% developed PPDR and 6% developed PDR after 1 year. Their classification was a simpler version of ETDRS. After 10 years, those with background DR had 56% progression to PPDR and 11% to PDR. But this may be an underestimate because referred patients were removed from the screening system. The data provide background to pre-proliferative progression rates.

TABLE 31 Prevalences of retinopathy in DCCT and EDIC, conventional arm

Retinopathy	At end of DCCT	EDIC year 18
None	17.3%	4.7%
Microaneurysms only	32.1%	26.8%
Mild NPDR	28.5%	18.3%
Moderate NPDR	14.3%	19.6%
Severe NPDR	7.8%	30.7%

Transition probabilities

The Markov model in *Chapter 7* uses transition probabilities for the progression through various stages of DR. Most clinical studies present information in the form of progression rates at a specified time. These rates were converted to transition probabilities using the formula below, where r is the progression rate and t is time:

$$p_{transition} = 1 - \exp\{-rt\} \tag{1}$$

Where progression rates were not available from the literature, we converted the probability of the event over a period of time to a constant rate using the formula below:

$$r = -[\ln(1-P)]/t \tag{2}$$

Then, the calculated rate was used, as above, to derive the transition probability.

This section reports on the sources of the progression rates of DR, the progression of CSMO and SVL, and methods used to derive the transition probabilities. These transition probabilities were derived from the literature and in consultation with clinical experts. We report on the progression rates used from the literature and the transition probabilities (progression and regression) calculated for the progression to various stages of DR. The limitations are discussed later. Ideally, we would have found data on progression and where relevant, regression to and from each stage, but many studies combined stages, for example jumping from moderate NPDR to HR-PDR. *Table 32* summarises the transition probabilities for the usual care and intervention arms, respectively. *Tables 33* and *34* summarise the post-treatment transition probabilities for the usual care and intervention arms, respectively.

Rates of progression (usual care)
In the UK, the current standard of care is to initiate PRP when the severity level of DR reaches HRCs.[42]

Moderate non-proliferative diabetic retinopathy
Progression rates for people who progressed from moderate NPDR to severe NPDR were obtained from a population-based study from Melbourne by McCarty *et al.* (2003).[153] These authors provided information on the 5-year probability (2 of 10) of developing severe NPDR for people categorised as moderate NPDR, at baseline. We converted this probability to a to a 6-month transition probability of 0.0221 to be used in the model. For people who progressed to severe NPDR and CSMO with/without visual impairment, we used the transition probability of progressing from moderate NPDR to severe NPDR in addition to the progression rate reported by Klein *et al.* (1998)[148] for people developing CSMO. Klein *et al.* (1998)[143] reported a 14-year progression rate of 17% (95% CI 14.1% to 19.9%) for people developing CSMO. From this information, we derived a transition probability of 0.0281 for people progressing from moderate NPDR to severe NPDR and CSMO.

Severe non-proliferative diabetic retinopathy
The progression rate for people developing severe NPDR and CSMO with/without visual impairment was obtained from Klein *et al.* (1998).[148] These authors reported a 14-year progression rate of 17% (95% CI 14.1% to 19.9%) for people developing CSMO. From this, we calculated a 6-month transition probability of 0.0061 for progressing from severe NPDR to developing severe NPDR with CSMO. Progression rate for people developing early PDR was taken from ETDRS #12.[6] These authors reported the 5-year progression rate to early PDR for people categorised as severity level 53, at baseline. From this, we derived a 6-month transition probability of 0.0214 for people developing early PDR from baseline severe NPDR.

TABLE 32 Transition probabilities required for the progression of DR (intervention and usual care)

	Moderate NPDR	Severe NPDR	Severe NPDR and CSMO ± VI	Early PDR	Early PDR and CSMO ± VI	HR-PDR	HR-PDR and CSMO ± VI	Severe PDR	Severe PDR and CSMO ± VI	SVL
Moderate NPDR	a	0.0221	0.0281	0	0	0	0	0	0	0
Severe NPDR	0	0	0.0061	0.0214		0	0	0	0	0
Severe NPDR and CSMO ± VI	0	0	0		0.0548	0	0	0	0	0
Early PDR	0	0	0	0	0.0061	0.0717	0.0778	0	0	0
Early PDR and CSMO ± VI	0	0	0	0	0	0.1434	0.1555	0	0	0.0258
HR-PDR	0	0	0	0	0	0	0.0061	0.0459	0.0520	0
HR-PDR and CSMO ± VI	0	0	0	0	0	0	0	0.0918	0.1039	0.0535
Severe PDR	0	0	0	0	0	0	0	0	0.0061	0.0535
Severe PDR and CSMO ± VI	0	0	0	0	0	0	0	0	0	0.0535
SVL	0	0	0	0	0	0	0	0	0	a

VI, visual impairment.
a Residual transition probability of remaining in that health state.
Transition probabilities used in the model changes every year due to an increase in probability of events and death as the cohort ages.

TABLE 33 Transition probabilities required for the progression of DR (usual care): post treatment

	Moderate NPDR	Severe NPDR	Severe NPDR and CSMO ± VI	Early PDR	Early PDR and CSMO ± VI	High-risk/ moderate PDR	High-risk/ moderate PDR and CSMO ± VI	Severe PDR	Severe PDR and CSMO ± VI	Severe visual loss
HR-PDR PT	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0061	0.0459	0.0520	0
HR-PDR and CSMO ± VI PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0918	0.1039	0.0252
Severe PDR PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0061	0.0252
Severe PDR and CSMO ± VI PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0252

PDR, proliferative diabetic retinopathy; PT, post treatment; VI, visual impairment.
Transition probabilities used in the model changes every year due to an increase in probability of events and death as the cohort ages.

TABLE 34 Transition probabilities required for the progression of DR (intervention): post treatment

	Moderate NPDR	Severe NPDR	Severe NPDR and CSMO ± VI	Early PDR	Early PDR and CSMO ± VI	High-risk/ moderate PDR	High-risk/ moderate PDR and CSMO ± VI	Severe PDR	Severe PDR and CSMO ± VI	Severe visual loss
Severe NPDR PT	0.0036	0	0.0061	0.0171	0	0	0	0	0	0
Severe NPDR and CSMO PT	0.0036	0.0036	0	0.0342	0.0464	0	0	0	0	0
Early PDR PT	0.0036	0.0036	0.0036	0	0.0061	0.0186	0.0247	0	0	0
Early PDR and CSMO PT	0.0036	0.0036	0.0036	0.0036	0	0.0284	0.0494	0	0	0.0092
HR-PDR PT	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0061	0.0459	0.0520	0
HR-PDR and CSMO ± VI PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0918	0.1039	0.0252
Severe PDR PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0061	0.0252
Severe PDR and CSMO ± VI PT	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0.0036	0	0.0252

PDR, proliferative diabetic retinopathy; PT, post treatment; VI, visual impairment.
Transition probabilities used in the model changes every year due to an increase in probability of events and death as the cohort ages.

Severe non-proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment

For the progression rate to early PDR and CSMO from the severe NPDR and CSMO health state, Pautler (2010)[47] suggested that people with DMO and PDR are at greater risk of developing more severe retinopathy than people with PDR alone. Owing to the lack of information on progression rates in the literature for people developing more severe retinopathy from the severe NPDR and CSMO health state, we assumed that the progression rate is twice that of severe NPDR developing more severe retinopathy. We derived a 6-month transition probability of 0.0548 for people with baseline severe NPDR and CSMO with/without visual impairment and progressing to early PDR and CSMO with/without visual impairment.

Early proliferative diabetic retinopathy

The progression rate for people developing early PDR and CSMO with/without visual impairment was taken from Klein *et al.* (1998).[148] Information on the progression rate to HR-PDR from baseline early PDR was obtained from ETDRS #18.[154] The authors reported a 5-year cumulative progression rate of 74.4% (95% CI 69.8% to 79.4%) to HR-PDR for people categorised as early PDR, at baseline. From this, we derived a 6-month transition probability of 0.0717 for people progressing to HR-PDR from baseline early PDR. For people progressing to HR-PDR and CSMO with/without visual impairment we used the progression rate of developing HR-PDR in addition to the progression rate for people developing CSMO. From this information, we derived a transition probability of 0.0778 for people progressing from early PDR to HR-PDR and CSMO.

Early proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment

For the progression rates to more severe retinopathy from the early PDR and CSMO health state, Pautler (2010)[47] suggested that people with DMO and PDR are at greater risk of developing more severe retinopathy than people with PDR alone. Owing to the paucity of information on progression rates for people developing more severe retinopathy from the early PDR and CSMO health state, we assumed that the progression rate is twice that of early PDR developing more severe retinopathy. We derived a 6-month transition probability of 0.1434 and 0.1555 for people developing HR-PDR and HR-PDR and CSMO, respectively, from baseline early PDR and CSMO with/without visual impairment. For progression to SVL, the transition probability was derived from information taken from DRS #14.[38] These authors presented a 4-year progression rate of 20.9% to SVL for untreated eyes categorised as proliferative without HRCs. We derived a 6-month transition probability of 0.0258 for people progressing to SVL from early PDR and CSMO.

High-risk proliferative diabetic retinopathy

The cumulative progression rate for people developing HR-PDR and CSMO with/without visual impairment from baseline HR-PDR was obtained from Klein *et al.* (1998).[148] From this, we calculated a transition probability of 0.0061 for people developing HR-PDR and CSMO. For people progressing to severe PDR, information was obtained from the McCarty *et al.* (2003).[153] These authors reported a 5-year transition probability for people treated for PDR and remaining in the PDR health state. At the 5-year follow-up, three out of eight people remained in the PDR health state. We assumed this transition probability for people developing severe PDR. The 5-year transition probability was converted to an annual rate and then re-converted to a 6-month transition probability of 0.0459. For people progressing to severe PDR and CSMO with/without visual impairment we used the progression rate of developing severe PDR in addition to the transition probability for people developing CSMO. The progression rate for people developing severe PDR was obtained from the study by McCarty *et al.* (2003)[153] in addition to the progression rate for people developing CSMO. From these studies, we derived a 6-month transition probability of 0.0520 of progressing to severe PDR and CSMO with/without visual impairment from baseline HR-PDR.

High-risk proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment

For the progression rates to more severe retinopathy from the HR-PDR and CSMO health state, Pautler (2010)[47] suggested that people with DMO and PDR are at greater risk of developing more severe retinopathy than people with PDR alone. Owing to the lack of information on the progression rates for people developing more severe retinopathy from the HR-PDR and CSMO health state, we assumed that the progression rate is twice that of HR-PDR developing more severe retinopathy. From this information, we derived a 6-month transition probability of 0.0918 for people developing severe PDR from baseline HR-PDR and CSMO. For progression to SVL, the transition probability was derived from information taken from DRS #14.[38] These authors presented a 4-year progression rate of 44.0% to SVL for untreated eyes categorised as proliferative with HRCs. We derived a 6-month transition probability of 0.0535 for people progressing to SVL from early PDR and CSMO.

Severe proliferative diabetic retinopathy

The cumulative progression rate for people developing severe PDR and CSMO with/without visual impairment from baseline severe PDR was taken from the study by Klein *et al.* (1998).[143] From this study,[143] we estimated a 6-month transition probability of 0.0061 for developing severe PDR and CSMO. For progression to SVL, the transition probability was derived from information taken from DRS #14.[38] These authors presented a 4-year progression rate of 44.0% to SVL for untreated eyes categorised as proliferative with HRCs (so not quite at severe stage). We derived a 6-month transition probability of 0.0535 for people progressing to SVL from severe PDR.

Severe proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment

For progression to SVL, the transition probability was derived based on information obtained from DRS #14.[38] These authors presented a 4-year progression rate of 44.0% to SVL for untreated eyes categorised as proliferative with HRCs. We derived a 6-month transition probability of 0.0535 for people progressing to SVL from severe PDR and CSMO with/without visual impairment.

High-risk proliferative diabetic retinopathy post treatment

For people developing HR-PDR and CSMO from HR-PDR at baseline, we derived a transition probability based on information obtained from Klein *et al.* (1998).[148] From this, we calculated a transition probability of 0.0061 for people developing HR-PDR and CSMO. For the progression to severe PDR, information was obtained from McCarty *et al.* (2003).[153] These authors reported a 5-year transition probability for people treated for PDR and remaining in the PDR health state. We assumed that this was the progression rate for people developing severe PDR. The 5-year transition probability was converted to an annual rate and then re-converted to a 6-month transition probability. For the progression rate to severe PDR and CSMO, we derived a transition probability from the McCarty *et al.* (2003)[153] study in addition to the transition probability of developing CSMO. From this, we calculated a 6-month transition probability of 0.0520 for people progressing to severe PDR and CSMO after treatment for HR-PDR. Information on the progression to SVL was taken from DRS #14.[38] These authors presented a 4-year progression rate of 20.4% to SVL for treated eyes categorised as proliferative with HRCs. From this progression rate, we derived a 6-month transition probability of 0.0258 for people developing SVL after treatment for HR-PDR.

High-risk and clinically significant diabetic macular oedema with/without visual impairment post treatment

The progression rate for people that received treatment for HR-PDR and CSMO with/without visual impairment to more severe health states were taken from the literature. For people progressing to severe PDR, we derived a transition probability based on information reported by McCarty *et al.* (2003).[153] The 5-year transition probability was converted to an annual rate and then re-converted to a 6-month transition probability of 0.0459. We assumed that people with PDR and CSMO are twice as likely to develop more severe retinopathy than people with PDR alone. We estimated a 6-month transition probability of 0.0918 for people developing severe PDR from baseline HR-PDR and CSMO. For people

progressing to severe PDR and CSMO, we derived a transition probability based on information reported by McCarty *et al.* (2003)[153] in addition to a transition probability of developing CSMO. Also, we assumed that people with PDR and CSMO are twice as likely to develop more severe retinopathy than people with PDR alone. The derived transition probability of 0.1039 is for progression to severe NPDR and CSMO from baseline HR-PDR and CSMO. Progression rates to SVL were obtained from DRS #14.[38] These authors reported a 4-year progression rate of 20.4% to SVL for people treated for PDR with HRCs. We derived a 6-month transition probability of 0.0252 to SVL for eyes in the HR-PDR and CSMO post-treatment health state.

Severe proliferative diabetic retinopathy post treatment

The progression rates for people that received treatment for severe PDR and progressing to more severe retinopathy health states were taken from the literature. For people progressing to severe PDR and CSMO, we derived a transition probability from the Klein *et al.* (1998).[148] Progression rates to SVL were obtained from DRS #14.[38] These authors presented a 4-year progression rate of 20.4% to SVL for people treated for PDR with HRCs. From this, we derived a 6-month transition probability of 0.0252 to SVL for eyes in the severe PDR post-treatment health state.

Severe proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment post treatment

The progression rates for people that received treatment for severe PDR and CSMO and progressing to more severe retinopathy were obtained from the DRS #14.[38] From this study,[38] these authors presented a 4-year progression rate of 20.4% to SVL for people treated for PDR with HRCs. From this, we derived a 6-month transition probability of 0.0252 to SVL for eyes in the severe PDR post-treatment health state.

Rates of regression (usual care)

Regression rates for people following treatment for DR were obtained from Klein *et al.* (2008),[155] who reported a 25-year cumulative rate of improvement in DR following laser treatment of 18% (95% CI 14.1% to 19.9%). We assumed this improvement to all regression health states, and converted this rate to a 6-month transition probability of 0.0036 to be used in the model.

Rates of progression (intervention: early pan-retinal photocoagulation)

People who have moderate NPDR are monitored, and then treated with PRP when they progress to the severe NPDR stage.

All transitions in the intervention arm were the same as the usual care arm except for the transitions that are listed below.

Severe non-proliferative diabetic retinopathy post treatment

The progression rate for people that received treatment for severe NPDR to more severe health states were taken from the literature. The progression rate to severe NPDR and CSMO with/without visual impairment was derived from the Klein *et al.* (1998)[148] study. These authors reported a 14-year cumulative progression rate of 17% (95% CI 14.1% to 19.9%) for developing CSMO. From this, we estimated a 6-month transition probability of 0.0061 for progressing to severe NPDR and CSMO. The progression rate for people developing early PDR was taken from ETDRS #12.[6] We assumed that PRP reduces the progression rate to early PDR by 20%. These authors reported a 5-year progression rate of 21.6% to early PDR for people categorised as severity level 53. From this, we derived a 6-month transition probability of 0.0171.

Severe non-proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment post treatment

For the progression rate to early PDR from the severe NPDR and CSMO post-treatment health state, we obtained information from the ETDRS #12.[6] These authors reported a 5-year progression rate of 21.6% for people developing early PDR from severe NPDR. Here, assumed that PRP will reduce the progression rate to early PDR by 20%. Additionally, we assumed that the progression rate to early PDR in people with CSMO, is twice that of severe NPDR without DMO. We derived a transition probability of 0.0342 for people developing early PDR from severe NPDR and CSMO post-treatment health state. For people developing early PDR and CSMO, we obtained information from the ETDRS #12.[6] These authors reported a 5-year progression rate of 21.6% for people developing early PDR from severe NPDR. Here, we assumed that PRP will reduce the progression rate to early PDR by 20%. Additionally, we assumed that people with PDR and CSMO are twice as likely to progress to more severe retinopathy than people with PDR but without CSMO. We derived a transition probability of 0.0463 for people progressing to early PDR and CSMO from the severe NPDR and CSMO post-treatment health state.

Early proliferative diabetic retinopathy post treatment

For people developing early PDR and CSMO, we derived a transition probability of 0.0061 from the 14-year progression rate of CSMO obtained from Klein *et al.* (1998).[148] For the progression to HR-PDR, the ETDRS #9[9] reported results on the 5-year progression rate of 18.8% to HR-PDR for people treated for moderate-severe NPDR or early PDR. We derived a 6-month transition probability of 0.0186 for people developing HR-PDR. The progression rate to HR-PDR and CSMO was obtained from the ETDRS #9 study.[9] These authors reported a 5-year progression rate of 18.8% to HR-PDR for eyes treated for moderate-severe NPDR. In addition, we added the derived transition probability of developing CSMO based on the progression rate reported by Klein *et al.* (1998).[148] From this we derived a 6-month transition probability of 0.0247 for the progression to HR-PDR and CSMO for eyes treated for early PDR.

Early proliferative diabetic retinopathy and clinically significant diabetic macular oedema with/without visual impairment post treatment

For the progression to HR-PDR, the ETDRS #9[9] reported results on the 5-year progression rate of 28.8% to HR-PDR for people treated for CSMO and more severe (severe NPDR or early PDR) retinopathy. We derived a 6-month transition probability of 0.0284 for people progressing to HR-PDR having received treatment for early PDR and CSMO. To calculate the progression rate to HR-PDR and CSMO, we obtained information on the progression rates from the ETDRS #9[9] and Klein *et al.* (1998)[148] studies. Also, we assumed that early PRP reduces the progression rate to HR-PDR and CSMO by 20%. Additionally, we assumed that the progression is twice that of early PDR developing more severe retinopathy. From this, we estimated a transition probability of 0.0494 for people progressing to HR-PDR and CSMO from the early PDR and CSMO post-treatment health state. The progression rate to SVL was obtained from DRS #14.[38] These authors presented a 4-year progression rate of 7.4% to SVL for people treated for PDR without HRCs. From this, we derived a 6-month transition probability of 0.0092 to SVL for eyes treated for PDR without HRCs.

Rates of regression (intervention)

Regression rates for people following treatment for DR were obtained from Klein *et al.* (2008),[155] who reported a 25-year cumulative regression rate of 18% (95% CI 14% to 21%) for improvement in DR following laser treatment. We assumed this improvement to all health states, and converted this rate to a 6-month transition probability of 0.0036 to be used in the model.

Limitations

We encountered a number of problems. Ideally, we would like to have had good population-based and recent data on progression rates, and hence transition probabilities, along the retinopathy pathway: moderate NPDR > severe NPDR > early PDR > HR-PDR > severe PDR > SVL.

However, many studies jumped stages, for example giving only progression from NPDR to HR-PDR.

Some of the studies with the most detailed information – such as the DRS,[38] ETDRS[6,154] and WESDR[143,155] (discussed in earlier chapters) – are now somewhat out of date. A meta-analysis by Wong *et al.* (2009)[2] showed that progression rates are now much lower than in decades past, which they attribute to improved control of blood glucose, BP and lipids, and to better eye care, with earlier identification of retinopathy through screening and better treatment. The 10-year incidence of PDR was 11.5% in the period 1975–85, and 6.6% in the period 1986–2008. For SVL, the corresponding figures were 6.0% and 2.6%.

Inevitably, data on progression may always be out of date because it takes 20 years to collect 20-year progression data, by which time advances in care may have reduced the risk.

The studies found provided useful information on progression rates, but varied in terms of the study population, sample size included, categories of diabetes, classification of DR, length of follow-up, outcome measures and clinical end points. These characteristics of the studies can have an impact on the transition probabilities used to model disease progression.

In our model, there were limitations which we must acknowledge. Firstly, the model was populated with transition probabilities derived from various sources. From these studies, authors may have followed up a cohort of people with type 1 diabetes only,[11,143,155] or type 2 diabetes[149] or a mixed group of type 1 and type 2.[38,153] Additionally, studies may have included people with DR in one eye only and both eyes. Scanlon *et al.* (2013)[156] reported that people with DR in both eyes are likely to progress to more severe retinopathy compared with people with retinopathy in one eye.

Secondly, in the baseline analysis, the progression rates were obtained from the ETDRS,[6,9,154] where the clinical end points were mainly progression to HR-PDR, vitrectomy or SVL. Hence, we had to seek information from other studies to derive transition probabilities of progressing to less severe health states. For example, progression from moderate NPDR to severe NPDR information was obtained from McCarty *et al.* (2003).[153] These authors followed up 121 diabetics. At baseline, majority of the people included in this study had no retinopathy or mild NPDR. Ten and eight people had moderate NPDR and PDR, respectively. Owing to the small sample size of people with moderate NPDR at baseline, this may not be an accurate representation of the progression rate to more severe retinopathy. Information on the progression rate to early PDR following treatment for severe NPDR was not available from the literature. Most studies assessed the impact of PRP in reducing the progression rate to HR-PDR or SVL.

Additionally, some studies (McCarty 2003[153]) did not differentiate between the severity level of PDR at baseline. Hence, in some cases, we assumed that the progression rate for people with early PDR, HR-PDR or severe PDR was the same for progressing to more severe health states. This may have the impact of underestimating/overestimating the progression rates, as we would expect an individual with early PDR to progress to more severe health states at a slower rate than an individual with HR-PDR.

Thirdly, due to the paucity of information on the progression rates for people with DR and CSMO developing more severe retinopathy, we assumed the progression rate is twice the progression rate for a person with DR alone. Paulter (2010)[47] suggested that people with PDR and DMO are likely to progress to more severe retinopathy compared with people without PDR. However, this progression was not quantified by Paulter (2010).[47] The impact of this assumption on our results may lead to an under/overestimation of the progression rates.

Fourthly, the progression rates were mainly obtained from studies pre-1998, and the management of diabetes, DR and blood glucose management has improved owing to a better understanding of the retinopathy disease process.[157]

The various uncertainties may lead to underestimating/overestimating the progression rates used in the model.

However, the largest uncertainty arises not from uncertainties over progression rates, but from the absence of recent data on the benefits of PRP at severe NPDR or early PDR compared with waiting till HR-PDR, using modern laser methods and adjuvant anti-VEGF treatment.

Chapter 7 Model for assessing cost-effectiveness of pan-retinal photocoagulation for non-proliferative diabetic retinopathy

Introduction

We built a Markov model in order to determine whether offering PRP treatment to patients with severe NPDR is cost-effective compared with delaying treatment till the PDR stages. This chapter describes the structure of the model, the inputs into the model, the assumptions made, the different scenarios that have been evaluated, the main results and sensitivity analyses.

Model structure

To assess the cost-effectiveness of early treatment versus delaying treatment of PRP, a Markov (state-transition) model was developed using Microsoft Excel version 2013 (Microsoft Corporation, Redmond, WA, USA). A Markov model was the most appropriate choice because progression of DR can evolve over time and during this time, patients can move to different stages of DR (health states) or can die.

The economic model was developed by determining the different clinical pathways for patients presenting with moderate NPDR through to irreversible severe vision loss and blindness (and to death). We have used information from the systematic review on the clinical effectiveness, but most notably the DRS (see *Chapter 2*), and the ETDRS (see *Chapter 2*), and from expert opinion to develop the different clinical pathways.

There are two treatment arms within the model:

1. *Current practice (usual care)* Patients are observed until they progress to the HR-PDR health state (and onwards) when they receive PRP.
2. *Early PRP (intervention)* Patients receive PRP once they progress to the severe NPDR health state.

Figures 4 and *5* show the model structure for people receiving current practice (usual care) and *Figures 6* and *7* show the model structure for people receiving early PRP (intervention arm). Health states in the model structure are shown in the ovals, the arrows represent the transitions that patients can make in the model, the recurring arrows show that patients can stay in that same health state for more than one cycle, and death is an absorbing health state.

Table 35 lists the different health states for the model. The four post-treatment health states for severe NPDR, severe NPDR and CSMO with/without visual impairment, early PDR and early PDR and CSMO with/without visual impairment do not apply to the usual care arm.

The model starts by assigning a cohort of 1000 patients presenting with moderate NPDR at an ophthalmology clinic. The model assumes that people progress through all stages of DR: moderate NPDR > severe NPDR > early PDR > HR-PDR > severe PDR > SVL.
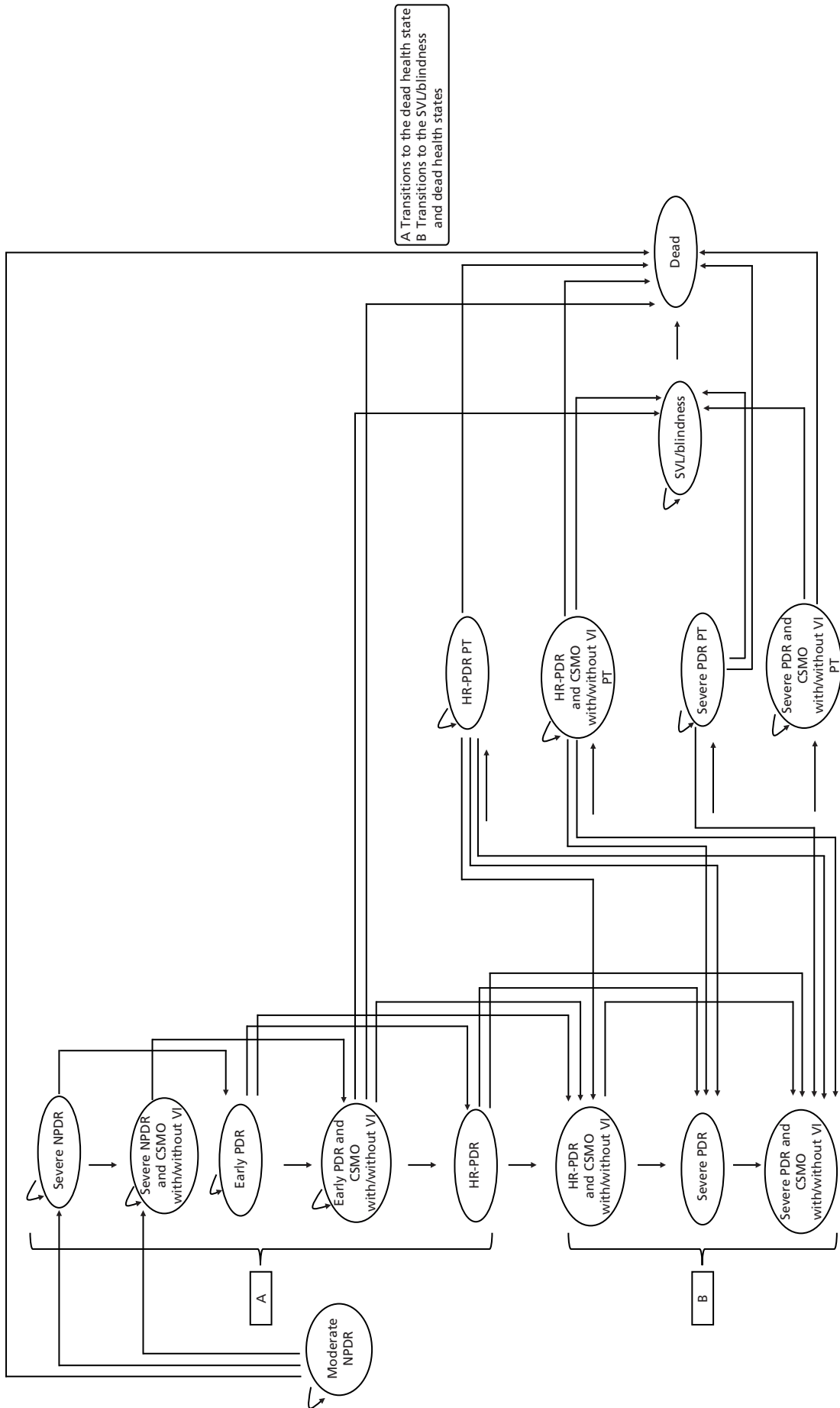
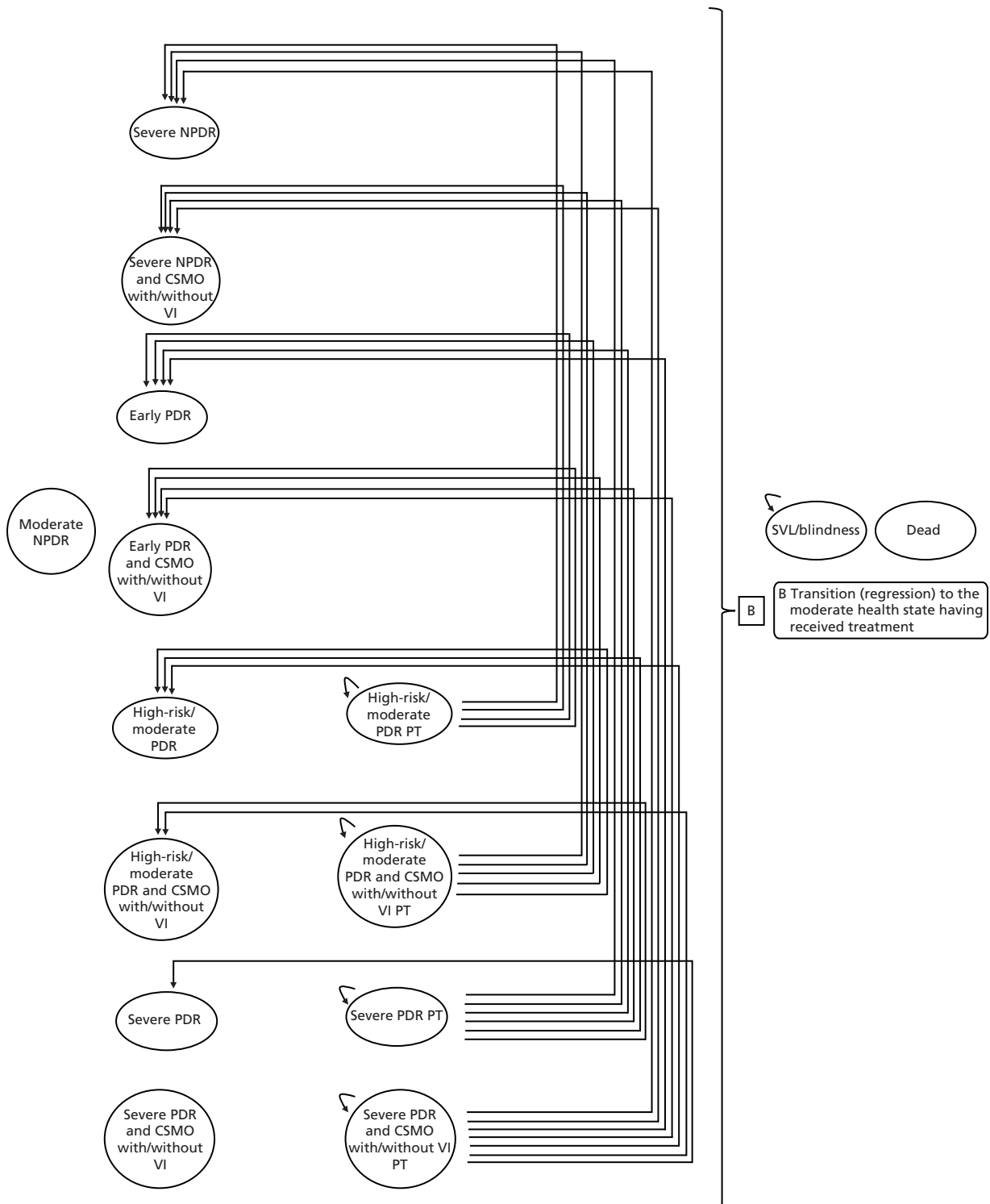**FIGURE 4** Current practice (usual care) progression. PT, post treatment; VI, visual impairment.

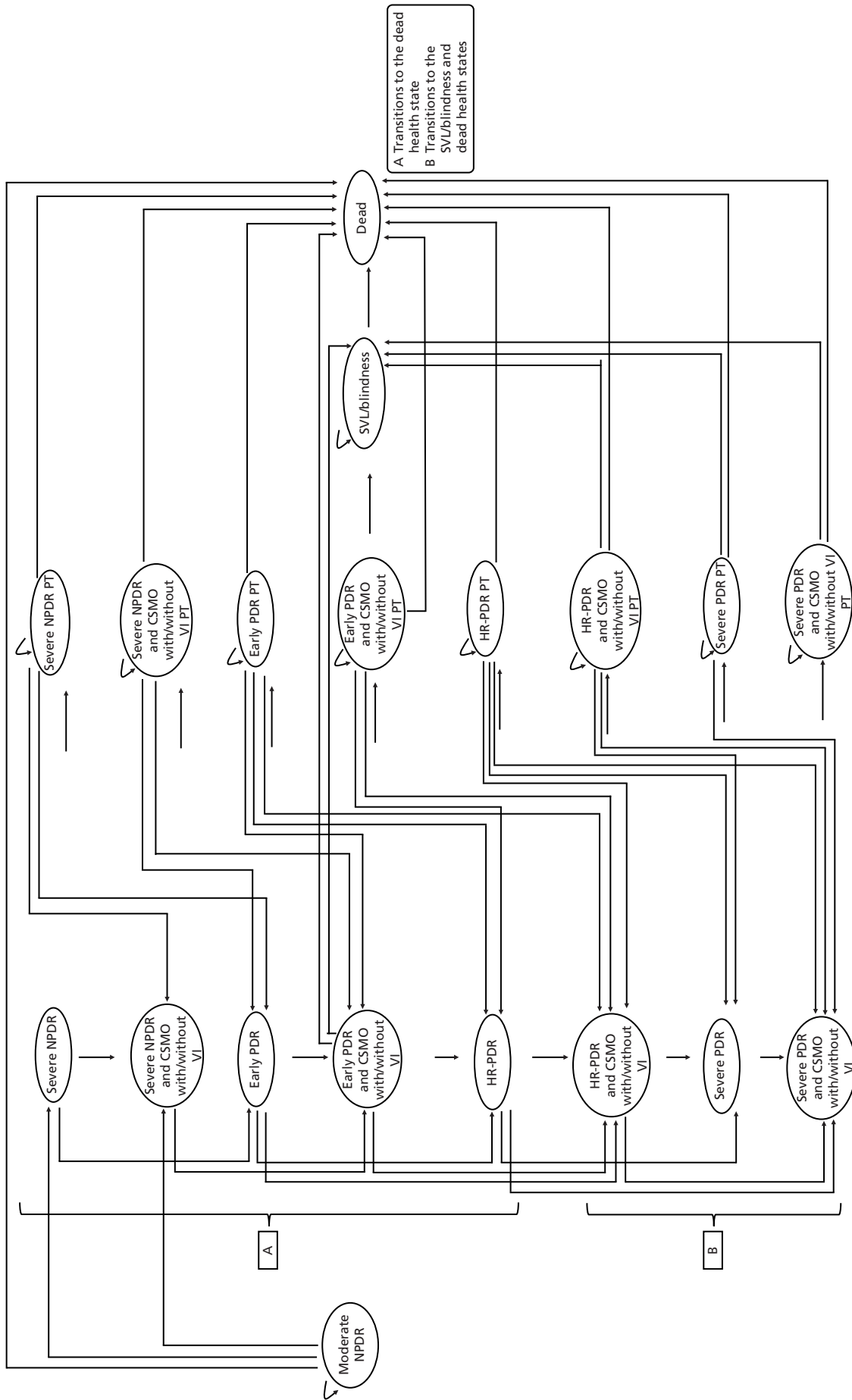**FIGURE 5** Current practice (intervention) regression. PT, post treatment; VI, visual impairment.

FIGURE 6 Early PRP (intervention) progression. PT, post treatment; VI, visual impairment.
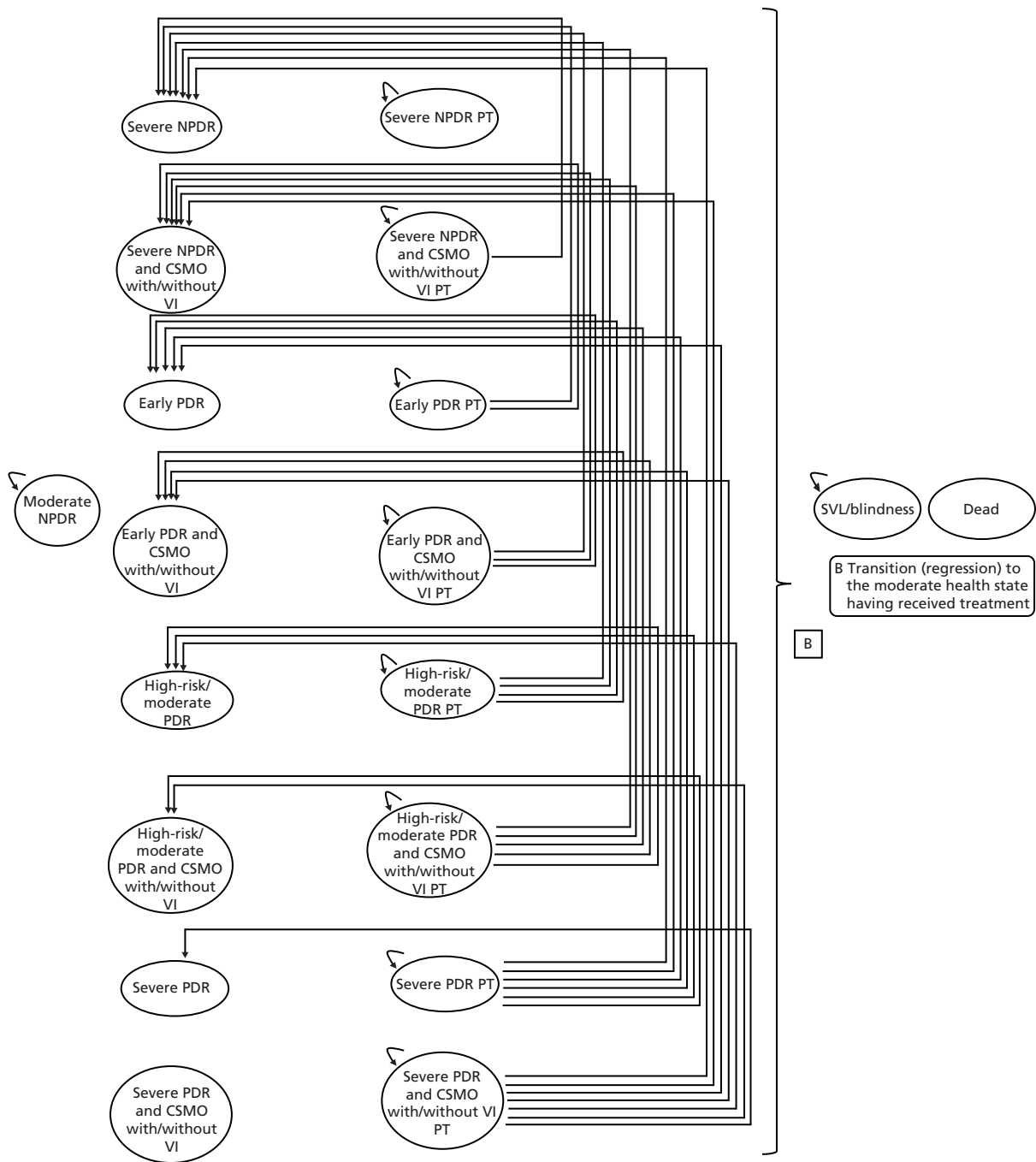
FIGURE 7 Early PRP (usual care) regression. PT, post treatment; VI, visual impairment.

TABLE 35 Health states in the NPDR model

Health state	Post-treatment health state
Moderate NPDR	
Severe NPDR	Severe NPDR PT
Severe NPDR and CSMO with/without VI	Severe NPDR and CSMO with/without VI PT
Early PDR	Early PDR PT
Early PDR and CSMO with/without VI	Early PDR and CSMO with/without VI PT
HR-PDR	HR-PDR PT
HR-PDR and CSMO with/without VI	HR-PDR and CSMO with/without VI PT
Severe PDR	Severe PDR PT
Severe PDR and CSMO with/without VI	Severe PDR and CSMO with/without VI PT
SVL/blindness	
Death	

PT, post treatment; VI, visual impairment.

In the first cycle, patients can either stay in the moderate NPDR health state or progress to either severe NPDR health state or to severe NPDR and CSMO with/without visual impairment health state or die from diabetes-related disease or from other causes. In the intervention arm, those patients in the severe NPDR health state or the severe NPDR and CSMO with/without visual impairment health state, receive treatment and at the end of the cycle they move to the corresponding post-treatment health state.

In the second cycle, patients in the usual care arm can stay in either the moderate or severe NPDR health states or progress to early PDR or early PDR and CSMO with/without visual impairment or die from diabetes-related disease or from other causes. In the next cycle, the patients can stay in either the moderate or severe NPDR or early PDR health states or progress to HR-PDR or HR-PDR and CSMO with/without visual impairment health states or die (note that the patients in the early PDR and CSMO with/without visual impairment can also progress to the SVL/blindness health state because of DMO). When the patient moves to the HR-PDR or HR-PDR and CSMO with/without visual impairment health states, they receive treatment and at the end the cycle they move to the corresponding post-treatment health state. Once the patients enter the post-treatment health states, they can either stay in this health state or progress to one of the more severe health states, regress back to earlier stages of the disease, or die. Patients can stay in the post-treatment health state for more than one cycle.

In the intervention arm, in the second cycle and onwards, patients can stay in the moderate NPDR health state or progress to either severe NPDR or severe NPDR and CSMO with/without visual impairment or die. For those patients who were in the severe NPDR health states in the second cycle, in the third cycle they can progress to early PDR or early PDR and CSMO with/without visual impairment and so forth. When the patients progress to one of these health states (i.e. severe NPDR or early PDR) they will receive treatment and at the end the cycle they move to the corresponding post-treatment health state. For those patients who received treatment in the previous cycle, they start in the post-treatment health state and they can either stay in this health state or progress to one of the more severe health states, regress back to earlier stages of the disease, or die. Patients can stay in the post-treatment health state for more than one cycle.

The cycle length for each model was set to 6 months[5] and transitions between each health state occur at the end of each cycle. The transitions that can be made from each health state for the usual care and intervention arms are highlighted in *Appendix 4*, *Table 49*. A number of assumptions were made in the model:

1. Patients progress through all stages of DR.
2. People can have advanced DR with no symptoms.
3. Treatment can lead to regression back to earlier stages (i.e. to less severe health states having received treatment).
4. Patients cannot regress from the SVL/blindness health state.
5. DMO can occur at most stages of DR.
6. DMO can lead to visual impairment in the absence of PDR.
7. In people with DR and CSMO, the latter is usually treated first.
8. In people with DR and CSMO, treatment might improve one but not the other.
9. PRP might precipitate DMO.
10. Proportion of patients in severe PDR or severe PDR and CSMO with/without visual impairment health states may also develop vitreous haemorrhage or pre-retinal haemorrhage, or both.

Base-case analysis

As DR is a bilateral disease, we have assumed that the model is a two-eye model and that the severity level is the same in each eye. For the base-case analysis, we have adopted a 30-year time horizon. A hypothetical cohort of 1000 diabetic patients with a starting age of 50 years were followed. We adopted a starting age of 50 years for the economic model, as this is the mean age of patients with DR. Treatment of retinopathy is in secondary care. The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS). All costs are in pounds sterling (£) in 2012–13 prices. Health outcomes were measured in QALYs. Results are expressed as incremental cost per QALY gained. An annual discount rate of 3.5% is applied to both costs and outcomes.

Model inputs

Transition probabilities

For the base-case analysis, transition probabilities were based on data derived from ETDRS, as this was the main source of data for the effects of administering PRP at the severe NPDR or early PDR stages (ETDRS did not report results for NPDR and early PDR separately) rather than waiting till HR-PDR develops. *Chapter 6* details the literature used and assumptions made for deriving these transition probabilities and *Tables 32–34* show the transition probabilities that have been used in the base-case analysis.

Utilities

Most of the health-state utility values for DR are based on different VA ranges. Although there are a few studies that have health-state values by the different DR severity levels, for example no retinopathy, background retinopathy, STDR, blindness,[158] background retinopathy, proliferative diabetic retinopathy, MO, severe vision loss/blindness,[159] and no retinopathy, non-STDR, STDR, blindness,[160] they do not provide enough detail for the different DR severity levels we need for the model. The most useful paper was by Ting *et al.* (2007)[157] who developed a Markov model of a novel DR prognostic device for DR progression. They had utility values for the following health states: no DR, microaneurysm, mild NPDR, moderate NPDR, severe NPDR, PDR, maculopathy and blind. The utility values used by Ting *et al.* (2007)[157] were a weighted

average based on two papers: Brown *et al.* (1999)[161] who provided utility values (time-trade off values) for a range of visual acuities associated with DR, and Fong *et al.* (2002)[162] who provided information on the range of VA for different stages of DR and data from the WSE was used. However, we have not used the values from Ting *et al.* (2007)[157] in our model because of two reasons: (1) we could not replicate their results; and (2) the utility values looked suspiciously high, for example a patient with no DR had a utility value of 0.8402 – this was very similar to the utility value for someone who was at a more advanced stage of DR, i.e. severe NPDR (0.8182) and PDR (0.8137).

We have used the same two studies that were used in Ting *et al.* (2007)[157] to estimate the health-state utility values for our economic model: Brown *et al.* (1999)[161] and Fong *et al.* (2002).[162] In addition, for patients with MO, we have used utility values from a study by Smith *et al.* (2008),[163] who estimated utility values for vision loss in a community-based population with type 2 diabetes.

In summary, Fong *et al.* (2002)[162] reported the number (distribution) of people by three VA ranges ($\geq$ 20/40, < 20/40 and > 20/200, $\leq$ 20/200) for the BSE for no/minimal retinopathy, background/mild NPDR, moderate/severe NPDR and PDR. Smith *et al.* (2008)[163] reported the number of people by five VA ranges ($\geq$ 20/20, 20/25 to 20/35, 20/40, 20/50 to 20/70, $\leq$ 20/80) for MO, which we then grouped into the same three VA ranges as Fong *et al.* (2002).[162]

Using the five VA levels from Brown *et al.* (1999)[161] we have linked these to the three VA levels in Fong *et al.* (2002)[162] in order to calculate an overall utility value for that VA group. Then, using the number of patients, we have estimated weighted utility values for the three severity levels: moderate/severe NPDR, PDR and MO. For patients who have MO, a disutility of –0.03 was applied to the utility value for MO obtained from Brown *et al.* (1999).[161] This value was the minimum QALY loss associated with acuity loss of at least 20/30 in one eye and was based on a paper by Rein *et al.* (2011)[164] who estimated the cost-effectiveness of three screening strategies for patients with no or early DR. For patients who move to a retinopathy health state with CSMO, the utility value for that health state was based on an average of the value of that DR health state and MO.

The utility value for severe vision loss/blindness was a weighted average of the two groups in the Brown *et al.* (1999)[161] paper for VA range 20/200 to 20/400 and for counting fingers to hand motion. The utility values for the two arms are shown in the *Table 36*. We have assumed that the pre-treatment utility values are the same as the post-treatment utility values for any health state. The benefits result from a re-distribution amongst health states.

Resource use and costs

Resource-use information for each of the health states was based on information from the RCOphth guidelines[5] and from expert clinical opinion. These eye appointments consist of the examination being conducted using a slit-lamp ophthalmoscope and the appointment will also include VA tests, administering of eye drops, and check of current treatments. *Table 37* shows the number of ophthalmology and monitoring visits for each 6-month cycle.

For patients who receive PRP treatment we have assumed that both eyes will be treated at the same time and PRP treatment will be given over two sessions, to reduce the risk of DMO. Patients who also have DMO will receive focal laser first for both eyes and also an OCT test will also be undertaken. These two treatments have been costed as separate visits.

TABLE 36 Health-state utility values for the NPDR model base-case analysis

Health state	Usual care arm	Intervention arm
Moderate NPDR	0.7915	0.7915
Severe NPDR	0.7915	0.7915
Severe NPDR and CSMO	0.7365	0.7365
Early PDR	0.7047	0.7047
Early PDR and CSMO	0.6930	0.6930
HR-PDR	0.7047	0.7047
HR-PDR and CSMO	0.6930	0.6930
Severe PDR	0.7047	0.7047
Severe PDR and CSMO	0.6930	0.6930
Severe NPDR PT		0.7915
Severe NPDR and CSMO PT		0.7365
Early PDR PT		0.7047
Early PDR and CSMO PT		0.6930
HR-PDR PT	0.7047	0.7047
HR-PDR and CSMO PT	0.6930	0.6930
Severe PDR PT	0.7047	0.7047
Severe PDR and CSMO PT	0.6930	0.6930
SVL/blindness	0.6218	0.6218

PT, post treatment.

TABLE 37 Frequency of ophthalmology and monitoring visits for each 6-month cycle for the base-case analysis

Health state	No. of ophthalmology and monitoring visits
Moderate NPDR	1
Severe NPDR/severe NPDR PT/severe NPDR and CSMO with/without VI/severe NPDR and CSMO with/without VI PT	1
Early PDR/early PDR PT/early PDR and CSMO with/without VI/early PDR and CSMO with/without VI PT	1.5
HR-PDR/HR-PDR PT/HR-PDR and CSMO with/without VI/HR-PDR and CSMO with/without VI PT	2
Severe PDR/severe PDR PT/severe PDR and CSMO with/without VI/severe PDR and CSMO with/without VI PT	2
Severe vision loss/blindness	0.5

PT, post treatment; VI, visual impairment.

For the different items of resource use, the associated unit costs are presented are in pounds sterling (£) in 2012–13 prices. We have used national reference costs where possible for items such as clinic visits, laser treatment, surgery and tests[165] (*Table 38*).

The annual cost of blindness was obtained from a study by Mitchell *et al.* (2012)[166] who looked at the cost-effectiveness of ranibizumab in treatment of DMO causing visual impairment. The annual cost of blindness comprised the following costs incurred by the NHS such as low-vision aids, low-vision rehabilitation (occupational health therapist), community care, depression and hip fracture/replacement, which were outlined in a previous costing study on blindness by Meads *et al.* (2006).[167] The costs were in pounds sterling (£) in 2010 prices and have been inflated to 2012–13 prices using the Hospital and Community Health Services Index.[168]

Complications

Some patients who receive PRP may develop complications. For the model we have assumed that a proportion of people (see below) who receive PRP will develop MO or, less often, vitreous haemorrhage for one cycle only.

Data on precipitation of DMO by PRP was obtained from the ETDRS #9,[9] which found that a third of eyes without MO at baseline who were assigned to early photocoagulation received focal photocoagulation when clinically significant MO developed during the 5-year follow-up.

A proportion of patients in the severe PDR or the severe PDR and CSMO with/without visual impairment may also develop vitreous or pre-retinal haemorrhage after PRP. The Diabetic Retinopathy Vitrectomy Study Report #1[169] found that vitreous haemorrhage occurred frequently in eyes treated for severe PDR or very severe PDR. Over a 2-year follow-up period, 25% of the people had undergone vitrectomy.

We have assumed that in the same cycle that patients receive PRP, they have a chance of developing either DMO or vitreous haemorrhage, and within this same cycle the patient would receive treatment: patients who get MO would get focal laser and many patients who get vitreous haemorrhage receive vitrectomy surgery (some vitreous haemorrhages may resolve). We have added in the appropriate cost and a disutility value of –0.03[164] has been included for that one cycle.

TABLE 38 Unit costs for the NPDR model base-case analysis

Resource use (HRG code)	National average unit cost (lower–upper quartile)	Source
First Ophthalmology clinic visit (WF01B)	£106 (£87 to £124)	NHS reference costs 2012–13[165]
Monitoring clinic visit (WF01A)	£80 (£67 to £89)	
PRP laser (OP BZ22B)	£131 (£69 to £145)	
Focal laser (OP BZ22B)	£131 (£69 to £145)	
OCT (OP BZ23Z)	£117 (£93 to £133)	
Vitrectomy surgery (DC BZ22B)	£989 (£589 to £1304)	
Annual cost of blindness[a]	£1483	Mitchell 2012[166]

HRG, Healthcare Resource Group.
a Excludes residential (home) care.

Mortality

Age-specific mortality rates used in the model were based on the UK general population lifetime tables from the Office for National Statistics (ONS).[170] Using the ONS data, the average probability of death for males and females were combined. As the cohort ages, mortality rates generally increase throughout the time horizon in the model. To reflect the higher mortality rates of people with diabetes than those with no diabetes we have used a weighted average of two all-cause mortality rates, which were based on UK population data to obtain a mortality multiplier: (1) Soedamah-Muthu *et al.* (2006)[171] estimated the all-cause mortality rate in patients with type 1 diabetes compared with a non-diabetic population from the UK general practice research database; and (2) Mulnier *et al.* (2006)[172] estimated the all-cause mortality rate in patients with type 2 diabetes in a large cohort selected from the general practice research database.

In addition, we have also included another mortality multiplier for people with diabetes with advanced retinopathy versus all people with diabetes. These mortality multipliers by severity level were obtained from two further papers:

- Cusick *et al.* (2005)[173] followed up a cohort of type 1 and type 2 diabetic patients from 1980 to 1985 to assess the association between diabetic complications and mortality in the ETDRS. The authors reported hazard ratios for people with moderate NPDR, severe NPDR, mild PDR and moderate/high PDR compared with a reference group of no/mild retinopathy using Cox proportional hazard models. The authors adjusted for age, sex, statistically significant baseline characteristics ($p < 0.05$) and all other diabetic complications and presented separate ratios for type 1 and type 2 diabetic patients. From these results, we calculated an average weighted mortality rates (hazard rates) by severity of DR for type 1 and type 2 diabetes combined. The mortality hazard ratios for people with moderate NPDR, severe NPDR, mild PDR and moderate/high PDR were 1.118, 1.422, 0.992 and 1.705, respectively, compared with diabetics with no/mild retinopathy.
- Klein *et al.* (1999)[174] followed up two groups of patients depending on when their diabetes was diagnosed (younger-onset or older-onset patients) to investigate the association of ocular disease and mortality. The authors reported age and sex adjusted hazard ratios for people with severe visual impairment (loss) compared with a reference group without visual impairment. For the model, we calculated an average weighted mortality hazard ratio of 3.321 for people with SVL.

Measuring cost-effectiveness

Using the Markov model we have calculated for a cohort of patients the expected quality-adjusted survival based on their likelihood of surviving each cycle, their expected health-state utility value, and their expected costs. We have adopted a 30-year time horizon and the starting age for the patient cohort is 50 years. The analysis is conducted from the perspective of the NHS and PSS. Cost-effectiveness was measured in terms of the incremental cost per QALY gained [incremental cost-effectiveness ratio (ICER)]. Discount rates of 3.5% were applied to both costs and outcomes.

We present both deterministic and probabilistic results. For the probabilistic analysis, the gamma distribution was used for costs and the beta distribution was used for utility values.[175] As the values for both costs and utilities used in the model were means or weighted averages an assumption was made for the standard error in order to calculate the alpha and beta values that are required for the probabilistic sensitivity analysis. For example, for utilities the standard error was assumed to be 0.1 of the mean value[176] and for the variation in mean cost, a coefficient of variation of 0.1 of the mean value was used to obtain the standard errors.[177]

To represent the uncertainty in the parameters used in the model and to illustrate sampling uncertainty, we undertook probabilistic sensitivity analyses using 1000 simulations. For the PSA to reflect the amount and pattern of the variation, results were calculated by selecting random values from each distribution. We used a gamma distribution for costs and beta distributions for utilities and transition probabilities. These bootstrapped simulations were plotted along the cost-effectiveness plane. Each point on the cost-effectiveness plane is a simulation from the probabilistic analysis. The cost-effectiveness plot represents the uncertainty surrounding the incremental costs and QALYs for the two arms that are being compared. In addition, these simulations were also used to obtain the cost-effectiveness acceptability curves (CEACs), which illustrate the effect of sampling uncertainty, in which individual model parameters were sampled from the appropriate probability distribution. CEACs were presented using a willingness-to-pay (WTP) threshold from £0 to £50,000.

Scenario and sensitivity analyses

As mentioned earlier for the base-case analysis, two treatment arms were modelled using progression data from the ETDRS studies:

1. *Current practice (usual care)* Patients are observed until they progress to the HR-PDR health state (and onwards) when they receive PRP.
2. *Early PRP (intervention)* Patients receive PRP once they progress to the severe NPDR health state.

Sensitivity analyses were conducted by altering base-case inputs to the model. Several types of scenario and sensitivity analyses were explored. Using ETDRS data for the transition probabilities, the following scenario analyses were conducted, and inputs for the scenario and sensitivity analyses are shown in *Table 39:*

1. *PRP and anti-VEGF drugs for DR (laser and drugs)* This scenario is the same as for the base-case analysis, that is, patients receive PRP for DR and focal laser for DMO. However, the difference is that patients also receive one round of anti-VEGF injections (two injections, one for each eye), in addition to their PRP treatment, in order to prevent or reduce the presence of MO after PRP. We used the cost of ranibizumab for one scenario and for the other scenario the cost of bevacizumab. We also included the cost of administering the drug.

TABLE 39 Inputs for the scenario and sensitivity analyses

Unit costs		
Resource use (HRG code)	National average unit cost (lower–upper quartile)	Source
Anti-VEGF – ranibizumab	£742	BNF[178]
Anti-VEGF – bevacizumab	£50 to £100	NICE[179,180]
Administration of anti-VEGF medications (WF01A)	£80 (£67 to 89)	NHS reference costs 2012–13[165]
Annual cost of blindness – including residential (home) care	£6972	Mitchell 2012[166]
BNF, *British National Formulary*; HRG, Healthcare Resource Group.		

2. *PRP for DR and anti-VEGF drugs for DMO (laser and drugs for DMO)* This scenario is the same as the base-case analysis, the only difference is that instead of patients receiving focal laser they get can now receive anti-VEGF medication for their DMO. We have assumed for those patients receiving anti-VEGF treatment, they have eight injections in the first 6 months (four injections for each eye). For the intervention arm, these patients then move to the corresponding post-treatment health state, where they receive six injections (three injections for each eye) and if they stay in the post-treatment state for each future cycle, they receive two further injections (one in each eye). For the usual care arm, these patients who remain in that health state they receive six injections (three injections for each eye) and if they stay in the same health state for each future cycle, they receive two further injections (one in each eye). For each visit, we have also included the cost of administering the anti-VEGF treatment. We used the cost of ranibizumab for one scenario and for the other scenario the cost of bevacizumab.

3. *For the intervention arm, we have assumed that PRP treatment will start at the severe NPDR stage* Patients with severe NPDR and CSMO have focal laser first. In this sensitivity analysis, we start treatment at the early PDR or early PDR and CSMO.

4. *We have assumed in the base-case analysis that PRP treatment will be administered over two sittings (in total, four laser treatments for the two eyes)* In this sensitivity analysis, we vary this assumption by using one sitting (two laser treatments for two eyes) and four sittings (eight laser treatments for two eyes). We have assumed that the risk of DMO remains the same.

5. *In the base-case analysis, the cost of blindness did not include any residential (home care) costs* In this sensitivity analysis, we add in the cost of residential care to the annual cost of blindness.

6. *In the base-case analysis, we have used Brown et al. (1999)[161] to estimate health-state utilities using the time-trade off method* In this sensitivity analysis we used health-state utility values from Lloyd *et al.* (2008).[181] The authors in this paper used EQ-5D to derive utility values. We know from previous work that generic measures such as the EQ-5D are insensitive to changes that are significant to patients.[182] As mentioned in the previous chapter, one further source of data for DR progression (transition probabilities) is used in this scenario analysis.

7. *In the base-case analysis, PRP was administered over two sittings* In another sensitivity analysis, we have assumed that PRP will be administered in one sitting and one round of anti-VEGF medication will also be administered, as PRP laser may exacerbate DMO.

Results

We present here the cost-effectiveness deterministic and probabilistic results for usual care (current practice) versus intervention (early PRP).

Base-case analysis: cost-effectiveness results

For the base-case analysis we compared the cost-effectiveness of administering PRP treatment to patients with severe NPDR compared with delaying PRP treatment till the HR-PDR stages. Using data from the ETDRS for progression rates, a time horizon of 30 years and with a starting age of 50 years for the patient cohort, *Table 40* shows the deterministic (undiscounted and discounted) and probabilistic (discounted) results.

For all scenarios, the cost for the usual care arm (i.e. delaying treatment till HR-PDR stages) was more costly than the intervention arm, and the mean QALYs were also lower (discounted deterministic results: incremental costs –£1101, incremental QALYs 0.1337). The ICER for usual care was dominated by the intervention; that is, offering PRP treatment to patients with severe NPDR was cheaper and more effective than delaying PRP treatment till the HR-PDR stages.

TABLE 40 Base-case cost-effectiveness results

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic – undiscounted		
Total mean costs	£5426	£3770
Total mean QALYs	10.3879	10.6306
Incremental costs	−£1657	
Incremental QALYs	0.2427	
ICER (cost per QALY gained)	Dominated	
Deterministic – discounted		
Total mean costs	£3853	£2753
Total mean QALYs	7.8236	7.9572
Incremental costs	−£1101	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – discounted		
Total mean costs	£3858	£2746
Total mean QALYs	7.8332	7.9624
Incremental costs	−£1112	
Incremental QALYs	0.1292	
ICER (cost per QALY gained)	Dominated	

Figure 8 shows the cost-effectiveness plane for usual care vs. intervention (early PRP). The graph clearly shows that the cost for intervention arm is much lower than the usual care arm. There is some uncertainty on the effect of early PRP, as the QALYs are scattered over the bottom two quadrants of the cost-effectiveness plane; however, as the majority of these iterations (58%) are in the south-east quadrant of the plane, this makes the intervention slightly more cost-effective. *Figure 9* shows the CEAC, for a WTP threshold from £0 to £50,000 per QALY. If a decision-maker is willing to pay between £20,000 and £30,000 per QALY, early PRP is likely to be 60% more cost-effective than usual care.
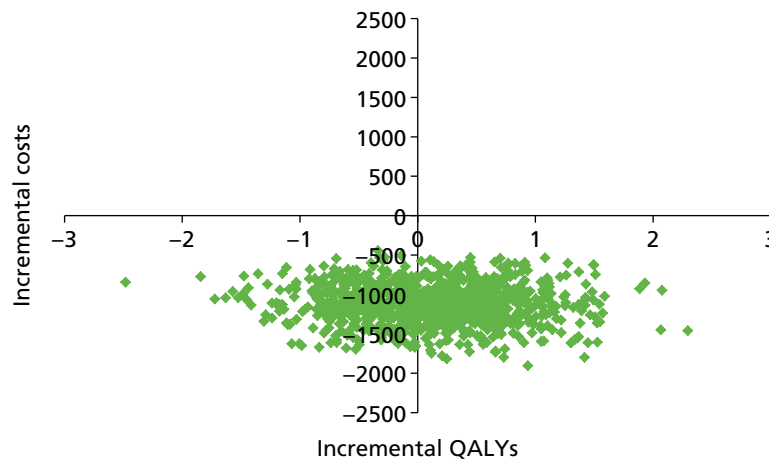

FIGURE 8 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP).
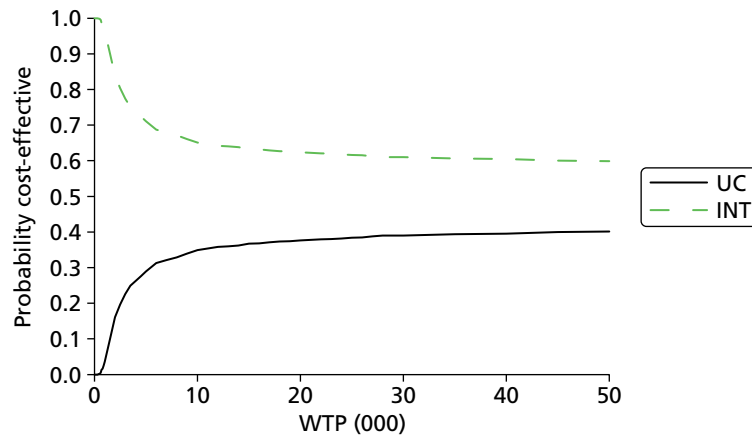
FIGURE 9 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP). INT, intervention; UC, usual care.

Sensitivity analysis: cost-effectiveness results

(a) Pan-retinal photocoagulation and anti-vascular endothelial growth factor drugs for diabetic retinopathy (laser and drugs)

In this scenario, patients also receive one round of anti-VEGF injections (two injections, one for each eye) in addition to PRP treatment for DR (and focal laser for DMO), in order to prevent or reduce the presence of MO after PRP. We have used the cost of ranibizumab for one scenario and for the other scenario we have used the cost of bevacizumab.

Table 41 presents the discounted results for the deterministic and probabilistic analyses.

The results in *Table 41* show that when one round of anti-VEGF medication ranibizumab is given in addition to PRP at an extra cost of £742 for each injection in each eye plus the administration cost, even though the intervention is slightly more effective, it is also slightly more costly. The incremental cost per QALY gained ratio is £1122 (deterministic results). When one round of anti-VEGF medication bevacizumab is given in addition to PRP at an extra cost of £75 for each injection in each eye plus the administration cost, early PRP is still cheaper and more effective than usual care, that is, intervention dominates usual care (in line with the base-case results).

Figure 10 shows the cost-effectiveness plane if ranibizumab is used as the anti-VEGF medication. Although the iterations are split across the four quadrants of the cost-effectiveness plane, the majority of the iterations are in the north-east quadrant (38%), indicating that the intervention is more costly and more effective than usual care. *Figure 11* shows the CEAC for using ranibizumab as the anti-VEGF medication and for a threshold £20,000–30,000, early PRP is approximately 55% more cost-effective than usual care. When bevacizumab is used as the anti-VEGF medication, the iterations fall in the bottom two quadrants (57.5% of iterations are in the south-east quadrant), even though it is cheaper, there is still some uncertainty around its effectiveness (*Figure 12*) and if a decision-maker is willing to pay between £20,000 and £30,000 per QALY, there is a 60% probability that early PRP is more cost-effective than usual care (*Figure 13*), in line with the base-case results.

TABLE 41 Sensitivity analysis cost-effectiveness results: laser and anti-VEGF drugs

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic – ranibizumab		
Total mean costs	£4396	£4546
Total mean QALYs	7.8236	7.9572
Incremental costs	£150	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	£1122	
Probabilistic – ranibizumab		
Total mean costs	£4396	£4538
Total mean QALYs	7.8332	7.9624
Incremental costs	£141	
Incremental QALYs	0.1292	
ICER (cost per QALY gained)	£1094	
Deterministic – bevacizumab		
Total mean costs	£3933	£3016
Total mean QALYs	7.8236	7.9572
Incremental costs	−£917	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – bevacizumab		
Total mean costs	£3931	£3010
Total mean QALYs	7.8242	7.9552
Incremental costs	−£921	
Incremental QALYs	0.1310	
ICER (cost per QALY gained)	Dominated	

FIGURE 10 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for ranibizumab.

FIGURE 11 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for ranibizumab. INT, intervention; UC, usual care.
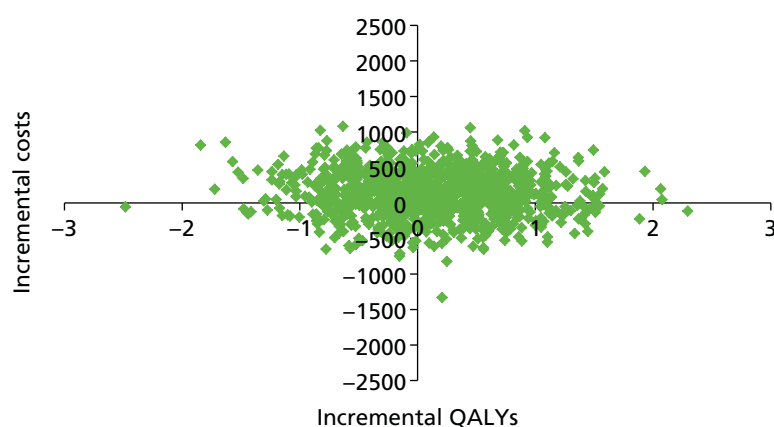

FIGURE 12 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for bevacizumab.
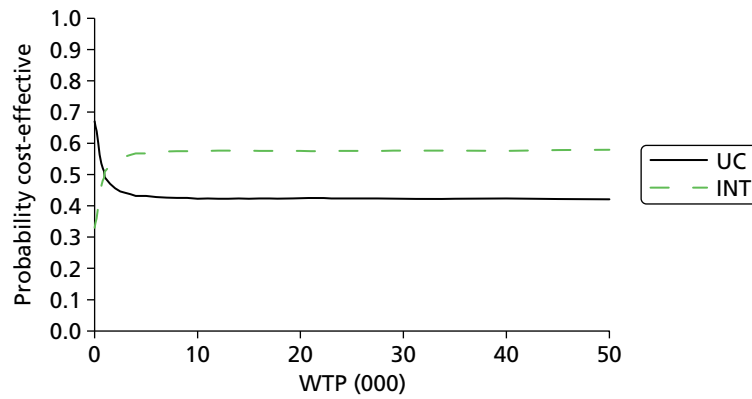

FIGURE 13 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for bevacizumab. INT, intervention; UC, usual care.
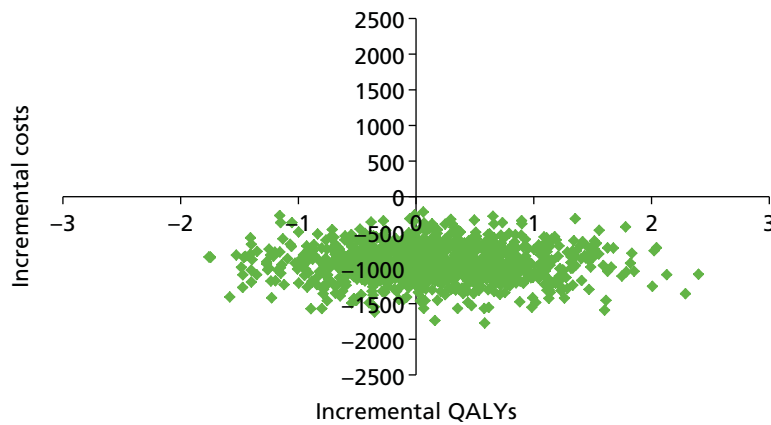
(b) Pan-retinal photocoagulation for diabetic retinopathy and anti-vascular endothelial growth factor drugs for diabetic macular oedema (laser and drugs)

In this scenario, patients also receive PRP for DR and anti-VEGF drugs for DMO instead of focal laser. We have used the cost of ranibizumab for one scenario and for the other scenario we have used the cost of bevacizumab. *Table 42* presents the discounted results for the deterministic and probabilistic analyses and *Figures 14–17* present the cost-effectiveness planes and the CEACs.

The results in *Table 42* show that using anti-VEGF medication (either ranibizumab or bevacizumab) for DMO and PRP for DR, for each scenario, the costs of the intervention arm are lower than with the usual care arm, and also there are more QALYs gained in the intervention arm (early PRP) compared with usual care. That is, early PRP dominates usual care. The corresponding cost-effectiveness planes are shown in *Figures 14* and *16*, where the majority of iterations are in the bottom two quadrants of the plane (approximately 58% of iterations are in the south-east quadrants). If ranibizumab is used to treat

TABLE 42 Sensitivity analysis cost-effectiveness results: laser and drugs for DMO

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic – ranibizumab		
Total mean costs	£22,803	£14,373
Total mean QALYs	7.8236	7.9572
Incremental costs	–£8430	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – ranibizumab		
Total mean costs	£22,843	£14,285
Total mean QALYs	7.8332	7.9624
Incremental costs	–£8558	
Incremental QALYs	0.1292	
ICER (cost per QALY gained)	Dominated	
Deterministic – bevacizumab		
Total mean costs	£5474	£4373
Total mean QALYs	7.8236	7.9572
Incremental costs	–£1101	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – bevacizumab		
Total mean costs	£5462	£4377
Total mean QALYs	7.8242	7.9552
Incremental costs	–£1085	
Incremental QALYs	0.1310	
ICER (cost per QALY gained)	Dominated	

FIGURE 14 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for ranibizumab.

FIGURE 15 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for ranibizumab. INT, intervention; UC, usual care.

FIGURE 16 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for bevacizumab.
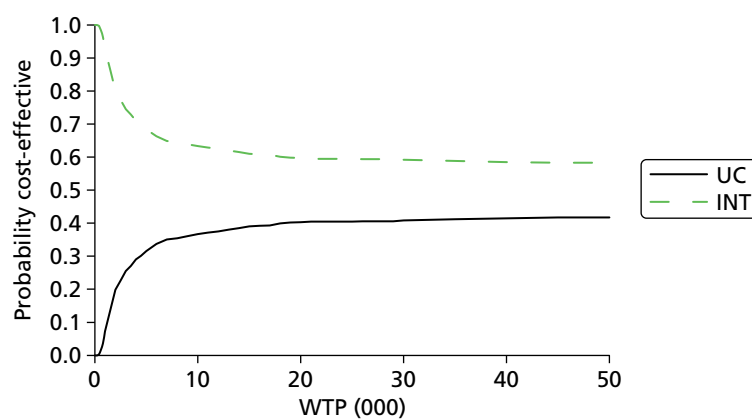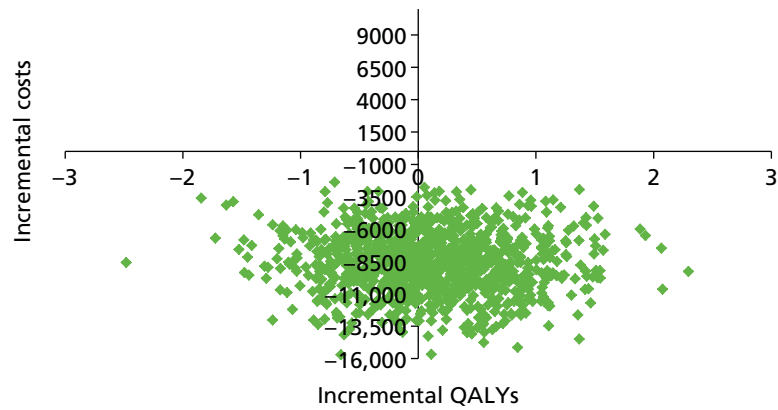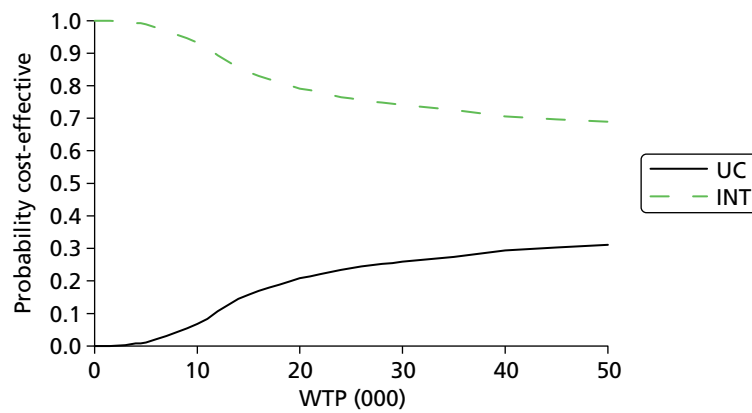
FIGURE 17 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for bevacizumab. INT, intervention; UC, usual care.
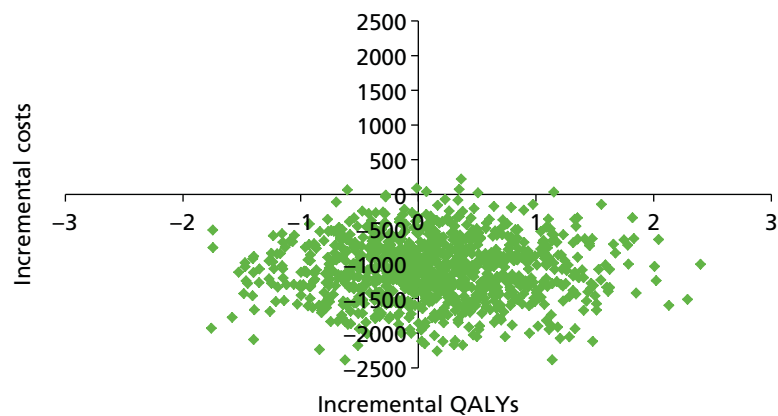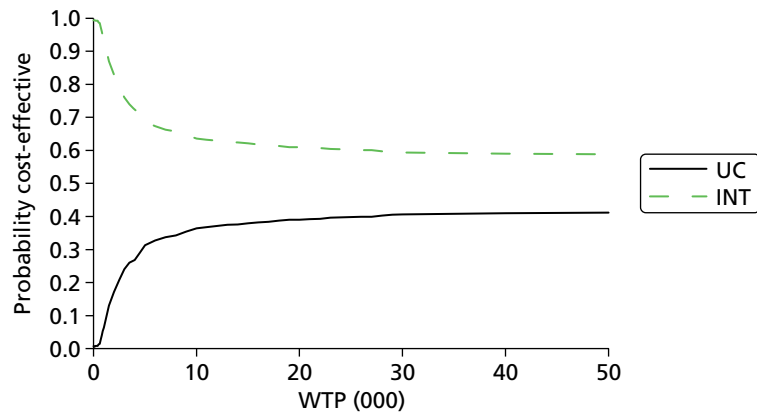
DMO, the corresponding CEAC shows that if the decision-maker is willing to pay £20,000 per QALY, there is nearly an 80% probability that the intervention is more cost-effective, and if they are willing to pay £30,000 per QALY then the probability that intervention is more cost-effective than usual care is 75% (see *Figure 15*). Whereas if bevacizumab is used for DMO, and if a decision-maker is willing to pay between £20,000 and £30,000 per QALY, there is a 60% probability that early PRP is more cost-effective than usual care (see *Figure 17*), which is in line with the base-case results. Note that these results assume multiple injections of anti-VEGF agents to treat DMO, in contrast with single injections to reduce the risk of DMO. So the cost-effectiveness depends on costs of anti-VEGF avoided.

(c) Pan-retinal photocoagulation treatment starts at early proliferative diabetic retinopathy

In this scenario, patients receive PRP for DR at the early PDR or early PDR and CSMO with/without visual impairment stages.

Table 43 presents the discounted results for the deterministic and probabilistic analyses for patients receiving PRP at the early PDR stage. For both scenarios, intervention is only slightly cheaper than usual care by approximately £120; however, the intervention is more effective. Owing to these small differences, the intervention has been found to dominate usual care.

Figure 18 shows the cost-effectiveness plane for usual care versus intervention (early PRP at the early PDR stage). The graph clearly shows the uncertainty as the iterations are scattered across the four quadrants. However, the majority of the iterations are in the south-east quadrant (34.3%), which emphasises the dominance (albeit small) of intervention over usual care. This uncertainty is also shown in the CEAC (*Figure 19*), if the decision-maker is willing to pay between £10,000 and £50,000 per QALY, early PRP at the early PDR stage is likely to be no more cost-effective than usual care.

TABLE 43 Sensitivity analysis cost-effectiveness results: PRP for early PDR

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic		
Total mean costs	£3853	£3725
Total mean QALYs	7.8236	7.8645
Incremental costs	−£128	
Incremental QALYs	0.0409	
ICER (cost per QALY gained)	Dominated	
Probabilistic – ranibizumab		
Total mean costs	£3858	£3738
Total mean QALYs	7.8332	7.8787
Incremental costs	−£120	
Incremental QALYs	0.0454	
ICER (cost per QALY gained)	Dominated	
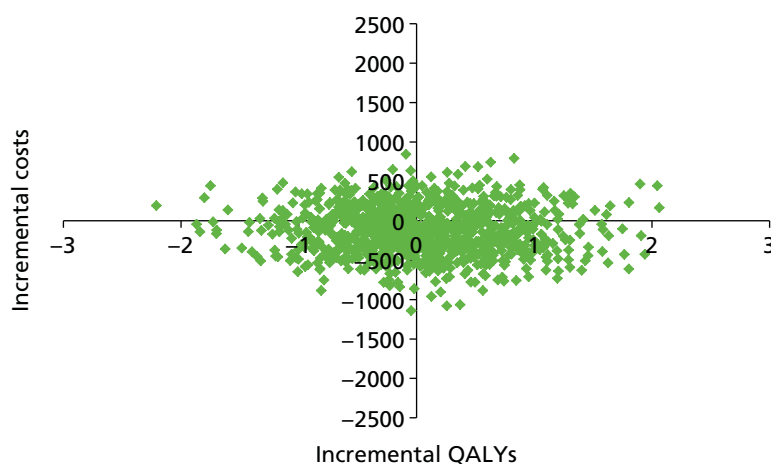
FIGURE 18 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP at early PDR stage).
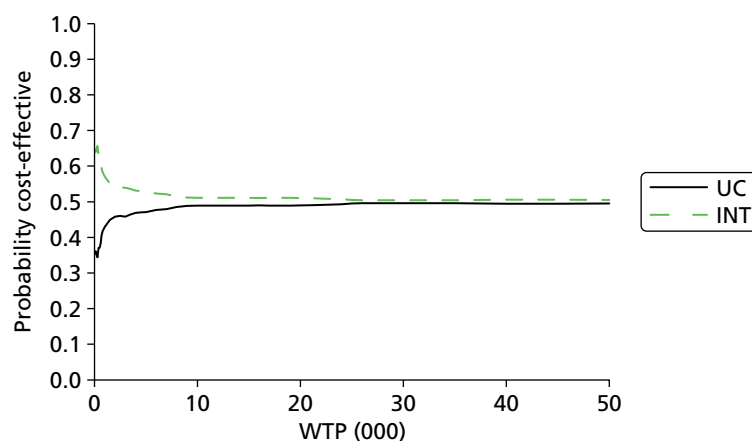
FIGURE 19 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP at early PDR stage). INT, intervention; UC, usual care.

(d) Pan-retinal photocoagulation treatment in one or four sittings

We have assumed in the base-case analysis that PRP treatment will be administered over two sittings (in total, four laser treatments for the two eyes). In this sensitivity analysis, we have varied this assumption by using one sitting (two laser treatments for two eyes) and four sittings (eight laser treatments for two eyes). We have assumed that the risk of DMO remains the same.

Table 44 shows the results when PRP is administered in either one or four sittings. For each scenario, the costs of the intervention arm are lower than the usual care arm and also there are more QALYs gained in the intervention arm (early PRP) than with usual care. That is, the intervention (early PRP) dominates usual care. When PRP is administered over four sittings compared with the one sitting, the difference in incremental costs falls by almost a half. *Figure 20* shows the cost-effectiveness plane if PRP is administered in one sitting and *Figure 21* shows the cost-effectiveness plane if PRP is administered over four sittings. Both graphs show that most the iterations fall in the bottom two quadrants (approximately 55% of iterations are in the south-east quadrants); even though it is cheaper there is still some uncertainty around its effectiveness. If a decision-maker is willing to pay between £20,000 and £30,000 per QALY, then there is a 55–60% probability that the intervention is more cost-effective than usual care (*Figures 22* and *23*), in line with the base-case results.

TABLE 44 Sensitivity analysis cost-effectiveness results: PRP treatment in one or four sittings

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic – one sitting		
Total mean costs	£3762	£2452
Total mean QALYs	7.8236	7.9572
Incremental costs	−£1310	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – one sitting		
Total mean costs	£3765	£2450
Total mean QALYs	7.8431	7.9482
Incremental costs	−£1316	
Incremental QALYs	0.1051	
ICER (cost per QALY gained)	Dominated	
Deterministic – four sittings		
Total mean costs	£4035	£3353
Total mean QALYs	7.8236	7.9572
Incremental costs	−£682	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – four sittings		
Total mean costs	£4026	£3346
Total mean QALYs	7.8416	7.9519
Incremental costs	−£680	
Incremental QALYs	0.1103	
ICER (cost per QALY gained)	Dominated	

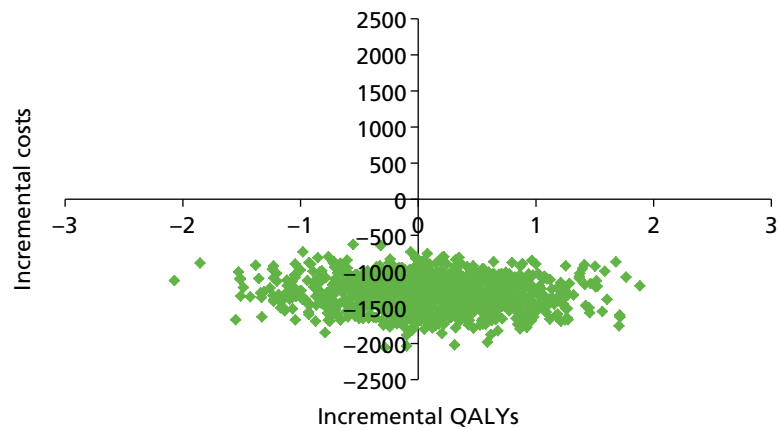**FIGURE 20** Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) – one sitting for PRP.
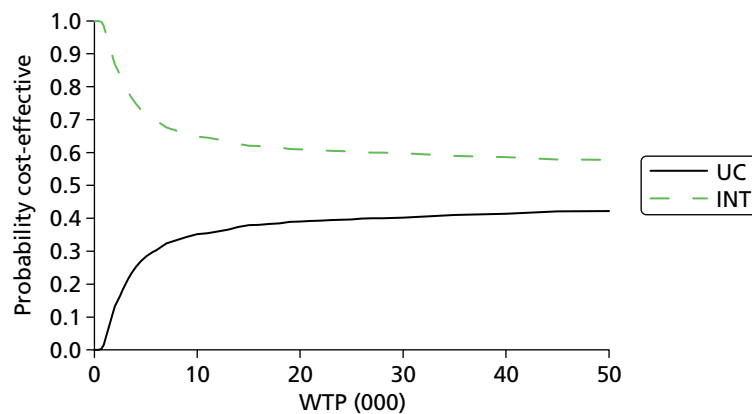

FIGURE 21 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) – four sittings for PRP. INT, intervention; UC, usual care.
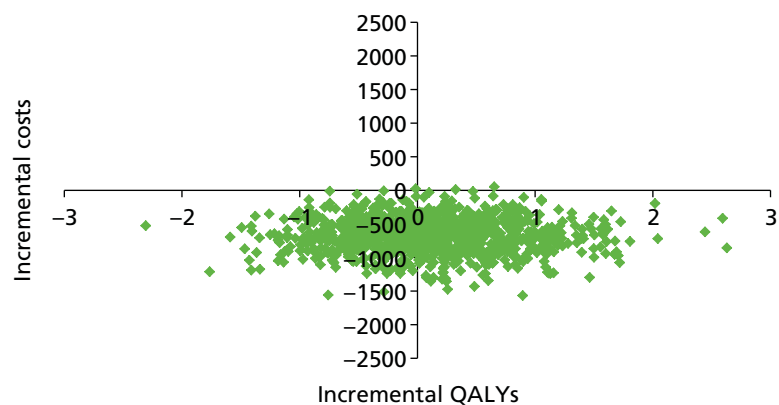

FIGURE 22 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) – one sitting for PRP.
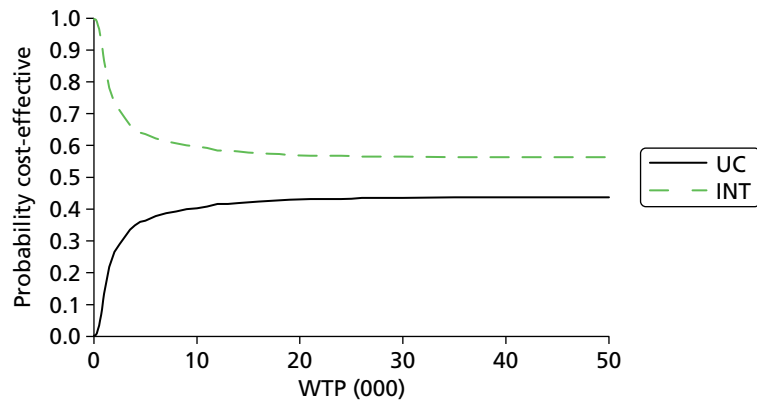
FIGURE 23 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) – four sittings for PRP. INT, intervention; UC, usual care.

(e) Including residential (home care) costs into the annual cost of blindness

In the base-case analysis, the cost of blindness did not include any residential (home care) costs. In this sensitivity analysis, we add in the cost of residential care to the annual cost of blindness.

Table 45 presents the discounted results for the deterministic and probabilistic analyses for usual care versus intervention inclusive of the residential care costs in the annual cost of blindness. For both scenarios, intervention is cheaper than usual care and is more effective. That is, the intervention (early PRP) dominates usual care. *Figure 24* shows the cost-effectiveness plane and the graph clearly shows that the intervention is cheaper; however, there is uncertainty in the effectiveness, as the iterations are scattered across the bottom two quadrants [the majority of the iterations are in the south-east quadrant (54.8%)]. This uncertainty is also shown in the CEAC (*Figure 25*), if the decision-maker is willing to pay £10,000 per QALY then there is a 66% probability that the intervention is more cost-effective than usual care; however, the cost-effectiveness falls slightly if the decision-maker has a higher threshold (at £30,000 per QALY the intervention is 58% more cost-effective).

TABLE 45 Sensitivity analysis cost-effectiveness results: annual cost of blindness inclusive of residential care costs

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic		
Total mean costs	£4951	£3135
Total mean QALYs	7.8236	7.9572
Incremental costs	–£1816	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic		
Total mean costs	£4942	£3134
Total mean QALYs	7.8386	7.9396
Incremental costs	–£1.808	
Incremental QALYs	0.1010	
ICER (cost per QALY gained)	Dominated	
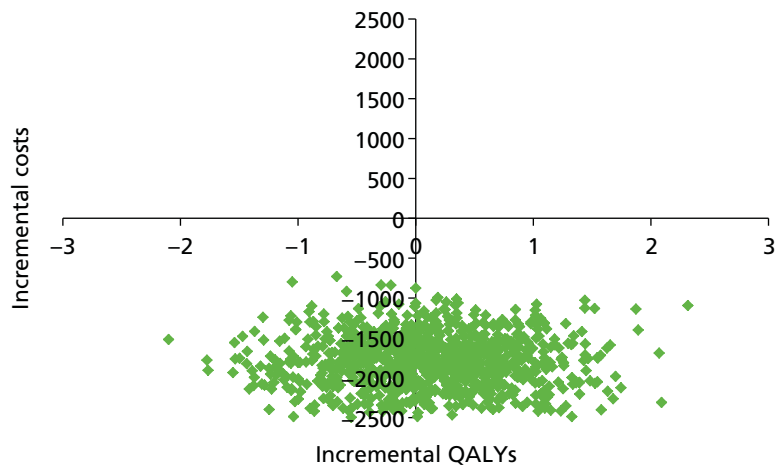
FIGURE 24 Cost-effectiveness plane: usual care (current practice) vs. intervention (annual cost of blindness inclusive of residential care costs).
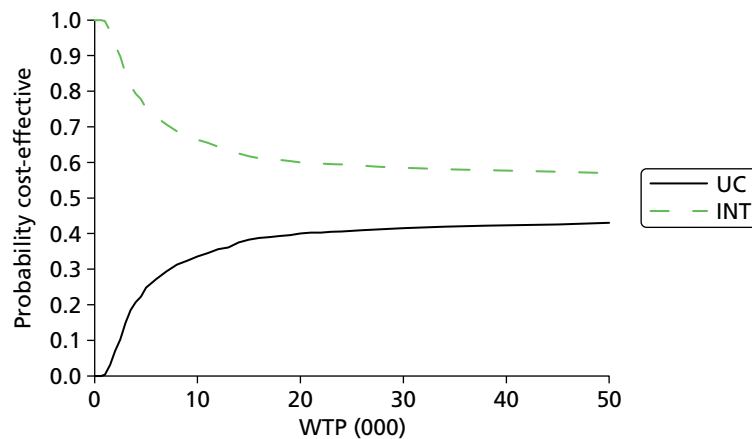
FIGURE 25 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (annual cost of blindness inclusive of residential care costs). INT, intervention; UC, usual care.

(f) Using health-state utilities from Lloyd *et al.* (2008)

In the base-case analysis, we have used utilities from Brown *et al.* (1999)[161] to estimate health-state utilities using the time-trade off method. In this sensitivity analysis we have used health-state utility values from Lloyd *et al.* (2008).[181]

Table 46 presents the discounted results for the deterministic and probabilistic analyses for usual care versus intervention when using health-state utility values from Lloyd *et al.* (2008).[181] For both scenarios, intervention is cheaper than usual care and is more effective. That is, the intervention (early PRP) dominates usual care. The utility values for both arms are approximately 1.3 QALYs lower than the base-case analysis. *Figure 26* shows the cost-effectiveness plane and the graph clearly shows that the intervention is cheaper; however, there is uncertainty in the effectiveness as the iterations are scattered across the bottom two quadrants [the majority of the iterations are in the south-east quadrant (58.9%)].

If a decision-maker is willing to pay between £20,000 and £30,000 per QALY, then the probability is around 60% that the intervention is more cost-effective than usual care (*Figure 27*; see also *Figure 23*), in line with the base-case results.

TABLE 46 Sensitivity analysis cost-effectiveness results: using health-state utilities from Lloyd et al. (2008)[181]

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic		
Total mean costs	£3853	£2753
Total mean QALYs	6.4845	6.6040
Incremental costs	−£1101	
Incremental QALYs	0.1195	
ICER (cost per QALY gained)	Dominated	
Probabilistic		
Total mean costs	£3851	£2749
Total mean QALYs	6.4925	6.6144
Incremental costs	−£1102	
Incremental QALYs	0.1220	
ICER (cost per QALY gained)	Dominated	

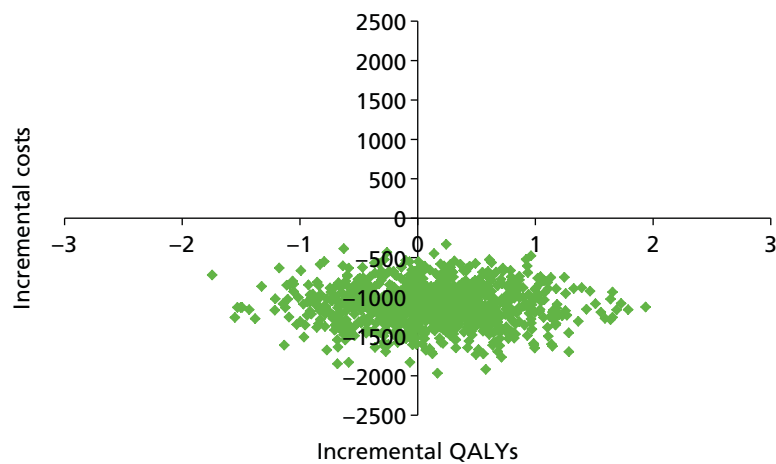FIGURE 26 Cost-effectiveness plane: usual care (current practice) vs. intervention (using health-state utilities from Lloyd et al. 2008[181]).
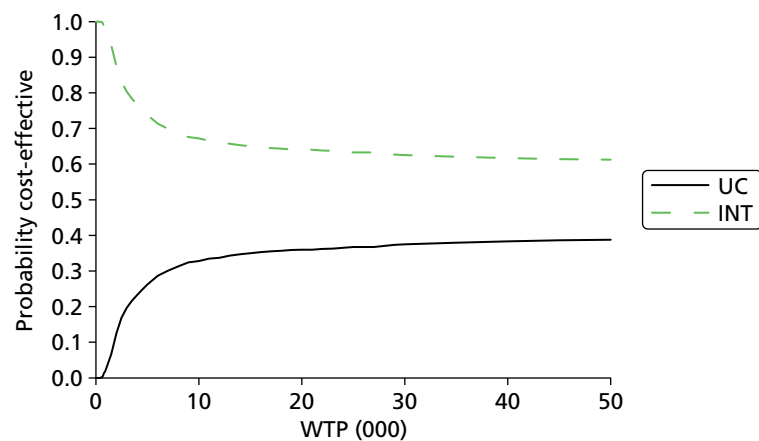
FIGURE 27 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (using health-state utilities from Lloyd et al. 2008[181]). INT, intervention; UC, usual care.

(g) Pan-retinal photocoagulation treatment in one sitting plus anti-vascular endothelial growth factor drugs

In this scenario, patients have PRP administered in just one sitting. To reduce or prevent the presence of MO after PRP, one round of anti-VEGF medication (two injections, one for each eye) will also be administered. We have used the cost of ranibizumab for one scenario and for the other scenario the cost of bevacizumab has been used. *Table 47* presents the discounted results for the deterministic and probabilistic analyses.

Table 47 shows that when PRP is administered in one sitting in addition to one round of anti-VEGF ranibizumab or bevacizumab, early PRP is still cheaper and more effective than usual care, that is, intervention dominates usual care (in line with the base-case results). There was a greater cost difference between the two arms when bevacizumab was used.

TABLE 47 Sensitivity analysis cost-effectiveness results: PRP laser treatment in one sitting plus one round of anti-VEGF medication

Costs and QALYs	Usual care (current practice)	Intervention (early PRP)
Deterministic – ranibizumab		
Total mean costs	£4305	£4245
Total mean QALYs	7.8236	7.9572
Incremental costs	−£60	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – ranibizumab		
Total mean costs	£4294	£4237
Total mean QALYs	7.8370	7.9674
Incremental costs	−£57	
Incremental QALYs	0.1304	
ICER (cost per QALY gained)	Dominated	
Deterministic – bevacizumab		
Total mean costs	£3842	£2716
Total mean QALYs	7.8236	7.9572
Incremental costs	−£1126	
Incremental QALYs	0.1337	
ICER (cost per QALY gained)	Dominated	
Probabilistic – bevacizumab		
Total mean costs	£3840	£2712
Total mean QALYs	7.8206	7.9626
Incremental costs	−£1128	
Incremental QALYs	0.1420	
ICER (cost per QALY gained)	Dominated	

Figure 28 shows the cost-effectiveness plane if ranibizumab is used as the anti-VEGF medication and PRP is administered in one sitting. Although the iterations are split across the four quadrants of the cost-effectiveness plane, the majority of the iterations are in the south-east quadrant (34%), indicating that the intervention is cheaper and more effective than usual care. *Figure 29* shows the CEAC for using ranibizumab as the anti-VEGF medication and when PRP is administered in one sitting, and for a threshold of £0–50,000, there is a 60% probability that early PRP is more cost-effective than usual care. When bevacizumab is used as the anti-VEGF medication, the iterations fall in the bottom two quadrants (58.3% of iterations are in the south-east quadrant) (*Figure 30*), and if a decision-maker is willing to pay between £20,000 and £30,000 per QALY there is again a 60% probability that early PRP is more cost-effective than usual care (*Figure 31*), in line with the base-case results.

Finally, we conducted some sensitivity analyses around the assumption that people with DMO and NPDR are at a greater risk of developing more severe retinopathy than people with NPDR alone. Owing to the lack of information, we assumed that the progression rate is twice that of people with severe NPDR alone developing more severe retinopathy (see *Chapter 6*). In the sensitivity analyses we varied this assumption by using values of 0.5, 1, 3 and 4, but we found that intervention (early PRP) still dominated usual care by being cheaper and more effective.

FIGURE 28 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for PRP in one sitting and one round of ranibizumab.
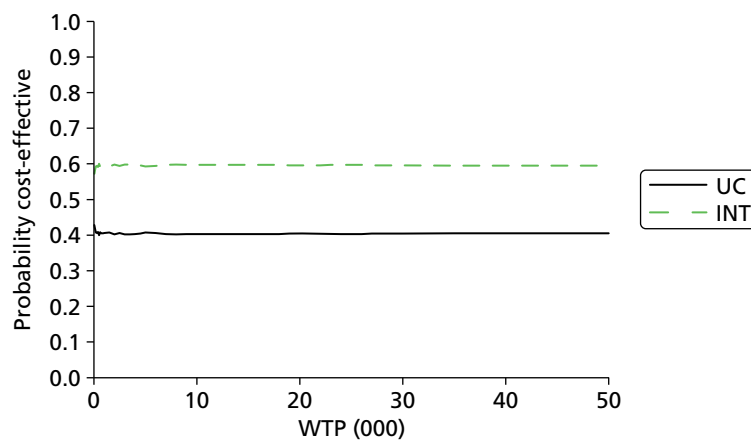
FIGURE 29 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for PRP in one sitting and one round of ranibizumab. INT, intervention; UC, usual care.
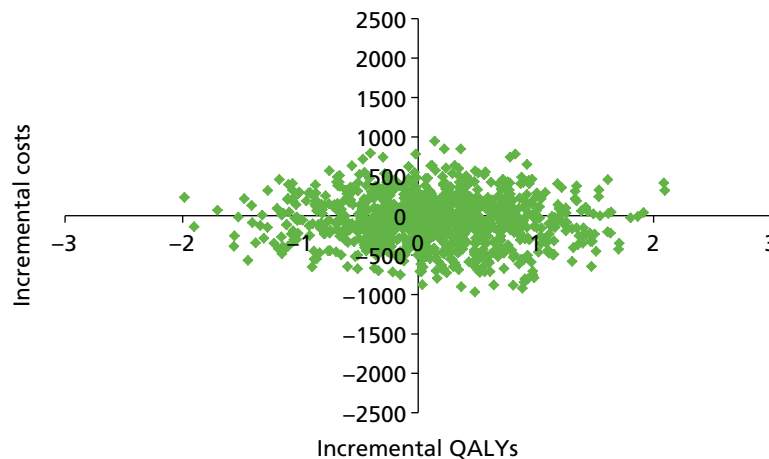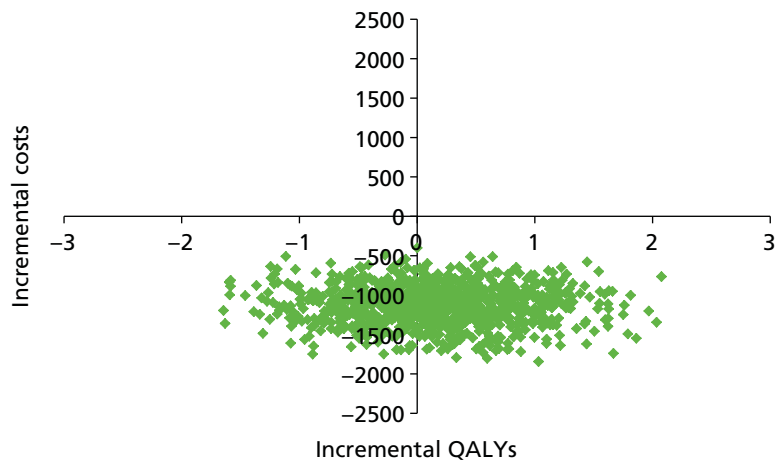
FIGURE 30 Cost-effectiveness plane: usual care (current practice) vs. intervention (early PRP) for PRP in one sitting and one round of bevacizumab.
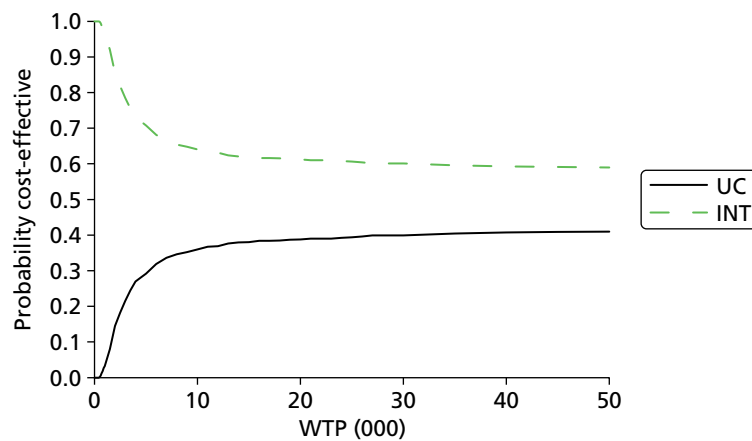
FIGURE 31 Cost-effectiveness acceptability curve: usual care (current practice) vs. intervention (early PRP) for PRP in one sitting and one round of bevacizumab. INT, intervention; UC, usual care.

Discussion

We have built a Markov (state-transition) model to assess the cost-effectiveness of observing patients until they progress to HR-PDR states where they receive PRP (usual care) versus patients receiving PRP treatment once they progress to the severe NPDR health states (intervention).

For the base-case analysis, we have adopted a 30-year time horizon. A hypothetical cohort of 1000 diabetic patients with a starting age of 50 years were followed. The cycle length for each model was set to 6 months, and transitions between each health state occur at the end of cycle. The analysis was conducted from the perspective of the NHS and PSS. The main source of data for the transition probabilities was the ETDRS studies.[9] Information on mortality rates for patients with diabetes and complications associated with PRP were obtained from the literature. Health-state utilities data were obtained from peer-reviewed published studies for DR and health outcomes were measured in QALYs. The majority of unit costs were obtained from the NHS reference costs database.[165] All costs are in pounds sterling (£) in 2012–13 prices. Results are expressed as incremental cost per QALY gained. An annual discount rate of 3.5% was applied to both costs and QALYs. We ran the model deterministically and probabilistically with 1000 iterations. We undertook various sensitivity analyses. These bootstrapped iterations were plotted onto cost-effectiveness planes and they were also used to calculate the CEACs. The CEACs were presented using a WTP threshold from £0 to £50,000.

Methods and summary of findings

For the base-case analysis, offering PRP treatment to patients with severe NPDR compared with delaying PRP treatment till the HR-PDR stages was cheaper and more effective, that is, the intervention was dominant. Treating earlier with PRP laser, at a cost of £131 per eye, meant that fewer people in the intervention arm than in the usual care arm progressed to more advanced stages of DR. Delaying treatment for patients in the usual care arm meant that more of them progressed to the higher stages of DR such as severe PDR health states including the severe vision loss/blindness state as compared with the intervention arm.

The annual cost of blindness excluding residential care cost was £1483, which partly explains the higher costs associated with the usual care arm than the intervention arm. Evidence from the cost-effectiveness plane showed that although costs were lower for the intervention arm, there was uncertainty in the effectiveness arm; as the majority of these iterations were in the south-east quadrant of the cost-effectiveness plane, this made the intervention slightly more cost-effective. The CEAC plane indicated that if a decision-maker is willing to pay £20,000–30,000 per QALY then treating earlier at the severe NPDR stage was more cost-effective than usual care (delaying treatment till HR-PDR stages).

A number of sensitivity analyses were undertaken to determine the cost-effectiveness of various options; the majority of results were in line with the base-case analyses. For example, assuming that the effectiveness remained the same, when adding the cost of one round of anti-VEGF injections (two injections, one for each eye) in addition to PRP treatment for patients with DR, when using bevacizumab at a cost of £75 per eye (plus administration costs), intervention dominated usual care. When ranibizumab was used as the anti-VEGF injection at a cost of £742 per eye (plus administration costs), even though it was effective, it was also more expensive. This additional cost of treating earlier is clearly shown in the increase in costs. This uncertainty was also highlighted in the cost-effectiveness plane, where the bootstrapped iterations moved up along the vertical axis (incremental cost axis). However, for both anti-VEGF medications, the CEACs showed that the intervention was slightly more cost-effective than usual care.

In another sensitivity analysis instead of patients receiving focal laser for their DMO, they received anti-VEGF medication (in total, patients would receive seven injections for each eye (14 injections in total) in their first year plus the administration costs), in line with the base-case results intervention dominated usual care. The main cost driver here was cost of the anti-VEGF drug; if ranibizumab was used the cost difference between the two arms was over £8000, this cost difference between the two arms falls to £1000 if bevacizumab was used. The CEACs showed that if a decision-maker was willing to pay £20,000 per QALY, there is an 80% probability that the intervention was more cost-effective than usual care if ranibizumab was used, whereas if bevacizumab was used the probability falls to 60% (see *Figures 15* and *17*).

In the base-case analysis we had assumed that PRP was administered over two sittings (four laser treatments for two eyes), we varied this assumption in the sensitivity analysis, where we had assumed that the risk of DMO remained the same and PRP was administered over one (two laser treatments for two eyes) or four sittings (eight laser treatments for two eyes); again, the results were in line with the base-case analysis, that is, intervention dominated care. When the cost of residential care (at a cost of approximately £5000) was added to the annual cost of blindness, assuming that the effectiveness remained the same, the cost difference between the two arms increased approximately by £700 as compared with the base-case analysis. However, the results were still in line with base-case analysis, as the intervention still dominated usual care.

When we assumed that patients would receive PRP treatment in the intervention arm in the early PDR stages as opposed to the severe NPDR stages (base-case analysis), the intervention was found to dominate usual care. Looking at this in more detail, the differences between the two arms was negligible – costs were approximately £100 lower in the intervention arm and there was a QALY gain of around 0.04 more QALYs in the intervention arm. The bootstrapped iterations were scattered across all four quadrants in the

cost-effectiveness plane and the CEAC found that treating at the early PDR stage is likely to dominate usual care. One reason for this may be due to the data that we used for the progression rates, as the ETDRS did not report results separately for NPDR and early PDR.

In the final sensitivity analysis we used health-state utilities from the Lloyd *et al.* (2008)[181] paper, as opposed to the Brown *et al.* (1999)[161] paper. The utility values in the base-case analysis were based on patients with DR elicited using the time-trade off method.[161] In the sensitivity analysis, utilities were elicited from patients with DR using the EQ-5D measure.[181] The EQ-5D measure is the preferred measure by NICE when eliciting utility values.[183] However, we know from previous work that generic measures such as the EQ-5D are insensitive to changes that are significant to patients in vision-related studies;[182] in addition to the EQ-5D, vision-related measures such as the NEI VFQ-25[139] and the Vision and Quality of Life (VisQoL) questionnaires[184,185] could be included in studies/trials to measure utilities. This may partly explain why the utility values in the paper that used EQ-5D[181] were a lot lower than those in the paper that used the time-trade off measure.[161] However, the overall direction and magnitude of results in the sensitivity analysis remained the same as the base-case analysis, and intervention dominated usual care.

Strengths and limitations
Although we undertook a thorough search for cost-effectiveness studies of the use of PRP and/or anti-VEGF medication for patients with moderate or severe NPDR or early PDR we could not identify any economic evaluations or modelling-based studies (see *Chapter 5*). The Markov model built here is novel, as it considers using PRP treatment at an earlier stage of DR as opposed to current practice (treat when a patient reaches HR-PDR stage). The model also contains more detailed health states differentiated by the different severity levels for DR than previous studies, which have focused on screening for DR and not necessarily PRP treatment for DR.[60,158,159] The model also considers using PRP laser in combination with anti-VEGF medication.

However, the model does have a number of limitations:

- Firstly, we populated the model with progression data mainly from the ETDRS trial.[9] Although this information from the ETDRS was useful, it is now dated – patients in the ETDRS had poorer glycaemic control, and the treatment of diabetes and laser treatment since the ETDRS studies were published have been greatly improved. More recent studies have since been conducted, but no trial has addressed the timing questions.
- Secondly, in the sensitivity analyses where the treatment for retinopathy was with the use of PRP laser and/or anti-VEGF treatment, we have assumed that the treatment effect, in terms of progressing to more severe retinopathy was the same as PRP treatment alone, as the effect of the anti-VEGF drugs is temporary, and we have found no evidence that their temporary effect increase the effect of PRP.
- Thirdly, in the model, we have assumed that patients can develop adverse events, the most important of which is MO, as a result of receiving PRP treatment for DR. We obtained these proportions based on information on from the ETDRS.[9] Although these studies are useful, these complication rates may not be accurate because laser treatment since then has improved (see *Chapter 3*). Owing to these changes, we expect that the rate of adverse events from PRP treatment would have decreased over time; although we believe that this would not have an overall impact on the magnitude and direction of cost-effectiveness ratio. Another side effect of PRP laser is pain; however, costs of pain treatment such as using a simple analgesia (e.g. paracetamol) are negligible and are unlikely to have a significant impact on the cost-effectiveness ratio. Also, in terms of complications, in the economic model we have not taken into account any adverse events due to focal laser or any adverse effects of anti-VEGF treatment. We know that there are few side effects from anti-VEGF treatment (see *Chapter 4*) and, again, this would not have any significant impact on the magnitude and direction of cost-effectiveness ratio.
- Fourthly, in the model we have assumed that the costs of PRP laser and focal laser are the same, and these unit costs were obtained from the NHS reference costs database.[165] However, although the reference costs may be the same, PRP takes much longer to do than focal or grid photocoagulation, and more sessions are required – focal/grid can be done in one session. To get a more accurate picture

of these costs it would have been better to have carried out 'bottom-up costing' and then analyses with different types of laser (i.e. multi-spot, argon) and their associated costs, including local anaesthetics for multi-spot. We believe having more accurate costs for the different types of laser will not alter the magnitude and direction of the ICER. For the anti-VEGF treatment we obtained costs for bevacizumab from NICE[179] for two NHS hospital trusts and for ranibizumab from the *British National Formulary*.[178] The cost differential between the two anti-VEGF treatments was about £650. Even though we used ranibizumab at the current list price, in the economic model the intervention (early PRP) was cost-effective compared with usual care (current practice); however, if we were to use the discounted price (which is confidential), the intervention should become even more cost-effective.

- Fifthly, in terms of utility estimates that we have used in the economic model, the literature search conducted in *Chapter 5* did not identify any studies with health-state utility values by the detailed severity levels that we have in our economic model. We used the studies by Fong *et al.* (2002)[162] and Smith *et al.* (2008)[163] to characterise the different VA levels into health states. Using this information we were then able to link these health states levels to the health-state utilities values for patients with DR as reported in the Brown *et al.* (1999)[161] paper. There were some drawbacks with this method, as the Fong *et al.* (2002)[162] paper reported only two diabetic severity levels that were applicable to our model: moderate/severe NPDR and PDR; hence, in our model we have the same utility value for a patient with early PDR as someone who has severe PDR. Likewise, Smith *et al.* (2008)[163] reported only MO; we did not have any information on whether this was clinically significant or not, and whether there was any visual impairment.
- We also applied a utility decrement of 0.03 to patients who move to a state with CSMO. This may be a conservative assumption based on data from a previous screening study for DR.[164] However, our literature review conducted in *Chapter 5* did not highlight any further data on disutilities associated with progressing through all the different stages of DR.
- Sixthly, we did not include in the model the impact on patients of losing the ability to drive.
- Seventhly, we did not include an analysis of systemic treatment aimed at improving glycaemic and BP control. A patient with an HbA_{1c} of 10%, a BP of 150/100 mmHg and renal problems is at much higher risk of progression to visual loss than one who achieves excellent metabolic and BP control.
- Finally, in the economic model we have not differentiated by gender or whether the patient had type 1 or type 2 diabetes owing to the insufficient information, such as progression rates and utility values, which we had available for the model. Although, some subgroup analyses could be done using some of the available literature, there is not enough evidence on the use of early PRP treatment in these patients and this will provide even further uncertainty to the cost-effectiveness estimates.

Other potential issues that may affect the cost-effectiveness

In the modelling, we do not include corticosteroid injections (steroids). The rationale for this is that we would want to include only short-acting ones with the aim of reducing the risk of post-PRP. No one is going to use long-acting steroids in this situation. So that means that the steroids licensed for DMO – long-acting dexamethasone and fluocinolone – would not be considered. That leaves only triamcinolone, and we should note that the preservative-free form of that used in the DRCRN trials, Trivaris, is no longer in production. It was made by Allergan who also make Ozurdex. So we are left with Kenalog. That is not licensed for use in the eye. It was designed for use in joints, but was widely used for eye conditions before the anti-VEGFs arrived.

However in *Chapter 4*, we report more adverse effects with triamcinolone (raised IOP) than with the anti-VEGFs. Its other advantages over the anti-VEGFs might be that is much less expensive than ranibizumab and aflibercept, though not than bevacizumab, that it lasts longer (3–4 months or more) and so requires fewer injections, and that in DMO it may work in patients in whom an anti-VEGF has failed. The anti-VEGFs are a considerable advance in DMO but they produce good results (gain of 10 or more letters) in only around half of eyes. So there may still be an occasional place for triamcinolone in the UK and we have retained the triamcinolone trials in *Chapter 4*. It is also worth noting that in many countries, the licensed anti-VEGFs are unlikely to be affordable.

The factors that would determine the cost-effectiveness of adjuvant anti-VEGF treatment include:

1. The frequency of development of CSMO after PRP. This appears to be less frequent with modern 'lighter' laser methods than was seen in ETDRS, as noted in some of the studies in *Chapter 3*. For example, in Bandello *et al.* (2001),[75] the proportion of patients with worsening CSMO was significantly greater in the classical PRP group than in the light PRP group (23% vs. 3%; $p = 0.023$).
2. Compared with older studies, the better detection of MO by OCT compared with clinical examination.
3. The usually temporary nature of MO after PRP, meaning that the disutility would also be temporary (and not influential if modelling involves 6-month cycles because it would usually have resolved before that time point?). However, as noted earlier, the visual loss is not always temporary, at least in older studies such as DRS and ETDRS.[9,10]
4. The utility weight given to modest changes in VA. The effect of a small change may have profound impact in QoL if it means that patients have to stop driving.
5. The disutility of pain, though that is transient, and a more important economic factor might be the disutility of less effective PRP if it could not be completed owing to pain. As reported earlier (see *Chapter 4*), pain may be reduced by administration of an anti-VEGF a week before PRP.[123] However administration of subconjunctival or sub-Tenon's anaesthesia should remove pain.
6. The cost of anti-VEGF treatment, both drug cost (high with ranibizumab, modest with bevacizumab) and administration. If using ranibizumab at list price (the discounted price is confidential), the cost might be in the region of £900.
7. The cost of PRP, if anti-VEGF cover allowed it to be given in one session rather than several. Patients could have sub-Tenon's anaesthesia, then the anti-VEGF injection, and then PRP, and then be seen in 3 months. This would be more convenient for them. It might also be safer to have one visit in hospitals where appointments may be postponed and treatment delayed, increasing the risk of vitreous haemorrhage before treatment is completed.
8. Any adverse effects of anti-VEGF treatment. In *Chapter 4*, it was found that anti-VEGF mainly caused transient adverse events related mainly to injection such as subconjunctival haemorrhage or foreign body sensation. The incidence of serious drug-related adverse events like endophthalmitis, uveitis, vitreous haemorrhage or retinal detachment was minimal. In DRCRN (2011),[120] there was one case of endophthalmitis in the ranibizumab group. In the same study,[120] more patients in the sham group had retinal detachment (3% vs. 1%) and vitreous haemorrhage (12% vs. 5%) than those in the ranibizumab group. None of the studies found that anti-VEGF drug caused thromboembolic adverse events. The overall pain score was also significantly lower in the group receiving PRP plus anti-VEGF than in those receiving PRP only (Lucena 2013[123] – VAS score 4.7 vs. 60.8).
9. The net gain in QALYs, taking into account reduced disutility from CSMO; any disutility from adverse effects including the injection into the eye itself; and possibly reduced disutility from fewer PRP sessions.

Comparisons with other studies

No studies were identified that had considered the cost-effectiveness of early treatment with PRP for severe NPDR, and, therefore, appropriate comparisons with other existing studies were not possible. For example, the cost-effectiveness studies of DR, which have been identified, assessed the cost-effectiveness of various screening strategies in a cohort of people where the starting point was people who diabetic with no or early retinopathy,[158,164] whereas in our model the starting point was patients with moderate NPDR, or studies that assessed the cost-effectiveness of various treatment options for DMO,[166,186,187] whereas our model primarily focused on treating patients who had severe NPDR.

Chapter 8 Discussion and research needs

Statement of principal findings

- The DRS[10] confirmed that laser photocoagulation was effective in reducing the risk of visual loss due to PDR.
- The ETDRS[9] addressed the timing question, and reported that earlier PRP, at severe NPDR and early PDR stages, was more effective then postponing PRP till later PDR. However, it did not report results separately for early PDR and severe NPDR, and the difference in the primary outcome of SVL did not quite reach statistical significance at the ETDRS level of 99% CIs: RR 0.77, 99% CI 0.56 to 1.06.
- A composite outcome of SVL and vitrectomy did give a statistically significant result: RR 0.67, 99% CI 0.52 to 0.97.
- There is currently insufficient evidence to recommend PRP for NPDR.
- There has been a trend towards lighter methods of PRP, where lighter refers to using lasers at lower power and producing less severe burns. PSC: The multi-spot laser allow more spots to be delivered in one application, hence shortening the procedure time, but more spots are needed as short-duration burns do not spread. The multi-spot lasers are also of shorter duration (10–20 ms as compared with 100 ms in older systems).
- Laser devices that can apply patterns of spots have advantages over single-spot devices. Newer lasers have other features that allow parameters to be controlled. However, in terms of visual outcomes, there is a lack of robust data favouring one laser over another, and there are no data to demonstrate superiority of any laser technology compared with argon laser, which was the laser used in the ETDRS. The SDM system shows promise in focal laser for DMO but there are very few data on use in PRP.
- There is accumulating evidence that combining PRP with either an anti-VEGF drug or triamcinolone may reduce the risk of PRP-associated MO. Whether this improves long-term results is not known. There would be advantages if it allowed PRP to be done in one session.
- There are uncertainties around the cost-effectiveness of PRP at NPDR or early PDR stage, but, in a range of analyses, earlier PRP either dominates delaying PRP till HR-PDR stage or is cost-effective with quite low ICERs.
- The uncertainty around the economic analysis and the limitations for the economic model indicate the need for more research. The results from the economic model should be treated with caution.

The deferred arms in the studies may not reflect routine care, where delays in treatment may result in patients having vitreous bleeds and presenting as emergencies. Even without delays, treatment at advanced PDR stage can have complications such as vitreous haemorrhage and tractional retinal detachment due to contraction of NV tissue. This would not be a problem with treatment at less severe stages.

Strengths and limitations

The strengths of this report include:

- wide-ranging searches for evidence
- extension of the original scope to include current laser technologies and new drug treatments, to add value to the review and make it more useful for planning future research
- a thorough review of adverse events of PRP, based on both RCTs and observational studies, and including outcomes important to patients, such as ability to drive
- recommendations of the specific research questions, underpinned by a thorough presentation of research currently under way
- a new economic model of DR.

The limitations included:

- Dependence on one trial, the ETDRS, for the critical issue of timing of PRP – whether to use it at NPDR stage. The ETDRS was carried out in the 1980s, before OCT was available, and it did not give results separately for NPDR and early PDR.
- Few trials comparing argon laser with newer laser technologies. So no data to show whether modern laser technologies are superior to the argon laser used in ETDRS.
- A lack of data on the most effective use of anti-VEGF drugs in combination with lasers – should they be given prophylactically to all or only to those who develop DMO after PRP?
- A lack of good, up-to-date, long-term data on progression and regression of retinopathy after treatment.

Research completed but not yet published in full

Several studies of combination treatment with anti-VEGF drugs and laser have been reported as abstracts. Inevitably details are sparse, till full publication.

In two studies, the anti-VEGF used was pegaptanib:

- In a small, three-armed trial, Estudillo and Gonzalez (2013)[188] [the same trial seems to have been reported by Gonzalez (2013)[189] alone but with slightly different figures] randomised 20 eyes to pegaptanib alone (three initial injections then repeats every 12 weeks; eight patients), pegaptanib (three initial injections only) plus selective laser treatment (eight), and standard PRP alone (four). The third group did better in BCVA after 12 months.
- Leal *et al.* (2013)[190] randomised 22 patients with HR-PDR into two arms in what was described as an exploratory Phase II study. One arm had standard PRP as per DRS. The other arm had 'progressive PRP' plus pegaptanib, The progressive PRP starts with the DRS third ring, followed if need be by further laser treatment moving inwards. (Full details are not given in the abstract but this sounds like the lighter PRP technique reported by Madeira *et al.* 2009[191] in an abstract from a EURETINA meeting.) They call it external ring photocoagulation, and the aim appears to be to minimise visual field defect and the risk of MO, and have less effect on night vision (argon green laser was used).

Eyes that received the combined treatment lost on average only one letter of BCVA compared with six in the PRP-alone group.

Two abstracts reported results with bevacizumab:[192,193]

- Preti *et al.* (2013)[192] randomised both eyes of 23 patients with HRC-PDR. One eye was treated with PRP plus bevacizumab (number of injections not given) and the other with PRP alone. No visual outcome results are given, only choroidal thickness.
- Another abstract from the same group with 30 patients appears to have come from the same study.[193] It reports no significant change in BCVA in either group.

Four studies reported on the use of ranibizumab;[194–197] three are by-products of DMO trials:[194–196]

- Lohmann *et al.* (2013)[194] reported that in the RELATION trial of ranibizumab + laser versus laser alone for DMO (so focal or grid laser, not PRP), a subgroup of 27 patients had PDR at baseline. Of those (20) in the combined group, eight (40%) showed regression of PDR, whereas none in the laser-alone group did. They conclude that anti-VEGF treatment may be effective in PDR.

- Ehrlich *et al.* (2013)[195] report findings from the RISE and RIDE trials in which patients with DMO were randomised to ranizumab (two doses) or sham injections. Patients could have macular laser or PRP if required. Secondary outcomes included progression of DR, expressed in ETDRS stages, vitreous haemorrhage and need for PRP. Regression by 36 months was commoner in the ranibizumab arms (3-step improvement 3% in sham arm, 15% and 13% in ranibizumab arms). Progression to PDR was reported in 34% in the sham arm, compared with 13% and 15% in the ranibizumab arms.

- The DRCRN carried out a RCT of IVR and triamcinolone for DMO, and in this abstract report effects amongst those with DR, outcomes being progression from NPDR to PDR, occurrence of vitreous haemorrhage, need for PRP or worsening of DR by at least two levels.[196] The advantage of this study is large numbers. In eyes without PDR at baseline ($n = 538$), the drug arms had lower (4%) progression than the sham injection plus laser arm (10%). (Note that laser was for DMO, so focal or grid, not PRP.) In eyes with PDR at baseline ($n = 254$), more (20%) progressed in the non-drug arm than in the drug arms (2–9%). The authors cautiously comment that 'These results suggest that use of these drugs to prevent worsening of DR is worth further investigation'.

- In a group of patients with bilateral PDR, Ferraz *et al.* (2013)[197] compared PRP alone, given in three sessions as per ETDRS guidelines, with PRP plus ranibizumab at weeks 1 and 4. Eyes were randomly allocated to ranibizumab or a sham injection. Results were reported separately for those with and without CSMO at baseline. In those with CSMO, after 6 months' follow-up, BCVA improved by four letters in the combined group and decreased by five letters in the PRP-alone group. In those without CSMO, VA improved by eight letters in the combined group and was unchanged in the PR-alone group. Vitreous haemorrhage was less common in the combined group (10%) than the PRP-alone group (23%).

Ongoing or recently completed research searches

Sources searched for ongoing or recently completed research were ClinicalTrials.gov, WHO (World Health Organization) Clinical Trials Registry Platform Search Portal, Current Controlled Trials, UK Clinical Trials Gateway, EU Clinical Trials Register, and UK Clinical Research Network Study Portfolio.

Searches were performed on 16 January 2014 using keywords: diabetic retinopathy AND (laser OR photocoagulation OR PRP OR scatter).

Studies selected were those in which the main condition being studied was DR (we excluded those that included patients with DMO only) and the intervention included PRP photocoagulation alone or in combination with another intervention, such as an intravitreal drug, and where the results had not been found published in full or as a meeting abstract. We selected only RCTs, apart from one observational study, which we considered to be investigating an outcome-important patients' QoL (i.e. being able to maintain a UK driving licence).

We included 16 studies in total: 15 RCTS and the one observational study. Eight studies include anti-VEGF drugs (one each with aflibercept, bevacizumab, and pegaptinib and five with ranibizumab) either given alone or as adjunctive therapy to PRP and seven involve different methods of laser delivery. All have a Clinical ClinicalTrials.gov Identifier (and will be identified by this number) apart from one that was identified in the UK Clinical Research Network Study Portfolio database (UKCRN ID 13472). Studies are briefly summarised in more detail in *Table 48*, and also described below.

TABLE 48 Ongoing or recently completed studies involving laser therapy

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Treatment with Intravitreal Aflibercept Injection for Proliferative Diabetic Retinopathy, The A.C.T. Study *Sponsor:* Ophthalmic Consultants of Long Island Collaborator: Regeneron Pharmaceuticals **NCT01813773**	To assess the safety of IAI in the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of adverse events Randomised open-label study, single centre, pilot study *Estimated enrolment:* 20	Retinal neovascularisation secondary to DR, BCVA in the study eye better than 20/320 using an ETDRS chart	*Arm 1:* IAI (2 mg) every 4 weeks. Following the 5 initial injections between day 1 and week 16, this group will continue to receive IAI every 4 weeks, beginning week 20, through week 48 *Arm 2:* IAI (2 mg) every 8 weeks. Following the 5 initial injections between day 1 and week 16, this group will receive IAI every 8 weeks, beginning week 24, through week 48	Incidence and severity of adverse events of IAI in the treatment of PDR *Time frame:* 52 weeks *Study start date:* March 2013 *Estimated study completion date:* March 2015 *Estimated primary completion date:* December 2014
Effect of Adjunctive Intravitreal Bevacizumab Before Panretinal Photocoagulation in Macular Thickness and Retinal Nerve Fiber Layer Thickness *Sponsor:* Kyungpook National University **NCT01504724**	To investigate the effect of adjunctive IVB before PRP compared with only PRP on CMT and retinal nerve fibre layer thickness in patients with severe diabetic retinopathy without MO Randomised, parallel assignment, open label *Enrolment:* 30	Patients with severe NPDR or early PDR without MO, BCVA of 20/25 or better. Patients followed up for at least 6 months after the first PRP	*Arm 1:* IVB group. Patients were treated with IVB injections approximately within 1 week before the first PRP. Then patients had PRP, which was done in three sessions at weeks 0, 1 and 2 according to ETDRS guidelines. The superior, inferior, and nasal and temporal areas were treated sequentially *Arm 2:* Only PRP group. Patients had PRP, which was done in three sessions at weeks 0, 1 and 2 according to ETDRS guidelines. The superior, inferior, and nasal and temporal areas were treated sequentially	CMT measured by Cirrus HD OCT *Time frame:* 6 months after first PRP session This study has been completed *Study start date:* August 2011 *Study completion date:* August 2013 *Primary completion date:* August 2012 (Final data collection date for primary outcome measure)

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Macugen for Proliferative Diabetic Retinopathy Study With Extended Dosing (M-PDRS ED) Sponsor: Valley Retina Institute Collaborator: Pfizer **NCT01486771**	To investigate if intravitreal injections of pegaptanib will induce the regression of PDR and reduce the need for retinal photocoagulation Pilot study, randomised, factorial assignment, open label *Enrolment: 30*	Active PDR with HRCs as defined by the DRS; ETDRS VA score ≥24 letters (approximately 20/320) and ≤85 letters (approximately 20/20) by the ETDRS VA protocol at the screening visit; eyes with mild pre-retinal haemorrhage or mild VH that does not interfere with clear visualisation of the macula and optic disc; evaluating physician believes that PRP can be safely withheld for 3 weeks	*Arm 1:* IV Macugen Q6. Receive 3 intravitreal pegaptanib injections at 6-week intervals, then 3 additional injections at 12-week intervals *Arm 2:* IV Mac Q6. Receive selective laser photocoagulation after 3 intravitreal pegaptanib injections *Arm 3:* PRP. Will act as the control group, subjects in this group will receive standard PRP (mETDRS protocol)	Efficacy of intravitreal pegaptanib sodium injections in inducing regression of HR-PDR (as determined by percentage of eyes without treatment failure) using standard PRP as the control arm *Time frame:* 54 weeks *Study start date:* November 2007 *Estimated study completion date:* February 2014 *Estimated primary completion date:* August 2013 (final data collection date for primary outcome measure)
Efficacy and Safety of Lucentis® Monotherapy Compared With Lucentis® Plus Panretinal Photocoagulation (PRP) and PRP in the Treatment of Patients With High Risk Proliferative Diabetic Retinopathy *Sponsor:* José Cunha-Vaz, Association for Innovation and Biomedical Research on Light and Image **NCT01280929**	To demonstrate superiority of one of the treatment arms over a 12-month treatment period in the regression of neovascularisation Prospective, randomised, multicentre, open-label Phase II study *Estimated enrolment: 54*	HR-PDR eye, BCVA at baseline > 20/320 in the study eye, clear ocular media and adequate pupillary dilatation to permit good quality fundus photography, IOP < 21 mmHg, type 1 or type 2 diabetes	*Arm 1:* PRP at month 0 that can be repeated after month 3 *Arm 2:* Intravitreous injection of ranibizumab every 4 weeks at month 0, month 1 and month 2 that can be repeated after month 3 *Arm 3:* Combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks ± 1 week after injection), at month 0, month 1 and month 2 that can be repeated after month 3	Regression of neovascularisation *Time frame:* 12-month treatment *Start date:* September 2010 *Estimated study completion date:* December 2013

TABLE 48 Ongoing or recently completed studies involving laser therapy (*continued*)

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Multicenter 12 Months Clinical Study to Evaluate Efficacy and Safety of Ranibizumab Alone or in Combination with Laser Photocoagulation vs. Laser Photocoagulation Alone in Proliferative Diabetic Retinopathy (PRIDE) *Sponsor:* Novartis Pharmaceuticals Collaborators: Cologne Image Reading Center & Laboratory (CIRCL) Spranger Laboratories **NCT01594281**	To assess the efficacy and safety of ranibizumab alone or in combination with laser treatment vs. laser treatment alone in proliferative diabetic retinopathy Randomised, parallel, single-blind (outcomes assessor), Phase IV study *Estimated enrolment:* 120	Proliferative diabetic retinopathy, BCVA ≥ 20 ETDRS letters, diabetes with HbA$_{1c}$ ≤ 12% (= 107 mmol/mol)	*Arm 1:* Ranibizumab *Arm 2:* Laser photocoagulation *Arm 3:* Ranibizumab and laser photocoagulation	Change of area of neovascularisations as measured by FA *Time frame:* 12 months *Study start date:* December 2012 *Estimated study completion date:* April 2015 (final data collection date for primary outcome measure)
Prospective, Randomized, Multicentre, Open-label, Phase II/III Study to Assess Efficacy and Safety of Ranibizumab 0.5 mg Intravitreal Injections Plus Panretinal Photocoagulation (PRP) vs. PRP in Monotherapy in the Treatment of Subjects With High Risk Proliferative Diabetic Retinopathy (PROTEUS) *Sponsor:* Association for Innovation and Biomedical Research on Light and Image **NCT01941329**	To compare the efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus PRP vs. PRP alone in the regression of the neovascularisation area in patients with high-risk proliferative diabetic retinopathy over a 12-month treatment period Prospective, randomised, multicentre, open-label, Phase I/III study *Estimated enrolment:* 94	High-risk proliferative diabetic retinopathy, neovascularisation in the disc ≥ ¼ DA or neovascularisation elsewhere ≥ ½ DA, NVE < ½ DA + vitreous and/or pre-retinal haemorrhage and/or rubeosis; NVD < ¼ DA + vitreous and/or pre-retinal haemorrhage and/or rubeosis, BCVA at baseline ≥ 24 ETDRS letters score (approximate Snellen equivalent 20/320)	*Arm 1:* Ranibizumab + PRP. 3 intravitreous injections of ranibizumab combined with standard PRP (2 ± 1 weeks after injection), at months 0, 1 and 2, which can be repeated after month 3, with always at least 1 month of interval between injections *Arm 2:* PRP monotherapy. PRP between months 0 and 2, with 1 mandatory laser session in month 0 and more laser sessions as needed until month 2 to complete the PRP treatment. After completing the PRP treatment, PRP sessions can be repeated from months 3 to 11	Regression of neovascularisation *Time frame:* 12-month treatment *Study start date:* January 2014 *Estimated study and primary completion date:* July 2015

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
PASCAL Laser vs. ETDRS Laser Associated with Intravitreal Ranibizumab (IVR) vs. Only IVR for Proliferative Diabetic Retinopathy *Sponsor:* University of São Paulo **NCT02005432**	To evaluate the effects on retinal morphophysiology of full scatter single target PRP vs. full scatter multiple target PRP (both combined with intravitreous injections of ranibizumab) vs. IVR alone in patients with PDR Randomised, parallel assignment, single blind (outcomes assessor) *Enrolment:* 31	Presence of PDR, presence of retinal neovascularisation, defined as active neovessels (fine retinal vessels with saccular dilatations or extremities covered with blood or associated with recurrent VH) with VA better than 20/800 and with no previous laser treatment	*Arm 1:* SS-PRP arm. PRP single shoot (ETDRS – green diode laser) + 0.05 ml IVR *Arm 2:* MS-PRP arm. Multiple shoot panphotocoagulation (PASCAL) plus IVR *Arm 3:* IVR arm. Only IVR	Mean change in the total area of active retinal neovessels, as measured by FA leakage area, in mm² *Time frame:* Baseline to week 48 *Study start date:* February 2012 *Estimated primary completion date:* November 2014
Prompt Panretinal Photocoagulation vs. Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy *Sponsor:* DRCRN Collaborators: NEI, Genentech **NCT01489189**	To determine if VA outcomes at 2 years in eyes with PDR that receive anti-VEGF therapy with deferred PRP are non-inferior to those in eyes that receive standard prompt PRP therapy Randomised, parallel assignment, open label *Estimated enrolment:* 316	Diagnosis of diabetes (type 1 or type 2), and meets at least all of the following ocular criteria: presence of PDR which the investigator intends to manage with PRP alone but for which PRP can be deferred for at least 4 weeks in the setting of IVR, in the investigator's judgement, electronic-ETDRS VA letter score > 24 (approximate Snellen equivalent 20/320) on the day of randomisation, media clarity, pupillary dilatation	*Arm 1:* Intravitreal injection of 0.5 mg ranibizumab (at baseline and up to every 4 weeks using defined retreatment criteria) with deferred PRP (PRP is deferred until failure/futility criteria for intravitreal injection are met) *Arm 2:* Prompt PRP alone at baseline (full session completed within 56 days)	Mean change in VA from baseline to 2 years *Time frame:* 2 years (primary outcome) *Total follow-up:* 5 years *Study start date:* March 2012 *Estimated study completion date:* December 2017 *Estimated primary completion date:* December 2014 (final data collection date for primary outcome measure)
Incidence of MO After Panretinal Photocoagulation (PRPC) Performed in a Single Session Versus Four Sessions in Diabetic Patients *Sponsor:* Centre Hospitalier Universitaire Dijon **NCT01766362**	To show that PRPC performed in a single session using a PASCAL laser leads to better management of the disease, a saving of time and better comfort for both patient and doctor Randomised, parallel, open-label, Phase III study *Estimated enrolment:* 90	Diabetes type 1 or 2, severe non-proliferative or early proliferative diabetic retinopathy (according to the Alfediam classification); CMT ≤ 350 μm according to spectralis OCT	*Arm 1:* PRPC using PASCAL laser – a single session *Arm 2:* PRPC using PASCAL laser – four sessions, with every session spaced out by a month	CMT at 9 months after the start of PRPC using PASCAL laser *Time frame:* 9 months *Study start date:* October 2011 *Estimated primary completion date:* October 2013

continued

TABLE 48 Ongoing or recently completed studies involving laser therapy (*continued*)

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Safety and Effectiveness Study of 532 nm Laser Subthreshold Panretinal Photocoagulation for Severe NPDR *Sponsor:* Sun Yat-sen University **NCT01759121**	To evaluate the therapeutic efficacy of 532-nm laser partially sub-threshold PRP with PASCAL end point management function for severe NPDR Randomised, parallel controlled, double-blind (subject, outcomes assessor), clinical trial *Estimated enrolment:* 84	Diagnosis of severe NPDR, age: 45–80 years, BCVA ≥ 20/100, myopia ≤ −6 degree (−6D), no previous PRP, and no major ocular surgery within 3 months	*Arm 1:* Traditional-PRP (T-PRP): 532-nm short-pulse PRP with PASCAL function *Arm 2:* Sub-threshold PRP (S-PRP): 532-nm partially subthreshold short-pulse PRP with PASCAL Endpoint Management function	Change of BCVA; probability of VH *Time frame:* 1 year *Study start date:* December 2012 *Estimated study completion date:* July 2014
Safety and Efficacy of Single-session, Low-Fluence Panretinal Photocoagulation for Proliferative Diabetic Retinopathy *Sponsor:* Asociación para Evitar la Ceguera en México **NCT01737957**	To determine the safety and efficacy of a single session of low-fluence PRP when compared with full-fluence PRP Randomised, single-blind study *Estimated enrolment:* 60	Type 1 or type 2 diabetes, proliferative diabetic retinopathy	*Arm 1:* Low-fluence PRP in a single session with 532-nm green laser (other name: PUREPOINT laser) *Arm 2:* Full-fluence PRP in two sessions with 532-nm laser (other name: PUREPOINT laser)	Measurement of macular thickness changes by spectral domain OCT *Time frame:* Baseline, 1 week, 6 weeks, 12 weeks, 16 weeks *Study start date:* November 2012 *Estimated study completion date:* March 2013
Morphological and Functional Retinal Changes Following Retinal Photocoagulation Using a Semiautomated Patterned Scanning Laser System in Proliferative Retinopathy or Macular Edema Secondary to Diabetes Mellitus or Retinal Vein Occlusion *Sponsor:* Medical University of Vienna **NCT00682240**	To measure imaging of retinal morphological changes with time secondary to laser treatment as assessed with high-definition OCT Randomised, crossover assignment, open label *Estimated enrolment:* 80	Patients with either retinopathy/ maculopathy secondary to diabetes type 1 or 2 with medical indication for segmental or pan-retinal laser coagulation or with necessity for completion of previous incomplete laser photocoagulation, patients with PDR requiring pan-retinal laser treatment (Arms 1, 2 and 3), patients with MO requiring central focal or grid laser treatment (Arm 4)	*Arm 1:* A single-session pan-retinal laser treatment using the PASCAL laser system *Arm 2:* Multi-session pan-retinal laser treatment using the PASCAL laser system *Arm 3:* Multi-session pan-retinal laser treatment according to the conventional protocol, using a conventional laser system *Arm 4:* Patients with persistent central or para-central DMO receiving focal or grid laser treatment	Retinal morphological changes with time secondary to laser treatment as assessed with OCT *Time frame:* 2007–14 *Study start date:* October 2007 *Estimated study completion date:* December 2015 *Estimated primary completion date:* June 2015

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Panretinal Photocoagulation for Diabetic Retinopathy with PASCAL Laser *Sponsor*: Federal University of São Paulo **NCT01304225**	To investigate the clinical efficacy and safety of the PASCAL laser for DR. Patients with proliferative or severe non-proliferative retinopathy will be treated with PRP utilising different treatment strategies Randomised, parallel assignment, single blind (subject) *Estimated enrolment*: 60	Proliferative or severe NPDR (type 1 or type 2), BCVA of 20/50 or better	*Arm 1*: 100-ms single-shot. PRP utilising 100-ms pulse duration, moderate intensity burns, in a single-shot fashion *Arm 2*: 20-ms multiple-shot. PRP utilising 20-ms pulse duration, moderate intensity burns, in a multiple-shot fashion *Arm 3*: 20-ms multiple-shot, barely visible. PRP utilising 20-ms pulse duration, barely visible intensity burns, in a multiple-shot fashion	Incidence of SVL after 1 year [SVL is defined as VA worse or equal to 5/200 in two consecutive visits (DRS/ETDRS primary outcome)] *Time frame*: 1 year *Study start date*: September 2010 *Estimated study completion date*: March 2013
PASCAL Pan Retinal Photo-Stimulation in Pre-Proliferative Diabetic Retinopathy: a Safety and Efficacy Study *Sponsor*: Central Manchester University Hospitals NHS Trust (CMFT) *Funder*: Optos Plc, OptiMedica Corporation **UKCRN ID 13472**	To find if treating patients using a single session of lower intensity laser (PASCAL® Pan Retinal PhotoStimulation, PRPhS), at an earlier stage in DR (during the severe NPDR stage) when the abnormal new vessels are not developed, will prevent diabetic patients developing PDR Randomised, single-centre, pilot, feasibility study *Global sample size*: 30	1. Treatment-naive severe NPDR 2. ETDRS VA equivalent to 35 letters or better 3. Any of the following: extensive (> 20) intraretinal haemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; prominent IRMA in 1+ quadrant 4. Mean CRT of ≤ 300 μm as measured by Deep Range Imaging OCT scans	*Arm 1*: Patients will be treated with the normal parameters used in PASCAL laser *Arm 2*: Patients will be treated with a lower intensity than normal, using the Endpoint Management system (a new software from the PASCAL laser, which allows operator to decrease the intensity of the burns (invisible burns), showing some landmarks with normal intensity; the area which has been treated can be seen) *Arm 3*: Patients will be observed, such as is being done in clinic routinely	Primary outcomes not specified *Closure date*: 3 March 2015

continued

TABLE 48 Ongoing or recently completed studies involving laser therapy (*continued*)

Title and sponsors	Aim and study design	Main inclusion criteria	Intervention	Primary outcome and key dates
Comparison of Two Laser Therapy Methods for PDR *Sponsor:* Shahid Beheshti Medical University NCT01232179	A comparison between results and side effects of treatment of proliferative diabetic retinopathy by conventional and extended targeted PRP Randomised, double-blind, Phase II trial	Patients with PDR suitable for photocoagulation therapy, pupil with dilatation ≥ 6 mm, no previous treatment with anti-VEGF drugs 3 months before study, no previous vitreoretinal surgery or laser therapy	*Arm 1:* Conventional PRP *Arm 2:* Targeted PRP: 1200–1600 spots in far periphery retina, anterior equator	No leakage in widefield FA *Time frame:* 3 months after laser therapy *Study start date:* October 2010 *Estimated primary completion date:* April 2011
A Prospective Clinical Study of the Effects of Panretinal Photocoagulation Delivered With a Multi-spot Photocoagulator on Retinal Sensitivity and Driving Eligibility in Patients With Diabetic Retinopathy *Sponsor:* Moorfields Eye Hospital NHS Foundation Trust Collaborator: Insulin Dependent Diabetes Trust NCT01383772	To determine the risk of failing the VA criteria to hold a driving licence following retinal laser treatment delivered with a multi-spot photocoagulator Observational, cohort study *Estimated enrolment:* 100	Patients of either sex aged 18 years or over, diabetes (type 1 or type 2), BCVA ≥ 6/60 in both eyes, requiring full bilateral PRP, no previous laser treatment	Patients will undergo baseline VA testing and complete a QoL questionnaire. All patients will receive their laser treatment as part of standard clinical care via the multi-spot photocoagulator, which will require approximately four 20-minute sessions. At 6 months following the completion of treatment the patients will undergo repeat VA testing as conducted at baseline and complete a QoL questionnaire	Risk of failing VA criteria to hold a driving licence *Time frame:* VAs at baseline and at 6 months *Study start date:* June 2012 *Estimated study completion date:* December 2013 *Estimated primary completion date:* August 2013

CRT, central retinal thickness; DA, disc area; IAI, intravitreal aflibercept injection; VH, visual haemorrhage.

NCT01813773 is a small randomised pilot study assessing the incidence and severity of adverse events with two different dosing regimens of intravitreal aflibercept injections for PDR. Both arms of the study have five initial injections between day 1 and week 16; Arm 1 will then continue to receive IAI every 4 weeks, beginning week 20, through week 48; and Arm 2 will receive intravitreal aflibercept injections every 8 weeks, beginning week 24, through week 48.

We also note that the Efficacy and Mechanism Evaluation (EME) programme is to fund a trial called CLARITY, which will look at the clinical effectiveness and cost-effectiveness of aflibercept used in combination with PRP for PDR.[198,199] CLARITY is short for 'Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy'.

NCT01504724 is a recently completed 6-month randomised study of 30 patients (60 eyes) looking at the effect of adjunctive IVB before PRP versus PRP only on CMT in patients with severe DR without MO. Patients had weekly PRP treatments in three sessions, and then were randomly assigned to either the IVB group (who had adjunctive IVB within 1 week before first PRP) or a control group who had only PRP (done in three sessions at weeks 0, 1 and 2 according to ETDRS guidelines).

NCT01486771 is a randomised three-arm pilot study, which aims to investigate if intravitreal injections of pegaptanib will induce the regression of proliferative diabetic retinopathy and reduce the need for retinal photocoagulation in patients with active PDR with HRCs. Arm 1 patients will receive three intravitreal pegaptanib injections at 6-week intervals, then three additional injections at 12-week intervals; Arm 2 will receive selective laser photocoagulation after three intravitreal pegaptanib injections; and Arm 3 will act as the control group and receive standard PRP (mETDRS protocol).

NCT01280929 is randomised, multicentre, open-label, three-arm Phase II study, with an estimated enrolment of 54 patients, looking at the efficacy and safety of IVR injections monotherapy compared with ranibizumab plus PRP and PRP alone, in the treatment of patients with HR-PDR. The primary outcome is regression of neovascularisation at 12 months.

NCT01594281 is another three-arm study assessing the efficacy and safety of ranibizumab alone or in combination with laser treatment versus laser treatment alone in patients with proliferative diabetic retinopathy. This Phase IV study plans to enrol 120 patients, and the primary outcome is the change of area of neovascularisation as measured by FA at 12 months.

NCT01941329 is a randomised, multicentre, open-label, Phase II/III study, with an estimated enrolment of 94 patients. The study aims to assess efficacy and safety of IVR plus PRP versus PRP in monotherapy in the treatment of subjects with HR-PDR over a 12-month treatment period. The primary outcome is regression of neovascularisation.

NCT02005432 is a three-arm pilot study that compares two different methods of laser (PASCAL laser vs. ETDRS laser) both with IVR versus IVR alone in patients with PDR. Arm 1 consists of single shoot PRP (ETDRS) plus 0.05 ml IVR; Arm 2 is multiple shoot PRP (PASCAL) plus IVR; and Arm 3 is IVR only. The primary outcome is the mean change from baseline in the total area of active retinal neovessels, as measured by FA leakage area at 48 weeks.

NCT01489189 is a trial sponsored by the DRCRN (DRCRnet) which compares prompt PRP with 0.5 mg IVR with deferred PRP. The aim is to determine if VA outcomes at 2 years in eyes with IVR plus deferred PRP are non-inferior to those in eyes that receive standard prompt PRP therapy. The inclusion criteria includes patients with type 1 or 2 diabetes with PDR (with or without DMO) in which the investigator intends to manage with PRP alone, but for which PRP can be deferred for at least 4 weeks, if an intravitreal injection is given. One arm will receive 0.5 mg IVR with deferred PRP (PRP is deferred until failure/futility criteria for intravitreal injection are met) and the other will receive prompt PRP alone (with the full session completed within 56 days).

NCT01766362 aims to show that PRP performed in a single session using a PASCAL laser leads to better management of PDR, with a saving of time and better comfort for both patient and doctor. This randomised, open-label, Phase III study aims to enrol 90 patients with severe NPDR or early PDR. One arm will include a single session of PRP using PASCAL laser and the other will receive four sessions of PASCAL laser, with sessions spaced out by a month. The primary outcome is CMT at 9 months.

NCT01759121 plans to include 90 patients is an open-label trial to investigate the safety and effectiveness of 532-nm laser sub-threshold PRP with PASCAL Endpoint Management function for severe NPDR. One arm will consist of traditional PRP (532-nm short-pulse PRP with PASCAL function) compared with another arm with sub-threshold PRP (532-nm partially sub-threshold short-pulse PRP with PASCAL Endpoint Management function). The main outcomes will be the change of BCVA and the probability of vitreous haemorrhage at 1 year.

NCT01737957 aims to test the safety and efficacy of single-session, low-fluence PRP for PDR when compared with full-fluence PRP. The hypothesis is that a single-session of low-fluence PRP will be safe regarding the progression of MO and the presence of adverse events, and will efficiently induce regression of neovascularisation in patients with PDR. Patients in one arm will received low-fluence PRP in a single session with 532-nm green laser (PUREPOINT laser) and the other arm will receive full-fluence PRP in two sessions with 532-nm laser (PUREPOINT laser). The primary outcome is macular thickness changes measured by spectral domain OCT at 1, 6, 12 and 16 weeks.

NCT00682240 is a four-arm, randomised, crossover trial to assess morphological and functional retinal changes following retinal photocoagulation using PASCAL laser in proliferative retinopathy or MO secondary to diabetes or retinal vein occlusion. Arm 1 will receive a single-session of PRP using the PASCAL laser system; Arm 2 will receive multi-session PRP using PASCAL, Arm 3 will receive multi-session PRP using a conventional laser system; and in Arm 4 patients with persistent central or para-central DMO will receive focal or grid laser treatment.

NCT01304225 is trial investigating the clinical efficacy and safety of the PASCAL laser for DR in patients with PDR or severe NPDR, utilising three different treatment strategies. The main outcome is the incidence of SVL after 1 year. The comparisons include: Arm 1 with PRP using a 100-ms pulse duration, moderate intensity burns, in a single-shot fashion; Arm 2 with PRP using a 20-ms pulse duration, moderate intensity burns, in a multiple-shot fashion; and Arm 3 with PRP using a 20-ms pulse duration, barely visible intensity burns, in a multiple-shot fashion.

UKCRN ID 13472 is a randomised, three-arm pilot study with a target recruitment of 24 patients looking at the safety and efficacy of PASCAL in patients with PPDR. It aims to find whether treating patients using a single session of lower intensity laser (PASCAL® Pan Retinal PhotoStimulation, PRPhS) at an earlier stage in DR (during the severe NPDR stage) will prevent diabetic patients developing PDR. Patients in Arm 1 will be treated with the normal parameters used in PASCAL laser; Arm 2 patients will be treated with a lower intensity laser than normal, using the Endpoint Management system (a way of marking target areas with visible burns followed by reduced energy and hence non-visible spots within the target area); and patients in Arm 3 will be observed, as done routinely in clinical practice.

NCT01232179 is a 3-month Phase II trial comparing two methods of laser therapy in patients with PDR suitable for photocoagulation therapy. One arm will receive conventional PRP and the other will receive extended targeted PRP, consisting of 1200–1600 spots in the far periphery retina. The primary outcome is no leakage in wide-field FA at 3 months.

NCT01383772 is a prospective observational cohort study looking at the effects of PRP, delivered with a multi-spot photocoagulator, on retinal sensitivity and driving eligibility in patients with DR. The primary outcome is the risk of failing visual field criteria to hold a UK driving licence. Eligible patients are those with diabetes (type 1 or type 2), BCVA ≥ 6/60 in both eyes, requiring full bilateral PRP, and no previous laser treatment. The anticipated enrolment is 100 patients. All will receive the multi-spot photocoagulator

laser as part of standard clinical care. Patients will undergo visual field testing and complete a QoL questionnaire at baseline and again at 6 months.

A novel development, some way away from use in humans, is topical delivery of anti-VEGFs by eye drops. Davis *et al.* (2014)[200] have shown that bevacizumab can be delivered into the eyes of rats by this method.

The HTA programme has part-funded the Cochrane Eyes and Vision Group to produce a review of laser photocoagulation for NPDR, which will include a review of PRP and anti-VEGF drugs for NPDR, but also photocoagulation for DMO.[201]

Summary of ongoing research and research needs

- There are several trials of different anti-VEGF drugs, either against photocoagulation or in combination with it.
- The anti-VEGF trials fall into two groups: those assessing the efficacy of anti-VEGFs given alone, and those assessing their ability to reduce adverse effects of PRP, notably MO.
- There are several trials investigating different methods of photocoagulation for patients with DR at different stages.
- Most concern later stages of PDR. Only five studies (NCT01504724, NCT01766362, NCT01759121, NCT01304225 and UKCRN ID 13472) specifically mention that they include patients at the NPDR stage. One involving IVB combined with PRP, and the other four are concerned with different methods of delivering laser.
- The most relevant study to the research question in this report is the UKCRN ID 13472, which is the only one addressing the question of timing of PRP. It is a pilot that aims to recruit only eight patients per arm.

If multiple studies are done, then, to allow comparisons to be made across studies or to allow studies to be combined:

- The studies should all have the same intermediate and final outcomes.
- The studies should clearly state the proportions of people over time who are at the different severity levels and also what their VA is.
- Details should be given for separately for type 1 and type 2 diabetes.

Economic studies

Long-term studies are needed, which measure the progression (and regression) of people with DR through all the different stages of retinopathy. These studies will include patients receiving treatments, such as PRP laser and/or anti-VEGF, which are administered at earlier time points, i.e. at the severe NPDR or early PDR stages as opposed to waiting till the retinopathy progresses to the HR-PDR stages.

These studies should also include health-related QoL (HRQoL) measures to enable calculation of QALYs which are needed for cost-effectiveness analyses. These could include the generic preference-based measures such as EQ-5D or SF-6D alongside some disease-specific measures such as NEI VFQ-25 and VisQol. As the generic-based measures are said to be insensitive to changes in DR progression, the disease-specific measures could be mapped onto generic measures to obtain health-state utility values which can then be used in future cost-effectiveness analyses.

Retaining ability to drive would be an important outcome, which can make the difference between being in employment or not.

The studies would also benefit from having accurate cost estimates for the treatment whether it is for the different types of PRP laser or the different anti-VEGF medications.

The economic model created here for treating patients early who have severe NPDR can be used for other treatments, such as oral fenofibrate to assess their likely cost-effectiveness in reducing retinopathy progression. In addition, this model can be extended to start at the no or mild DR stage.

Therefore, there remains a need for a trial sufficiently large to address the decision problem posed for this review. Such a trial would use best modern laser technologies. We think there is accumulating evidence that use of single-dose anti-VEGF drugs in combination with PRP reduces the adverse effects and may allow PRP to be administered in a single session, and a trial could test this hypothesis.

So the features of a trial would include:

- Randomisation to PRP at severe NPDR and early PDR stages, reported separately, compared with deferring laser till HR-PDR stage.
- A multi-spot laser device.
- Randomisation to prophylactic anti-VEGF treatment to prevent MO versus treating only the minority who develop MO. There would need to be subgroups: those who have never had DMO; those who have DMO; and those who have had DMO in the past.
- Adequate numbers, which would need to be large to have power to take account of the various factors.
- At least 2 years' follow-up.

Other research needs include:

- Better and up-to-date data on progression and regression of retinopathy at each stage. This will always be somewhat problematic, as, for example, 20-year progression rates take 20 years to collect, by which time treatment and outcomes may have changed.
- Data on the best way to administer PRP taking into account confluence, intensity and location – whether to apply to the midperipheral retina versus focusing on areas of ischaemia using wide-angle FA, as the more selective approach may limit the damage caused by laser treatment.
- Data on optimum frequency of follow-up. This might be based on risk factors such as glycaemic control, BP and kidney function. Such factors might also influence decisions on when to administer PRP.
- If anti-VEGFs are to be used in adjuvant treatment, when is the best time to give them? There would be resource advantages in giving at the same visit as PRP. Some patients might appreciate having everything done at once, others might find it too much.
- Our focus was on the use of short-term, usually single, anti-VEGF treatment to reduce the risk of PRP-associated DMO. Anti-VEGF therapy could also be used longer term to reduce progression of retinopathy, but at the cost of multiple injections. The value of this is currently unclear but studies are under way.
- An alternative use of anti-VEGF drugs would be in people needing PRP, but who have DMO. Anti-VEGF treatment could be used instead of focal laser to clear macular fluid, after which PRP would be applied, though as DMO may take some time to clear after anti-VEGF treatment, PRP might have to be given at the same time. This might require close follow-up in case the anti-VEGF caused rapid regression of neovessels and scarring that might lead to tractional retinal detachment.
- Determining whether those with DMO but who require PRP, might benefit from a single injection of the dexamethasone implant to provide stability for several months.

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Contribution of authors

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Appendix 1 Classification of diabetic retinopathy in the early treatment of diabetic retinopathy study

Adapted from the ETDRS Research Group.[6,40,202]

Disease severity level	Findings observable upon dilated ophthalmoscopy
Mild non-proliferative retinopathy	At least one microaneurysm, and definition not met for moderate non-proliferative retinopathy, severe non-proliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Moderate non-proliferative retinopathy	Haemorrhages and/or microaneurysms ≥ standard photograph 2A;[a] and/or soft exudates, venous beading, or IRMAs definitely present; and definition not met for severe non-proliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Severe non-proliferative retinopathy	Soft exudates, venous beading, and IRMAs all definitely present in at least two of fields 4 through 7; or two of the preceding three lesions present in at least two of fields 4 through 7 and haemorrhages and microaneurysms present in these four fields, equalling or exceeding standard photo 2A in at least one of them; or IRMAs present in each of fields 4 through 7 and equalling or exceeding standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy (see below)
Early proliferative retinopathy (i.e. proliferative retinopathy without DRS HRCs)	New vessels; and definition not met for high-risk proliferative retinopathy (see below)
High-risk proliferative retinopathy (proliferative retinopathy with DRS HRCs)	New vessels on or within one DD of the optic disc (NVD) ≥ standard photograph 10A[a] (about ¼ to ⅓ disc area), with or without vitreous or pre-retinal haemorrhage; or vitreous and/or pre-retinal haemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ ¼ disc area
Less severe retinopathy	Mild or moderate non-proliferative retinopathy
More severe retinopathy	Severe non-proliferative or early proliferative retinopathy

a ETDRS Research Group. Grading diabetic retinopathy from stereoscopic colour fundus.

Appendix 2 Search strategies

Search strategies

In order to capture the wide range of evidence relating to PRP, other forms of laser treatment, and drug treatments in the treatment of all stages of DR, 10 separate types of search (as outlined below) were designed and performed:

 (a) systematic reviews and meta-analyses of PRP for DR
 (b) RCTs for treatment of DR
 (c) all studies on NPDR
 (d) all studies on lasers in DR
 (e) progression or natural history of DR
 (f) side effects of lasers from non-RCT studies
 (g) QoL in DR after PRP
 (h) cost-effectiveness of treatment in DR
 (i) ongoing or recently completed research
 (j) additional sources searched.

(a) Searches for previous systematic reviews or meta-analyses on the treatment of diabetic retinopathy

Ovid MEDLINE 1946 to August Week 2 2013

1. exp *Diabetic Retinopathy/
2. (diabet* and retinopathy).m_titl.
3. 1 or 2
4. (systematic review or meta-analysis).tw.
5. meta-analysis.pt.
6. 4 or 5
7. 3 and 6

EMBASE 1980 to 2013 Week 34

1. exp *Diabetic Retinopathy/
2. (diabet* and retinopathy).m_titl.
3. 1 or 2
4. (systematic review or meta-analysis).tw.
5. 3 and 4

Cochrane Database of Systematic Reviews July 2013
(diabet* and retinopathy) in Title

(b) Searches for randomised controlled trials for the treatment of diabetic retinopathy

These searches included all aspects of treatment – including laser surgery and drug treatment.

Ovid MEDLINE 1946 to August Week 2 2013; Ovid MEDLINE In-Process & Other Non-Indexed Citations August 26, 2013

1. exp *Diabetic Retinopathy/
2. (diabet* and retinopathy).m_titl.
3. randomized controlled trial.pt.
4. random*.tw.
5. 3 or 4
6. 1 or 2
7. 5 and 6
8. 1 or 2
9. 3 or 4
10. 5 and 6

EMBASE 1974 to 2013 August 27

1. exp *diabetic retinopathy/
2. (diabet* and retinopathy).m_titl.
3. 1 and 2
4. (random* adj3 trial*).tw.
5. (random* adj3 control*).tw.
6. 4 or 5
7. 3 and 6

The Cochrane Library

Cochrane Central Register of Controlled Trials: Issue 7 of 12, July 2013.

Search strategy "diabetic retinopathy" in title, and laser or photocoagulation or photo-coagulation in title abstract keywords in Trials".

After deduplication, resulted in **383** in the database and **92** were selected for full text.

Additional searches for non-randomised controlled trial evidence

(c) Searches for studies on non-proliferative diabetic retinopathy

Additional searches of any study design were done to find any studies that specifically mentioned DR at the non-proliferative or pre-proliferative stage, in order to find additional information for the clinical background section or data on progression or natural history. The searches below were run and downloaded into EndNote and resulted in 928 records in the database after removal of duplicates; the full text of 59 articles was requested and further examined.

Ovid MEDLINE 1946 to August Week 2 2013; Ovid MEDLINE In-Process & Other Non-Indexed Citations August 27, 2013

1. ((non-proliferative or nonproliferative or preproliferative or pre-proliferative) adj3 retinopathy).tw.
2. early retinopathy.tw.
3. NPDR.tw.

4. 1 or 2 or 3
5. exp *Diabetic Retinopathy/
6. 4 and 5
7. limit 6 to English language

Ovid EMBASE 1974 to 2013 August 27=569

1. ((non-proliferative or nonproliferative or preproliferative or pre-proliferative) adj retinopathy).tw.
2. early retinopathy.tw.
3. NPDR.tw.
4. 1 or 2 or 3
5. exp *Diabetic Retinopathy/
6. 4 and 5
7. limit 6 to English language

(d) Searches for studies on laser in diabetic retinopathy

Ovid MEDLINE 1946 to August Week 2 2013, Ovid MEDLINE In-Process & Other Non-Indexed Citations August 27, 2013; EMBASE 1974 to 2013 August 27

1. exp *diabetic retinopathy/
2. diabetic retinopathy.m_titl.
3. (laser or photo-coagulation or photocoagulation or panretinal or pan-retinal or PRP).m_titl.
4. 1 and 2
5. 3 and 4
6. limit 5 to English language

The Cochrane Library

Cochrane Central Register of Controlled Trials: Issue 8 of 12, August 2013.

There are 79 results from 71,0762 records for your search on "(laser or photocoagulation or photo-coagulation) and diabetic retinopathy and (NPDR or non-proliferative or non-proliferative or pre-proliferative or preproliferative) in title abstract keywords in Trials".

(e) Searches of progression of diabetic retinopathy
These searches below were done to inform the background section and the model.

EMBASE 1974 to 2013 September 19; Ovid MEDLINE 1946 to September Week 2 2013; Ovid MEDLINE In-Process & Other Non-Indexed Citations September 19, 2013

1. diabetic retinopathy.m_titl.
2. exp Disease Progression/
3. (progression or natural or course).m_titl.
4. exp Diabetic Retinopathy/
5. 1 and 4
6. 2 and 3 and 5
7. limit 6 to English language

Resulted in 300 records.

(f) Searches for adverse effects of lasers from non-randomised controlled trial studies

The EndNote database created from previous searches for PRP and lasers was searched using the following keywords:

(adverse or risk* or harm* or side effect* or safety or pain or visual loss or complication*) and (laser or (photocoagulation or panretinal or pan-retinal or scatter or PRP).

The results of this search were then supplemented with searches of MEDLINE and EMBASE.

Ovid MEDLINE 1946 to November Week 3 2013

1. exp Diabetic Retinopathy/
2. Laser Coagulation/ae, ct [Adverse Effects, Contraindications]
3. 1 and 2
4. limit 3 to English language

EMBASE 1974 to 2014 Week 02

1. exp Diabetic Retinopathy/
2. exp laser coagulation/ae [Adverse Drug Reaction]
3. limit 1 to English language

(g) Quality of life searches for diabetic retinopathy after pan-retinal photocoagulation

Searches of existing databases created from the previous searches above were done using the keywords 'quality of life' and 'laser or photocoagulation'. These records were exported into a new EndNote database and also supplemented with the following database searches.

Ovid MEDLINE In-Process & Other Non-Indexed Citations February 10, 2014; Ovid MEDLINE 1946 to January Week 5 2014; EMBASE 1974 to 2014 February 10 – Retrieved 36

1. exp "Quality of Life"/
2. quality of life.tw.
3. 1 or 2
4. exp Laser Coagulation/
5. (laser or photocoagulation).tw.
6. 4 or 5
7. 3 and 6
8. limit 7 to English language
9. exp Diabetic Retinopathy/
10. diabetic retinopathy.mp.
11. 9 or 10
12. 8 and 11
13. limit 12 to English language

The resulting EndNote database had 80 references, of which 16 were selected for the section on the quality for DR after PRP.

(h) Searches for ongoing or recently completed research

Searches were done on 16 January 2014 using the keywords "diabetic retinopathy AND (laser OR photocoagulation OR PRP OR scatter)".

Sources searched were ClinicalTrials.gov, WHO, Clinical Trials Registry Platform Search Portal, Current Controlled Trials, UK Clinical Trials Gateway, EU Clinical Trials Register, UK Clinical Research Network Study Portfolio.

Selected those where the condition being studies was diabetic retinopathy (but excluded those where it was only DMO) and the intervention included scatter or PRP laser alone or in combination with something else and where the results had not been found published in full or as a meeting abstract. Selected only those that had a RCT study design – apart from one observational study.

Also searched the Association for Research in Vision and Ophthalmology (ARVO) meeting abstracts website for recently completed RCTs from 2002 to present using the keywords *(randomized and laser) or (randomized and photocoagulation)* and selected those that were published between 2011 and 2013 and which were about PRP laser for DR.

(i) Cost-effectiveness search strategies

MEDLINE and EMBASE searches

1. exp quality adjusted life year/
2. quality adjusted life year.mp.
3. (QALY or QALYs).mp.
4. utilit$.mp.
5. (EuroQol or Euro Qol or Euro-Qol or EQ 5D or EQ5D or EQ-5D).mp.
6. (health utilities index or health-utilities-index or HUI).mp.
7. (SF 6D or SF6D or SF-6D).mp.
8. (short form 36 or short-form 36 or SF 36 or SF36 or SF-36).mp.
9. (quality of wellbeing or quality of well-being or QWB).mp.
10. (healthy years equivalent or hyes or hye).mp.
11. (time trade off or time trade-off or time-trade-off or TTO).mp.
12. (standard gamble or standard-gamble or SG).mp.
13. (15 D or 15D).mp.
14. ((willing$ adj2 pay) or WTP).mp.
15. Health Status/
16. exp Quality of Life/
17. (quality adj2 life).mp.
18. (health state* or health status).mp.
19. (hrql or hrqol or disability$ or disutility$).mp.
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp Cost-Benefit Analysis/
22. (cost effective$ or cost-effective$).mp.
23. (cost utility$ or cost-utilit$).mp.
24. (cost benefit$ or cost-benefit$).mp.
25. (willingness to pay or wtp or willingness-to-pay or willingness to accept or willingness-to-accept or net benefit or net-benefit or contingent valuation).mp.
26. (Pharmacoeconomic$ or pharmaco-economic$ or Economic analy$ or Economic evaluation$).mp.
27. (economic adj2 (evaluation$ or analy$ or study or studies)).mp.
28. (cost adj2 (evaluation$ or analy$ or study or studies or effective$ or benefit$ or utili$)).mp.
29. ((markov or decision) adj2 model).mp.
30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31. exp cost$/
32. exp Economics/
33. cost*.tw.
34. (resource adj2 unit).mp.
35. (resource adj2 item).mp.
36. resource$.mp.
37. 31 or 32 or 33 or 34 or 35 or 36
38. 20 or 30 or 37
39. diabetic retinopathy.m_titl.
40. exp Diabetic Retinopathy/
41. 39 or 40
42. 38 and 40
43. limit 42 to English language

Web of Knowledge/Web of Science

diabetic retinopathy AND ("quality of life" or Qol or hrqol or quality adjusted life year* or QALY* or cost* or economic* or pharmacoeconomic* or model* or euro-qol or utilit* or EuroQol or Euro Qol or EQ5D or EQ-5D or SF-36 or SF36 or time trade* or TTO or standard gamble or markov or visual analog* or discrete choice or health stat* or "willingness to pay").

(j) Additional sources searched

- *Auto-alerts* Weekly auto-alerts in Ovid MEDLINE and EMBASE were run for all of the above search strategies from August 2013 to March 2014 in order to capture new studies added after the initial searches.
- *Value in Health website* Also searched the website of the journal *Value in Health* using the search term "diabetic retinopathy" in the title or abstract for full text articles and meeting abstracts.
- *ARVO meeting abstracts* Searched the ARVO website for meeting abstracts (2002 to present) indexed in the *Investigative Ophthalmology & Visual Science* (*IOVS*) journal using the keywords "diabetic retinopathy and (laser or photocoagulation or PRP)".
- *Contact with authors* Contacted authors of some published and ongoing trials for further clarification.

Appendix 3 Major features of Early Treatment Diabetic Retinopathy Study early photocoagulation

(Taken from table 2, ETDRS #7.[40])

Scatter	Full	Mild
Burn characteristics		
Size	500 μm (at retina)	500 μm (at retina)
Exposure	0.1 seconds	0.1 seconds
Intensity	Moderate	Moderate
Number	1200–1600	400–650
Placement	Half burn apart > 2 DDs from fovea out to equator	≥ 1 burn apart > 2 DDs from fovea out to equator
No. of episodes	≥ 2	1
Lesion treated directly	Patches of NVE < 2 disc areas	Patches of NVE < 2 disc areas
Indications for follow-up treatment	Recurrent or new NVE or high-risk proliferative retinopathy	Recurrent or new NVE or high-risk proliferative retinopathy
Focal	**Direct**	**Grid**
Burn characteristics		
Size	50–100 μm	< 200 μm (at retina)
Exposure	0.05–0.1 seconds	0.05–0.1 seconds
Intensity	Sufficient to whiten or darken large microaneurysms	Mild
Number	Sufficient to satisfactorily treat all focal leaks	Sufficient to cover all areas of diffuse leakage and non-perfusion
Placement	500–3000 μm from centre of fovea	Spaced > 1 burn width apart 500–3000 μm from centre of fovea
No. of episodes	1	1
Indications for follow-up treatment	Presence of CSMO and treatable lesions at ≥ 4 months	Presence of CSMO and treatable lesions at ≥ 4 months

Appendix 4 Health-state transitions for the model (usual care and intervention)

TABLE 49 Transitions for treating all patients who develop moderate NPDR

Usual care arm	Intervention arm
Moderate NPDR will remain in that health state or progress to: 1. Severe NPDR 2. Severe NPDR and CSMO with/without VI 3. Dead	Moderate NPDR will remain in that health state or progress: 1. Severe NPDR 2. Severe NPDR and CSMO with/without VI 3. Dead
Severe NPDR will remain in that health state or progress to: 1. Severe NPDR and CSMO with/without VI 2. Early PDR 3. Dead	Severe NPDR will progress to: 1. Severe NPDR PT 2. Severe NPDR and CSMO with/without VI 3. Early PDR 4. Dead Severe NPDR PT will remain in that health state or progress to: 1. Severe NPDR and CSMO with/without VI 2. Early PDR 3. Dead Or regress to: (a) Moderate NPDR
Severe NPDR and CSMO with/without VI will remain in that health state or progress to: 1. Early PDR and CSMO with/without VI 2. Dead	Severe NPDR and CSMO with/without VI will progress to: 1. Severe NPDR and CSMO with/without VI post treatment 2. Early PDR and CSMO with/without VI 3. Dead Severe NPDR and CSMO with/without VI PT will remain in that health state or progress to: 1. Early PDR 2. Early PDR and CSMO with/without VI 3. Dead Or regress to: (a) Severe NPDR (b) Moderate NPDR
Early PDR will remain in that health state or progress to: 1. Early PDR and CSMO with/without VI 2. HR-PDR 3. HR-PDR and CSMO with/without VI 4. Dead	Early PDR will progress to: 1. Early PDR PT 2. Early PDR and CSMO with/without VI 3. HR-PDR 4. HR-PDR and CSMO with/without VI 5. Dead Early PDR PT will remain in that health state or progress to: 1. Early PDR and CSMO with/without VI 2. HR-PDR 3. HR-PDR and CSMO with/without VI 4. Dead

TABLE 49 Transitions for treating all patients who develop moderate NPDR (*continued*)

Usual care arm	Intervention arm
	Or regress to:
	(a) Severe NPDR and CSMO with/without VI (b) Severe NPDR (c) Moderate NPDR
Early PDR and CSMO with/without VI will remain in that health state or progress to: 1. HR-PDR 2. HR-PDR and CSMO with/without VI 3. SVL/blindness 4. Dead	Early PDR and CSMO with/without VI will progress to: 1. Early PDR and CSMO with/without VI PT 2. HR-PDR 3. HR-PDR and CSMO with/without VI 4. SVL/blindness 5. Dead Early PDR and CSMO with/without VI post treatment will remain in that health state or progress to: 1. HR-PDR 2. HR-PDR and CSMO with/without VI 3. Severe visual loss/blindness 4. Dead Or regress to: (a) Early PDR (b) Severe NPDR and CSMO with/without VI (c) Severe NPDR (d) Moderate NPDR
HR-PDR will progress to: 1. HR-PDR PT 2. HR-PDR and CSMO with/without VI 3. Severe PDR 4. Severe PDR and CSMO with/without VI 5. Dead	HR-PDR will progress to: 1. HR-PDR PT 2. HR-PDR and CSMO with/without VI 3. Severe PDR 4. Severe PDR and CSMO with/without VI 5. Dead
HR-PDR PT will remain in that health state or progress to: 1. HR-PDR and CSMO with/without VI 2. Severe PDR 3. Severe PDR and CSMO with/without VI 4. Dead	HR-PDR PT will remain in that health state or progress to: 1. HR-PDR and CSMO with/without VI 2. Severe PDR 3. Severe PDR and CSMO with/without VI 4. Dead
Or regress to: (a) Early PDR and CSMO with/without VI (b) Early PDR (c) Severe NPDR and CSMO with/without VI (d) Severe NPDR (e) Moderate NPDR	Or regress to: (a) Early PDR and CSMO with/without VI (b) Early PDR (c) Severe NPDR and CSMO with/without VI (d) Severe NPDR (e) Moderate NPDR
HR-PDR and CSMO with/without VI will progress to: 1. HR-PDR and CSMO with/without VI PT 2. Severe PDR 3. Severe PDR and CSMO with/without VI 4. SVL/blindness 5. Dead	HR-PDR and CSMO with/without VI will progress to: 1. HR-PDR and CSMO with/without VI PT 2. Severe PDR 3. Severe PDR and CSMO with/without VI 4. SVL/blindness 5. Dead
HR-PDR and CSMO with/without VI PT will remain in that health state or progress to: 1. Severe PDR 2. Severe PDR and CSMO with/without VI 3. SVL/blindness 4. Dead	HR-PDR and CSMO with/without VI PT will remain in that health state or progress to: 1. Severe PDR 2. Severe PDR and CSMO with/without VI 3. SVL/blindness 4. Dead

TABLE 49 Transitions for treating all patients who develop moderate NPDR (*continued*)

Usual care arm	Intervention arm
Or regress to:	Or regress to:
(a) HR-PDR (b) Early PDR and CSMO with/without VI (c) Early PDR (d) Severe NPDR and CSMO with/without VI (e) Severe NPDR (f) Moderate NPDR	(a) HR-PDR (b) Early PDR and CSMO with/without VI (c) Early PDR (d) Severe NPDR and CSMO with/without VI (e) Severe NPDR (f) Moderate NPDR
Severe PDR will progress to:	Severe PDR will progress to:
1. Severe PDR PT 2. Severe PDR and CSMO with/without VI 3. SVL/blindness 4. Dead	1. Severe PDR PT 2. Severe PDR and CSMO with/without VI 3. SVL/blindness 4. Dead
Severe PDR PT will remain in that health state or progress to:	Severe PDR PT will remain in that health state or progress to:
1. Severe PDR and CSMO with/without VI 2. SVL/blindness 3. Dead	1. Severe PDR and CSMO with/without VI 2. SVL/blindness 3. Dead
Or regress to:	Or regress to:
(a) HR-PDR and CSMO with/without VI (b) HR-PDR (c) Early PDR and CSMO with/without VI (d) Early PDR (e) Severe NPDR and CSMO with/without VI (f) Severe NPDR (g) Moderate NPDR	(a) HR-PDR and CSMO with/without VI (b) HR-PDR (c) Early PDR and CSMO with/without VI (d) Early PDR (e) Severe NPDR and CSMO with/without VI (f) Severe NPDR (g) Moderate NPDR
Severe PDR and CSMO with/without VI will progress to:	Severe PDR and CSMO with/without VI will progress to:
1. Severe PDR and CSMO with/without VI PT 2. SVL/blindness 3. Dead	1. Severe PDR and CSMO with/without VI PT 2. SVL/blindness 3. Dead
Severe PDR and CSMO with/without VI PT will remain in that health state or progress to:	Severe PDR and CSMO with/without VI PT will remain in that health state or progress to:
1. SVL/blindness 2. Dead	1. SVL/blindness 2. Dead
Or regress to:	Or regress to:
(a) Severe PDR (b) HR-PDR and CSMO with/without VI (c) HR-PDR (d) Early PDR and CSMO with/without VI (e) Early PDR (f) Severe NPDR and CSMO with/without VI (g) Severe NPDR (h) Moderate NPDR	(a) Severe PDR (b) HR-PDR and CSMO with/without VI (c) HR-PDR (d) Early PDR and CSMO with/without VI (e) Early PDR (f) Severe NPDR and CSMO with/without VI (g) Severe NPDR (h) Moderate NPDR
SVL/blindness will remain in that health state or progress	SVL/blindness will remain in that health state or progress
1. Dead	1. Dead
Dead will remain in that health state	Dead will remain in that health state

PT, post treatment; VI, visual impairment.

**EME
HS&DR
HTA
PGfAR
PHR**

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