The Royal College of Ophthalmologists

Diabetic Retinopathy Guidelines

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Preface

Since the previous edition of the Royal College of Ophthalmologists Diabetic Retinopathy Guidelines, population based digital image photographic DR screening programmes have become established throughout the United Kingdom. A number of clinical studies have expanded the understanding of the condition and management of DR. Similarly technological advances in retinal imaging especially the high definition OCT scans, wide field retinal angiography and new laser technology using multispot and micropulse abilities have widened clinical knowledge and treatment options. Medical interventions – systemic as well as ocular have revolutionised the way diabetic patients are managed in the eye clinics. The new guidelines reflect on all these changes and aim to provide up to date guidance for busy clinicians. These guidelines will be kept up to date with on line updates of major developments in the field.

The aim of the guidelines is to provide evidence-based, clinical guidance for the best management of different aspects of diabetic eye disease. The foundations of the guidelines are based on evidence taken form the literature and published trials of therapies as well as consensus opinion of a representative expert panel convened by the Royal College of Ophthalmologists with an interest in this condition. The scope of the guidelines is limited to management of diabetic retinopathy with special focus on sight threatening retinopathy. It offers guidance regarding service set up to facilitate delivery of optimal clinical care for patients with retinopathy. The guidelines are prepared primarily for ophthalmologists, however they are relevant to other healthcare professionals, service providers and commissioning organisations as well as patient groups. The guidelines do not cover rare, complex, complicated or unusual cases. It is recommended that readers refer to other relevant sources of information such as summaries of product characteristics (SPCs) for pharmaceutical products as well as NICE and GMC guidance.

The new guidelines incorporate established and applicable information and guidance from the previous version with revision while some chapters are extensively revised and some new chapters are added. As stated in the previous version, the guidelines are advisory and are not intended as a set of rigid rules, since individual patients require tailored treatment for their particular condition. However, it is hoped that if used appropriately, the guidelines will lead to a uniformly high standard of management of patients with diabetic retinopathy.

Search Strategy:

Medline was used by individual authors of each section using search terms relevant to subject mater voered in the chapter, scanning the database for duration up to 2011. Previous edition of the RCOphth guidelines were used as reference source.

EVIDENCE is graded on three levels:

Level 1: evidence based on results of randomised controlled trials (RCTS) power calculations or other recognised means to determine statistical validity of the conclusion.

Level 2: evidence based on results of case studies, case series or other non-randomise prospective or retrospective analysis of patient data.

Level 3: evidence based on expert opinion, consensus opinion or current recognised standard of care criteria where no formal case series analysis was available.

RECOMMENDATIONS for practice are based on treatment protocols and measures which were recognised to improve patient care and/or quality of life based on:

Level A: where strength of evidence was universally agreed

Level B: where the probability of benefit to the patient outweighed the risks

Level C: where it was recognised that there was difference of opinion as to the likely benefit to the patient and decision to treat would be based after discussion with the patient

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SECTION 1: TERMINOLOGY AND DISEASE DEFINITION

Diabetes mellitus is defined as a metabolic disorder of multiple aetiologies characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both[1].

1.1 DEFINITION OF DIABETIC RETINOPATHY

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.

1.2 CLASSIFICATION OF DIABETIC RETINOPATHY

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. Classification and severity grading of diabetic retinopathy 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. However, this grading may not accurately reflect functionally severe disease since maculopathy with severe visual loss may occur in the presence of moderate ophthalmoscopic signs. Two different approaches to classification have emerged: (a) those designed to cover the full range of retinopathy and aimed at the ophthalmologist that are based on the original Airlie House / EDTRS classification and (b) those which are proposed for use in population screening.

1.2.1 Full disease classifications

Full dissease classifications have developed from the original Airlie House classification classification that was modified by the Diabetic Retinopathy Study (DRS)[2] developed for the Early Treatment Diabetic Retinopathy Study (ETDRS)[3] aimed at grading retinopathy in the context of overall severity of ophthalmoscopic signs. Modified and simplified versions have been developed and used for research programmes and in clinical practice. A simplified version was developed for the first version of these guidelines in 1997 [4]. A reduced version of the ETDRS classification aimed at countries without systematic screening programmes was endorsed in 2003 by the American Academy of Ophthalmology Guidelines Committee[5] and used in clinical trials (e.g. ETDRS). The latter classification was developed in recognition of the need for a clinical grading system that would reflect the vision threatening risk of diabetic retinopathy. This describes three stages of low risk non-proliferative retinopathy, a fourth stage of severe non-proliferative retinopathy and a fifth grade of proliferative retinopathy. In addition macular oedema

is determined as absent or present and further sub classified on the basis of involvement of the centre of the macula.

1.2.2 Population screening classifications

The National Screening Committee (NSC)[6] has adopted a classification for use in England and Wales aimed at detection of that level of retinopathy sufficiently severe to merit referral of the patient for expert ophthalmological opinion and possible treatment. A Scottish Diabetic Retinopathy Grading Scheme has also recently been introduced[7.] The NSC classification adopts a simplified approach to grading retinopathy based on features which a non-ophthalmologist / accredited photographic grader might be faced with in a population of diabetic patients. This classification identifies four types of presentation of fundus disease, namely retinopathy (R), maculopathy (M), photocoagulation (P) and unclassifiable (U) (see Appendix).

1.2.3 Differences between classification systems

There is considerable overlap between the various classifications. They all recognise the two basic mechanisms leading to loss of vision: retinopathy (risk of new vessels) and maculopathy (risk of damage to the central fovea).The differences between classifications relate mainly to levels of retinopathy and also to terminology used. Below are described the similarities and differences in various classifications, with the aim of permitting ready cross-reference. Alternative terminology in common use is shown in parentheses.

1.2.3.1 Retinopathy

Diabetic retinopathy is classified according to the presence or absence of abnormal new vessels as:
• Non-proliferative (background/preproliferative) retinopathy
• Proliferative retinopathy
Each has a different prognosis for vision.

1.2.3.2 Non-proliferative diabetic retinopathy (NPDR) (background/preproliferative)

In the international (AAO) classification, NPDR is graded as:
• Mild
• Moderate
• Severe

In the NSC-UK classification, NPDR is graded as:
• Background (Level R1)
• Pre-proliferative (Level R2)

In the Scottish Diabetic Retinopathy Grading Scheme, NPDR is graded as:
• Mild background (Level R1)
• Moderate background (Level R2)
• Severe background (Level R3)

1.2.3.3 Proliferative diabetic retinopathy (PDR)

PDR (Level R3 in the NSC-UK grading and R4 in Scotland) is described according to:

(a) location

• new vessels on the disc (NVD) or within 1 disc diameter (DD)of the margin of the disc
• new vessels elsewhere in the retina (NVE) (more than 1DD from the disc)

(b) severity

early PDR, PDR with high risk characteristics, florid PDR and gliotic PDR.
"Involutionary" PDR is used to describe new vessels which have regressed in response to treatment or (rarely) spontaneously.

The different classifications referred to above can be approximately mapped to each other as shown in Table 1.1

Table 1.1
Approximate equivalence of currently used alternative classification systems for diabetic retinopathy

ETDRS (ref 1)	**NSC (ref 4)**	**SDRGS (ref 5)**	**AAO (ref 3) International**	**RCOphth (ref 2)**
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			Mod NPDR	
43 moderate NPDR	R2 preproliferative	R2 moderate BDR		High risk
47 Moderately severe NPDR				
53A-D severe NPDR		R3 severe BDR	Severe NPDR	
53E very severe NPDR				
61 mild PDR	R3 proliferative	R4 PDR	PDR	PDR
65 Moderate PDR				
71, 75 High risk PDR				
81, 85 Advanced PDR				

Legend:

ETDRS = Early Treatment Diabetic Retinopathy Study; AAO = American Academy of Ophthalmology; NSC = National Screening Committee; SDRGS = Scottish Diabetic Retinopathy Grading Scheme; NPDR = non-proliferative diabetic retinopathy; BDR = background diabetic retinopathy; PDR = proliferative diabetic retinopathy; HRC = high risk characteristics

1.2.4. Diabetic maculopathy (DM)

Retinopathy which affects the macula is separately described as diabetic maculopathy. DM is further classified as:
• Focal oedema
• Diffuse oedema
• Ischaemic or
• Mixed
DM may be tractional due to vitreoretinal pathology or non-tractional (intraretinal). In the classification systems described above various definitions of maculopathy have been given.**(Level 1)**

1.3 DEFINITIONS OF THE OCULAR COMPLICATIONS ASSOCIATED WITH DIABETIC RETINOPATHY

The ocular complication of diabetes may be specific to progression of the ocular disease or, more commonly, may be non-specific recognised associations of diabetes in the eye.

Table 1.2 Complications linked to Diabetic Retinopathy

Specific	Non-Specific
Retinal Detachment Cataract	
Rubeosis Iridis	
Cataract	Glaucoma
	Retinal Vein Occlusion/Optic Disc Swelling
Optic Neuropathy	

1.3.1 Non-specific ocular disease associations

1.3.1.1 Cataract

Cataract is defined as opacification of the lens and is common in older age populations. Age-related cataract occurs earlier in patients with diabetes.

1.3.1.2 Glaucoma

Glaucoma is defined as loss of vision due to raised intraocular pressure and occurs in two forms: primary or secondary. Primary glaucoma may present as acute glaucoma or chronic glaucoma. Patients with diabetes were previously thought to have a greater risk of developing primary chronic glaucoma with loss of visual field (side vision).[8] However, more recent papers suggest that diabetes is not a greater risk factor, but simply that glaucoma was found more readily. [9-11] Patients with PDR are at risk of developing secondary glaucoma, particularly neovascular (rubeotic) glaucoma (see below).

1.3.1.3 Retinal Vein Occlusion / Optic disc swelling

Patients with diabetes are at higher risk of developing optic nerve disease due to vascular occlusion, which is distinct from diabetes-specific optic neuropathy (see below) and usually occurs in older patients with Type 2 diabetes and hypertension. This may be a form of ischaemic optic neuropathy.

1.3.2 Specific complications

1.3.2.1 Retinal Detachment

Retinal detachment is caused by the accumulation of fluid between the neural retina and the retinal pigment epithelium and in non-diabetic patients most commonly results from a tear in the retina (rhegmatogenous retinal detachment). In patients with PDR, tractional retinal detachment may occur due to condensation and contraction of the vitreous gel in association with haemorrhage and fibrosis (plus gliosis). Tractional retinal detachment may progress to combined tractional and rhegmatogenous retinal detachment. Central vision is lost when the macula is involved.

1.3.2.2 Rubeosis iridis and rubeotic glaucoma

Rubeosis iridis is the growth of new vessels on the iris in eyes with advanced retinal ischaemia. Rubeosis – neovascularisatiion of iris (NVI) may induce a severe form of intractable glaucoma (see below) with growth of new vessels in the anterior chamber angle (NVA). If uncontrolled, NVA leads to closure of the aqueous fluid drainage route in the anterior chamber angle of the eye by fibrovascular tissue.

1.3.2.3 Cataract

A specific form of “snow-flake” cataract is recognised in younger diabetics. In addition, a rare form of “osmotic” reversible cataract occurs in young diabetic patients, including infants, due to rapid changes in fluid electrolyte balance in severe uncontrolled diabetes.

1.3.2.4 Optic neuropathy

Patients with diabetes may rarely experience optic neuropathy, which presents as swelling of the optic discs associated with gradual reduction in visual acuity.

1.3.2.5 Other ocular pathology in diabetes

Ocular muscle palsies are not uncommon in association particularly with Type 2 diabetes. In addition, corneal epitheliopathy is common and a cause of poor epithelial wound healing especially after ocular surgery.

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SECTION 2: THE EPIDEMIOLOGY OF DIABETES AND DIABETIC RETINOPATHY

2.1. INTRODUCTION

Diabetes is a chronic debilitating metabolic disorder that has reached epidemic proportions in the developed and developing world. Both the prevalence and incidence of diabetes continues to rise inexorably with no country in the world spared. Diabetes poses the most important threat to public health in the 21st century consuming a disproportionate share of health care resources owing to its deleterious effects on the micro and macro vasculature with effects on every organ in the body[1] .

2.2 DEFINITIONS OF INCIDENCE AND PREVALENCE

2.2.1 Disease Incidence

Disease incidence is the number of new cases of a particular disease occurring over a defined time period. It may also be expressed as the percentage of cases progressing to the next stage of a disease over a defined time period. It may also be expressed as the number of patients per 100 or per 1000 patient years

2.2.2 Prevalence

Point prevalence: the proportion of cases of a disorder or disease in a particular population at a particular point in time.

Lifetime prevalence: the proportion of the population who have a history of a given condition at a particular point in time.

2.3 INCIDENCE AND PREVALENCE OF DIABETES

2.3.1 Worldwide reports

The incidence of type 2 diabetes in particular has risen dramatically[2] driven by longevity combined with sedentary lifestyles and increasing levels of obesity. In 2004, Wild[3] suggested that the most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age. (**Level 3**)

The International Diabetes Federation (IDF) published data[4] in 2006 which showed that diabetes affects 246 million people worldwide, with 46% of all those affected in the 40-59 working age group. The new data (http://www.idf.org/diabetesatlas/5e/the-global-burden) predict that the total number of people living with diabetes will rise to 552 million by 2030. (**Level 3**)

In 2009, the International Diabetes Federation launched a 5-year programme[5] on education and prevention. Every year there are 4 million deaths worldwide due to diabetes. They estimated that 285 million people across the world are living with diabetes; an estimated 70% are in low-income and middle-income countries (LMIC). Around 90% of the burden is caused by type 2 diabetes, which is a preventable chronic disease. (**Level 3**)

2.3.2 Reports from the UK

1. In 2000, Ehtisham[6] reported the first cases of insulin resistant diabetes (type 2) in young obese female pubertal children mainly of South Asian origin living in the UK. (**Level, 2**)

2. In 2002, Feltbower[7] reported an increasing incidence of type 1 diabetes in South Asians in Bradford. (**Level 2**)

3. In 2007, Evans[8] interrogated a diabetes clinical information system in Tayside, Scotland, and showed a doubling in incidence and prevalence of type 2 diabetes between 1993 and 2004, with statistically significant increasing trends of 6.3 and 6.7% per year respectively. (**Level 2**)

4. Gonzalez[9] used the Health Improvement Network database in the UK to estimate the incidence and prevalence of type 1 and type 2 diabetes in the UK general population from 1996 to 2005 showing an increase in prevalence from 2.8% in 1996 to 4.3% in 2005. (**Level 2**)

5. The Office for National Statistics[10] estimated that resident population of the UK was 61,792,000 in mid-2009. The UK population is projected to increase by an average annual rate of growth of 0.7 per cent, an increase of 4.3 million by 2018. The Office for National Statistics estimated[11] that resident population of England was 51,456,400 in 2008. With a 0.7% increase per year, the total population in England in 2010 is estimated to be 52,176,789. From DH screening figures[12] we know that practices have identified 2,379,792 people with diabetes over the age of 12 years in England in 2010. A survey[13] conducted by the Royal College of Paediatricians between January and March 2009 identified approximately 9296 children in England with diabetes under the age of 12 years. Hence the total number of people with diabetes in 2010 in England is estimated to be 2,389,088. (**Level 2**) The percentage of known people with diabetes in England in 2010 is, therefore, estimated to be 4.58% of the total population. In the Diabetes UK report 'Diabetes in the UK 2010: Key statistics on diabetes', it is quoted that in 2009, the prevalence of diabetes in the adult population across the UK was 5.1% based on a number of people with diabetes of 2,213,138.

6. The United Kingdom Asian Diabetes Study[14](UKADS) was a cluster randomized controlled trial designed to evaluate the benefits of an enhanced diabetes care package for people of south Asian ethnicity with type 2 diabetes in Coventry and Birmingham, U.K. In a sub study of UKADS[15], comprising a cross-sectional prevalence survey using retinopathy screening data from 10 general practices in the Foleshill area of Coventry in central England, the

grade of retinopathy was compared between 421 patients of south Asian ethnicity and 614 white European patients. Patients of south Asian ethnicity had a significantly higher prevalence of diabetic retinopathy and maculopathy, with significantly elevated systolic and diastolic blood pressure, haemoglobin A1C, and total cholesterol; lower attained age; and younger age at diagnosis. Earlier onset of disease and higher levels of modifiable risk factors in south Asians make early detection of diabetes, annual referral for retinal screening, and intensive risk factor control key elements in addressing this health inequality (**Levels 1,2**)

2.4 INCIDENCE & PREVALENCE OF DIABETIC RETINOPATHY

2.4.1 Prevalence of diabetic retinopathy and sight threatening diabetic retinopathy

In 1992, Klein[16] reported results from the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR study), which was a population-based study in southern Wisconsin of 996 insulin-taking younger-onset diabetic persons (given diagnoses of diabetes under 30 yrs.) and 1,370 patients given diagnoses of diabetes at age 30 years or older who were examined using standard protocols to determine the prevalence and severity of diabetic retinopathy and associated risk variables. Proliferative diabetic retinopathy (PDR) was found to be a prevalent complication - 23% in the younger-onset group, 10% in the older-onset group that takes insulin, and 3% in the group that does not take insulin. In 1995 Klein[17] reported the incidence of macular oedema over a 10 year period to be 20.1% in the younger-onset group, 25.4% in the older-onset group taking insulin, and 13.9% in the older-onset group not taking insulin. (**Level 1**)

In 1998, Kohner[18] reported baseline retinopathy levels in 2964 patients with newly diagnosed type 2 diabetes enrolled in the United Kingdom Prospective Diabetes Study (UKPDS). Retinopathy, defined as microaneurysms or worse lesions in at least 1 eye, was present in 39% of men and 35% of women. Marked retinopathy with cotton wool spots or intraretinal microvascular abnormalities was present in 8% of men and 4% of women. (**Level 1**)

In 2002, Younis[19] reported baseline results from population screening in Liverpool of 831 people with Type 1 diabetes and 7231 people with Type 2 diabetes. The results showed a baseline for Type 1 of any DR 45.7%, PDR 3.7% and STED 16.4%. Baseline for Type 2 group of any DR 25.3%, PDR 0.5% and STED 6.0%. (**Level 1**)

Individual case reports exist to show that children as young as 12 years of age can present with pre-proliferative DR[20] or as young as 8 years with a duration of diabetes of some 5.6 years, with background diabetic retinopathy[21] . (**Level 3**)

Many studies exist on diabetic eye disease in different parts of the world[22] -[33] all of which provide a picture of increasing concern with respect to the prevalence of this disorder (**Levels 2 and 3**)

Two studies[34] [35] have demonstrated that, if one screens for type 2 diabetes, the prevalence of diabetic retinopathy in screen positive patients (7.6% and 6.8%) is

much lower than the prevalence in the known population of people with diabetes. (**Level 3**)

Beulens[36] reported that baseline retinopathy levels (ETDRS ≥20) of 1602 patients with type 2 diabetes in the ADVANCE study was 40.1% indicating a high prevalence of the early features of microvascular damage. (**Level 1**)

2.4.2. Incidence and progression of DR

In 1981, Palmberg[37] described a study of the natural history of diabetic retinopathy in 461 people with juvenile-onset insulin-dependent diabetes mellitus (IDDM). At diagnosis no DR was found, with prevalence of 50% at 7 yrs duration and 90% at 17-50 yrs duration. Proliferative diabetic retinopathy (PDR) was first seen at 13 yrs, with 26% prevalence at 26-50 yrs duration. (**Level 1**)

In a longitudinal analysis of the WESDR study in 1984 and 1989, Klein[38-41] reported that for the 154 people with IDDM diagnosed > 30 yrs. with no DR at first visit, 47% developed DR after 4 yrs. For the 418 people with IDDM diagnosed > 30 yrs. with no PDR at first visit, 7% developed PDR after 4 years and worsening of DR in 34%. For the 320 non IDDM diagnosed > 30 yrs. with no DR at first visit, 34% (developed DR after 4 yrs. For the 486 non IDDM diagnosed > 30 yrs. with no PDR at first visit, 2% developed PDR after 4 years and worsening of DR in 25%. (**Level 1**)

Further studies that have shown clear evidence that sight-threatening diabetic retinopathy has a recognisable latent or early symptomatic stage [42-53] .

The Diabetes Control and Complications Trial[54-56] (DCCT) included 1441 people with type 1 DM, 726 with no DR at base line (the primary-prevention cohort), and 715 with mild to moderateretinopathy (the secondary-intervention cohort), with mean follow-up of 6.5 years. For the primary-prevention cohort, intensive therapy reduced the mean risk for the development of DR by 76 % (CI 62-85 %), compared with conventional therapy. For the secondary-intervention cohort, intensive therapy slowed the progression of DR by 54 % (CI 39-66 %) and reduced the development of PDR or severe NPDR by 47 % (CI 14-67 %). (**Level 1**)

The United Kingdom Prospective Diabetes Study[18 57-60] recruited 3867 with type 2 DM and the effect of intensive blood-glucose control with sulphonylureas or insulin was compared with conventional treatment. Compared with the conventional group, there was a 25% risk reduction (7-40, p=0.0099) in the intensive group in microvascular endpoints, including the need for retinal photocoagulation. Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint. (**Level 1**)

A systematic review published by Williams[27] in 2004 on the epidemiology of diabetic retinopathy and macular oedema concluded that studies of sufficient size to stratify for age and duration of eye disease show an increase in DR in older age groups with long-standing disease.(**Level 1**)

Grauslund[61] reported the 25 year incidence of proliferative retinopathy among population-based cohort of 727 type 1 Danish diabetic patients was 42.9%.(**Level 2**)

In 2008 and 2009, Klein[62 63] reported on the 25-year cumulative progression and regression of diabetic retinopathy (DR) and on the 25-year cumulative incidence of macular edema (ME) and clinically significant macular oedema (CSME) in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Klein demonstrated a reduction in incidence of PDR in more recently diagnosed cohorts. (**Level 2**)

In 2009, Wong[64] conducted a systematic review of rates of progression in diabetic retinopathy during different time periods. The authors concluded that since 1985, lower rates of progression to PDR and severe visual loss (SVL) were being reported by the studies included in the review. These findings may reflect an increased awareness of retinopathy risk factors; earlier identification and initiation of care for patients with retinopathy; and improved medical management of glucose, blood pressure, and serum lipids. (**Level 1**)

In 2010, Varma[65] demonstrated that the 4-year incidence and progression of DR and the incidence of clinically significant macular oedema (CSMO) are high among Latinos compared to non-Hispanic whites. (**Level 2**)

The incidence and progression of DR can be seen to be related to a variety of risk factors and these are considered further in Section 6.

2.4.3 Incidence and prevalence of cataract in people with diabetes

In 1995, Klein[66] reported the occurrence of cataract surgery in people in the WESDR study. In the younger-onset group there was an 8.3% (95% confidence interval, 6.2%, 10.8%) cumulative incidence, and in the older-onset group there was a 24.9% (95% confidence interval, 21.3%, 28.5%) cumulative incidence of cataract surgery in the ten-year interval. Statistically significant characteristics related to cataract surgery in the younger-onset group in multivariate analysis were age, severity of diabetic retinopathy, and proteinuria. In the older-onset group, age and use of insulin were associated with increased risk. (**Level 1**)

Studies by Henricsson[67] , Chew[68] , Mittra[69] , Chung[70] , Somaiya[71] and Liao[72] have shown an increased risk of ocular complications in diabetics after cataract surgery but the same studies and those by Dowler[73] , Flesner[74] , Squirrell[75] and Hauser[76] have shown that modern surgical techniques have minimised risks. Macular oedema before surgery is the most common condition that limits post-operative visual recovery[68 70 73] . Thus, pre-operative and or perioperative management of DMO needs careful planning. (See Sections 11 and 13).

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SECTION 3: DIABETIC RETINOPATHY IN CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS

3.1 PREVALENCE OF DIABETIC RETINOPATHY IN TYPE 1 DIABETES MELLITUS (T1DM)

The incidence of diabetic retinopathy in children has been studied by several groups over the last decade. Owing to differences in technique and study population, there is a range of prevalence from "snap shot" studies published in the medical literature **(Level 2)**.

Table 1 Prevalence of Diabetic Retinopathy during adolescence[1]

Age at fundus photography	Prevalence of DR
10-13 years	1%
14-15 years	5.8%
16-18 years	17.7%

Massin et al (see table 1) undertook retinal photographic screening of 504 T1DM children at summer camp, aged between 11 and 17 years (mean 15.5 years). Of this self-selected group, 4.6% had DR on fundus photography, only one of whom was under age 12 years.

Table 2 Prevalence of Diabetic Retinopathy six years after diagnosis[2]

Children under age 11	8%
Pre pubertal children	12%
Adolescents	25%
Pubertal adolescents	19%

Donaghue et al found that retinopathy was commonly found in children with T1DM six years after diagnosis (table 2)[2].

Maguire et al studied 1000 children with T1DM performing annual examinations. At baseline examination, 20% had some retinopathy. In children age under 11 years at last review, retinopathy regressed in 80% and progressed in 0%. In children over 11 years at final review, it regressed in 36% and progressed in 13%. No child developed PDR nor needed laser photocoagualtionor surgical treatment[3].

The incidence of reported complications in many areas with specialised clinics has declined due to major changes in diabetes management and regular screening[4] **(Level 2)**. Following this decline in early retinopathy from 1990-2002 from 16% to 7%), rates have remained static[5].

3.2 PREVALENCE OF DIABETIC RETINOPATHY IN TYPE 2 DIABETES MELLITUS (T2DM)

There is sparse literature regarding DR in children and adolescents with T2DM, although the worldwide increased incidence is widely acknowledged, with between 8 and 45% of newly diagnosed diabetes in childhood being T2DM[4].

Data reported by the National Paediatric Diabetes Audit show that T2DM accounts for 1.5% of the 25,000 young (under age 25 years) diabetic persons in England and Wales[6].

In young people, T2DM develops at around 13.5 years during the peak of physiological puberty insulin resistance. It occurs more commonly in non-Caucasian races. There is insufficient data at present to comment upon relative incidence of retinopathy in young people with T1DM vs. T2DM[7].

In terms of prevalence, Eppens et al compared fundus photographs of 1433 children with T1DM and 68 with T2DM. Those with T2DM had shorter duration DM, older age at diagnosis and higher rates of obesity and hypertension. Those with T1DM had higher rates of DR (20% vs. 4%) although for all T2DM patients in the study, duration of DM was less than 3 years[8] **(Level 2)**.

3.3 RISK FACTORS

3.3.1 Non modifiable

a) Duration and age at onset

Duration of diabetes is a major risk factor in the development of DR in children. In children diagnosed before age 5, the survival period without retinopathy was longer compared with those diagnosed after age 5 years. The risk of clinical retinopathy increased by 28% for every prepubertal year of duration and 36% for each postpubertal year of duration[9].

The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) showed that in patients diagnosed before age 30 years, 97% had retinopathy and 25% had PDR at 15 years post diagnosis. However with improved management of diabetes in the past decade, these rates of DR development are thought to be in decline[10].

Botero et al review the risk of developing DR in young people who are diagnosed with T2DM before the age of 20 years[11]. In PimaIndians 45% of T2DM had retinopathy by age 30 years, although the risk of developing DR is lower than in patients diagnosed with T2DM later in life. In Japanese young diabetic persons, DR occurs more frequently than in T1DM and was found to progress more rapidly than in T1DM[11].

Olsen et al found that after 20 years duration T1DM, 70-90% patients will develop DR regardless of HbA1c[12]. After adjustment for age, only duration of diabetes is significantly associated with DR[1]. **(Level 2)**

b) Puberty

Pre pubertal children younger than twelve years rarely develop complications of diabetes[13]. Puberty is a risk factor for developing retinopathy because of the physiological increased resistance to insulin that everyone acquires at this age. Insulin like growth factor, growth hormone and poor control in adolescence may have an accelerating effect on progression of DR. Adolescence is often associated with deterioration in metabolic control due to a variety of physiological and psychosocial factors. Klein et al found that diabetes duration post menarche was associated with 30% increase risk or retinopathy compared with diabetes duration before menarche[14] **(Level 2)**.

WESDR identified adolescents age 15-19 as having the highest rate of progression to sight threatening disease within 10 years compared with paediatric or adult patients[15].

There has been some discussion in the literature as to the protective effect of prepubertal years of T1DM on the development of DR. There is some consensus that prepubertal years may delay onset of DR but do not protect against it. Donaghue et al found the survival free period from DR was significantly longer for those diagnosed before age 5 than for those diagnosed after age 5 years. Time to onset of complications increased progressively with longer diabetes duration before puberty[9]. Olsen et al consider that years after puberty carry double the risk of years before puberty in terms of onset of DR[16].

Adolescents have a higher risk of progression to vision threatening retinopathy compared to adult patients with diabetes. The progression may be rapid especially in those with poor glycaemic control. Adolescence is a time when efforts should be directed to screening for early signs of DR and modifiable risk factors[3].

3.3.2 Modifiable Risk Factors

a) Diabetic control/ HbA1c

Within the DCCT was a cohort of 195 adolescents. Compared with conventional treatment, those on intensive treatment reduced the risk of and progression of background (nonproliferative) retinopathy by 53%[17]. The long lasting effects of good control were demonstrated in the EDIC study which followed these children after cessation of the study. It found that although there was no longer any difference in HbA1c between the two groups, those who have previously been in the "intensive" treatment group were less likely to have retinopathy [18] **(Level 1)**.

The American Academy of Paediatrics considers those adolescents with T1DM for more than 10 years and an HbA1c of >10% are at risk of developing "florid" DR which may progress in a few months to sight threatening disease, and these patients should be seen frequently for fundus examination[19].

It is important however to consider the adverse effect hypoglycaemia can have on the developing brain and intensive therapy should be balanced against this risk, especially in young children.

b) Blood Pressure

Massin et al study of 504 T1DM at a summer camp also looked at the effect blood pressure may have on likelihood of developing DR. Those children found to have DR had higher blood pressure than those without DR[1]. Gallego et al examined the relationship between blood pressure and the development of early DR in adolescents with childhood onset T1DM. 1869 children under the age of 15 years underwent fundus photography. The median duration of T1Dm was 4.9 years. Over the course of the study, 36% developed DR, with 0.02% (35 patients) developing moderate-severe PPDR. Only 1 patient developed PDR. They found that diastolic and systolic BP, duration of DM and HbA1c were higher in patients who developed DR[20] **(Level 2).**

c) Body Mass Index(BMI)

High BMI has been shown to be a risk factor for developing retinopathy in adolescence[7] **(Level 2)**.

d) Vitamin D

There has been recent research interest in the role of Vitamin D in the development of DR in children. Kaur et all found 25-hydroxyvitamin D levels were more likely to be reduced in children and adolescents with DR, and postulate this reduction to be due to the inflammatory and angiogenic effects of vitamin D deficiency[21]. **(Level 2)**. This may have implications for areas with a south Asian population, in whom vitamin D deficiency in childhood is common.

e) Smoking

The effect of smoking on retinopathy in children is not clear[4].

f) Pregnancy

There are no studies which look at the effect of pregnancy in adolescence on DR in T1DM

3.4 SCREENING FOR DIABETIC RETINOPATHY IN CHILDREN AND ADOLESCENTS

The method of screening for DR is covered elsewhere in this guideline.

There are various recommendations in the literature regarding the age at which screening for DR should commence **(Level 3)**.

Organisation/author	Recommendation
American Academy of Ophthalmology[22]	Annual screening to start 5 years after onset of diabetes
American Diabetic Association[23]	Screening to commence 3-5 years after diagnosis, and once the patient is 10 years old
American Academy of Pediatrics[19]	Initial examination at 3-5 years after diagnosis if over age 9, and annually thereafter
Maguire et al[3]	Adolescents with reasonable metabolic control to be screened every 2 years. Those with duration of diabetes >10 years, poor control or significant DR should be screened more frequently
ISPAD Clinical Practice Consensus Guideline 2009[4]	Annual screening from age 11 after 2 years duration, and from age 9 years for those with 5 years duration. Ophthalmological monitoring is recommended before initiation of intensive treatment and at 3 month intervals for 6-12 months thereafter for patients with long-standing poor glycaemic control particularly if retinopathy severity is at or past the moderate non-proliferative stage at the time of intensification.
American Association for Paediatric Ophthalmology and Strabismus[19]	Concerning T2DM: "There are no guidelines regarding screening for DR in this groups of children"

3.5 MANAGEMENT AND TREATMENT OF DIABETIC RETINOPATHY IN CHILDHOOD AND ADOLESCENCE

Children and adolescents with DR should be managed by an ophthalmologist with expertise in diabetic retinopathy, an understanding of the risk for retinopathy in the paediatric population and experience in counselling the young person and family on the importance of early prevention and intervention. [24] **(Level 2)** While serum VEGF concentrations are increased in prepubertal and pubertal children with diabetes and, as in adults, marked increases are associated with microvascular complications[25], there is a paucity of published literature on the management of sight threatening diabetic retinopathy in children and adolescents.

3.6 CARE RECOMMENDATIONS

1) Children and adolescents with diabetes should be under the care of a multidisciplinary team with experience in managing the many aspects of this chronic condition. This care includes blood pressure monitoring, dietary advice, monitoring of BMI, advice regarding smoking and pregnancy. The importance of control in reducing the risk of onset and progression of DR and preventing visual loss should be discussed. Responsibility for referral to the screening service lies with the general practitioner**. (Level B)**

2) Children and adolescents with T1DM should undergo dilated fundus photography annually from age 12 years, emergence of cases with early

onset diabetic retinopathy may help to guide initiating screening at earlier age of 10 in future. **(Level B)**

3) Children and adolescents with T2DM should undergo dilated fundus photography annually from diagnosis. **(Level B)**

4) Fundus photography should be analysed by a trained professional with referral for care and followup according to the same criteria as adults. **(Level B)**

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SECTION 4: DIABETIC EYE DISEASE IN PEOPLE WITH LEARNING DISABILITIES

Published literature relating to the prevalence, management and outcomes of diabetic retinopathy in the Learning Disability Community in the UK is not available. There are however several resources at www.lookupinfo.org developed for patients with learning disability and their carers to explain the importance of regular eye screening and to help the patient and carer prepare for the visit to clinic[1,2].

The Department of Health and NHS Diabetes have published guidance on Commissioning Services for people with learning disability and diabetes[3].The Royal College of Ophthalmologists has published an Ophthalmic Service Guidance Chapter "The management of visual problems in people with learning disability (PWLD)"[4]. The following recommendations are adapted from these two documents.

Recommendations (Level C)

1) **Access to screening**

   General Practitioners should ensure PWLD are not excluded from diabetic eye screening.

2) **Appointments**

   Appointments should be made to accommodate the patient and at a time when a carer can attend to support them.

   The person may benefit from visiting the clinic before theappointmentto become familiarised with the waiting area, the examination room, and equipment to be used. PWLD may need extra time for appointments. It may be necessary to adjust the appointment time of best suit the patient's special needs (e.g first appointment in the morning, to avoid the person waiting for long periods).

3) **Dilation**

   It may be preferable to dilate the patient at home prior to the visit to minimise waiting times and reduce the patient's distress. Where possible, non mydriatic cameras should be used.

4) **Referral into Secondary Care**

   When a PWLD requires assessment at a hospital, either because of difficulties with local screening or because of a positive screen, it should be clearly stated on the referral that the patient has learning difficulties so that pre-appointment information and/or visits can be facilitated.

5) Consent

Capacity to consent is procedure-specific. Clinicians should judge, in conjunction with carers, if the patient is able to consent to each procedure. For example a patient may be able to consent to eye drops and fundus examination or photography, but not to laser treatment. Concerns about consent should not be a barrier to screening or treatment.

6) Communication

Information about screening and treatment of diabetic eye disease should be provided in a format which is accessible by the patient. It is advisable to provide EasyRead leaflets which will help people with learning disability understand and prepare for eye examinations and clinic visits[1,2].

PWLD often have multiple care providers. Medical and personal information is held in a personal care plan. In addition to communicating with the GP it is important to include feedback about managing diabetic eye disease within the care plan. For example, the importance of blood glucose and blood pressure control should be shared with the whole care team, not just the carer attending clinic.

7) Did Not Attend Policies

People with learning disability are "vulnerable patients" and should be exempt from DNA policies for missed appointments.

8) Visual Impairment Registration

People with learning disabilities can benefit from low vision services: an inability to read should not preclude registration for visual impirement (CVI) and/or referral to low vision services for support.

Section 4 References:

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4. http://www.rcophth.ac.uk/page.asp?section=293&sectionTitle=Ophthalmic+Services+ Guidance

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SECTION 5: THE PUBLIC HEALTH ASPECTS OF DIABETIC RETINOPATHY

5.1 INTRODUCTION

Public health is described as the "The science and art of promoting and protecting health and well-being, preventing ill-health and prolonging life through the organised efforts of society" As such, public health brings a population perspective to our understanding of a condition. There are two aspects to this, firstly, public health (PH) practitioners consider the impact of a condition in a population rather than an individual; secondly, they develop and implement interventions for populations to improve outcomes.

In the case of diabetic retinopathy (DR), the population analysis of the condition includes an understanding of:

- The epidemiology of diabetes
- The epidemiology of DR
- The burden of disease from DR
- Socio-economic aspects of the condition
- The economic impact of the condition and its treatment

These factors are important in developing public health interventions that use resources effectively to deliver improved outcomes at a population level.

These interventions include prevention of diabetes through lifestyle changes, optimal care of people with diabetes by the primary and secondary care teams to reduce risk of developing or worsening DR, risk reduction through population screening and the public health contribution of clinicians, including ophthalmologists, to reduce the impact of this condition in people with diabetes.

Several of these aspects have been addressed in other parts of the guidelines including epidemiology, prevention- see section 2 and screening for DR – see section 8. This chapter therefore focuses on those public health aspects not covered in other sections.

5.2 THE BURDEN OF DISEASE FROM DIABETIC RETINOPATHY

Vision loss due to DR is an important cause of disability in the working age population. The public health impact of DR can be assessed using methodology developed by The World Health Organisation to measure and value the burden of disease. The disability adjusted life year (DALY) measures the loss in a healthy life year and is used to quantify non-fatal health outcomes.

In a study of the costs of sight loss commissioned by the Royal National Institute for Blind People (RNIB) (Access Economics, 2009)[1] it was estimated that 190,000 DALYs were lost in 2008 in the UK due to disability associated with partial sight and

blindness. Of this visual disability, 6%, (equivalent to 11,300 DALYs in 2008) was attributed to DR. This figure compares to 31% attributed to aged-related macular degeneration (AMD). However, if just the working age population is considered, DR accounted for 17.5% of disability, compared to 0.5% due to AMD.

Further studies are required to provide up to date data to quantify the burden of disease due to DR in 2012.

5.3 QUALITY OF LIFE

DR has a negative impact on quality of life, particularly in the advanced stages[2,3,4] although variations in assessment tools and outcomes (quality of general health -HRQoL vs. quality of vision) make comparisons of studies difficult. At similar levels of visual acuity loss, the impact on quality of life related to DR was shown to be comparable to that related to AMD[5] , which has implications for cost utility analyses of ophthalmic interventions.

Bailey and Sparrow[6] (2001) also described significant levels of co-morbidity in patients with DR, including angina, myocardial infarction and renal impairment, which has an impact on the clinical management of eye disease. Brown[7] , however, indicated that the presence of co-morbidities in patients with ocular disease did not affect ocular utility values. Depression has also been shown to be more prevalent in the diabetic population compared to the non-diabetic population (24% vs. 17%) and is an important co-morbidity that should be considered in the treatment of patients with diabetes[8].

5.4 SOCIO-ECONOMIC INEQUALITIES

The impact of socio-economic status on the outcome from DR may be mediated through a number of mechanisms:

- The prevalence of diabetes
- The prevention, diagnosis, treatment and control of diabetes,hypertension and other co-morbidities
- The uptake of screening for DR
- The prevalence of sight threatening DR
- The diagnosis, control and treatment of DR

5.4.1 Socio-economic status and prevalence of diabetes.

There is a significant body of evidence that demonstrates that the prevalence of type 2 diabetes but not type 1 diabetes is adversely affected by deprivation [9,10,11,12] . Robbins (2005) [12] also found that in women the incidence of diabetes was inversely associated with educational status, income and occupational status. Scanlon[13](2008) demonstrated that prevalence of diabetes also increased with increasing deprivation quintiles and that prevalence of sight threatening DR amongst those screened also increased.

5.4.2 Socio-economic influences on the prevention, diagnosis, treatment and control of diabetes

Ricci-Cabello[14] in a review of the literature in 2010 concluded that in Organisation for Economic Co-operation and Development (OECD) countries which have universal healthcare systems there is evidence that socio-economic inequalities were found in the diagnosis and control of disease and the existence of ethnic inequalities in treatment, metabolic control and use of healthcare services.

Earlier studies in the UK indicate similar findings. Robinson in 1998 found a significant association between social deprivation and mortality in people with type 2 diabetes (OR 2.0 CI 1.41 – 2.85) but not in people with type 1 diabetes[15]. In 2000 Weng et al in London showed that patients with diabetes living in more deprived areas had significantly worse glycaemic control and a higher BMI[16].

In 2001 Roper et al[17] showed that the risk of premature death in people with diabetes in South Tees increased significantly with increasing material deprivation.

In 2004, Hippisley-Cox reported on quality indicators for diabetes in GP Practices. On many indicators, scores were worse for women, those from BME communities and those with high levels of material deprivation[18].

5.4.3 Socio-economic status and uptake for DR screening

In 2006 Millet and Dodhia looked at screening uptake in South East London. Ages younger than 40 years, Type 1 diabetes and deprivation were all risk factors for non-attendance[19]. In 2008, Scanlon had similar findings in a study in Gloucestershire, with increasing deprivation associated with poorer uptake[13]. Similarly, a more recent study indicated that non-attendance for screening was particularly poor amongst those aged 18-34 and those over 85 years but suggested that the DR screening inequalities attributed to socio-economic factors (primarily deprivation), although still evident, may not be quite as marked as previously reported[20].

5.4.4 Implications for policy

It is notable that these factors all act in the same direction. Those from more deprived communities are more likely to develop type 2 diabetes, have poorer control and be less likely to access care and take up offers of screening.

Achieving a reduction in the burden of disease from DR therefore requires a focus on those from more deprived communities. Failure to develop strategies to address the needs of those known to be at higher risk of developing diabetes and its complications will mean that approaches such as screening will not deliver their potential to reduce sight loss and will have the potential to increase health inequalities.

Recommendation:

Further research should be undertaken to understand the impact of socio-economic status on DR and what steps can be taken to reduce inequalities in access and outcome. (**Level B**)

5.5 PREVENTION

Modifiable risk factors for DR are discussed in detail in the following chapter and include control of glycaemia, blood pressure and lipid levels. On a population level, modifying lifestyle factors can play a significant role in reducing the risk associated with these factors. The effectiveness of population interventions to address healthy eating, obesity and physical activity are addressed in NICE guidelines[21].

Effective individual lifestyle support on diet and physical activity remains important in the management of the patients with diabetes and the prevention of complications such as retinopathy (NICE clinical guideline 43 (2006), NICE public health intervention guidance 2 (2006)). Although the association between smoking and DR is to reduce the incidence and prevalence of DR in those who smoke, the considerable morbidity and mortality associated with smoking in people with diabetes associated cardiovascular disease and neuropathic complications, means that the importance of giving effective advice and interventions to reduce smoking cannot be underestimated[22].

5.6 REDUCTION OF POPULATION RISK THROUGH SCREENING

Screening is a population approach to reduce risk from a particular condition within an identified population. Its purpose is to identify those people who have early signs of disease but who do not yet exhibit symptoms and to provide an effective treatment which will lead to an overall reduction in the condition of interest.

As screening invites individuals to participate in a process that may not benefit them as an individual and could harm them, it is important that screening programmes are well constructed and evaluated to ensure they deliver more benefit than harm and that they remain cost-effective.

DR screening is a population screening programme; it is not a diagnosis and treatment service. Screening will not detect every individual with DR and it will not be possible to offer screening to all people with diabetes. However, the intention is to deliver an overall reduction in sight loss due to DR in the population at risk.

The four nations offer screening through their national screening programmes. (England: NHS Diabetic Eye Screening Programme www.diabeticeye.screening.nhs.uk; Scotland: National Diabetic Retinopathy Screening Programme, www.ndrs.scot.nhs.uk; Wales: Diabetic Retinopathy Screening Service for Wales,www.cardiffandvaleuhb.wales.nhs.uk/drssw; Northern Ireland: Northern Ireland Diabetic Retinopathy Screening).

To deliver effective screening, the test must be part of a well-organised system to ensure that appropriate interventions occur following screening and rigorous quality assurance of the whole process. It is generally accepted that screening for DR is clinically good practice and Jones (2010) suggested that, in terms of sight years preserved, systematic screening for DR is cost effective compared with no screening[23]. However, the changing epidemiology of the condition and the improvement in care of people with diabetes means that the UK National Screening

Committee must constantly review the population eligible for screening, the screening model and key policies such as screening intervals to ensure it remains a cost-effective programme that reduces the risk of sight loss from DR in the population screened.

Recommendations:

- Policy-makers and commissioners must ensure that DR screening programmes are constructed to deliver cost-effective systematic screening that reflect emerging evidence, changing epidemiology of DR and advances in technological developments. (**Level B**)

- Policymakers and commissioners of public health programmes should ensure that screening programmes are commissioned in the context of a broad approach to preventing sight loss from DR. This will include effective partnership working with primary care, diabetology and ophthalmology services. (**Level B**)

5.7 THE PUBLIC HEALTH ROLE OF THE OPHTHALMOLOGIST

The ophthalmologist has two key public health roles:

- Reducing the overall morbidity and mortality associated with diabetes by contributing to the effective management of eye problems in patients with diabetes

- Contributing to the collection, analysis and dissemination of information which underpins patient management and the monitoring of quality and outcomes for an effective screening programme

5.7.1 Reducing morbidity and mortality associated with diabetes

The ophthalmologist is a member of a team that cares for a patient with diabetes. Early signs of retinopathy or maculopathy may be the first signs of tissue damage from poor control of diabetes and/or blood pressure in a patient.

The ophthalmologist should provide effective advice to patients on how they can change their behaviour to reduce the risks associated with unhealthy lifestyles and poor diabetic control. (ref *section on medical management*)

Information on retinopathy and/or maculopathy should be fed back to the physician with a responsibility for overall diabetic care for a patient. Communication between physicians caring for patients with diabetes is essential to create clear messages for patients.

Recommendation:

Consultant ophthalmologists caring for patients with DR should develop strong links with local primary care and diabetology services to ensure that patients have effective integrated care plans for the management of their condition. (**Level B**)

5.7.2 Collection and analysis of data

The ophthalmologist is in a unique position to collect information on sight loss. Without the collection and analysis of this kind of data it is not possible to understand the changing epidemiology of DR as well as other important conditions leading to sight loss and blindness.

Collection of outcome data is essential for a screening programme to:

- Undertake audit to ensure that systems are working effectively
- Demonstrate cost-effectiveness of screening as an intervention
- Understand inequalities in access to services and use the information to improve services for the future

Recommendation:

Ophthalmologists should ensure that they collect information on sight loss and severe sight loss and submit data to national collection systems. (**Level B**)

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SECTION 6: MANAGEMENT OF DIABETES AND RETINOPATHY

6.1 INTRODUCTION

Visual impairment is the most feared long-term consequence of diabetes. Several conditions contribute to the problem of loss of vision in diabetes, including diabetic and hypertensive retinopathy, and increased risks of retinal vascular occlusion, cataract formation and glaucoma. The rise in number of people with diabetes to an estimate of 4 million in UK by 2025, together with increasing life expectancy, are daunting prospects if retinopathy prevalence remains at 40%. However, some optimism is warranted as reversal of retinopathy is possible in the earlier stages and there is evidence from several studies that both proliferative retinopathy and/or severe visual loss have been reduced in recent years. For example in a metanalysis of reports on Type 1 diabetes progression to proliferative retinopathy and severe visual loss was reduced by approximately two-thirds when 1975-85 was compared with 1986-2008[1](level 2). New therapies such as intravitreal treatments may also affect outcome. As management of diabetes and retinopathy improves, other ocular problems may become more dominant as causes of visual loss in diabetes[2].

6.2 RISK FACTORS

Risk factors for diabetic retinopathy

- Non-modifiable:
  Genetic factors, gender and duration of diabetes

- Modifiable:
  Glycaemia, blood pressure and lipid levels

- Additional factors:
  Carotid arterial disease, pregnancy, renal impairment and smoking

6.2.1 Glycaemia

Level of control

The Diabetes Control and Complications Trial (DCCT)[3] studying known Type 1 diabetes and the UK Prospective Diabetes Study (UKPDS)[4-6] involving newly diagnosed type 2 diabetes have provided good evidence on the importance of glycaemic control on the development of retinopathy and its progression (level 1). After a mean duration of follow-up of 6.5 years DCCT intensive therapy achieved a reduction in mean HbA1c from 76 mmol/mol (9.1%) to 56 mmol/mol (7.3%) with significant reduction in progression of retinopathy (3-step increase on the ETDRS scale) by 76% in the primary prevention group and by 54% in the secondary intervention cohort (**Level 1**). Importantly no glycaemic threshold was identified at which the risk of retinopathy was eliminated and benefits were seen at all levels of HbA1c. After a mean duration of follow-up of 10 years in the UK Prospective Study reduction of HbA1c from 63 mmol/mol (7.9%) to 53 mmol/mol (7.0%) was associated with a 25% risk reduction of microvascular complications (**Level 1**).

Further confirmation of the value of good glycaemic control in type 2 diabetes was obtained in the ACCORD Eye study where reduction of HbA1c from mean 58 to 46 mmol/mol was associated with reduced primary outcome (3-step increase on the ETDRS scale or development of proliferative retinopathy requiring photocoagulation or vitrectomy) from 10.2% to 6.5% and progression of retinopathy was reduced by 42%[7] (**Level 1**).

Metabolic memory and legacy effects

Importantly, the idea of metabolic memory or legacy effect of good glycaemic control on retinopathy has been demonstrated by both the DCCT study and UKPDS. In the DCCT/EDIC[8] after ten years follow-up where the glycated haemoglobin levels had converged completely, the former intensive treatment group still had 24% reduction in progression of retinopathy and 59% reduction in proliferative retinopathy but the risk reductions at ten years were attenuated compared with the first four years of follow-up. In UKPDS despite glycated haemoglobin differences being lost after the first year in the sulfonylurea–insulin treatment group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and for microvascular disease (24%, P=0.001)[9].(**Level 1**)

Risks of diabetes therapy (tight glycaemic control and thiazolidinediones)

Some risk is associated with very tight glycaemic control, not from an ophthalmic point of view, but from increased risk of hypoglycaemia and its possible association with cardiovascular events. In the ACCORD study hypoglycaemia requiring third party assistance was increased from 3.5% to 10.5% ($p<0.001$) and there was an increased rate of death from any cause (4.0% vs. 5.0%) (**Level 1**). The main glycaemia trial was therefore stopped early after a mean 3.5 years follow-up, potentially underestimating the reported effect of glycaemia treatment on diabetic retinopathy. It was of interest that it was the median times from the onset of severe hypoglycaemia to the first major macrovascular event, the first major microvascular event and death that were significantly different in the intensively treated group, with no relationship being found between repeated episodes of severe hypoglycaemia and vascular outcomes and death (**Level 1**). Thiazolidinediones were widely prescribed in the ACCORD study (92% in the intensive therapy group vs. 58% in the standard therapy group) and there have been concerns that rosiglitazone, now withdrawn, was not cardioprotective. Similar findings were noted in the ADVANCE study[10] of intensive glycaemic therapy in type 2 diabetes based on sulphonylureas with less than 20% use of thiazolidinediones in which a mean glycated haemoglobin level of 48mmol/mol (6.5%) was achieved in the intensive-control group compared with 56 mmol/mol (7.3%) in the standard-control group. Severe hypoglycaemia, although uncommon, was more common in the intensive-control group (2.7%, vs. 1.5% in the standard-control group; hazard ratio, 1.86; 95% CI, 1.42 to 2.40; $P<0.001$). The incidence of combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control) was reduced. However owing to the possible 2.6-fold increase in macula oedema associated with the use of thiazolidinediones, but not with other anti-diabetic drugs[11] (**Level 1**), current advice is to withdraw pioglitazone when macula oedema has developed. (**Level A**)

Summary

- It is recognised that the benefit of good glycaemic control may be seen at any stage in the development of retinopathy – for preventing retinopathy, for regression in the early stages of retinopathy and for reducing the progression to proliferative retinopathy and to severe visual loss. (**Level A**)
- Good glycaemic control early in the course of diabetes has an important impact on long-term outcome of retinopathy. (**Level A**)

Recommendations for management of glycaemia

i. A personalised HbA1c target should be set, usually between 48-58 mmol/mol (6.5-7.5%). No threshold level of glycaemia has been shown in any of the larger studies of retinopathy. (**Level A**)
ii. Less strict targets should be set (NICE quality standards June 2011) in patients with established cardiovascular disease and in older subjects. (**Level A**)
iii. Patients should receive an on-going review of treatment to minimise hypoglycaemia. (**Level A**)
iv. Pioglitazone should be avoided in the presence of macula oedema. (**Level A/B**)

6.2.2 Blood pressure

Blood pressure control plays an important role in prevention and management of diabetic retinopathy. The UKPDS showed that a reduction of mean systolic blood pressure from 154 to 144 mmHg reduced microaneurysm count at 4.5 years follow up, reduced hard exudates and cotton-wool spots at 7.5 years, and was aasociated with less need for photocoagulation and less deterioration of 2-step or more on the ETDRS retinopathy scale[12]. No legacy effect was demonstrated so blood pressure control should be maintained to be effective[13]. (**Level 1**)

In the ACCORD Eye study[7] intensive blood pressure control aiming for systolic blood pressure <120mmHg was compared with standard control <140mmHg in the context of good glycaemic control, using all the standard hypotensive medications. The ACCORD Eye study failed to demonstrate a significant effect of intensive blood pressure control on the progression of retinopathy. It is possible that the median systolic pressure of 133mmHg in the non-intensive treatment group was an effective level for preventing progression or that the duration of follow-up was insufficient. (**Level 1**)

A role for angiotensin as an angiogenic growth factor has been suggested. Specific therapies blocking the renin-angiotensin system (RAS) therefore may have additional benefits particularly for mild retinopathy. An early trial using the ACE inhibitor lisinopril was tested over 2 years of follow-up in the EUCLID) study [14](**Level 1**). This study demonstrated that patients with type 1 diabetes treated with an ACE inhibitor had a significant reduction of 50% in the progression of DR (p=0.02), but the findings were weakened owing to differences in initial and final HbA1C levels favouring lisinopril. The more recent Diabetic Retinopathy Candesartan Trials (DIRECT) programme assessed the effect of treatment of oral candesartan 32 mg daily, an

angiotensin-receptor blocker (ARB), on the incidence and progression of diabetic retinopathy. The programme enrolled over 5,000 patients in three arms of the trial, DIRECT-Prevent 1 and -Protect 1in type 1 diabetes[15], and DIRECT-Protect 2[16] in type 2 diabetes (which included treated hypertensive patients), to examine the incidence and progression of diabetic retinopathy over a 5-year period. The primary endpoints for all three arms of the trial were two-step progression of DR or the *de novo* development of retinopathy in Prevent 1, and no statistically significant changes in these primary endpoints were shown (**Level 1**). In patients with Type 1 diabetes, candesartan had a borderline effect on reducing the incidence of retinopathy by two or more steps in severity by 18%, but had no effect on progression of retinopathy (**Level 1**). In *post hoc* analyses, the incidence of DR of three steps (EDTRS scale) was significantly reduced by 35%. In patients with type 2 diabetes (Protect 2), candesartan treatment resulted in a significant increase in regression of DR by 35% (**Level 1**). However, an overall significant change towards less severe DR in all three trials was observed (p=0.03–0.003). It is more likely that these effects were specific to RAS blockade rather than an effect of lower blood pressure as baseline blood pressure were 116-117/72-74 in the type 1 diabetes studies and 123-139/75-80 in the type 2 diabetes study with very small changes on treatment. It is reasonable to conclude that RAS blockade in general and candesartan specifically have a place in the medical management of diabetic retinopathy, to prevent the problem in Type 1 diabetes and to treat the early stages in Type 2 diabetes[17].

Guidelines for hypertension in diabetes

- Intensify therapy aiming for systolic ≤130mmHg in those with established retinopathy and/or nephropathy (**Level A**).
- Encourage regular monitoring of blood pressure in a health care setting and at home if possible.
- Recognise that lower pressures may be beneficial overall but evidence is lacking for retinopathy. (**Level B**)
- Recognise that specific therapies blocking the renin-angiotensin system (RAS) may have additional benefits, particularly for mild retinopathy, but should be discontinued during pregnancy. (**Level B**)
- Establish a personalised mean systolic blood pressure target in all patients who do not have retinopathy, usually < 140mmHg (**Level A**).

6.2.3 Lipids

Lipid-lowering is another approach that may reduce the risk of progression of diabetic retinopathy, particularly macular oedema and exudation. The possibility of an effect of statins has been investigated over the last 10 years with some encouraging results. For example 2838 patients in CARDS followed over a median follow-up of 3.9 years with atorvastatin 10mg daily, showed a trend to reduced laser therapy but no influence on diabetic retinopathy progression[18,19](**Level 1**). Better evidence on the effects of larger doses of statins with longer follow-up is required but, if statins modify retinopathy, the effect is likely to be small.

Two large randomised controlled trials of fenofibrate have subsequently confirmed benefit in established retinopathy. Firstly, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[20], fenofibrate (200 mg formulation /day) reduced the requirements for laser therapy (both macula and pan retinal/scatter laser)

and prevented disease progression in patients with pre-existing diabetic retinopathy (**Level 1**). These benefits did not appear to be related to changes in lipid levels as there were no reported clinically relevant differences in mean plasma HDL cholesterol or triglyceride concentrations in those with or without laser treatment.

Secondly the ACCORD Eye study [7] showed a 40% reduction in the odds of having progression of retinopathy over four years in patients allocated to fenofibrate (160 mg formulation/day) in combination with a statin, compared to simvastatin alone. This occurred with an increase in HDL-cholesterol and a decrease in the serum triglyceride level in the fenofibrate group, as compared with the placebo group, and being noted in the first year of treatment and maintained. Additionally, in ACCORD eye study the effect of fenofibrate was independent of glycaemia (**Level 1**). However, no data is available to indicate which features of retinopathy progressed or whether any evidence of regression was noted. In interpreting these studies and their clinical implications[21], it must be noted that DR was not the primary endpoint by design, a tertiary endpoint in FIELD, and DR endpoints recorded in a sub study cohort of the ACCORD study population. Hence, the exact beneficial action of fenofibrate on DR remains to be elucidated.

Recommendations for lipid management in diabetes

- Consider statins in secondary prevention of macrovascular disease as well as in primary prevention. (**Level A**)
- Avoid statins in pregnancy (**Level A**)
- Consider Ezetimibe for patients intolerant of statins.
- Consider adding fenofibrate to a statin for non-proliferative retinopathy in type 2 diabetes. (**Level B**)

6.2.4 Smoking

Although smoking contributes to the development but not progression of nephropathy in Type 1 diabetes, no clear association of smoking and retinopathy has been demonstrated. Smoking may be important in some patients with Type 1 diabetes as current smoking has been shown to be associated with microangiopathy when complications occur early in the course of type 1 diabetes[22]. In a specific study of smoking a univariate analyses showed a significant association of pack-years and progression to proliferative diabetic retinopathy in older-onset subjects on insulin[23]. After controlling for known risk factors for the incidence and progression of retinopathy, pack-years smoked was borderline significant in predicting incidence of retinopathy in younger-onset subjects. Smoking was not associated with incidence in older-onset subjects or with progression or progression to proliferative diabetic retinopathy in any of the groups (**Level 2**). Counselling and treatment for smoking is cost effective in diabetes management[24] (**Level 1**).

Guidelines for patients with diabetes who smoke

- Patients with DR should be made aware that they are at higher risk of cardiovascular disease (**Level A**)
- All smokers should be encouraged to quit as part of healthy life-style advice. (**Level A**)

6.3 INTERACTIONS OF RISK FACTORS FOR DIABETC COMPLICATIONS

The interaction of different risk factors has been well documented in two long-term studies of patient with Type 2 diabetes. In the UKPDS, the risk of complications was associated independently and additively with hyperglycaemia and hypertension with risk reductions of 21% per 1% HbA1c decrement and 11% per 10 mmHg systolic blood pressure decrement [25](**Level 1**). In another smaller study of Type 2 diabetes over a period of 7.8 years intensified, multi-targeted medical treatment aiming for HbA1c < 6.5%, fasting serum total cholesterol level <4.5 mmol/L, fasting serum triglyceride level of <1.7 mmol/L, systolic blood pressure of <130 mm Hg, and diastolic blood pressure <80 mm Hg, cardiovascular outcome was improved and fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; P=0.02)[26]. (**Level 1**)

6.4 PREGNANCY (based on NICE guidelines)

Progression of retinopathy is a significant but relatively low risk in pregnancy. This has been well documented in patients with type 1 diabetes[27] with reported rates in the older literature ranging from 17-70%[,28,29,30]. Recent prospective studies have confirmed these older studies for example 64/102 (63%) patients having retinopathy in at least one eye in early pregnancy and progression occurring in 27% with laser therapy being required in 6 patients[31]. (**Level 2**)

The known duration of diabetes in a pregnant type 2 patient is often short but retinopathy was noted in 11/80 patients (14%) in early pregnancy and progressed in a minority[32] (**Level 2**). Pregnancy is not associated with post-partum worsening of retinopathy in type 1 diabetes in patients followed for five years after delivery[33] (**Level 2**).

Pre-conception care of women with known diabetes

- Diabetic patients planning pregnancy should be informed on the need for assessment of diabetic retinopathy before and during pregnancy (**Level A**)
- Statins and drugs blocking the renin-angiotensin system should be discontinued before conception and always at first antenatal booking if still being taken. (**Level A**)
- Rapid optimisation of poor glycaemic control should be deferred at least until after retinal assessment. (**Level B**)

Retinal assessment during pregnancy

- Pregnant women with pre-existing diabetes should be offered retinal assessment by digital imaging following their first antenatal clinic appointment and again at 28 weeks if the first assessment is normal. If any diabetic retinopathy is present, additional retinal assessment should be performed at 16–20 weeks. (**Level A**)
- Diabetic retinopathy should not be considered a contraindication to rapid optimisation of glycaemic control in women who present with a high HbA_{1c} in early pregnancy but retinal assessment is essential (**Level A**).
- Women who have pre-proliferative diabetic retinopathy diagnosed during pregnancy should have ophthalmological follow-up for at least 6 months following the birth of the baby. (**Level A**)
- Diabetic retinopathy should not be considered a contraindication to vaginal birth. (**Level A**)
- Tropicamide alone should be used if mydriasis is required during pregnancy. (**Level A**)

6.5 COUNSELLING

Patient education and counselling plays an important role in management of diabetic patients, in physicians' clinics as well as in the eye clinics. Patients with sight threatening retinopathy need additional counselling on impact on vision as well as retinal treatment options.

- Counselling on diabetic retinopathy is required as soon as diabetes is diagnosed and retinal screening commenced (**Level A**).
- Studies have shown significant reduction of quality of life scores at diagnosis of diabetic retinopathy and when vision is impaired[34,35,36]. (**Level 2**).
- Patient education plays an important role in management of retinopathy as increased awareness is linked with motivation. Ophthalmic consultation provides an opportunity to explain what retinopathy is, why it develops, what can be done to prevent progression and reduce the risk of blindness. Such counselling may improve compliance with screening and clinic visits. (**Level B**)
- Careful explanation of the risks and benefits of laser therapy is required as it is commonly assumed that such therapy will improve vision. (**Level A**)
- Detailed discussion and explanation about potential intraocular pharmacologic interventions is necessary, emphasising the need for repeated and frequent attendance for further interventions to maintain benefit of the therapy. (**Level A**)
- Ophthalmologists need to be aware of psychological need of their diabetic patients. Psychological support for children and adults with diabetes is recommended. In children this should include eating disorders, behavioural, emotional problems. In adults this should include anxiety, depression and eating disorders. (**Level B**)
- Healthcare professionals should be aware of cultural differences and psychological problems in different ethnic communities (**Level B**).

6.6 OPHTHALMOLOGIST AND MANAGEMENT OF DIABETES

In the UK, most patients have their diabetes care in a primary medical or nursing setting so the ophthalmologist often provides the first specialist consultation. Ophthalmologists have an important role in the management of diabetic patient since retinopathy heralds a significant stage of diabetes with evidence of microangiopathy.

- Systems can be set up (see later) to provide enhanced care for diabetic patients in eye clinics. For example in addition to visual acuity and ocular assessments, blood pressure measurements and survey of other diabetes related care and outcomes can be performed routinely. (**Level B**)

- The ophthalmologists can take the opportunity to ensure appropriate care and medical targets are being pursued. A number of simple, key questions (table) may help determine whether patients have been lost to regular supervision or whether more specialised diabetes interventions are required. The same principles also apply to on-going follow-up of patients in the hospital eye service, especially if laser therapy or intravitreal injection therapy is being considered.

Medical questions for patients with diabetic retinopathy

- Counselling on diabetic retinopathy is required as soon as diabetes is diagnosed and retinal screening commenced (Level A).
- Studies have shown significant reduction of quality of life scores at diagnosis of diabetic retinopathy and when vision is impaired[34,35,36]. (Level 2).
- Patient education plays an important role in management of retinopathy as increased awareness is linked with motivation. Ophthalmic consultation provides an opportunity to explain what retinopathy is, why it develops, what can be done to prevent progression and reduce the risk of blindness. Such counselling may improve compliance with screening and clinic visits. (Level B)
- Careful explanation of the risks and benefits of laser therapy is required as it is commonly assumed that such therapy will improve vision. (Level A)
- Detailed discussion and explanation about potential intraocular pharmacologic interventions is necessary, emphasising the need for repeated and frequent attendance for further interventions to maintain benefit of the therapy. (Level A)
- Ophthalmologists need to be aware of psychological need of their diabetic patients. Psychological support for children and adults with diabetes is recommended. In children this should include eating disorders, behavioural, emotional problems. In adults this should include anxiety, depression and eating disorders. (Level B)
- Healthcare professionals should be aware of cultural differences and psychological problems in different ethnic communities (Level B).

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Medical questions for patients with diabetic retinopathy

1. Who helps you to look after your diabetes?

General practitioner

Specialist diabetes nurse in community/GP surgery

in hospital or diabetes centre

Diabetes specialist

2. When is your next appointment?

3. What is your long-range diabetes test result?

glycated haemoglobin (HbA1c) or fructosamine

when was the last test done?

3. What is your usual blood pressure? How often it is checked?

measured at home

measured in surgery or clinic

4. Do you know what your blood cholesterol level is?

5. What is your current treatment?

Diabetes

Blood pressure

Cholesterol

6. Does your current treatment include any of the following?

pioglitazone (Actos)	aspirin
ramipril or sartan family of drugs	warfarin
fenofibrat	

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SECTION 7: CLINICAL FEATURES OF DIABETIC RETINOPATHY

7.1 INTRODUCTION

Diabetic retinopathy (DR) is essentially, but not exclusively, a microvascular disease. Individual DR features helps the clinician to evaluate the risk of imminent visual impairment (e.g. subfoveal macular oedema, new vessels) as well as that of significant future risk (e.g.extra/juxtafoveal macular oedema, surrogate markers of capillary non-perfusion or leakage), thus assisting in developing a management plan for an individual patient. The classification of diabetic retinopathy has a dichotomous approach- the presence or absence of new vessels, the presence or absence of sub-foveal macular oedema. Yet in spite of its importance, the pathogenesis of many retinopathy features is not fully understood.Much of our knowledge about individual features has come from studying fluorescein angiography of the retinal circulation. The role of the retinal pigment epithelium and choroidal circulation in diabetic retinopathy is largely unknown.

Since the previous edition of the RCOphth diabetic retinopathy guidelines, both population based digital image photographic DR screening programmes and optical coherence tomography have become established throughout the United Kingdom.

7.1.1 Traditionally, for ophthalmologists the term maculopathy has meant the presence of exudates, haemorrhages or retinal thickening, within a two disc diameter radius centred on the fovea - in isolation or in conjunction with one another. This terminology requires updating- optical coherence tomography may show intra-retinal fluid in the absence of retinal thickening and there is added confusion with screening programmes using a different terminology for maculopathy.

7.1.2 To avoid confusion, this guideline recommends that the term maculopathy is used in the context of the diabetic retinopathy screening programme (UK)., while for clinical use more specific descriptions of the features of clinically significant maculopathy such as macular oedema (centre involving or otherwise), exudation with or without thickening, and ischaemia. (See section 11)

7.2 FEATURES OF NON-PROLIFERATIVE DIABETIC RETINOPATHY

Recognising features of non-proliferative retinopathy enables to predict an individual's risk of future new vessel formation, and to recommend a safe review interval. The importance of localising macular changes in the non-proliferative stage of retinopathy is to ascertain risk to the fovea (and vision) of macular oedema and lipid deposition.

The first clinical signs of diabetic retinopathy are a consequence of isolated capillary occlusion (reference) with adjacent non-occluded capillaries forming saccular or fusiform swellings called microaneurysms. The capillary circulation is only visible on fluorescein angiography.

7.2.1 Microaneurysms

These appear as isolated, spherical, red dots of varying size. There are a number of theories to explain their presence- they may reflect an abortive attempt to form a new vessel or may simply be a weakness of capillary vessel wall through loss of normal structural integrity.

Individual microaneurysms may leak resulting in dot haemorrhage, oedema and exudate. Spontaneous thrombosis may lead to resorption of haemorrhage oedema and exudate. The thrombosed microaneurysm usually disappears from clinical view, but occasionally remains visible as a white dot.

7.2.2 Dot Haemorrhages

Dot haemorrhages cannot always be differentiated from microaneurysms as they are similar in appearance but with varying size. Hence it is traditional not to attempt differentiate them on clinical examination. Instead the term dot haemorrhage/ microaneurysm (H/Ma) is used.

7.3 DIFFUSE CAPILLARY OCCLUSION

Progressive capillary occlusion leads to the development of blot haemorrhages, intraretinal microvascular anomalies and venous changes. More extensive capillary occlusion can lead to a featureless retina, followed by neovascularisation.

7.3.1 Blot haemorrhages

Where clusters of capillaries occlude, intraretinal blot haemorrhages develop. Such haemorrhages may occur throughout the full thickness of the retina.

Blot haemorrhages are considered to represent a deep retinal infarct. The lesion can be seen to be in the outer plexiform layer on fluorescein angiography where it does not mask the overlying capillary bed unlike dot and flame haemorrhages which lie more superficially in the retina.

More peripheral, round, large blotch haemorrhage is a common feature of ocular ischaemia. Such patients often develop rubeosis iridis -proliferative iridopathy and consequent neovascular glaucoma.

7.4 COTTON WOOL SPOTS

Cotton wool spots are believed to represent the swollen ends of interrupted axons where build-up of axoplasmic flow occurs at the edge of the infarct. Cotton wool spots occur most frequently where the nerve fibre is densest such as the nasal side of the optic nerve.

Such features are not exclusive to diabetic retinopathy and do not in themselves appear to increase the risk of new vessel formation. Hence, unless extensive areas

affected by cotton wool spots are found they are considered to be a change of no proliferative retinopathy.

Cotton wool spots often have abutting looping microvascular anomalies, which are probably a variant of collateral formation, as seen with retinal vein occlusion, rather than the typical IRMA seen with capillary occlusion.

7.5 INTRA-RETINAL MICROVASCULAR ANOMALIES (IRMA)

Extensive closure of capillary network between arteriole and venule leads to dilated capillary remnants. These remaining stumps and vascular channels appear as spiky tortuous micro-vascular abnormalities in the areas of capillary occlusion, within retina, the changes are easier to identify on fluorescein angiography. Another possible mechanism for development of IRMA is a variant of collateral formation and may be seen in association with localised arteriolar occlusion and cotton wool spot. In young patients IRMAs may be confused with dilated telangiectatic vessels in the nerve fibre bundles, which reflects state of generalised hyperaemia.

In contrast to IRMA, telangiectasia that arise as a consequence of retinal vein occlusion leak fluorescein along their length resulting in retinal oedema and exudate formation. IRMA only leak from their growing tips, are less often associated with exudate and appear to develop endothelial cell tight junctions indicating a probable role in retinal repair.

7.5.1 Venous Beading

Where veins run through areas of extensive capillary closure, venous beading occurs. Venous beading may represent foci of venous endothelial cell proliferation that have failed to develop into new vessels. Fluorescein angiography shows vessel wall staining as the vein passes through ischaemic retina and ‘pruning’ where side branches appear occluded shortly after branching from the main vessel.

7.5.2 Venous Reduplication

Venous reduplication is rare and usually occurs in conjunction with venous beading.

7.5.3 Venous Loops

Venous loops are infrequent and though to develop due to small vessel occlusion and opening of alternative circulation.

7.5.4 Retinal pallor

Retinal pallor is a non-specific feature that is best appreciated in hindsight on red-free photographs and on fluorescein angiography, particularly temporal to the macula in patients who appear to have the unexplained presence of new vessels.

7.5.5 White lines

White lines may represent vessel wall staining or thrombosed arterioles , which often accompany retinal pallor and are similarly found in areas of extensive capillary closure.

7.6 MACULAR CHANGES IN NON-PROLIFERATIVE RETINOPATHY

7.6.1 Macular Oedema

Thickening of retina takes place due to accumulation of exudative fluid from damaged outer blood-retina barrier (extracellular oedema) or as a result of hypoxia leading to fluid accumulating within individual retinal cells (intracellular oedema). Both mechanisms are consequences of capillary closure (ischaemia), either indirectly (extracellular) or directly (intracellular).

The appearance of macular oedema can be appreciated on stereoscopic examination or inferred by the presence of intraretinal exudate (reference). Leakage from isolated microaneurysms or clusters of microaneurysms may appear as a discrete area of surrounding oedema (focal oedema) radiating out from the leaking microaneurysms. Exudate may delineate the advancing edge of the oedema, much like the tide mark of the sea, Such exudates are usually found in the outer plexiform layer on an OCT scan though the area.

The mechanism of more widespread oedema (diffuse oedema) is more complex. In its most simplistic form it may be envisaged to occur as a result of widespread capillary leakage, often from capillary segments with impaired autoregulation rather than discrete microaneurysms. Other mechanisms include retinal pigment epithelium dysfunction or the presence of ischaemia especially that affecting the perifoveal vascular zone.

7.6.2 Macrovascular disease

Although classically thought of as a microvascular disorder, some features of a macrovascular origin may be seen in diabetic retinopathy. Arteriolar occlusion, without capillary occlusion, frequently affects the horizontal nerve fibre layer of the retina resulting in flame haemorrhage and cotton wool spot formation.

7.7 OPTIC DISC CHANGES

Occasionally swollen optic discs may be seen (diabetic papillopathy) in diabetic patients with poor correlation to retinopathy levels. Diabetic papillopathy would need to be differentiated from ischaemic optic neuropathy and cases with new vessels on the disc (NVD). In patients with diabetic papillopathy, vision is largely not impaired however visual acuity may be affected.

7.8 PROLIFERATIVE DIABETIC RETINOPATHY

Proliferative diabetic retinopathy (PDR) is the angiogenic response of the retina to extensive capillary closure. New vessels grow at the interface of perfused and non-perfused retina and are described as new vessels on the disc (NVD) or new vessels elsewhere (NVE).

Appearance
Depending on the stage of development, new vessels vary in appearance. New vessels usually grow from post-capillary venules and differ from the normal vasculature in that they do not obey the law of fractals.

7.8.1 New Vessels at the Disc (NVD)

New vessels at the discs usually arise from the venous circulation on the disc or within 1 disc diameter of the disc NVD are sometimes difficult to distinguish from fine normal small blood vessels. The latter however, always taper to an end and do not loop back to the disc. New vessels always loop back, may form a chaotic net within the loop, and have the top of the loop of wider diameter than the base. New vessel formation at the disc may be a consequence of generalised retinal ischaemia. Macular ischaemia if wide spread, may contribute to NVD formation. Macular ischaemia can be described as be central (involving the foveal avascular zone) or peripheral (involving the temporal vascular arcade watershed zone).

7.8.2 New vessels elsewhere NVE

New vessels elsewhere (NVE) may be confused with intra-retinal microvascular anomalies (IRMA). However, new vessels occur along the border between healthy retina and areas of capillary occlusion whereas IRMAs occur within areas of capillary occlusion. Although IRMAs do not always obey the laws of fractals, they never form loops. Any unusual blood vessel forming loops should always be considered to be a new vessel until proven otherwise.

7.8.3 Other sites of new vessels

New vessel formation on the iris - NVI (proliferative iridopathy) is uncommon but represents potentially more advanced ischemic changes. NVI indicates more widespread ischaemia and sometimes occurs in association with ocular ischaemia (e.g carotid stenosis, atherosclerosis of the ophthalmic artery etc) or with central retinal artery/vein occlusion.

It is useful to perform gonioscopy in such cases to exclude new vessels in the anterior chamber angle (NVA) which can lead to neovascular glaucoma.

7.8.3 New vessel formation on the anterior hyaloid surface is uncommon and usually occurs post-vitrectomy if insufficient laser has been applied to the peripheral retina.

7.8.4 Relationship to non-proliferative diabetic retinopathy

The speed and site of onset of new vessels formation depends on the extent and nature of the underlying retinal capillary closure. A large, isolated area of occlusion may lead to the early appearance of new vessels compared to the relatively milder retinal changes which may lead to erroneous grading on the screening episode.
Similarly, widespread, small clusters of capillary occlusion, may not lead to new vessel formation, until relatively late in the clinical grading stage where such patients present with retinal pallor, venous beading and white lines.

The amount of capillary occlusion as identified from clinical features and/or retinal angiogram is a good indicator as to the potential aggressiveness of any new vessel formation. Patients presenting with more severe degrees of non-proliferative retinopathy tend to require more laser than those presenting with milder degrees.

7.9 ANGIOGENESIS AT THE VITREO-RETINAL INTERFACE

New blood vessels themselves are asymptomatic. The symptoms arise from complications which occur because of the dynamic interaction at the vitreo-retinal interface.
New vessels grow between the inner surface of the retina and the posterior hyaloid face of the vitreous gel which is most strongly adherent to the pars plana, the optic disc and the major retinal arcades in decreasing order.

The interaction results in an inflammatory response and scar formation. Initially transparent, the contracting scar elevates the new vessel off the retinal surface (forward new vessels). Further contraction can cause bleeding (vitreous haemorrhage), and if the vitreous is adherent to the retina, it leads to traction retinal detachment.The stronger the adherence of the vitreous to the retina, the more likely a haemorrhage and/or traction to occur.

The resulting vitreous haemorrhage may be confined to the potential space between the retina and vitreous gel (pre-retinal or sub-hyaloid haemorrhage) or into the middle of the gel itself (intra-gel vitreous haemorrhage). Pre-retinal or sub-hyaloid haemorrhage can only occur if the vitreous is still attached to the retina and "holding the blood up against it". When the vitreous detaches, the blood falls into the vitreous cavity converting itself into a vitreous haemorrhage. Vitreous haemorrhages often clear the visual axis, as the vitreous detaches further (posterior vitreous detachment) and the blood collects inferiorly If this does not occur the blood must be surgically removed (vitrectomy).

7.10 FIBROUS PROLIFERATION

In proliferative retinopathy, new vessels grow on a platform of glial cells. If the new vessel component predominates vitreous haemorrhage is the predominant feature.

In cases of repeated vitreaous haemorrhages, glial component becomes predominant. Glial cells associated with new vessels growing along major vascular arcades are particularly at risk of scar contraction, causing the vitreous to pull on the retina and resulting in retinal folds and sometimes in detachment of the retina (traction retinal detachment). Traction retinal detachments are concave and progress only slowly unless a hole forms in the detached retina leading to a combined traction/ rhegmatogenous retinal detachment.

7.11 INACTIVE ANGIOGENESIS

New vessels may occasionally auto-infarct spontaneously. Most patients with proliferative retinopathy need treatment either in the form of laser or intra-vitreal injection of anti-vascular endothelial growth factor, to cause involution of the new vessels.

Where incomplete regression occurs, inactivity can be inferred by the development of gliosis, reduction in size of the NV, and decrease in the distal lumen. If new vessels persist, another good sign of inactivity is the presence of pan-retinal laser burns in conjunction with the disappearance of retinal haemorrhages, normalisation of retinal venous changes and resolution of IRMAs.

7.12 ISOLATED POSTERIOR VITREOUS DETACHMENT

Regression of angiogenesis may accelerate scarring (gliosis) at the vitreo-retinal interface which in turn may induce posterior vitreous detachment.

As an early complication of pan-retinal laser, posterior vitreous detachment may convert a sub-hyaloid haemorrhage into an intra-gel haemorrhage making further laser difficult.

More commonly, it is a late complication of pan-retinal laser, leading to a self-limiting intra-gel vitreous haemorrhage as the vitreous detaches from inactive new vessel remnants.

7.13 IMAGING

Imaging is playing an increasingly important role in the classification of diabetic retinopathy. The classification of diabetic retinopathy will need to be reflect the rapid technological advances.

7.13.1 Digital photography

Digital photographyhas become the mainstay of documentation of diabetic retinopathy and is the methodology of choice for retinal screening.

Colour photography is best for demonstrating the presence of white lesions such as exudate and cotton wool spots. All other lesions are best visualised using red-free images. Although most features can be ascertained as long as third order vessels at

thefovea are also visible, intra-retinal microvascular anomalies can only be confidently documented if the nerve fibre layer is also visible.

7.13.2 Fluorescein angiography

Historically, fluorescein angiography has had an important role in demonstrating the presence of subtle new-vessel formation and guiding laser, particularly macular laser for oedema and fill-in laser for proliferative retinopathy. Only fluorescein angiography can readily demonstrate the extent and location of capillary drop out. However, the use of fluorescein angiography is waning with the advent of OCT and antiVEGF medications.

7.14 PATTERNS OF LEAKAGE

7.14.1 Neovascular

New vessels of proliferative diabetic retinopathy unlike those formed in utero, are fenestrated. As a result fluorescein leakage throughout the angiogram run occurs.

Occasionally early new vessels leak minimally, despite their obvious clinical appearance, most often noted with early NVD. Unlike collaterals, the lumens of these non-leaking new vessels at the disc are very narrow (fine) compared to other vessels at the disc. Clinical acumen should take precedence, particularly if such non-leaking new vessels are noted at the disc where extent of peripheral significant capillary drop out should be assessed to decide if pan-retinal laser should be considered.

7.14.2 Macular

Unlike age-related macular degeneration the classification of fluorescein leakage at the macula is not established. There are, however, some similarities.

7.14.3 “Focal” leakage

In diabetic macular oedema, some patients may show early leakage in transit phase of angiogram which may be “discrete” (focal) with progressive leakage from “culprit” microaneurysms. These patients often have accompanying circumferential exudates (circulate exudates); such discrete leaky spots respond well to macular laser, especially those in extrafoveal areas.

7.14.4 “Indeterminate”

In many patients with diffuse diabetic macular oedema, a similar “indeterminate” appearance in the late phase of the angiogram occurs and which shows little or no correlation to the presence of microaneurysms. These patients often have diffuse retinal thickening, sometimes with intra-retinal cysts (cystoid macular oedema) and often without exudate formation. These patients respond poorly to macula laser, particularly if leakage is subfoveal.

7.14.5 "Mixed"

Many patients, with diabetic macular oedema have a mixed pattern of leakage. Additionally, there may be additional component of ischaemic maculopathy.

7.15 PATTERNS OF MACULAR ISCHAEMIA

Both – focal and diffuse – patterns of macular leakage may be associated with areas of capillary occlusion seen as discrete zones of capillary drop out in macula. Indeed all patients with macular oedema, by the very nature of the pathogenesis of diabetic retinopathy, would have some degree of ischaemia.

Macular ischaemia may be central (involving the foveal avascular zone -FAZ) seen as enlarged foveal avascular zone or peripheral (i.e. involving the temporal vascular arcade watershed zone or extra foveal areas of macula).

If the perifoveal capillaries of the foveal avascular zone are affected then visual prognosis is poor and laser is ineffective in restoring macular function.

7.16 RETINAL ISCHAEMIA

Peripheral retinal ischaemia, in the absence of surrogate markers or capillary drop out (blot haemorrhage, venous beading, intra-retinal microvascular anomalies) may not always be readily discernible clinically and hence retinal angiography especially wide field retinal angiography is useful in detecting ischaemic changes.

Angiography readily identifies such areas and is particularly useful in identifying potential areas of retreatment for persistent or recalcitrant new vessel formation. It is also useful in classifying those patients with isolated intra-retinal microvascular anomalies into those with significant capillary dropout who required close supervision, and those without capillary dropout, who do not.

7.17 OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT has complemented our understanding of maculopathy and highlighted shortcomings of the slit lamp examination alone in identification of retinal thickening and intra-retinal oedema. OCT has revolutionised the identification of macular oedema, however, it is limited by its inability to identify the source of leakage, nor the degree of capillary drop out present. It is particularly suited to determining whether retinal fluid is centre involving or not, thus helping to select those patients which are best suited for intravitreal injection therapy (centre involving) or best suited for laser (extrafoveal). Fluorescein angiography may still be necessary in some cases to guide treatment, for example in cases of juxta foveal leakage and retinal thickening – cyst formation.

In addition to identification of fluid collection, optical coherence tomography will reveal the presence of haemorrhage, exudate and photoreceptor atrophy which can be enhanced by colour photography. OCT is very useful in assessing vitreo-retinal

interface at macula in differentiating Vitreo retinal attachment from vitreo retinal traction, such as viteo macular traction (VMT).

7.18 RETINAL THICKENING

Retinal thickening can result from vitreo-macular traction, glycation of the nerve fibre layer, intra-retinal oedema/cysts and sub-retinal fluid.

Vitreo-retinal traction may occur with or without epiretinal membrane formation and with or without intra-retinal fluid. Its identification is important as it may be amenable to surgery.

Thickening of the nerve fibre layer occurs early and results in a different normal reference range for people with diabetes. This does not affect vision.

Intra-retinal oedema/cysts in the absence of retinal thickening occur more frequently than previously appreciated, although it has been known for some time that fluorescein angiography may show leakage in the absence of retinal thickening. Ophthalmic management in such cases is uncertain as all clinical trials, whether of laser or intra-vitreal therapy, has used increased retinal thickness as an entry requirement. Neurosensory retinal detachments with subretinal fluid accumulation may be revealed on OCT scans.

Optical coherence tomography readily shows the consequence of prolonged oedema on the retinal structure in the form of large cysts with thin intervening pillars, ruptured cysts and pseudo hole formation; however OCT changes do not always correlate with the effect of oedema on visual function.

7.19 FUNDUS AUTOFLUORESCENCE

The role of fundus autofluorescence has yet to be fully elucidated in diabetic retinopathy. Unlike other modalities, autofluorescence is a form of functional imaging, giving insights into the metabolic activity of the retinal pigment epithelium.

Autofluorescence may have a role in laser retreatment of diabetic macular oedema, particularly with sub-threshold laser where burns may not be clinically discernible yet easily apparent with autofluorescence.

Although autofluorescence can identify areas of the cysts with cystoid macular oedema, it is unlikely to replace the role of optical coherence tomography.

Autofluorescence may, however, have a role in judging the visual potential of patients, with long standing diabetic macular oedema, by assessing the health of the underlying retinal pigment epithelium, and by inference, the health of the adjacent photoreceptors.

SECTION 8: SCREENING FOR DIABETIC RETINOPATHY

8.1 INTRODUCTION

National screening programmes for diabetic retinopathy based on digital retinal photography were developed and implemented in England[1] , Scotland[2] , Wales[3] and Northern Ireland[4] between 2002 and 2007. This section of the revised RCOphth guidelines covers background issues in screening and makes specific recommendations of relevance to ophthalmologists. It does not cover detailed differences between UK screening programmes and expects ophthalmologists involved in the screening and assessment of screen positive patients to be familiar with the relevant detail (e.g. the National Grading form) of their own National Programme.

8.2 DEVELOPMENT OF SCREENING IN THE UK

The development of screening in Europe was first encouraged by the St. Vincent Declaration[5]which, in 1989, set a target for reduction of new blindness by one third in the following 5 years.

In 2002, the Health Technology Board for Scotland[6] recommended that a National Diabetic Retinopathy Screening Programme for Scotland be established to detect referable (sight-threatening) retinopathy using a three-stage process based on single-field non-mydriatic digital photography, with the use of mydriasis and slit-lamps, where necessary.

The National Institute of Clinical Excellence (NICE) recommended that those with type 2 diabetes(2002 guideline[7] and type 1 diabetes (2004 guideline[8] have their eyes screened at the time of diagnosis and at least annually thereafter. NICE reviewed their guideline[9] for type 2 diabetes in 2008 and produced a similar recommendation.

In 2002, Wales announced a National Screening Programme based on two field digital photography after mydriasis and Northern Ireland announced a National Screening Programme using the same methodology with selective mydriasis for those under age 50 years.

In 2003, the National Service Framework for Diabetes: Delivery Strategy[10] announced the introduction of a National Screening Programme for Sight-Threatening Diabetic Retinopathy in England using two field digital photography after mydriasis with tropicamide.

A consensus grading protocol has been developed in England[1] , Scotland[2] , Wales[3] and Northern Ireland[4] and details are available on the relevant websites.

8.3 EVIDENCE FOR THE EFFECTIVENESS OF SCREENING

The *definition of screening* that was adapted by the WHO[11] in 1968 was ‘the presumptive identification of unrecognised disease or defect by the application of

tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.'

The principles for screening for human disease derived from the public health papers produced by the WHO[11] in 1968 were:

1. The condition sought should be an important problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of the case-finding programme (including early diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'one-time' project.

Much of the evidence that was given for diabetic retinopathy being an important condition that comes under these criteria above is presented in this guideline.

Evidence of the cost effectiveness of screening came from a number of sources [6, 12] - [20] .

In the Four Nations there is unequivocal support for the use of digital photography as the best method of screening. The use of selective mydriasis and the number of fields captured have been more controversial [6, 21] -[24] for evidence base for digital photography and required fields .

It is important to recognise that screening acts as a sieve and, as with all screening programmes, not every case of sight threatening retinopathy will be detected with the screening test used.

8.4 ORGANISATION OF SCREENING SERVICES AND METHODOLOGIES USED IN THE UK

The introduction of National Screening Programmes in England, Scotland, Wales and Northern Ireland demonstrated differences in the health care systems at that time.

All Four Nations agreed a minimum specification for cameras to be used across the UK which is updated at approximately 3 yearly intervals. Any new cameras coming onto the market are tested to check that they comply with the relevant minimum standard.

The implementation of the English National Screening Programme is overseen by a Programme Advisory Committee. In the English Scheme guidance was given on recommended software to be used, the method of two field mydriatic digital photography, the minimum grading classification and further information is provided on a website[1]. The screening test uses technician screeners or optometrists. Fixed locations are used or screening may be undertaken in a van based mobile unit transported to GP surgeries or other locations. It is recommended that screening in any area is overseen by a Programme Board that has representation from Ophthalmology, Public Health, Commissioners and the local Screening Team.

In Scotland the DRS Collaborative has been formed to bring together individuals from all the NHS Boards in Scotland involved in the delivery of the retinopathy screening programme, including representatives of the various professions involved as well as patient representatives and other stakeholders. The aim of the DRS Collaborative is to facilitate the delivery of diabetic retinopathy screening across Scotland as part of a National Programme. The National Screening Programme in Scotland uses a three-stage process based on one field non-mydriatic digital photography, with the use of mydriasis and slit-lamps, where necessary. In 2010, NHS Quality Improvement Scotland recommended the use of automated grading for distinguishing retinopathy from no retinopathy, providing validated software is used (http://www.sign.ac.uk/pdf/sign116.pdf, 2011). The DRS Collaborative has since commenced implementation of automated grading within the National Screening Programme.

In Wales, a Programme Board established by Cardiff and Vale NHS Trust oversee the Diabetic Retinopathy Screening Service for Wales which is centrally funded by the Welsh Assembly. The screening methodology in Wales is two field mydriatic digital photography using technicians travelling in mobile units to fixed locations across Wales. All grading in Wales is undertaken in a single centre.

The Northern Ireland DRSP was implemented by a project board. The screening programme uses a mixed model, with the screening test delivered primarily in GP practices in the legacy Eastern, Northern and Southern Boards using mobile equipment, and in six fixed community sites in the legacy Western Board. The methodology is two field digital photography through dilated pupils, with selective mydriasis under the age of 50 years. All images are transferred and graded centrally at the screening programme centre at Belfast Health and Social Care (HSC) Trust.

Monitoring of programme performance against a set of Quality Assurance standards is key to successful National Screening Programmes in all Four Nations. England has developed Quality Assurance Standards and Key Performance Indicators against which individual Screening Programmes are monitored. Wales and Northern Ireland are working to similar standards to the English Screening Programme. NHS Quality Improvement Scotland has produced a set of standards against which screening programmes in Scotland are monitored. Links to relevant documents are available from the English[1] and Scottish[2] websites.

The key feature of these standards is rigorous quality control at all stages of the screening and assessment process. Screening services are required to produce annual reports and continuous internal and external monitoring of quality should enable year on year improvements to occur.

A key requirement for systematic DR screening in the UK is accurate identification in primary care of all those known to have diabetes and the transfer of this information to invite the target population for screening. This is essential to achieve full coverage. In Scotland, GPs register all people with diabetes on the SCI-DC Network, which, in addition to providing a single web based patient record for diabetes also registers patients on the national diabetes retinopathy screening system (Soarian). In England a system called GPtoDRS is being developed to allow electronic transfer of data from GP diabetes registers to screening programmes.

With rapid advancements in technology new approaches to screening may prove effective including the use of computerised methods for detection and assessment of retinopathy[25 26] or optical coherence tomography in the first line assessment of screen positive patients with diabetic maculopathy.

When new technologies are assessed for use in the English Screening Programme they need to demonstrate:

1. That the device can match the sensitivity and specificity of digital photography in the detection of referable retinopathy in a screening programme environment where ungradable images are test positive.
2. That the device should be able to detect microaneurysms (display so that they can be graded) to the same level as modern digital cameras.
3. That the device compares favourably in terms of cost effectiveness and affordability compared to digital photography when used in a screening programme.

8.5 GRADING AND REFERRAL

A national consensus grading protocol was agreed for England and Wales[27] with the following key principles:

- to detect any retinopathy
- to detect the presence of sight threatening diabetic retinopathy(STDR)
- to allow precise quality assurance at all steps
- to minimise false positive referral to the hospital eye service

The grading and referral protocol is available on the English Programme website[1].
A Grading and Assessment Sub-Committee of the English National Screening Programme Advisory Group is currently working to tighten up some of the definitions within the current grading protocol and any updates will be circulated to Programme Managers and Clinical Leads of Screening Services in England.
The Scottish Diabetic Retinopathy Grading Scheme protocol is available on the Scottish Collaborative website[2] and on the Scottish Government website[28].

8.6 ROLE OF THE OPHTHALMOLOGIST IN SCREENING

The role of the ophthalmologist in the delivery of screening and management of patients with diabetes is pivotal. The responsibilities of the ophthalmologist are:

- to form a team with one or more diabetologists to lead the delivery of the screening programme. A specific linked ophthalmologist is required for each individual programme.
- to involve local management structures at PCT and SHA level
- to act as higher level grader as appropriate to local methodology
- to act as quality assurance reference standard after suitable training
- to ensure the training and accreditation of local screening staff
- to agree and monitor local quality assurance
- to ensure access to prompt treatment within agreed quality standards
- to organise the collection and prompt transfer of data on vision and disease outcome within the minimum data set to central data collection networks. This will be best achieved through the establishment of dedicated clinics for the management and
follow-up of cases detected through screening.

In September 2010 the Royal College of Ophthalmologists produced Preferred Practice Guidance[29] on Diabetic Retinopathy Screening (DRS) and the Ophthalmology Clinic set up in England, which produces useful extra information for Ophthalmologists working in England.

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SECTION 9: RETINAL LASERS

Photocoagulation for diabetic retinopathy is performed with the use of a variety of ophthalmic lasers. The technological advances in this field have made efficient laser equipment that can deliver effective treatments in both clinical set up as well in operating theatre.

9.1 METHOD OF LASER APPLICATION

Laser energy may be applied to the retina either through the dilated pupil using a contact lens or the indirect ophthalmoscope, or externally through the sclera. Transpupillary laser is normally applied using the slit lamp bio-microscope and a contact lens. The superiority of the modern wide-angled contact lenses has made use of 3 mirror contact lens very infrequent in clinical practice. Contact lenses such as the VOLK®, MAINSTER® or RODENSTOCK® lenses give a good view of the macula, the equatorial and pre- and post- equatorial regions of the retina. These lenses give an inverted image but provide easy access to the retina even in the presence of media opacity such as mild to moderate cataract.

Lasers can also be applied using a non-contact indirect method such as the 90 dioptre or 66 dioptre or superfield lenses again using a biomicroscopy technique with the slit-lamp biomicroscope. These lenses may also be used with special adaptation of an indirect ophthalmoscope, however a 20D lens is usually used for laser treatment (PRP) with indirect ophthalmoscope; this technique offers the advantage of good access to peripheral retina and is the method of choice when applying laser during a general anaesthetic. It is very important to remember that the spot size may vary with the different types of lenses that are used and the operator should be familiar with the lens he or she normally uses. A sample of different spot sizes achieved with different lenses is shown in Appendix 1, Section 10. Trans-scleral laser therapy may also be used and a special attachment for the DIODE laser is available for this application. The laser intensity is monitored through an indirect ophthalmoscope and lens.

9.2 LASERS

Optical radiations produced by gas or solid lasers are unique in that they are emitted at effectively one wavelength. Dye lasers are produced with inorganic dyes and have varying wavelengths. Gas lasers (ARGON and KRYPTON) produce optical radiations in the visible spectrum while the newer Diode lasers produce energy in the infrared band. The infrared lasers can be either continuous or multipulsed (Micropulse).

Lasers act by inducing thermal damage after absorption of energy by tissue pigments. The three main retinal pigments are luteal pigment, haemoglobin and melanin and the appropriate laser wavelength can be used to be selectively absorbed in one or more of these three pigments. The main target cell, however, is the pigment epithelium and it is this site where much of the tissue damage is induced.

9.2.1 The Argon Laser

The Argon laser has been in wide use for treatment of diabetic retinopathy. The Argon laser produces two major peaks of energy in the 488nm and 514nm wavelengths. The 488nm wavelength has been shown by reflection off the contact lens to cause operator blue colour vision damage and this wavelength is now filtered out of the system[1-4]. The 514nm wavelength has a potential for causing similar damage but this has as yet not been proven; to prevent reflection of this wave band there is a barrier filter and the aiming beam is replaced with a HeNe (helium neon) laser which is coaxial with the treating laser beam. This green laser energy is absorbed both by haemoglobin and by pigment epithelium. It is therefore possible with this wavelength to directly close microaneurysms or close new blood vessels and if applied over a retinal vessel, may cause spasm or closure of the vessel. However in clinical practice, although it is possible to close vessels, the main application of the laser is to the underlying pigment epithelium where it produces a visible burn. A burn if gently applied causes a blanching of the outer neural retina; a more intense laser burn will produce marked whitening of the entire retinal thickness, a pigment ring surrounding the laser spot develops later. The energy applied to the pigment epithelium raises the temperature by approximately 10□C with a temperature gradient from the centre of the burn to the adjacent retina resulting in enlargement of the visible area of RPE cell loss, damage to the neural retina and progressive choriocapillaris atrophy. It is therefore important that the laser energy should be set to induce a minimal reaction at the time of application. Although the second peak from the Argon laser is the 488nm, this wavelength has now fallen into disuse. The disadvantage of this wavelength was that it is absorbed by the luteal pigment in the nerve fibre layer in the macular area risking damage to the perimacular nerve fibre layer. The 514 nm wavelength is minimally absorbed by the luteal pigment and therefore is safer for treatment of retina close to the macula[5-7] and should be used for macular laser treatment.

9.2.2 The Krypton Laser

Krypton laser peaks at 647 nm and 568 nm and thus emits in the red and yellow wavebands. The red waveband was initially thought to be useful in treating parafoveal lesions because it is not absorbed by luteal pigment. However, this colour is no longer used because of the sensitivity of the pigment epithelium to changes in power. A small increase in power changed a white RPE reaction either to a haemorrhage or to disruption of the pigment epithelium. A slight tilting of the lens leading to a change in the spot size had the same effect. The yellow peak of the krypton laser is similar to the yellow of the dye laser which has become more readily available now.

9.2.3 The Dye Laser

The dye laser (570nm – 630nm) was developed to provide a variable wavelength laser in the green, yellow and red wavebands. In the green waveband the dye laser has no advantage over the Argon laser and the red waveband is similar to the krypton laser and has the same complications. However the yellow wavelength (577 nm) has gained some popularity because it is absorbed by haemoglobin and therefore allows direct closure of microaneurysms and blood vessels. In addition, much less power is required compared to the argon laser to achieve a satisfactory burn and therefore in those patients with a low pain threshold or very thin retinas, this wavelength can be

very helpful[8,9]. Some operators feel that they are most comfortable treating with this wavelength.

9.2.4 The Diode Laser

The diode laser at 810 nm in the infrared or invisible spectrum is delivered via a portable machine. The lack of a bright flash provides increased patient comfort. Additionally, the laser producing minimal bleaching of the retina allows rapid recovery from the laser treatment. However with the diode laser the end point being a greyish lesion at the level of the pigment epithelium rather than more obvious white lesion produced by other wavelengths, it is more difficult to assess. If the laser surgeon is unaware of this difference, there may be a tendency to raise the power of the diode laser to produce a white lesion similar to that produced with the argon laser and that such more intense lesion may cause pain and excessive damage to the retina[10,11]. Around 9% of the energy from the diode laser is absorbed by the pigment epithelium, the remaining energy penetrates into the choroid to be absorbed by choroidal melanocytes compared to the 50% energy uptake by the RPE from the argon laser[12,13]. The diode laser has been adapted to fire in a rapid sequence micropulse mode (Micropulse laser). In this mode there are short applications of laser of approximately 100 micro-seconds in duration with an interval in the region of 1900 micro-seconds. Thus 100 micro-bursts of the laser can be applied into an envelope of 0.2 seconds. The method of application of this laser is to increase the power of the laser to achieve a whitening of the retina and then to reduce the energy levels by around 50% to continue treatment. The effect of this laser is to raise the temperature within the retinal pigment epithelium only; thus minimising collateral damage to both neuroretina and choroid. In addition, unlike the conventional mode of diode laser in which pain may occur, usually there is no associated pain with the micropulse mode. Initial non-randomised clinical studies in particular for diabetic maculopathy are encouraging[14,15] and there is currently a large multi-centre study in progress comparing this laser with the argon laser.

9.2.5 The Frequency-Doubled Yttrium Aluminum Garnet (YAG) Laser

Recent application of the frequency doubled YAG laser has shown that it is as effective in treatment of diabetic macular oedema as other laser types and that it is gaining some popularity [16,17.] In particular, the Pascal (PAttern SCAn Laser) frequency-doubled neodymium-doped yttrium aluminum garnet solid-state laser with a wavelength of 532 nm is increasingly used. Usual laser lenses appropriate for use are Mainster® 165 PRP, Mainster® Focal Grid, 1X Mainster®, Area Centralis®, Quadraspheric® & Super Quadraspheric® and similar lenses. A laser indirect ophthalmoscope can also be attached for single spot delivery only. Power settings for Pascal are in general twice that of argon for comparable treatments. However, pulse duration is one fifth that of conventiaonl argon laser treatment, [e.g. for Pascal laser PRP, 20ms (0.02sec) versus 100ms (0.10sec) for conventional argon laser]. [18]

9.2.6 Lasers – Principles in Practice

The goal of retinal photocoagulation is to target the RPE with minimal photoreceptor damage and RPE cell loss, and perhaps barely-visible scar formation within the outer retina. In the decade following the guidelines published by the DRS and ETDRS,

although visible endpoint DRS/ETDRS laser photocoagulation remains the gold standard for the treatment of PDR, different laser strategies can help reduce ocular side-effects, such as laser burn scarring and visual field loss[19]. As discussed above, the sub threshold diode micropulse (SDM, 810nm) laser targets the melanin within the RPE for photothermal effects, with minimisation of functional and structural damage to the outer retina since there is no absorption by photoreceptors and haemoglobin[20] **(**Level 2**).** A major issue for clinicians is that ophthalmologists have found laser titration difficult in the absence of visible laser uptake, with risks of overlapping re-treatment burns. Additionally, the SDM laser burns are not visualised using fundus autofluorescence (FAF) or OCT techniques [21,22]

There are few multisport laser delivery systems available with FDA clearance, such as the Pascal Photocoagulator Topcon[23, 24] the Suprascan 532nm (Quantel Medical), and recently, the MC-500 Vixi (Nidek) with 532nm green, 577nm yellow, or 647nm red. Such systems allow a pulse duration of 10-30ms compared with 100-200ms with conventional laser. Additionally the procedure can be semi-automated by delivering multiple laser burns to the retina with a single depression of the foot pedal.

Multispot laser treatment for PDR has been shown to be safe and effective, preserving central visual acuity as well as peripheral visual field [25](**Level 1**). Shorter duration of laser pulse has been demonstrated to be more favourable for pain [26, 27]. It is recognised that if laser treatment is applied using shorted duration of pulse (e.g. 20ms) a larger number of burns are needed to achieve control of PDR, either in a single session or multiple sessions[28,29,30] (**Level 2)** .

9.2.7 Healing Responses

The in vivo effects of 20ms burns have been demonstrated in animal studies[31]. A potential explanation for laser burn healing responses is related to fluence, which is calculated as (power x time)/area. The fluence required to produce a threshold ETDRS type PRP burn on the retina is significantly lower for a pulse duration of 20ms compared with conventional 100ms pulse duration. A lower fluence laser dose results in fewer structural alterations in the outer retina[31]. At shorter and longer pulse durations, the RPE absorbs the laser light and is destroyed, and the adjascent RPE proliferates to fill the area destroyed. However, at shorter pulse duration, there is photoreceptor in-filling to sites of laser injury with healing responses produced over time. The *MAPASS* study showed that 20ms burns allow the tissues to undergo a healing response that may not occur after standard-duration (100-200ms) photocoagulation[19] .This healing response is associated with a significant reduction in burn size across time for 20ms pulse duration, with no significant disruption to either the inner retina or the basal RPE. Higher-fluence 100ms burns developed larger defects due to thermal blooming and collateral damage, with no alteration in burn size across time or any healing laser-tissue interactions. Furthermore, at 6-months, the 20ms laser burns reduced in size without any overlapping laser scars, as the laser burns show healing responses over time[32] (Level 2). Hence, at different pulse durations, fluence should be titrated to achieve threshold burns in the outer retina, allowing for healing of laser burns and minimisation of photoreceptor injury.

9.2.8 Retinal Laser Ablation Area

Calculation of the total retinal area has produced estimates between 1100 and 1368mm^2 [34]. Barr reported that a maximal number of 5500 laser burns could be applied to the retinal surface using a 500μm laser spot size[35]. In 1995, Reddy and co-workers quantified the ablation areas using 500μm conventional argon PRP laser and reported that 2600–6500 laser burns, with a retinal coverage of 510–1280mm^2, is required to treat PDR with PRP dosage proportional to the number of retinopathy risk factors[36] (**Level 2**).

The ETDRS recommended multi-session 500μm PRP laser extending into far-peripheral zones in high-risk eyes[37] (**Level 1**) .The DRS study recommended a minimum laser ablation area of 236mm^2 (range 157–314mm^2) for standard PRP, and the ETDRS suggested a minimum area of 236 mm^2 for PRP treatment (**Level 1**). In the UK, a snap-shot of single-session PRP reported a median treatment area of 98.2mm^2 (range 6.7–682.5mm^2) [38] (**Level 2**). At the time of the UK study in 1995, there appeared to be a trend to initially undertreat eyes compared with the DRS and ETDRS recommendations; however, subsequent PRP was often needed in clinical practice[39].

The use of 1500, 20ms PRP burns in a single session was shown to be a safe regimen in the *MAPASS* trial. However, for long-term PDR regression, 72% of eyes required top-up PRP treatment[27], and the laser burn treatment density and final treatment areas varied according to the risk profile of the PDR[40]. Using 20ms PRP treatment, the retinal ablation areas needed to produce complete disease regression ranged from 292 to 657mm^2 [27]. Following primary PRP treatment of 1500 treatment burns, an additional 1000- to 2000-burn PRP was required in a single session to completely regress mild PDR (total 2500-3500 burns). The laser burn density and retinal ablation areas increase significantly for moderate PDR (approximately 4000 burns) and severe PDR (approximately 7000 burns). Overall regression rates for PDR showed between 67% and 75% for mild/moderate PDR and 43% in severe disease. Allowing for the laser healing responses that reduces the burn sizes of 20ms PRP burns over time, the retinal ablation area required to treat PDR using micropulse mode should be increased [33] (**Level 2**).

9.3 LASER APPLICATION: GENERAL PROTOCOLS

Laser treatment can be carried out either as a single session or in multiple sessions. Both eyes can be treated in the same session for the macula as well as for the peripheral retina. Caution should be taken when treating in the macular area when there are associated exudates lying immediately adjacent to the fovea as sometimes when the oedema has been treated, the exudates increase and these can encroach into the fovea and permanently affect foveal function. Under these circumstances, the treatment should be fractionated. (**Level B**) The aim of treatment of panretinal photocoagulation (PRP) is to destroy the areas where there is capillary nonperfusion and retinal ischaemia. In some eyes this may mean an initial treatment of over 2000 burns of 500 μm size, or more if the burn size is smaller. If there is an inadequate response without full regression of new vessels, then re-treatment can be carried out. This re-treatment can be performed within one to three months of the initial treatment, depending on clinical response. If there has been insufficient laser prior to vitrectomy,

then further laser can be applied during the vitrectomy via the indirect ophthalmoscope or the endolaser (see section 12).

9.4 SIDE EFFECTS OF LASERS

9.4.1 Pain

Delivery of laser energy to the ocular fundus may in some cases be associated with pain or discomfort. Diode lasers may be more painful than conventional lasers. The cause of the pain is unclear but may be due to direct thermal damage to branches of the posterior ciliary nerves. Pain may be prevented with the use of simple analgesia but on occasion may require periocular anaesthesia, or less frequently general anaesthesia, to achieve a satisfactory full PRP particularly in patients with florid proliferative retinopathy in whom a delay in therapy must be avoided. Pain may also 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. It is therefore important when applying repeat laser therapy to try to avoid the previously treated areas.

9.4.2 Vitreous Haemorrhage

Laser therapy in patients with forward new vessels may be sufficient to cause marked regression of vessels which separate from the posterior hyaloid face and produce vitreous and subhyaloid haemorrhage. In most cases this is a rare event but patients require information concerning this risk prior to initiation of therapy. (see Section 7.12)

9.4.3. Effect on Visual Function

There is evidence that the risk of causing reduction in visual field is around 40-50% after full PRP. Some later papers suggest the risk of losing one's driving licence after bilateral PRP is less than 20%. The reduction in debarring visual field loss may reflect changing strategies of PRP with smaller (200μm) and lighter burns (see above). Possible loss of peripheral field of vision has implications for fitness to drive safely and driving licence regulations, hence this potential side effect should form part of the information provided to patients prior to treatment[41-48]. Additionaly, there may be other more subtle side effects of PRP on visual function such as some loss of contrast sensitivity and a reduction in the ERG[49]. Finally, it must be remembered that visual function may also be lost through inadvertent laser application to the foveal and parafoveal regions, or through the development of secondary neovascular membranes after focal treatment of microaneurysms. Other persistent side effects that may occur following laser treatment are reduction of visual acuity, a possible reduction in accommodative power, some dimness of vision like looking through a neutral density filter andsome degree of nyctalopia [50]. Loss of colour vision in the blue spectrum may occur following extensive peripheral laser treatment and photophobia may also occur after laser therapy. This photophobia is due to halation and although it may be helped by dark glasses, it is possibly helped more by shading the eyes.

9.4.4 Secondary Choroidal Neovascularisation

If laser application is applied very close to the macula and is of a high energy, then there is a risk of loss of central vision due to disruption of the pigment epithelium and Bruch's membrane, giving rise to foci of chorioretinal neovascularistation, such as occurs spontaneously in neovascular age-related macular degeneration (the disciform response). This neovascularisation may occur rapidly following laser treatment and may result in loss of central vision. There is an increased risk of choroidal neovascularisation when moving from a peripheral region to a more central region without appropriately reducing the power of the laser or taking account of possible effects of lens tilt.

9.4.5. Macular Burn

It is crucial to prevent the development of a foveal burn by constantly referring back to the macula to be sure that the laser does not stray into the central macular area. In addition, recognition is growing of the risk of extension of laser burn size with time into the foveal zone.

9.4.6. Macular Oedema

Scatter peripheral pan-retinal photocoagulation has been reported to be followed by development or worsening of macular oedema which fortunately is transient but it is important to warn the patient that there may be some loss of vision following the laser treatment. It is advisable to treat the maculopathy either at the same time or prior to peripheral scatter retinal photocoagulation (PRP)[51-54.]

9.4.7 Other side effects

Rare complications such as corneal burns, raised intraocular pressure or angle closure (associated with shallowing of the anterior chamber, choroidal effusion and accompanying myopia)[55] and preretinal or subretinal fibrosis have been reported. Full panretinal laser photocoagulation may be followed by pallor of the optic disc as a result of loss of some of the nerve fibre layer and corresponding loss of vision, particularly with relatively heavy burns. Such patients have poor pupillary reactions and dilate poorly with short-acting mydriatics. This reduced mydriasis can compromise examination of the fundus and increase difficulty with intraocular surgery, if required post laser. There is also the recognised potential risk of traction retinal detachment with PRP. Rarely, some patients develop increasing vitreo retinal traction following laser treatment and would require VR surgical opinion.

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SECTION 10: MANAGEMENT OF DIABETIC RETINOPATHY

10.1 INTRODUCTION

This chapter discusses the management of peripheral (non-macular) diabetic retinopathy (the R grade in Diabetic Retinopathy Screening Programmes' grading classification) to reduce the risk of vision loss. Loss of vision from diabetic retinopathy mainly occurs by 2 mechanisms:

- Complications of proliferative retinopathy (PDR) affecting the macula
- Loss of peripheral field of vision that results from ischaemia and as a result of laser treatment related damage

The laser treatment protocol used in clinical practice is largely based on the combined findings of 2 landmark clinical trials from the 1980s[1,2] Since that time further management strategies have evolved. However the principle behind treatment is to reduce the stimulus for retinal neovascularisation by pan retinal/scatter laser phot ocoagulation (PRP).

This section:

- summarises landmark trials' (1980s) recommendations
- discusses subsequent management strategies and
- provides recommendations

10.2 MANAGEMENT STRATEGIES FROM THE LANDMARK TRIALS OF 1980S

10.2.1 The Diabetic Retinopathy Study (DRS) and the Early Treatment for Diabetic R etinopathy Study (ETDRS) were randomised clinical trials that compared the visual o utcome of patients treated with PRP compared with no treatment. The DRS recruited eyes with PDR and reported a 60% reduction of severe visual loss (SVL: vision less than 5/200 at 2 or more consecutive follow-up visits) in eyes treated with argon laser or Xenon arc PRP compared with control at 2 years[3]. The principle side effect of treatment with Xenon arc retinal photocoagulation was peripheral visual field loss due to retinal ablation[4]. The ETDRS recruited patients with non-proliferative retinopathy or proliferative retinopathy without high –risk characteristics to determine the stage at which PRP laser should be given using argon laser. Overall the 5 year risk of severe visual loss or vitrectomy was 2-6% in eyes assigned to early photocoagulation and 4-10% in those assigned to deferral. The conclusion was that laser PRP could be deferred until eyes approached the high risk stage (see table 1) provided maintenance of adequate follow up evaluation. . There was concern about laser related side effects especially in the cases with concurrent maculopathy[5]. These trials established the basis for treatment protocols for diabetic retinopathy that have subsequently been adopted worldwide **(LEVEL 1).**

10.2.1.1 No intervention was recommended for mild – moderate diabetic retinopathy which should be monitored annually with the patient encouraged to maintain as good diabetes control as possible (**Level 1**).

10.2.1.2 Moderately severe – very severe retinopathy (pre-proliferative retinopathy) was to be monitored at 4-6 monthly intervals with intervention by peripheral scatter laser treatment as high risk stage approaches (**Level 1**).

10.2.1.3 High risk proliferative diabetic retinopathy should be treated with pan-retinal/scatter peripheral retinal laser photocoagulation (PRP) to reduce risk of severe visual loss[3, 6] (**Level 1**)

Table 1: Four risk factors for severe visual loss in untreated eyes: modified from 3rd Report DRS[7]

No of risk factors	Risk factor	2y risk of SVL (%)
0		3.6
1	VH *or* NVE	4.2-6.8
2 (NB: presence of any NV is a risk factor)	Mod / sevNVE *or* NVD	6.9 – 10.5
3	NVD+VH *or* m/sNVE+VH	25.2-29.7
4	M/sNVE+NVD+ VH	36.9

Key: NVD: New vessels on disc or within 1 disc diameter
NVE: New vessels elsewhere
VH: Vitreous or preretinal haemorrhage

10.3 POST DRS AND ETDRS MANAGEMENT STRATEGIES

10.3.1 Earlier treatment: Recognition that earlier laser prevents progression to high risk retinopathy[8,] and that PDR has higher risk of blindness[9] 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[10] **(Level A)**

10.3.2 New laser technology and techniques: In the decade following publication of DRS and ETDRS recommendations, investigators have revisited the underlying mechanisms of laser photocoagulation and tried different laser strategies to reduce impact on peripheralfield of vision from scarring and enlargement of retinal burns. Retinal lesion size shows a logarithmic increase as a function of increasing pulse duration from 1 to 100 ms [11]. By using shorter pulse duration there is less thermal spread; PRP treatment is less painful[12] and creates a lighter, smaller burn with less collateral damage to the outer retina[13]. With shorter pulse duration there is stability of burn size over time and evidence of healing with less scarring[14], though more burns may be needed for equivalent therapeutic effect[15] (**Level 2**). Since introduction of pattern multishot laser delivery in 2005, PRP treatment can be

delivered faster with multiple retina laser burns being given with a single depression of the foot pedal[16]. In clinical studies good short term control of PDR has been shown for single session pattern multishot PRP treatment, but top-up laser has been required with overall more laser burns delivered than with conventional laser technique[17] (**Level 2)**.

10.4 CURRENT RECOMMENDATIONS: MONITORING, INVESTIGATION AND TREATMENT

10.4.1 *Background retinopathy (Mild-moderate nonproliferativeretinopathy)*

As recommended in ETDRS[5], no treatment is indicated for background DR (**Level 1**). In the UK, this level of retinopathy is monitored with annual digital photography in population-based Screening Programmes for Diabetic Retinopathy (**Level A**). In the English screening programme (ENSPDR) two standard photographic fields are used on the basis that at least 80% of the sight threatening retinopathy will be seen as is present in 7 field stereo colour photographs of the same fundus[18]. Progression to more advanced retinopathy is related to control of diabetes[19] and its risk can be reduced by intesive blood sugar control in type 1[20] and by both intensive blood pressure and blood sugar control in type 2[21] **(Level 1**). It is important that ophthalmologists encourage patients to optimise care of their diabetes (**Level A**).

10.4.2 *Pre-proliferative diabetic retinopathy (Severe nonproliferative diabetic retinopathy)*

It is recommended that those with more advanced nonproliferative retinopathy have regular slit lamp biomicroscopic examination by an expert to look for features of retinal ischaemia (**Level A**). Wide angle retinal examination outside standard screening photographic fields is advisable. The interval between examinations depends on level of retinopathy – DRS and ETDRS patients were examined at 4 monthly intervals, though many consider 6 months to be safe for referral grade retinopathy (R2 in England: level 43 ETDRS) in clinical practice with an approximate first year rate of progression to PDR of 3.2%[22] **(Level B**). Digital fundus colour photography is a useful adjunct to clinical examination (**Level B**). Digital images can be manipulated and magnified and enable correlation of examination with retinal features, improve grade accuracy, monitor progression and record response to treatment. Although colour photographs and slit lamp biomicroscopy are often sufficient to identify initial features of ischaemia, the extent of capillary non-perfusion is more accurately assessed using fundus fluorescein angiography (FFA) [23] though this is mostly not necessary FFA is particularly useful to identify new vessels where doubt exists (**Level B**). Indocyanine green angiography (ICG) is not indicated unless there are outer retinal changes, for exampleto diagnose post laser choridal neovascularisation where haemorrhage obscures the underlying problem.

As retinopathy approaches the proliferative stage, laser scatter treatment (PRP) should be increasingly considered to prevent progression to high risk PDR. In ETDRS very severe non-proliferative retinopathy (ETDRS 53E) had a 48.5% risk of progressing to high risk PDR within 1 year and it was recommended that even where follow-up was possible PRP treatment should be considered in these eyes because they showed

increased risk of severe visual loss (SVL) and need for vitrectomy(V)[22] (**Level 1**). Early PRP reduced progression to high risk PDR by 50% in the full scatter and 25% in the mild scatter groups. The overall rate of SVLV was low at 2.6% of treated and 3.7% of deferred eyes at 5 years[5]. This findings contrasts with DRS where the 2 year SVL rate of untreated eyes was 20%[3]. The lower risk in ETDRS was attributed to careful follow-up and prompt treatment as soon as high risk retinopathy developed and this is an important consideration where treatment of ischaemic eyes has to be deferred for any reason.

PRP treatment should be considered for pre- proliferative (severe- very severe) DR:

- in older patients with type 2 diabetes[24] (**Level 1**)
- where retinal view is difficult
- prior to cataract surgery: inflammation possibly associated with progression[25]
- in only eye where first eye lost to PDR
- where regular clinic attendance is likely to be poor
- difficult to examine patient for other reasons

10.4.3 *Proliferative diabetic retinopathy (PDR)*

Full PRP treatment is indicated for retinal new vessels (NVD, NVE). Wherever possible PRP should be delivered the same day or should be arranged within 2 weeks of diagnosis of high risk proliferative diabetic retinopathy (**Level A**). Although treatment should not be delayed by failure to obtain fluorescein angiography, patients with PDR will benefit from baseline fluorescein angiography to assess macular perfusion, retinal ischaemia, and neovascular activity even after initiating PRP treatment (**Level B**). A full scatter PRP is defined as treatment of all quadrants of pre- and post-equatorial retina outside the macular vascular arcades. The usual technique is to deliver the initial treatment posterior to the ora serrata outside the vascular arcade with emphasis on ischaemic retina near NVE but avoiding direct NV application. The DRS showed that the risk of severe visual loss in patients with high risk characteristics is reduced by 50% at 2 and 5 years by pan retinal photocoagulation laser therapy and by up to 70% in moderate risk patients[6]. (**Level 1**)

Initial treatment should avoid exacerbating pre-existing macular oedema or sites of retinal traction. Scatter laser treatment is titrated to the patient: with burn power sufficient to create an immediate grey-white retinal response and number of burns appropriate to the extent of NV and capillary non-perfusion. (**Level B**) This minimises adverse effects on visual field while still achieving regression of NV.

10.4.4 *Advanced PDR*

Some retinopathy is so advanced at presentation that laser PRP may appear to have little effect on new vessel progression, development of traction retinal detachment, haemorrhage and progression to anterior segment neovascularisation. In these cases early vitrectomy preserves sight in type 1 diabetes[26]. If there is delay in applying PRP due to vitreous haemorrhage or other inability to visualise the retina, vitrectomy

should be considered. Recent reports recommend intravitreal anti-VEGF injection just prior to vitrectomy to reduce risk of intraoperative complication and surgical time[27]. (**Level 1**)

10.5 PRP: GOALS AND TECHNIQUE

10.5.1 *Intensity,duration and spot size*

The ETDRS recommended 500µm spot size, 100ms duration, moderate burn intensity, 0.5 - 1 laser burn spacing for conventional primary PRP has been widely practiced in the UK. With currently available lasers (532nm argon-green laser or frequency-doubled YAG), shorter duration (10-50mseconds), smaller burns (300 - 400µm) and less close spacing (1-1.5) burns are recommended [section 10, Appendix 2]. (**Level 1**)PRP laser lesions should be visible as an immediate grey – white mark on the retina avoiding direct treatment of major blood vessels and retina within the temporal arcade. The retinal response may be difficult to see in lightly pigmented fundi or where there is extensive retinal ischemia or media opacity. Laser power should be reduced to avoid producing excessively intense PRP lesions in the far periphery where retina is thinner (**Level B**)

10.5.2 *Treated retinal area*

The DRS and ETDRS recommended laser ablation a covering a minimum of 236mm^2(range 157–314mm^2) of retinal area. (**Level 1**) This translates in to an indicative number of 1200-1600, 500µm burns would be delivered over 2 or more sessions[28]. In the United Kingdom, a snap-shot of single-session PRP in 1995 reported a median treatment area of 98.2mm^2 (range 6.7–682.5mm^2)[29]. In the absence of subsequent outcome data for this cohort it is not possible to comment on treatment adequacy. Unlike the previous studies, the ablation area of retina required to treat PDR was subsequently quantified at 510–1280mm^2 (2600–6500 500µm conventional laser) with PRP dosage proportional to number of retinopathy risk factors [30]. Using the adjusted laser duration parameters of 20ms PRP the smaller laser burns size over time might be predicted to require increased retinal ablation area to be effective [32], though this has yet to be reported in practice [16].

10.5.3 *Laser delivery*

Laser treatment can be delivered in out patient setting by a trained ophthalmologist-laser surgeon with appropriate technical skills needed for particular laser equipment as well as experienced in identifying and modulating tissue responses of laser treatment on retina. Occasionally, patients may need laser treatment delivered in operating theatre using indirect ophthalmoscope by skilled laser surgeon.

- Slit lamp biomicroscopy: most frequently used, with topical anaesthesia and corneal contact lens often giving wide view, inverted virtual retinal image. It is essential to know the magnification of laser spot size induced by the contact lens (see Appendix)

- Head-mounted binocular indirect ophthalmoscope. Used for peripheral PRP laser treatment in theatre or outpatient department when a patient is unable to co-operate with slit lamp delivery; some patients and practitioners prefer head-mounted binocular indirect ophthalmoscope delivery. This technique facilitates scleral indentation. It is used in theatre immediately following cataract surgery when PRP has previously been inadequate because of poor view.

- Endolaser is given during vitrectomy for advanced PDR.

10.5.4 *Anaesthesia*

Topical anaesthesia is usually sufficient for PRP. Unusually, patients may require orbital anaesthesia (subtenons or peribulbar lignocaine 2-5%) especially if there have been previous treatments. Out-patient department anaesthesia should be given with medical cover as appropriate to the general health of the patient (see RCOphth Local Anaesthesia in Ophthalmic Surgery 2012[33]).

10.5.5 *Consent*

Written consent requires careful (often time-consuming) discussion of patient concerns about treatment side effects including potential for peripheral visual field loss that may have implications for driving licence. Consent for course of treatment is common place now since establishment of intravitreal injections Where repeated laser treatments are perfomed, consent for course of laser treatments may be sought and clearly documented in medical records. In such circumstances, verbal affirmation of consent should be established at each treatment episode (**Level A**).

10.5.6 *Reducing treatment side effects*

Field defects and impaired night vision are frequently reported side effects of conventional laser treatment[4]. These side effects are less common if large confluent burns are avoided and less commonly reported with short pulse duration laser parameters. Vitreous haemorrhage and increased vitreo-retinal traction may worsen after effective PRP because regression of new vessels may be accompanied by contraction of fibrovascular tissue[34]. Advanced retinopathy may fail to respond to full retinal PRP and appropriate counselling is essential when re-treating previously treated areas of the retina since there is potential to damage the visual field and compromise legal driving requirements. Accidental macular burn during PRP is avoided by (placing demarcation lesions temporal to the macula before treating temporal retina, using wide angle rather than 3 mirror contact lens, and checking frequently for retinal landmarks e.g. position of disc and macula especially when lasering retina without evidence of previous treatment.

10.5.8 *When to stop*

Regression of new vessels is characterised by blunting of the NV growing tips, or replacement with fibrosis. It is considered that peripheral retinal destruction is not

necessary for successful control of vasoproliferation and in advanced cases new vessels may persist despite a full PRP (**Level A**). 'Stable' NVs require monitoring but probably do not require further PRP. If clinical appearances change, with fine new blood vessel growth and associated retinal haemorrhages, FFA may be repeated to investigate activity and look for retinal ischaemia and areas of untreated retina. In the ENSPDR the grade of 'stable PDR' (R3s) will be used to denote eyes that have been fully treated and may be monitored in the annual digital photography programme. If neovascularisation is still active despite comprehensive laser treatment, vitrectomy with endolaser may be required (see Section 12).

10.6 MANAGEMENT OF ADVANCED PROLIFERATIVE DIABETIC RETINOPATHY

10.6.1 Vitreous haemorrhage: See Section 12

10.6.2 Rubeosis iridis is neovascularisation occurring on the iris (NVI) and in the drainage angle (NVA) and is a manifestation of severe retinal ischaemia heralding the onset of rubeotic (neovascular) glaucoma. This can progress to blindness unless treated promptly.

10.6.2.1 Management of NVI alone: In patients with clear media, immediate full retinal photocoagulation should be given to induce iris vessel regression.(**Level A**)

10.6.2.2 Management of NVI and NVA: These cases should be considered for prompt treatment with PRP. There have been recent favourable case reports of the benefits of intravitreal antiVEGF injection in preventing blindness from progression to neovascular (rubeotic) glaucoma- NVG- in these high risk eyes and this is becoming standard of care[35] (**Level 3**).

10.6.2.3 Further treatments for NVG include cycloablative laser, cryotherapy, implantation of drainage tube and trabeculectomy enhanced with anti-proliferative agents, the patients with NVG and useful vision would need co-management with glaucoma specialists for such treatments.(**Level A**)

10.6.2.4 Eyes that are blind from NVG should be kept pain-free. Palliative topical steroids with atropine may be required, though steroids are thought to increase risk of corneal infection and perforation and hence if possible, atropine drops alone should be used. (**Level B**)

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Section 10 Appendices:

Appendix 1: Table of commonly available laser contact lens magnifications and fields of view

Name of lens	Field of view (in degrees)	Image magnification	Laser spot magnification
Area Centralis®	70-84	1.06	X0.94
Mainster focal/grid®	90-121	0.96	X1.05
TransEquator®	110-132	0.70	X1.44
Quadraspheric®	120-144	0.51	X1.97
Superquad 160®	160-165	0.50	X2
Mainster PRP 165®	165-180	0.51	X1.96

Notes
1. The field of view depends on patient's refractive error.
2. Anterior segment irradiance is higher than retinal irradiance for 1000 microns spot size settings with a Panfundoscope or Mainster lens, and this setting should be avoided, especially in patients with hazy ocular media

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Appendix 2: An Example of Laser Titration Step

Anaesthesia
3 drops of G.Oxybuprocaine (Benoxinate). The use of subtenon's block is not indicated for routine PRP. If there is a significant pain issue with PRP, then the patient can undergo indirect PRP in theatre using subtenons block. (**Level A**)

Pulse Duration

A 20ms exposure time is preferable for PRP as it is more patient friendly and effective. This pulse duration can be achieved with standard laser systems as well as with the pattern scan laser systems (**Level B**). Exposure time should be titrated for individual patient as well as depending on laser reaction observed at given laser power setting. (**Level A**)

Spot Size
Use a 400μm retinal spot size. The laser contact lens has variable laser spot magnification powers (Appendix 1), and these magnification powers must be factored in before selecting the spot size on the laser system. (**Level A**)

As an example, if 200μm is pre-selected on the laser interface, a Mainster 165 PRP lens (Ocular Instruments Inc, Bellevue, Washington, USA) with spot magnification factor of 1.96 will produce a theoretical retinal spot size 392μm.

Smaller retinal spot size, e.g. 200μm and 300μm may lead to excessive higher fluence and risks of Bruch's rupture at 20ms exposure time. Furthermore, following laser burn healing, the final laser spot (burn) may be <100-150μm. Over time, the patient will require much more PRP treatment (Palanker et al, Retina 2011).

Larger retinal spot size of ≥500μm may lead to excessively high laser powers being required, as the larger spot will further reduce laser fluence, and the operator will require to increase laser power and/or duration making procedure uncomfortable for the patient.

Since 20ms reduces the fluence per laser spot, and laser burns reduce in size by up to 50% over time, the choice of a 400μm spot is a compromise between delivering moderate laser power/laser fluence and maintaining adequate retinal ablation area to treat PDR.

Laser burn spacing
Laser burns should be placed 1-burn widths apart for mild and moderate PDR (**Level A**). The space between the laser burns can be reduced for example, 0.5-burn widths apart for severe PDR, TRD and vitreous haemorrhage. These cases are known have severe retinal ischaemia, and closer laser burns will help increase the therapeutic effect of the PRP.

Laser burn intensity
Laser surgeon should aim for a barely-visible, grey/white burn reaction on retina after laser application as the designated threshold (**Level A**). The laser surgeon should be aware that the laser burn intensity at 20ms can continue to increase up to 1 minute following retinal application, so patience is required during the laser titration period to avoid excessive threshold power.

Laser power titration can be attempted anywhere outside the vascular arcades and should be continually moderated as per response through out PRP session. Using the 20ms pulse duration, the laser power would need to be reduced by up to 50mW in the

pre-equatorial retina. Failure to continually titrate laser power in the retinal periphery will lead to excessively intense PRP burns.

Retinal surface coverage
The PRP should be applied as far peripheral as possible using the laser contact lens, up to the ora serrata as the main areas of retinal ischaemia in PDR exist in the far-peripheral retina while area of ischaemic penumbra is likely to be in pre-equatorial zones..
In cases of hazy view of retina and cataract cases, an alternative strategy will involve the indirect laser with/without scleral indentation

Laser Strategy for Primary PRP

Early PDR
Includes early NVE and NVD, where the NV complexes are flat and less than third of disc diameter.

Primary PRP should be completed by 2 weeks, fractionated if needed (1200- 1800 burns ETDRS strategy). If shorter duration of laser pulse (20ms) used, consider increasing number of laser burns appropriately. (**Level A**)
Review: 4 months [in non-pregnant patient].

Moderate PDR
NVD: greater than third of disc diameter, and forward NVD extending beyond the disc margin or NVE: complexes in all quadrants, forward NVE in any quadrant.

Primary PRP should be completed by 2 weeks, fractionated if needed (2000 -2500 burns ETDRS strategy). If shorter duration of laser pulse (20ms) used, consider increasing number of laser burns appropriately and should be completed over 4 weeks with aiming to deliver more laser spots in initial sessions. (**Level A**)
Review: 3 months [in non-pregnant patient], however in poorly controlled diabetics, review interval should be shortened.

Severe PDR

Large, NVE complexes in any quadrant, NVE with tractional retinal detachment, large, forward NVD covering whole optic disc surface, NVD with tractional retinal detachment.These cases are high risk of continued traction and haemorrhagic complications following PRP.

Laser surgeon should aim to deliver full PRP coverage of peripheral retina (3000 burns ETDRS) over 2-3 sessions in 3-4 weeks. If shorter duration of laser pulse (20ms) used, consider increasing number of laser burns appropriately and should be completed over 4 weeks with aiming to deliver more laser spots in initial sessions. (**Level A**)

In cases of inferior vitreous haemorrhage with a retinal view, and tractional subhyaloid/retrohyaloid haemorrhages laser surgeon should aim for complete retinal

coverage in visible retinal quadrants, if possible. Once the vitreous haemorrhage clears, the inferior retinal laser treatment should be completed.

If there is any delay in applying PRP due to vitreous haemorrhage and inability to visualise the fundus, then antiVEGF injections may be considered in addition to referral to vitreoretinal service for vitrectomy (**Level A**).

PDR in Pregnancy

PDR in pregnancy can deteriorate rapidly and hence requires closer monitoring. Prompt laser treatment according to strategy outlined above should be completed where possible. Post laser treatment review should be done at 2-weeks following completed primary PRP treatment (**Level A**). Adequately treated PDR during pregnancy, is not a contraindication to normal vaginal delivery. Close liaison between the obstetrician, diabetologist and ophthalmologist is essential in planning management of such cases (**Level A**).

Special Cases

Young patients with type-1 diabetes with PDR often show macular ischaemia on pre-laser fluorescein angiography. There is an increased risk of developing macular oedema post-PRP if too many laser burns are delivered in a single-session hence the total laser burns should be delivered over 3 – 4 sessions within 4 weeks.

SECTION 11: MANAGEMENT OF DIABETIC MACULOPATHY

11.1 INTRODUCTION

There have been significant recent advances in the treatment of diabetic macular oedema (DMO). This is an area of active research and it is likely that other new therapeutic options will become available over the next few years. This chapter will be updated periodically to take into account changes in clinical practice.
The classification of diabetic maculopathy has been described earlier. The diagnosis and monitoring of DMO has been facilitated and modified by the advent of optical coherence tomography (OCT) and there are now new classification systems based on the location and amount of retinal thickening on OCT assessment. These new classification systems take into account various parameters: retinal thickness, extension of retinal thickening, macular volume, retinal morphology and vitreo-retinal relationship[1]. The level of central retinal thickness on OCT is increasingly used in treatment decisions.

This chapter will describe the evidence base for treatment, with a short summary thereafter to provide a current therapeutic strategy.

11.2 EVIDENCE BASE FOR THE TREATMENT OF DIABETIC MACULAR OEDEMA

11.2.1 Control of systemic risk factors

The importance of systemic risk factors in the development and progression of retinopathy has been discussed previously (Section 6). Patients with diabetic maculopathy should work to achieve optimum blood pressure and glycaemic control and for such patients consideration should be given to statin treatment unless there are medical contraindications, with consideration of the addition of a fenofibrate for those with type 2 diabetes (Section 6).

11.2.2 Photocoagulation treatment

Laser photocoagulation treatment for DMO has been the mainstay of treatment for diabetic macular oedema since the early 1980s. In 1979, Blankenship et al reported lower frequency of visual loss after 2 years with laser in patients with symmetrical macular oedema and preproliferative retinopathy as 23% of treated group vs 43% of control group deteriorated by 2 lines or more of vision.[2] The Early Treatment Diabetic Retinopathy Study (ETDRS) was a landmark trial that firmly established laser photocoagulation as a treatment for diabetic maculopathy. 2244 patients were randomly assigned to receive either early treatment with focal and grid photocoagulation or deferral of photocoagulation.[3] The laser photocoagulation was performed as follows:

- Focal treatment of microaneuysms and other sites of focal leakage with a 50-100μm spot size to obtain adefinite whitening around the area of leakage.
- Diffuse leakage and areas of capillary closure (that were not contiguous with the foveal avascular zone) within 2 disc diameters of the centre were

treated in a grid fashion using spot sizes of 50-200μm, a space of 1 burn width apart.

- Lesions within 500μm of fovea were not treated initially but treatment was allowed to within 300μm of the fovea on repeated sessions, as needed.

The study showed that for eyes with clinically significant macular oedema (CSMO), the rate of moderate visual loss [a doubling of the visual angle (15 or more letter loss on ETDRS charts)] was reduced from 24% to 12% at 3 years (**Level 1**). Eyes without CSMO had a low rate of visual loss without treatment. CSMO was defined as one or more of the following:

1. Retinal thickening at or within 500μm of the fovea.
2. Hard exudates at or within 500μm of the fovea if associated with adjacent retinal thickening.
3. An area or areas of retinal thickening one disc area in size, at least part of which is within one disc diameter of the fovea.

Although patients with normal central vision and CSMO were included in the study, clear benefit was achieved when pre-treatment visual acuity was < 6/9 and was most beneficial when vision was between 6/12 and 6/24. In patients with CSMO and normal visual acuity, the ETDRS data indicated a trend towards benefit in laser treated patients; i.e., a 10% to 5% reduction in incidence of visual loss of 2 lines of Snellen acuity equivalent (**Level 1**). It is important to note that benefit in the ETDRS was taken as a delay in progression of visual loss; i.e., that even when photocoagulation treatment was applied there was still an increasing incidence of visual loss, albeit at a slower rate. It is also worth noting that 'treatable lesions' (i.e. leaking microaneurysms or diffuse macular leakage) were identified by fluorescein angiography. In the absence of clinically detectable retinal thickening (CSMO) fluorescein angiographic evidence of leakage is not normally regarded as an indication for treatment in routine clinical practice. The advent of OCT has altered the situation somewhat, in that very early intra- retinal fluid may be visualized on OCT that may not be seen on fundal examination, and the data from the ETDRS cannot necessarily be extrapolated to that group of patients.

In a subsequent study, Olk et al found significant improvement in VA in patients with diffuse maculopathy treated with grid laser to zones of retinal thickening.[4]

The DRCR.net group[5] carried out a randomised control trial on 323 eyes comparing mild macular grid laser and conventional modified ETDRS direct/grid laser for DMO.

The modified ETDRS focal/grid was performed as follows:

- All leaking microaneurysms 500 to 3000μm from fovea treated directly with 50μm spot size, duration 0.05-0.1s.
- Direct whitenening of the micronaneurysm was not required, but a greyish reaction beneath the microaneurysm was needed. Grid treatment was performed to areas of retinal thickening.
- Grid was performed from 500 to 3000μm superiorly and inferiorly and to 3500μm temporally. The spots were 2 burn widths apart and no burns were performed within 500μm of the disc.

The mild macular grid laser was performed with

- spots 2-3 burn widths apart throughout, regardless of the site of microaneurysms.
- A total of 200-300 burns of barely visible 50μm size were given (including unthickened retina).

At 12 months, the central subfield thickness had reduced by 88μm in the modified ETDRS group vs 49μm in the grid only technique (p =0.02) and retinal volume decreased by 0.8mm and 0.4 mm respectively (p=0.03). The visual acuity outcome between the two groups was not substantially different, although the modified ETDRS focal/grid was more effective in reducing retinal thickness. This study therefore supported the continued use of a modified ETDRS regime for laser (**Level 1**).

11.2.3 Subthreshold laser

Subthreshold micropulse laser was developed as a treatment that theoretically avoids damaging the inner neurosensory retina, thereby reducing potential complications such as paracentral scotomas and enlargement of post-treatment scars. This technique was first described in the late 1990s and since then there has been some RCT data comparing this technique to modified ETDRS laser treatment [6-18]. Sivaprasad et al reported a case series of 25 eyes with 3-year follow-up and found that vision improved or stabilised in 92% of cases and the oedema resolved in year 2 in 92% but with recurrence of oedema in 28% in year three (**Level 2**). Figueira et al. carried out a prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green argon laser in 84 eyes. This group demonstrated that at 12 months there was no statistically significant difference in visual acuity (p=0.88), macular thickness (p=0.81) or contrast sensitivity (p=0.87) between the study groups (**Level 1**).

Vujosevic et al. carried out a prospective randomised trial on 62 eyes of 50 patients undergoing either subthreshold micropulse diode or modified ETDRS photocoagulation for DMO, evaluating microperimetry and fundus autofluorescence (FAF) pre and post treatment. At 12 months follow-up, there was no significant difference in either best-corrected visual acuity or central retinal thickness between the 2 treatment groups (p = 0.48 and p = 0.29). Central retinal sensitivity improved with micropulse laser while deteriorated with modified ETDRS laser. Additionally, fundus autofluorescence was preserved in the micropulse group. Micropulse laser therefore may offer a new, less aggressive laser therapeutic approach in the treatment of clinically significant DMO. (**Level 1**) A micropulse facility is now also available on a yellow laser, although there is not yet any published RCT data for its use here. The precise optimum treatment parameters for micropulse diode have not yet been established and its use has not yet been adopted in a widespread manner. For most units, standard suprathreshold laser is still the mainstay of laser treatment for macular oedema.

In clinical practice, the outcome of laser photocoagulation for DMO is not as good as in research studies. A number of factors influence results of the laser treatment such as the laser equipment, patient factors and the laser operator. The retinal laser should be performed by an experienced operator to maintain consistency of results (**Level A**).

11.2.4 Summary: There is **level 1** evidence for benefit of photocoagulation using the modified ETDRS protocol vs no treatment, or compared to mild modified grid laser. There is emerging evidence to suggest that similar outcomes can be achieved with subthreshold micropulse diode laser therapy (**Level 2**).

Overall, while photocoagulation treatment reduces the risk of visual loss, and works over a long timescale, it is clear that recovery of vision is much harder to achieve with laser alone. Current treatments using intravitreal antiVEGF agents with prompt or delayed focal laser photocoagulation are most effective in preserving vision and restoring vision when centre-involved macular oedema is present and acuity is reduced to 20/32 or less (**Level 1**).

11.3 INTRAVITREAL STEROID TREATMENT

A variety of processes have been implicated in the pathogenesis of DMO, including increased levels of vascular permeability factors (such as VEGF), loss of endothelial tight junction proteins, and production of inflammatory mediators. Corticosteroids can inhibit all of the above processes and have therefore been investigated as a potential therapeutic option for DMO. There had been numerous case series documenting potential benefits from intravitreal steroid treatment, but little randomized controlled trial evidence until more recently.

The DRCRnet [19,20] undertook a randomized controlled trial with 3-year follow-up comparing modified ETDRS laser photocoagulation (as defined above) with either 1mg or 4mg of *preservative-free* intravitreal triamcinolone (Allergan USA). All patients were eligible for re-treatment at 4 monthly intervals if oedema persisted. At 4 months, the mean visual acuity was better in the 4mg triamcinolone group compared to both the 1mg triamcinolone and laser group ($p<0.001$). At 1 year, there was no significant difference in mean visual acuity between the groups. At 2 years the mean visual acuity was better in the laser group than in the other 2 groups. The OCT results paralleled the visual acuity results, with the 4mg triamcinolone group demonstrating a greater beneficial effect at the 4 month visit compared to the other 2 groups (**Level 1**). This study further demonstrated with subanalysis of pseudophakic patients that cataract was not a confounding factor, confirming a beneficial effect in the laser group despite lens status. The 3-year follow-up of 306 eyes was reported in 2009. The change in visual acuity letter score from baseline to 3 years was +5 in the laser group and 0 in each trimcinolone group. The 3-year cumulative probability of having cataract surgery was 31% in the laser group, 46% in the 1mg group and 83% in the 4mg group ($P<0.001$ for all pairwise comparisons). A limitation of this 3-year study was that only 36% of patients were able to achieve the 3-year follow-up.

Gillies et al [21] conducted a randomized placebo controlled trial of intravitreal triamcinolone (IVTA) vs placebo for patients with *refractory* DMO, in 69 eyes from 43 patients. Repeated injections were given as required and photocoagulation treatment could be given according to prospectively designed rules. There were significant improvements in best corrected VA and central macular thickness after 3 months in the IVTA group. After 2 years, these differences were still significant but reduced. An improvement of at least 5 letters was found in 56% of those treated with IVTA vs 26% of those treated with placebo ($p=0.006$), with mean gain of 5.7 letters more in the IVTA group than the placebo group (**Level 1**). After 2 years the study

became open label and patients in the original placebo group could be treated with IVTA according to prospectively designed guidelines. By five years, improvement of ≥5 letters was found in 42% of those eyes initially treated with intravitreal triamcinolone compared to 32% initially treated with placebo, but this finding was not statistically significant (p=0.4). There was also no difference in the mean central macular thickness reduction between the 2 groups. The earlier use of IVTA did not reduce the need for retreatment between years 3-5.

This study differs from the DRCRnet study in that most patients had failed laser treatment at inclusion. Less than half of the placebo group was treated with more laser according to the protocol, as further laser was thought to be futile. In contrast, the DRCRnet had excluded eyes not thought to benefit from laser treatment. The authors concluded that intravitreal triamcinolone may have a place for certain eyes, otherwise refractory to laser treatment; i.e., as a salvage therapy (**Level 2**).

11.4 STEROIDS AND LASER PHOTOCOAGULATION

Various studies have looked at the role of intravitreal triamcinolone (IVTA) as an adjunct to focal macular laser[22,23]. Gillies et al. carried out a prospective, double-masked placebo controlled trial comparing 4mg IVTA versus placebo 6 weeks prior to laser photocoagulation for DMO. Improvement in ≥5 letters of BCVA was no different between the two groups (p=0.8) despite a mean 50μm reduction in central macular thickness in the IVTA group compared to the control group at 6 months (p=0.016). The study concluded that there was no evidence of synergistic benefit. The DRCRnet compared focal macular photocoagulation 4 weeks after sub-tenon's injection of 40mg triamcinolone to laser alone in 129 eyes with visual acuity of 20/40 or better. There were no statistical differences between any group in terms of visual acuity (p=0.94) or central retinal thickness (p=0.46), and they concluded that there was unlikely to be any significant benefit, and did not recommend proceeding to phase III trial for this group of patients[24] (**Level 1**).

The DRCR-net group has also compared the use of intravitreal triamcinolone combined with laser vs laser alone and vs two ranibizumab groups for centre-involving DMO (see section under Ranibizumab for more details, DRCR.net 2010). This study showed that the visual outcomes for the Ranibizumab treated groups were better that the steroid treated group except for those eyes that were pseudophakic at baseline when the results were similar (**Level 1**).

Side-effects are a major drawback for the use of intravitreal triamcinolone[25,26]. In Gillies study at 2 years, 44% of treated eyes were on glaucoma medication (with 5.9% undergoing trabeculectomy) vs 3% on glaucoma medication in the placebo group. Cataract surgery had been performed in 54% of the treated eyes vs 0% of the placebo group. By 5 years, 9% of initial IVTA group had had a trabeculectomy (vs 0% initial placebo group), 56% were on glaucoma medication, and 71% had cataract surgery. In the DRCRnet study described above, 83% had undergone cataract surgery in 4mg IVTA group by 3 years vs 31% in the laser group. Intraocular pressure had risen by more than 10mm Hg at any visit in 33% of 4mg group vs 4% laser group. IOP lowering treatment was being used in 12% of the 4mg group vs 3% of laser group, and 5% had undergone glaucoma surgery (**Level 1**).

Recently, the advent of intravitreal slow release biodegradable drug delivery systems has proved of interest in the management of DMO. A 700µg dexamethasone intravitreal drug delivery system (available as Ozurdex ® Allergan) was compared with a 350µg dexamethasone intravitreal drug delivery system and observation (171 eyes, 57 in each group, 180 day follow-up) for eyes with DMO [27]. The mean baseline visual acuity was 54 letters in each group. At 90-day follow-up, a statistically significant difference in the proportion of eyes achieving at least a 10-letter improvement in BCVA was evident between the 700µg dexamethasone group and the observation group (33% vs. 12%; p=0.007). This difference was not statistically significant at day 180 (30% vs 23% respectively). The 350µg dose showed a statistically significant effect at 60 days (23% vs 9% 10 letter improvement), but not at 90 or 180 days. At day 90, there was also a statistically significant improvement in both central retinal thickness ($p<0.01$) and fluorescein leakage ($p<0.001$) in eyes that received the 700µg dexamethasone DDS compared with eyes in the observation group (**Level 1**). This study has only short follow-up which will underestimate potential side-effects such as cataract and further studies are ongoing.

Fluocinolone acetonide has been recently developed as a non-biodegradable intravitreal insert (Iluvien ®) with sustained release of fluocinolone for up to 36 months for treatment of DMO. The Fluocinolone acetonide intravitreal implant for diabetic macular edema (FAME) study included 956 patients randomised to receive a low dose fluocinolone insert, a high dose fluocinolone insert or a sham injection. [28] At 24 months, results demonstrated an improvement in best corrected visual acuity (BCVA) of 15 or more letters in 28.7% of the low dose group vs 16.2% controls and these results were sustained for the third year [29]. (**Level 1**) For those eyes phakic at baseline, 75% of the low dose group had undergone cataract surgery vs 23% of the control group, 16.3% had developed IOP greater than 30 and 3.1% undergone IOP lowering surgery. Pre planned subgroup analysis showed a particular benefit compared to control in those patients with duration of macular oedema of more than 3 years. This drug is now licenced for use for diabetic macular oedema in the UK, for cases unresponsive to other treatment options. The longer acting nature of fluocinolone acetonide does potentially have a benefit in terms of treatment rates over regular intravitreal anti-VEGF treatments, but this benefit has to be balanced against the greater risk of side-effects.

Other emerging steroid drug delivery systems in development include a triamcinolone acetonide trans-scleral helical implant (I-vation). The results of these are awaited.

11.4.1 Summary

There is **level 1** evidence that preservative free intravitreal triamcinolone monotherapy is inferior to laser treatment at 3-year follow-up. There is also **level 1** evidence that intravitreal preservative free triamcinolone combined with laser is also inferior to ranibizumab with immediate or deferred laser, except in patients who are pseudophakic. There is **level 1** evidence that fluocinolone slow release implant is effective in treatment of DMO. The longer acting steroid preparations are of particular interest due to the reduced frequency of treatment required, which may give a practical advantage compared to VEGF inhibitors. The high rate of increased IOP and cataract need to be considered when using intravitreal steroid preparations and patients who are already pseudophakic are particularly suitable.

11.5 INTRAVITREAL VEGF INHIBITORS

It is known that the VEGF levels are elevated in the vitreous and retina in patients with diabetic retinopathy.[30] The VEGF increases vessel permeability by affecting tight junction proteins and is an important factor in development of macular oedema.

11.5.1 Pegaptanib

Pegaptanib (Macugen) was the first anti VEGF treatment (specific to the 165 isoform of VEGF A) to show a favourable effect on DMO. In a randomised control trial in 172 eyes, different doses of pegaptanib (0.3mg, 1mg, 3mg) were compared with sham injection at study entry, week 6 and week 12. Additional injections and/or laser could be given as required for another 18 weeks after week 12. At week 36, all 3 pegaptanib subgroups had better visual acuity than the sham group. At week 36, the median visual acuity was better with 0.3mg group as compared with sham (34% improved visual acuity vs 10% in sham) p=0.04). In addition, mean central retinal thickness decreased by 68μm in the 0.3mg group, versus an increase of 4μm in the sham group (p=0.02). There was no statistical difference between the pegaptanib doses, although the authors attributed this finding to small numbers within the study[31]. There are theoretical potential benefits in avoiding targeting all the isoforms of VEGF A, especially for on going treatment regimes, in that some VEGF is needed for the maintenance of normal retinal vasculature and for the health of the RPE. However, Pfizer pharmaceuticals is no longer pursuing further studies for Macugen in diabetic macular oedema.

11.5.2 Ranibizumab

The READ-2 study (Ranibizumab for Edema of the mAcula in Diabete**s)** [32-33] compared the effect of 0.5mg intravitreal ranibizumab versus laser photocoagulation versus combined ranibizumab and laser photocoagulation in 126 treatment naive eyes. This study demonstrated that the mean gain in best corrected visual acuity was significantly better in the ranibizumab monotherapy group at the primary end point of 6 months (+7.24 letters compared to the laser photocoagulation group of -0.43 letters, p=0.0001 at 6 months). There was no statistically significant difference between the ranibizumab monotherapy group and the combination group. The study protocol allowed for all groups to be treated as necessary with ranibizumab after 6 months. The 2-year results showed that the visual outcomes in the ranibizumab groups were maintained with a PRN regime every 2 months (**Level 1**).

The RESOLVE (Safety and efficacy of ranibizumab in diabetic macular edema) study was a randomised controlled double-masked, multicentre phase II study evaluating the safety and efficacy of ranibizumab in the treatment of DMO at 12 months. Patients were randomised to 3 treatment arms: 0.3mg ranibizumab, 0.5mg ranibizumab or sham injection and received 3 initial monthly injections. Thereafter, all patients could receive laser photocoagulation if required depending on specified treatment criteria. After month 1, the ranibizumab dose could be doubled by increasing the injection volume from 0.05ml to 0.1ml if the central retinal thickness was >300μm or was >225μm and the reduction in retinal oedema from the previous assessment was <50μm. At 12 months, the ranibizumab treatment arms had a mean gain of 10.3 letters compared to the sham group, which had a mean decline of 1.4

letters ($p<0.0001$). In addition, the mean central retinal thickness reduced by 194.2μm compared to 48.4μm with sham injection ($P<0.0001$) [34]. (**Level 1**)

A phase III study evaluating the efficacy and safety of ranibizumab in patients with visual impairment due to DMO (RESTORE) was a randomised, double-masked, multicentre trial with 3 treatment arms: Ranibizumab 0.5mg in addition to sham laser, ranibizumab in addition to active laser, and sham injection in addition to active laser[35]. Patient's visual acuity was 78-39 letters at baseline. Over one year, patients treated with combination ranibizumab and laser gained a mean average additional 5.9 letters. Those who received ranibizumab monotherapy gained mean average 6.1 letters. This compared to a mean average gain of 0.8 letters in patients who received laser therapy alone ($P<0.0001$). The subgroup with at least 400μm central retinal thickness on OCT showed a greater benefit compared to laser therapy compared to those eyes with lesser degrees of oedema.

In the USA the RISE and RIDE studies evaluated the efficacy of ranibizumab in diabetic macular oedema. There have been no additional adverse events identified in any of the studies using ranibizumab in people with diabetic retinopathy.

In 2010, the landmark DRCR.net study[36] was published comparing 0.5mg intravitreal ranibizumab with prompt focal/grid laser photocoagulation, 0.5 mg ranibizumab with deferred laser photocoagulation (at least 24 weeks later), 4mg intravitreal triamcinolone with prompt laser, or a sham injection with prompt laser. The importance of this study necessitates understanding the specific inclusion criteria and treatment regimens given to guide our clinical care. Patients with diabetic macular oedema, with baseline visual acuity between 78 and 24 letters (6/9 – 6/90 approx.) and central subfield thickness on OCT of ≥250μm were recruited. This study demonstrated that at 1 year, 0.5mg intravitreal ranibizumab combined with either prompt or deferred laser photocoagulation, showed superior improvements in best corrected visual acuity (BCVA) compared with laser treatment alone (**Level 1**). At 1 year there was a mean 9 letter gain in both ranibizumab groups vs 3 letter gain in the laser /sham group and a 4 letter gain in the triamcinolone/laser group. The group treated with 4mg intravitreal triamcinolone with prompt laser did not demonstrate a significant improvement in BCVA compared with laser alone. However, this group did result in a greater reduction in retinal thickness on OCT compared with the laser group. When a subgroup analysis was carried out for those patients pseudophakic at baseline, there was an improvement in BCVA similar to that of the ranibizumab group for those treated with 4mg triamcinolone with laser, suggesting that the initial finding of no significant BCVA improvement in the whole triamcinolone group may have been the result of cataract formation/cataract surgery or both in phakic patients. The results were similar at 2-year follow-up (**Level 1**). There was a gain of at least 15 letters in approximately 30% of ranibizumab arms, vs 15% for the laser monotherapy group, and 21% for the triamcinolone group. There was a greater than 15 letter loss in 2% of the ranibziumab groups vs 8% in the laser and triaminolone groups. For those eyes with 2 year data available, the laser monotherapy group showed a mean gain of +2 letters, the ranibizumab and prompt laser a mean gain of +7 letters, and the ranibizumab and deferred laser showed a mean gain of +10 letters.

Table: The DRCR-net treatment regime for intravitreal ranibizumab

The patients were given four ‘loading’ doses of ranibizumab at 1 month intervals.
Retreatment was then continued at each monthly assessment for those in the ‘improvement category’: i.e., if the visual acuity was <84 letters with evidence of improvement (10% reduction of CSF thickness or VA improved by 5 letters or more).
One injection was given at each decision point to retreat (rather than a further course as per ranibizumab license below)
If the visual acuity was ≥ 84 letters, or CSF thickness < 250μm, retreatment could be given at the investigator discretion. (‘Success criteria’)

The median number of ranibizumab injections by year 1 was 8 in the prompt laser group and 9 in the deferred laser group. For those with complete follow-up to year 2, the median number of additional treatments for those with data was 2 in the ranibizumab and prompt laser group vs 3 in the ranibizumab and deferred laser group. The ranibizumab treated groups were also found to have a reduced progression of overall retinopathy grade (**Level 1**).

The combined IVTA and laser was better than laser alone for the pseudophakic group. However, this preservative-free version of triamcinolone (Trivaris) is not available in the UK. If ranibizumab is to be given as it was applied in this study, the data indicates a need to follow-up eyes monthly undergoing this treatment.

Ranibizumab is licensed in the EU for the treatment of centre involving DMO. NICE initially did not recommend treatment with Ranibizumab on the NHS, but they have reviewed the situation again and have issued an Appraisal Consultation Document (ACD) stating that Ranibizumab is recommended as an option for treating eyes with diabetic macular oedema and greater than 400μm central retinal thickness on OCT. It would therefore be anticipated that Ranibizumab would be available on the NHS for this subgroup of patients with centre-involving DMO during the first half of 2013.

There are currently several further on going clinical trials assessing the use of ranibizumab in DMO, results of which are awaited. Work is also underway to develop methods of slowly releasing anti-VEGF treatment from within the eye.

11.5.3 Bevacizumab

Bevacizumab is not licensed for intraocular use, but as is the case for AMD, it has been used extensively for the treatment of retinal vascular pathology. Doses of either 1.25 mg or 2.5 mg (or both) have been used in various studies. Some studies have used only a single injection, showing a short-term effect, but it is apparent that the effect is not sustained. There have been a number of published trials/case series with short follow-up, and using various different treatment doses/regimes and different comparison groups[37, 38]. The BOLT study (A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema) was a prospective randomized controlled trial comparing bevacizumab to laser treatment (standard of care). This trial involved 80 patients with diabetic macular oedema, randomized to 1.25mg intravitreal bevacizumab injections or laser. Patients had a visual acuity of 69-35 letters (6/12- 6/60) at baseline. In the bevacizumab group, 3 injections were performed at 6-week intervals as a loading

phase, and then prn 6 weekly thereafter. At one-year follow-up the bevacizumab group gained a median of 8 ETDRS letters compared to the laser group which lost a median of 0.5 ETDRS letters (p=0.0002). This finding correlated with the reduction in central retinal thickness at 12 months[39] (**Level 1**).

The Pan-American Collaborative Retina Study Group (PACORES) reported a retrospective case series of the 2-year outcomes for bevacizumab for diffuse macular oedema in 139 eyes, with a follow up logMAR vision of 0.57 compared to baseline of 0.88. There also appeared to be no significant differences in outcome between those given the 1.25 mg dose and the 2.5mg dose[40] (**Level 2**).

Lam et al. compared the efficacy of 3 monthly injections of 1.25mg versus 2.5mg of intravitreal bevacizumab for diabetic macular oedema in 52 eyes [41]. Significant reduction in mean central foveal thickness was observed in both groups at all follow-up visits (p<0.013). At 6-month follow-up, the mean logMAR BCVA improved from 0.63 to 0.52 in the 1.25 mg group and 0.60 to 0.47 in the 2.5 mg group and no significant difference in BCVA was observed between the 2 groups at any time point.
Ahmadieh et al undertook a randomised controlled trial comparing three groups: 1) three injections of 1.25mg intravitreal bevacizumab vs 2) combined intravitreal injection of 1.25mg bevacizumab and 2mg triamcinolone, followed by 2 injections of intravitreal bevacizumab at 6-week intervals vs 3) sham injection [42]. A total of 115 eyes were recruited. At week 24, central macular thickness was reduced significantly in both the intravitreal bevacizumab group (p=0.012) and the combined intravitreal bevacizumab and triamcinolone group (p=0.022) compared to the sham group. With regard to visual acuity, change from baseline to week 24, there was a significant difference between combined intravitreal bevacizumab and triamcinolone group and the sham group (p=0.006) as well as a significant difference between the intravitreal bevacizumab group and the sham group (p=0.01). There was no significant change detected between both treatment groups, although the combination group demonstrated an earlier beneficial effect (**Level 1**).

A further randomised controlled trial involving 150 eyes with a follow-up of 36 weeks compared 1) 1.25mg intravitreal bevacizumab vs 2) combined intravitreal injection of 1.25mg bevacizumab and 2mg triamcinolone vs 3) macular laser photocoagulation. [43] Retreatment was performed at 12-week intervals when required. Compared with baseline, visual acuity improvement was significantly better in the intravitreal bevacizumab groups at all follow-up visits up to 36 weeks (p<0.001). A visual acuity improvement of >2 Snellen lines at 36 weeks was detected in 37%, 25%, and 14.8% of patients in the intravitreal bevacizumab (IVB), intravitreal bevacizumab/triamcinolone (IVB/IVT), and laser groups, respectively. In the combined IVB/IVT group, visual acuity improved significantly only at 6 and 12 weeks (p=0.002 and 0.019, respectively). In the macular photocoagulation group, visual acuity did not significantly change compared to baseline (**Level 1**). In another study 62 eyes were randomised to 1) bevacizumab monotherapy, vs 2) modified grid monotherapy, vs 3) bevacizumab and subsequent modified grid laser 3 weeks later. No retreatments with bevacizumab were given [44]. One month after treatment, there was significant improvements in both groups treated with bevacizumab. By 3 months the improvement in the mean BCVA was significant only in the IVB and the combined groups (P < 0.05) but by 6 months there were no significant improvements in BCVA compared to baseline in any group. The mean reduction in central retinal

thickness (CRT) was significant only in the combination group at 3 and 6 months (**Level 1**).

There has not yet been any reported data directly comparing the efficacy of ranibizumab vs bevacizumab in diabetic macular oedema but studies are on-going.
Based on the above data intravitreal anti-VEGF treatment (with or without laser) achieves superior visual outcomes compared to laser treatment alone for patients with similar criteria to those involved in the clinical trials i.e. centre-involving DMO, CRT on OCT of at least 250 μm, with visual acuity in the region of 78-24 letters due to DMO (**Level A**). It is not yet clear whether bevacizumab has the same level of efficacy as ranibizumab for DMO, as there is not the same level of RCT evidence and no data so far directly comparing the two in DMO (**Level B**).

11.5.4 Aflibercept (VEGF-Trap-Eye)

Aflibercept (VEGFTrap-Eye) is a soluble VEGF receptor fusion protein that binds to all isoforms of VEGF-A as well as placental growth factor. It has a higher binding affinity compared to that of ranibizumab and bevacizumab and thus potentially has a longer duration of action[45-46]. Stewart et al. demonstrated that 79 days after a single VEGF Trap (1.15 mg) injection, the intravitreal VEGF-binding activity would be comparable to ranibizumab at 30 days. This finding may be a key advantage due to the chronicity of DMO as well the burden associated with regular intravitreal anti-VEGF injections.

A double-masked randomized controlled study evaluating the safety and efficacy of intravitreal VEGF Trap-Eye for DMO (DAVINCI) recruited patients with a visual acuity of 20/40 to 20/320. Four different regimes were evaluated vs laser treatment: 0.5mg monthly, 2mg monthly, 2mg 8 weekly after 3 monthly loading doses, and 2mg PRN after 3 monthly loading doses. DAVINCI has reported positive results at 1-year [47]. The mean gain in visual acuity at 1 year was 9.7 letters in the 2mg 8 weekly group, 12 letters in the 2mg PRN group and 13.1 letters in the 2mg 4 weekly group, vs -1.3 letters in the laser treated group (**Level 1**). The licence for VEGF-Trap-Eye is expected in Europe for AMD during 2012, and a licence for diabetic retinopathy in 2014.

11.5.5 PKCβinhibitors

Protein Kinase C has been implicated in increased vascular permeablilty in diabetic maculpathy. Studies in rats illustrated that there was reduction in VEGF induced permeability by PKC inhibitors[48]. Other groups have confirmed that inhibition of classical PKC isoforms, such as PKC β, reduced VEGF induced permeability by approximately half[49]. A prospective randomised trial evaluating the effect of the PKCβ, inhibitor (ruboxistaurin) compared to placebo in treating DMO was undertaken (PKC DRS2). 685 patients were recruited with follow-up to 36 months. Moderate visual loss occurred in 5.5% of ruboxistaurin treated patients compared to 9.1% of placebo treated patients (P=0.034). In addition, treatment with ruboxistaurin was associated with less progression of DMO to within 100 μm of the macular centre in eyes with CSMO at baseline and with less frequent laser photocoagulation[50]. Ruboxistaurin has demonstrated a 30% reduction in visual loss compared to placebo[51]. Another ruboxistaurin study [52] showed some delay in progression of DMO to the sight threatening stage, although it did not meet its

primary outcome in significantly reducing the time to laser treatment. The manufacturer, Eli Lilly, has received an approval letter from the U.S. Food and Drug Administration (FDA) for the prevention of vision loss in patients with DR with ruboxistaurin, but at this time the medication is not available for clinical use pending results of additional trials for this indication and it is not thought likely that the drug will be brought to licence.

There are other preparations under investigation for diabetic macular oedema, but results from phase III clinical trials are awaited for these.

11.6 THE TREATMENT OF MACULOPATHY IN THE PRESENCE OF RETINAL NEOVASCULARISATION

Maculopathy may co-exist with disc or retinal neovascularisation. Whether to treat the new vessels with PRP or to treat the maculopathy first depends on a number of factors, including the age of the patient and the relative severity of the retinopathy. In young patients with active new vessels it is generally recommended to treat the new vessels first with PRP (or concurrently with macular laser) since new vessels in these patients may run an aggressive course. It is recognised that VEGF overproduction in peripheral ischaemic retina drives macular changes in some cases, based on wide field angiography studies. Therefore, treatment of the peripheral ischaemic retina may actually help the macular oedema by reducing VEGF production (**Level A**). Traditionally, fractionating PRP into multiple sessions of several hundred burns has been advised in such circumstances to reduce the chance of exacerbation of oedema. However, with the advent of the pattern scanning laser systems this technique may no longer be necessary as some data has shown that single session treatment does not cause an increase in macular oedema [53]. In patients with lower risk PDR, it is reasonable to treat the macula first or concurrently with PRP.

11.7 THE MANAGEMENT OF DIABETIC MACULOPATHY IN THE CONTEXT OF CATARACT SURGERY

Close monitoring of diabetic maculopathy is required prior to and following cataract surgery. Ideally, maculopathy would be fully treated with resolution of oedema prior to cataract surgery, but for some cases macular oedema persists despite treatment at the time of cataract surgery. In these cases, it is reasonable to consider adjunctive treatment at the time of cataract surgery; otherwise, surgery is likely to exacerbate the oedema. Various studies have described benefit of concurrent treatment of macular oedema at the time of cataract surgery[54-56]. Funding availability and concurrent ocular morbidity such as glaucoma or ocular hypertension will affect the potential choice of treatment. The DRCRnet results suggest good outcome with preservative-free triamcinolone for pseudophakic patients; hence, intravitreal triamcinolone can potentially be injected at completion of cataract surgery. Similarly, the data on anti-VEGF treatment would support the use of intravitreal steroids as an adjunct to minimise oedema prior to cataract surgery and for any post-op exacerbation. If none of these options are available, macular laser treatment could be considered prior to or soon after the cataract surgery (**Level A**).

Close monitoring is required post-operatively for all these patients by the medical retina team. If an adequate assessment of the macula could be done just prior to surgery and no oedema noted at that stage, then the development of cystoid macular oedema (CMO) in the first few weeks post cataract surgery may be due to an Irvine-Gass type reaction, potentially exacerbated by the presence of diabetic microvascular changes at the macula. Such post- operative CMO may resolve without further treatment. If there is no adequate fundus view prior to cataract surgery, patients should be seen within a few days (ideally within 2-3 days) of the cataract surgery to fully assess their retinopathy prior to the development of any exacerbation that may be induced by surgery. [57-59]

Vitrectomy for diabetic macular oedema: see Section12.

11.8 CONCLUSIONS

We have entered a new era with regard to the management of DMO where treatment decisions are going to be based on OCT scans. Until recently, focal and focal/grid laser photocoagulation have been the mainstay of treatment and the benchmark to which all treatments for DMO were evaluated. However, there is growing evidence that intravitreal VEGF inhibitors (with or without combination with laser photocoagulation) provide better visual outcome with a potential to improve visual acuity. Hence, anti-VEGF injections are considered the new gold standard of therapy for eyes with centre-involving macular oedema and reduced vision (**Level A**). In terms of treatment protocols for anti-VEGF treatment, it currently seems reasonable to follow a retreatment protocol similar to the DRCRnet study with a loading phase of treatment followed by PRN injections depending on disease activity. Further studies assessing different treatment regimens are underway which will help refine clinical care pathways in future.

11.9 MACULOPATHY: RECOMMENDATIONS

Background comments:

All the potential treatment options for an individual patient should be discussed with the patient concerned (including whether NHS funding is available locally for them or not) and treatment should be tailored to meet individual patient. Some patients may choose different treatment options depending on their individual circumstances; e.g., some patients, especially those with relatively good vision who feel they are managing well, may prefer and choose not to be treated with intravitreal injections. There should be close attention to systemic factors for all cases.

Maculopathy recommendations

CSMO	Centre-involving	Visual acuity	Phakic /pseudophakic	OCT	Treatment options
Yes	No		Either		Photocoagulation (**level A**)
Yes	Yes	Normal, or minimally reduced by macular oedema (eg greater than 78 letters).	Either		Photocoagulation or observe if the source of leakage is very close to fovea and there are no other treatable lesions suitable or safe to laser (**Level C**)
Yes	Yes	VA in region of 78-24 letters (but eyes with better vision may under certain circumstances warrant treatment if oedema progressing and symptomatic)	Phakic	≥250μm central subfield thickness §	Intravitreal anti-VEGF treatment (*see comment below) with or without laser (**Level A**). For eyes unresponsive to other treatments, intravitreal fluocinolone implant may be considered, but bearing in mind the potential side-effects (**Level A**)
Yes	Yes	VA in region of 78-24 letters	Pseudophakic	≥250μm central subfield thickness §	Intravitreal anti-VEGF treatment *, OR Intravitreal triamcinolone (preservative –free) with or without adjunctive laser may also be considered . (**Level A**) OR intravitreal fluocinolone implant may be considered if available, and eye unresponsive to other treatments (**level A**)

Yes	Yes	<24 letters	Pseudophakic	≥250μm central subfield thickness	Observation may be appropriate, especially if longstanding and no response to previous laser, or if considerable macular ischaemia . Otherwise may consider anti-VEGF treatment or intravitreal steroid after careful consultation and consent. (**Level B**)
Yes	Yes		Either	Vitreo-macular traction	Consider vitrectomy with/without adjunctive intravitreal anti-VEGF or steroid treatment (**Level C**)

- **Anti-VEGF treatment regime**: Initial loading phase of monthly injections for 4-6 months, followed by PRN phase with continued treatment until the macula is dry or until there is no further improvement.
- * Monthly follow-up of patients undergoing anti-VEGF treatment with OCT scan and visual acuity assessment is required to decide on retreatments. If the patient has been stable off treatment for several monthly assessments, in year 2 onwards the period between follow-up appointments may be increased gradually, ultimately to a maximum of 12- 16 weeks as long as there are no other features requiring more frequent follow-up.
- Patients unwilling or unsuitable for injections should be offered macular laser treatment if appropriate. (**Level A**)

§ - The NICE ACD refers to >400 μm central retinal thickness in patients with DMO for whom Ranibizumab may be considered. (http://guidance.nice.org.uk/TA/Wave23/41/Consultation/DraftGuidance). A final guidance is expected in February 2013 (http://guidance.nice.org.uk/TA/Wave23/41), if the NICE confirms this in final guidance (FAD), Ranibizumab would be the antiVEGF agent of choice for the subgroup of patients approved by NICE in England.

Follow-up regimes

- 3-4 months follow-up is appropriate following macular laser as long as no other features are present that require more regular follow-up.
- For patients undergoing anti VEGF treatment, patients will require monthly follow-up at least in the first year
- For patients undergoing intravitreal steroid treatment, regular monitoring of intraocular pressure is required

- Patients with R1M1 but no CSMO: These patients are suitable for an ophthalmic imaging assessment clinic: Follow-up with photography (meeting ENSP standards) and spectral domain OCT scan. (**Level 2)**.

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Section 11 Appendix:

Summary: Management of DMO

11. A: MANAGEMENT OF DIABETIC MACULOPATHY

Ophthalmic management of diabetic maculopathy depends on the location and extent of macular thickening, and the guidelines provide paradigms based on the current evidence and consensus of opinion.

For the NHS in England and Wales, NICE have recently reviewed again the use of Ranibizumab for diabetic macular oedema. They have issued an Appraisal Consultation Document (ACD) stating that Ranibizumab is recommended as an option for treating eyes with diabetic macular oedema and greater than 400 μm central retinal thickness on OCT. It can therefore be anticipated that Ranibizumab would be available on the NHS for this subgroup of patients with centre-involving diabetic macular oedema during the first half of 2013.
In the meantime, or for those eyes which do not meet the 400 μm threshold, clinicians may use available alternative options in the best interest of their patients (**Level C**).

11.A.1 Patients with non centre-involving clinically significant macular oedema (CSMO) may be treated with laser photocoagulation according to modified ETDRS criteria (**Level A**)

11.A.2 Patients with centre-involving macular oedema and reduced vision would benefit most from anti-VEGF (Ranibizumab as licenced) treatment (with or without combination laser treatment at the outset) (**Level 1, Level A**) . Intravitreal Bevacizumab has also been used to reduce macular oedema (**Level B**). Intravitreal steroid treatment (preservative-free) combined with post-treatment argon laser treatment may be considered particularly in pseudophakic patients, but bearing in mind the risk of raised intraocular pressure (**Level B**). For those patients who have been unresponsive to other treatment, the intravitreal fluocinolone implant may be considered but taking into consideration the side-effect profile (**Level B**).

11.A.3 Patients unwilling or unsuitable for intravitreal injections may be offered macular laser treatment, if thought appropriate by the treating ophthalmologist. (**Level 1, Level A**)

11.A.4 Patients with centre involving macular oedema and good visual acuity e.g. >78 letters (>6/10) may be observed if the leaking microaneurysms are very close to fovea and there are no other treatable lesions suitable or safe to laser, otherwise laser photocoagulation treatment may be considered. (**Level A**)

11.A.5 Patients with poor visual acuity (below 24 letters- 6/90) may be observed especially if the macular oedema is long standing and there is considerable macular ischaemia. (**Level B**) Alternatively intravitreal anti-VEGF or intravitreal steroid preparations may be considered with full consultantion and informed consent of the patient, if the ophthalmologist feels there may be some benefit from intervention (**Level C**).

11.A.6 If there is evidence of vitreomacular traction on the OCT scan, vitrectomy may be considered with or without adjunctive anti-VEGF/steroid treatment (**Level 2, Level B**). Microplasmin injections may be considered as an option when available (**Level C**).

11.A.7 Intravitreal Injections:
Intravitreal injections should be delivered by ophthalmologists competent in the procedure as per the RCOphth guidance. In the absence of robust evidence, intravitreal injections by non-medical staff should be limited to research. (**Level B**)

11.A. 8 Follow-up regimes
3 (-4) months follow-up is appropriate following macular laser, as long as no other features are present that require more regular follow-up. (**Level A**)

For patients undergoing anti-VEGF treatment the evidence shows that patients should be treated with an initial loading phase of 4-6 monthly injections, followed by monthly follow-up with OCT, with continued treatment until the macula is dry or until there is no further improvement. After year 1, the period of time between follow-up appointments may be gradually increased if the eyes are stable off treatment, to a maximum of 12-16 weeks in years 2-3. (**Level A**)

For patients undergoing intavitreal steroid treatment, regular follow up will be required with OCT scans, IOP monitoring and repeated treatments as required with the aim to keep macula dry. (**Level 1**)

Patients with early maculopathy (but no CSMO) and background retinopathy (R1) may be followed up in Ophthalmic Imaging assessment Clinics with colour images and spectral domain OCT, at 4- 6 monthly intervals. (**Level 2, Level B**)

SECTION 12: VITRECTOMY IN DIABETIC EYE DISEASE

12.1 SURGICAL OBJECTIVES

Vitrectomy is a specialised procedure which is the domain of appropriately trained vitreo-retinal surgeons. Vitrectomy surgery is used to achieve specific goals, which may limit or halt the progress of advanced diabetic eye disease. These goals are:

- To remove vitreous opacity (commonly vitreous haemorrhage, intra-ocular fibrin, or cells) and/or fibrovascular proliferation (severe extensive proliferative retinopathy and/or anterior hyaloidal fibrovascular proliferation)

- To allow completion of panretinal laser photocoagulation (with the endolaser, introduced into the vitreous cavity or with the indirect laser ophthalmoscope), or direct ciliary body laser photocoagulation. Peripheral cryoptherapy may sometimes be used to ensure extensive peripheral retinal ablation.

- To relieve retinal traction, tractional displacement or ectopia; traction detachment by removal or dissection of epiretinal membranes, in cases of non-rhegmatogenous retinal detachment or recurrent vitreous haemorrhage in the presence of adequate panretinal photocoagulation due to visible vitreo-vascular adhesions.

- To achieve retinal reattachment by closure of breaks and placement of internal tamponade (in cases of combined traction/rhegmatogenous detachments).

- To remove the posterior hyaloid face or the internal limiting membrane (ILM) in some cases Optical Coherence Tomography (OCT)-documented vitreomacular traction or diffuse macular oedema with a taut posterior hyaloid confirmed on OCT.

12.2 VITREOUS / SUBHYALOID HAEMORRHAGE

12.2.1 Definition

Vitreous haemorrhage is defined as bleeding into the vitreous cavity from ruptured normal or new retinal vessels, usually caused by forward detachment of the vitreous gel and leading to loss of vision from vitreous opacification. Vitreous haemorrhage may be intragel (i.e. into the vitreous substance) or retrogel (subhyaloid) when it occurs into the space between the detached vitreous gel and the retinal surface.

12.2.2 Simple vitreous haemorrhage.

Simple vitreous haemorrhage occurs in the absence of other intravitreal pathology. It is a relative indication for vitreous surgery. DRVS studies[1,2] have shown that several factors should be considered: the patient's age, the rapidity of progress and degree of severity of diabetic eye disease in the affected or the contralateral eye. The patient's appreciation of risks, and benefits of surgery, and the patient's ability to co-operate with surgery, in particular with postoperative positioning should it be necessary are

also important considerations. The need for supplemental laser photocoagulation where indicated should also be considered.

12.2.3 Severe non-clearing vitreous haemorrhage.

Mild vitreous haemorrhage -where ophthalmoscopic examination and confirmation of an attached retina is possible- often clears within a matter of days to weeks. such clearing is more likely if is the haemorrhage is retro-hyaloidal and it is usually possible to achieve delivery of initial or supplemental panretinal laser photocoagulation without vitrectomy (cross ref to lasers). If laser photocoagulation is not possible, anti-VEGF intravitreal injection and early vitrectomy for vitreous haemorrhage that persists for more than one month should be considered since maculopathy and/or proliferative disease may progress unchecked, thus compromising the final visual result.

Patients with type 2 diabetes are less likely to have severe progressive proliferative retinopathy. Over the last few years the threshold for surgical intervention has progressively decreased. Type 2 diabetes patients with PDR and vitreous haemorrhage also gain benefit from early surgery (less than 3 months), as opposed to deferred surgery. These patients should nonetheless have surgery within 3 months from onset of persistent non-clearing vitreous haemorrhage or earlier in the presence of multiple recurrent vitreous haemorrhages in spite of adequate laser treatment.

Regular weekly ultrasonographic examinations are required to ensure early detection of retinal detachment, and clinical biomicroscopy and applanation tonometry to detect iris or irido-corneal angle neovascularisation, or haemolytic/ghost cell glaucoma, while awaiting spontaneous clearing of haemorrhage or vitrectomy surgery. Patients who develop any of these complications should be considered for early vitrectomy [1,2] and/or anti-VEGF injections[3](**Level A**).

Surgical Goals and Procedure

For non-clearing or significant vitreous haemorrhage the surgical goal is to remove the vitreous opacity through a 3-port pars plana vitrectomy procedure. The posterior hyaloid face should be removed (this is a structural support for fibrovascular proliferation and its removal usually prevents subsequent re-proliferation), and initial or supplemental panretinal laser photocoagulation (up to the ora serrata in cases with neovascularisation of iris NVI - iris rubeosis) should be performed to help prevent re-bleeding, re-proliferation, anterior hyaloidal fibrovascular proliferation, entry site complications (fibrovascular ingrowth) and NVI.

12.2.4 Non-clearing Post-vitrectomy Haemorrhage

Intravitreal blood is common (14-38%) in the first post-operative day but usually clears spontaneously within a short time (~ 2-4 weeks). Usually it takes the form of a diffuse vitreous haze generated by widespread fibrin deposition. Clearance is associated with spontaneous fibrinolysis which is often delayed in patients with diabetes. In all cases where the retina cannot be adequately visualised, it is essential to confirm the absence of underlying retinal detachment with ultrasonography. If cavity haemorrhage does not start to clear within the first few post-operative weeks (3-4

weeks), revision surgery with vitreous cavity lavage and possible supplemental endolaser should be considered. (**Level A**)

Surgical Goals and Procedures

The surgical goal is to remove the haemorrhage, and treat the cause. Surgery normally requires a 3-port pars plana vitrectomy to allow an adequate internal search for the source of bleeding. In particular, examination of the previous entry sites is important to search for possible bleeding sources, and top up endolaser is indicated if previous laser treatment is found to be inadequate. Cryotherapy to areas immediately posterior to the entry sites may also be considered.

12.2.5 Dense Pre-macular Haemorrhage

Subhyaloid premacular haemorrhages may be seen with or without associated intra-gel vitreous haemorrhage usually in immediate vicinity of neovascular complexes. Limitation of blood to this site indicates incomplete vitreous detachment, providing a ready surface for continued forward proliferation of the new vessels and risk of tractional retinal detachment. Early vitrectomy should be considered to clear premacular haemorrhage. Anti-VEGF can also be considered as a pre-operative adjunct 1 week prior to the surgery. Some surgeons have promoted in the past the use of YAG laser vitreolysis based on a number of small case series[4-10] however this technique has largely been abandoned.

Indications for vitrectomy in this type of haemorrhage include severe visual loss (for example inmonocular- 'only eye' cases), failure of regression or resumption of haemorrhage after supplemental laser photocoagulation and the presence of significant subhyaloid pre-macular haemorrhage in eyes with good preexisting panretinal laser photocoagulation or the suspicion of underlying treatable macular oedema. (**Level B**)

Surgical Goals and Procedures

A 3-port pars plana vitrectomy is performed taking care to remove the posterior hyaloid face, particularly from the posterior pole and the temporal arcades. Haemorrhage is removed, residual membrane dissected and supplemental panretinal endolaser photocoagulation is placed if needed. Long standing cases are more likely to require significant membrane dissection with its attendant risk of iatrogenic retinal break formation. Tissue-dyes are now used to highlight the presence and extent of gliotic epiretinal tissue thus facilitating its complete removal in a safer way while reducing the risk of intraoperative iatrogenic retinal breaks.

12.3 HAEMOLYTIC GHOST-CELL GLAUCOMA

Elevated intra-ocular pressures may be caused by partially lysed red cells (red cell ghosts or "erythroclasts") particularly in those eyes with a disrupted anterior hyaloid face after previous vitrectomy for vitreous haemorrhage[11], or in aphakic eyes with vitreous haemorrhage. "Erythroclasts" pass from the vitreous cavity into the anterior chamber and obstruct the trabecular meshwork. After a vitrectomy for diabetic vitreous haemorrhage, ghost cell glaucoma should be suspected in patients with

elevated intraocular pressure in the early post-operative period (2-6 weeks)[12]. It is important to differentiate this condition from steroid induced glaucoma, since many of these patients may also be using topical steroid drops. The physical signs of fine pigmented cells and flare in the anterior chamber indicate ghost cell glaucoma, however this appearance may be subtle. Ghost cell glaucoma is particularly common if vitrectomy is performed for removal of dense vitreous haemorrhage (ochre membrane). If the intra-ocular pressure remains elevated despite medical therapy after one to three weeks, surgery should be considered. (**Level B**)

Surgical Goals and Procedures

Revision pars plana vitrectomy with removal of all vitreous cavity and anterior chamber haemorrhage is the preferred surgical procedure. Glaucoma filtering surgery is usually not required. (**Level B**)

12.4 RETINAL DETACHMENT

12.4.1 Tractional Macular Ectopia and Detachment

Traction retinal detachment (TRD) arises from tension caused by contraction of the fibrovascular proliferations. Because peripheral or midperipheral traction retinal detachments progress to involve the macula in only about 15% of cases per year[13], vitrectomy in TRD is generally limited to those eyes with one of the following:

(a) involvement of the macula in the TRD as confirmed by OCT

(b) evidence of a progressive, extensive extra-macular traction retinal detachment;

(c) combined traction rhegmatogenous retinal detachment which threatens to involve the macular area (see below).

Traction retinal detachment involving the macula is a main indication for vitrectomy surgery and should be carried out at the earliest possible irrespective the duration of the macular involvement.

Surgical Goals and Procedures

In addition to removal of media opacity, specific goals include release of tractional components by removal of cortical vitreous and the posterior hyaloid vitreous face, a taut ILM, dissection and removal of fibrovascular membranes, endodiathermy of persistently bleeding vessels and treatment of any iatrogenic retinal breaks. Cases with pure tractional elevation will experience spontaneous post-operative retinal reattachment and macular remodelling as a result of successful surgery. Anatomic success has been reported in between 64% to 83% of patients (with a 6 month follow-up) with visual function improvement in 26% to 71%[14,15]. It is important to differentiate macular tractional detachment from macular schisis as the latter do not tend to show an improvement in vision following surgery. OCT is a very useful diagnostic tool to help make this differentiation.

12.4.2 Combined Traction - Rhegmatogenous Retinal Detachment

Most extra-macular traction retinal detachments are only relative indications for surgery since they may remain stable for indefinite periods. In some patients the force of the fibrovascular traction is sufficient to create a retinal tear, often in relation to previous laser photocoagulation scars. These tears can be difficult to identify pre-operatively. Clinically, a rhegmatogenous retinal detachment caused by fibrovascular proliferation presents with a convex configuration rather than the concave contour of a tractional, non-rhegmatogenous detached retina. In addition, white (hydration) lines in the inner retina, are more characteristic of a rhegmatogenous component. Surgery is indicated if there is sudden visual loss, evidence of progressive combined traction/rhegmatogenous retinal detachment, or evidence of progressive iris rubeosis, as the detached retina turns ischaemic. (**Level B**)

Surgical Goals and Procedures

Pars plana vitrectomy techniques are used to gain access to the retinal surface, to dissect fibrovascular membranes and thickened hyaloid face structures or taut ILM and thereby to relieve traction on and around retinal breaks. Vitrectomy also allows the performance of an internal search to help the identification of the retinal breaks. Subretinal fluid is removed and the retina reattached, followed by delivery of endolaser to both the break(s) and peripherally as supplemental or initial panretinal photocoagulation. Internal tamponade (gas, or silicone oil) will be necessary. Lensectomy has been largely abandoned in favour of leaving the patient phakic or combining vitrectomy with phacoemulsification and IOL implantation in the bag. If a combined approach is pursued then silicon IOLs should be avoided. Accurate post-operative positioning is of critical importance.

12.5 SEVERE WIDESPREAD FIBROVASCULAR PROLIFERATION

Some patients (typically young adult Type 1 diabetics with a history of diabetes since childhood) are seen with a pattern of active fibrovascular proliferation that progresses despite extensive panretinal laser photocoagulation. These eyes have a high risk of severe visual loss and blindness. The Diabetic Retinopathy Vitrectomy Study Group[16] compared standard laser and vitrectomy indications (with vitrectomy for vitreous haemorrhage, or traction macular detachment) in a randomised fashion with early vitrectomy surgery, in a total of 370 eyes. The number of patients experiencing preservation of good visual function (6/12 or better) was almost twice as high in the early vitrectomy group (surgery carried out within 3 months) (44%) compared to the conventional management group (28%) after 4 years of follow-up. However, the proportion of eyes with severe visual loss or blindness was similar in both groups and this stage was reached earlier in the early vitrectomy group. Clinical characteristics which warrant referral for early vitrectomy, even in the absence of extensive laser photocoagulation, include widespread fibrovascular proliferation (three disc diameters or more of fibrovascular tissue). (**Level B**)

Later studies have shown that rates of severe visual loss following early vitrectomy are drastically reduced. It is also important to note that with current vitreoretinal techniques, most cases of severe loss of vision are due to progressive aggressive ischaemic diabetic disease rather than the surgical procedure itself.

It is to be emphasised that these patients frequently have extensive proliferation as their sole indication and do not necessarily have vitreous haemorrhage or macular tractional displacement. While these patients should receive panretinal laser photocoagulation, the presence of high risk characteristics should indicate vitreoretinal referral at an early stage. (**Level B**)

Surgical Goals and Procedures

A 3-port pars plana vitrectomy is performed, with great care being taken to remove all detectable posterior hyaloid face which is typically adherent to the retina.

12.6 IRIS / ANGLE NEOVASCULARISATION WITH VITREOUS OPACITY

Anterior segment neovascularisation which is mild and non-progressive may be monitored or treated with anti-VEGF injections. Progressive iris or angle neovascularisation may require additional panretinal laser photocoagulation, and if vitreous haemorrhage prevents adequate and effective panretinal laser photocoagulation, vitrectomy with or without endolaser photocoagulation is indicated. If the haemorrhage is believed to be of tractional origin then vitrectomy without additional endolaser may suffice. (**Level C**)

Patients with established neovascular glaucoma may undergo combined surgery, comprising pars plana vitrectomy, with endolaser photocoagulation and in some cases with additional direct ciliary body photocoagulation. This surgery is combined with silicone oil exchange in some eyes or with glaucoma filtration surgery or a shunt procedure in others.

12.7 ANTERIOR HYALOIDAL FIBROVASCULAR PROLIFERATION / RETROLENTAL FIBROVASCULAR PROLIFERATION

Fibrovascular proliferation on the anterior hyaloidal surface or its remnant is typically seen after vitrectomy in severely ischaemic eyes of patients with type 1 diabetes mellitus. This fibrous tissue, which causes contraction of adjacent tissue and may cause peripheral traction retinal detachment, posterior iris displacement and lens displacement or recurrent vitreous haemorrhage, is highly vascular and difficult to treat. In some patients this process may be localised to the area of the entry site and is associated with typical sentinel vessels on the adjacent episclera and sclera[17]. Anterior hyaloidal fibrovascular proliferation may also occur after cataract extraction in patients with active proliferative disease[18]

This complication is becoming rarer with modern vitrectomy equipment and surgical technique with complete peripheral vitreous removal at primary vitrectomy. (**Level B**)

Surgical Goals and Procedure

The surgical goal is to remove all fibrovascular tissue, requiring vitrectomy sometimes combined with phacoemulsification, membrane dissection and complete

panretinal photocoagulation up to the ora and the use of endotamponade such as long-acting gas or silicone oil.

12.8 VITRECTOMY FOR DIABETIC MACULAR OEDEMA

Vitrectomy for removal of hard exudates has been proposed, but such surgery is only supported by small case series. Further work in this area is required. Vitrectomy with posterior hyaloid face removal, with or without inner limiting lamina removal[19] has been advocated for non-ischaemic diffuse diabetic macular oedema which is not responsive to at least one macular grid laser treatment, and when the posterior hyaloid is attached.

Vitrectomy surgery has been documented to be associated with improved visual acuity in other types of macular oedema, including pseudophakic macular oedema[20], and retinitis pigmentosa[21]. In vitrectomy for diabetic macular oedema, case selection has varied, with initial studies attempting only to include cases with a taut posterior hyaloid, while later studies have not used this criterion. OCT demonstrated vitreomacular traction is probably a valid indication for vitrectomy surgery with ILM excision[22] (**Level 2**).

Surgery is associated with a reduction in foveal thickness, as measured with OCT, in many studies [23-28.] One study reports that the mean perifoveal capillary blood flow velocity was significantly increased after vitrectomy for macular oedema (2.19 mm per second to 2.68 mm per second postoperatively, P =.02), and that this increased flow was associated with complete regression of oedema in the 9 eyes studied [29]. Many studies report visual benefit [30,31] and approximately 40 to 50% of cases experience an improvement in acuity of 2 lines or more (LogMAR)[32-35]. A recent study reports encouraging results with the final visual acuity improved by 2 or more lines in 32 of 65 eyes (45%), while remaining unchanged in 49%, and worse in 6%[23]. These apparently encouraging results were from a retrospective study with no control cases. There is a small fellow eye study[32] using cases with bilateral macular oedema, one eye operated. A controlled study of 15 operated eyes and 16 controls found an improvement in acuity in the treatment group, although the numbers were small and differences not statistically significant (**Level 2**).

Most studies have significant design flaws. Statistical significance at the level of 0.02 or better is reported in most studies, but the small numbers mean that the confidence intervals are large. Since significant numbers of eyes are undergoing this surgery, with one group reporting follow up data on 485 eyes of 325 patients [36], the need for a large prospective randomized controlled trial is apparent.

12.9 TIMING OF VR SURGERY

Traditional management includes vitrectomy surgery for non-clearing vitreous haemorrhage within 3 months for a type 2 diabetic and 6 months for a type 1 diabetic patient. Such practice has largely been based on the early vitrectomy for severe vitreous haemorrhage in diabetic retinopathy study [37] and the early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision [38]. These studies actually showed favourable results for the early intervention group, with vision of

better than 6/12 in over 20% of operated eyes, however over 20% of operated eyes ended up with severe complications leading to complete visual loss (no perception of light). Because of the then high risk profile of vitrectomy surgery, the risk-benefit ratio advocated a conservative approach in recommending intervention surgically. One must also keep in mind that at the time of DRVS up to one third to one half of patients had no PRP at presentation, hence the cohort at that time is not comparable to the cohorts of patients we are dealing with in the present era. However, as vitrectomy techniques have evolved and become safer a series of studies[39,40] has shown that earlier surgical intervention may be of benefit, mainly because the recorded rates of eyes suffering serious complications of vitrectomy have gone down (**Level B**).

12.10 USE OF ANTI-VEGF AS A SURGICAL ADJUNCT

Tractional retinal detachments with active fibrovascular elements pose a significant risk of intraoperative or early post-operative haemorrhage with vitrectomy surgery. Pre-operative (within a few days) intravitreal injection of anti-VEGF has been shown to reduce this risk and facilitate the surgical procedure [3,41-43] (**Level 3**). Timing of the vitrectomy surgery after anti-VEGF injection is crucial to avoid rebound revascularisation and worsening of the tractional component.

12.11 MICROPLASMIN

Microplasmin is a promising new pre-operative adjunct which can induce a gentle PVD[44] which could potentially make the surgical procedure easier and perhaps avoid the need for surgery in selected cases[45] . Microplasmin is not yet commercially available in the UK. This new pharmacological aid needs further assessment and its role in the treatment of diabetic eye disease needs to be clarified by future studies.

12.12 REDUCTION IN THE INTENSITY OF INTRAOPERATIVE LASER

In the absence of a scaffold for neovascularisation to grow onto, as a PVD is present (or has been surgically induced) and the vitreous has been removed with no further possibility of traction, there may no longer be a need for intense endolaser treatment as long as it reaches the peripheral retina. Treatment around the areas adjacent to the entry sites is especially important in eyes the very advanced proliferative states[46] (**Level B**).

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SECTION 13: CATARACT IN DIABETES

13.1 INTRODUCTION

Diabetes is known as a risk factor for development of cataract. The diabetic patients develop cataract at earlier age than the background population. Though metabolic cataract is rare in diabetes, cataract prevalence is higher in diabetic population.

13.2 INCIDENCE

Cortical and posterior subcapsular cataracts are associated with diabetes; posterior sub capsular change is reported to be reflective of blood sugar levels[1]. The average prevalence of cataract in young diabetics is 8% while in older diabetics it is 25%. The cataract prevalence increases with the duration of diabetes and is linked with poor diabetic control[2-5]. The prevalence of cataract in type II diabetic population in India is reported to be nearly 66%[4]. In the Blue Mountain Study the cataract surgery rate in diabetic population is noted to be 17.8%[5] while Danish study of type 1 diabetics, a mortality adjusted incidence of cataract surgery was 29 %. The study identified that the cataract surgery took place 20 years earlier in the diabetic group compared to general population[6]. A US study reported that 40% of patients undergoing cataract surgery were diabetics, of which 14% had diabetic retinopathy.

13.3 CATARACT MANAGEMENT

It is recognised that cataract surgery is beneficial in visual rehabilitation in diabetic patients. Diabetic patients without pre-existing retinopathy or with retinopathy but not laser treatment can expect similar visual outcome as patients without diabetic retinopathy following cataract surgery (on average two lines of improvement) [7]. Pre-existing retinopathy and laser treatment prior to cataract surgery seem to have an adverse impact for visual improvement following cataract surgery[7].

13.3.1 The cataract surgery in diabetic patient has increased risk of ocular complications (OR 1.8)[8] which may be related to patient specific factors such as poor dilation of pupil, neovascularisation of iris -rubeosis and uveitis in this patient group potentially increasing risks. (**Level 2**)

13.3.2 Diabetic patients have increased risk of posterior capsule thickening[9-11]. (**Level 2**) Meticulous cortical clean up and newer lens designs with hydrophobic acrylic lenses with square edge design can help reduced such risk.

13.3.3 The diabetic patients can be at increased risk of postoperative infection and are more likely to be culture positive[12].

13.3.4 Endophthalmitis is more severe and leads to a poorer visual outcome in diabetic patients[13]. (**Level 1**). The EVS had noted that diabetic patients were more likely to have severe media opacities, resulted in 39% patients achieving final visual acuity of 6/12 or better compared to nondiabetic patients with post op endophthalmitis.

13.3.5 It is suggested that uncontrolled diabetes at the time of surgery may increase the risk of endophthalmitis. As the overall incidence of endophthalmitis is low, it is difficult to ascertain the true risk in poorly controlled diabetics. Surgeons need to pay specific attention to known surgical risk factors such as pre-existing ocular surface infection, wound construction, minimising tissue trauma and avoiding surgical complications (**Level A**).

13.3.6 Over the last decade the incidence of postoperative endophthalmitis is reported to be on the decline compared to previous decades. It is good practice to follow the ESCRS study based[14] (**Level 1**) guidelines especially in patients with diabetes (**Level A**). Postoperative vigilance need to be tailored to each patient's circumstances. (**Level A**)

13.4 DIABETIC RETINOPATHY AFTER CATARACT SURGEY

Diabetic retinopathy may progress more after cataract surgery. Such progression may be observed in up to 20% of patients within 12 months of cataract surgery[8] (**Level 2** , however a much higher rate had been reported in a number of studies in the past (previous guideline). The progression of retinopathy was noticed in 28 % eyes at 12months after cataract surgery compared to 14% of the phakic eyes. In patients undergoing monocular surgery the difference was 36% for pseudophakic eyes vs 20% phakic eyes [15] (**Level 2**). The observed difference in the rates of progressive diabetic retinopathy may be due to disparity between studies, improved technique as well as improved diabetic care. It is therefore advisable to monitor the eyes closely for progression of DR following cataract surgery[16] (**Level A**).

13.4.1 Coexisting PDR should be treated with laser PRP preoperatively where possible if visualisation is allowed otherwise indirect laser treatment may be performed at the conclusion of cataract surgery. (**Level A**) It may be useful to minimise corneal wound hydration so as to allow good visualisation of the retina for PRP at the conclusion of phaco-emulsification. Alternatively, retinal laser treatment can be performed prior to insertion of IOL (**Level B**).

13.4.2 Such patients need careful evaluation in early post-operative period to consider for additional laser treatment and to monitor for macular changes as both PRP and cataract surgery may increase the risk of macular oedema (**Level B**).

13.5 DIABETIC MACULOPATHY WITH CATARACT

Diabetic macular oedema (DMO) may worsen postoperatively; however uncomplicated phacoemulsification surgery does not lead to accelerated diabetic retinopathy[17] (**Level 2**). The pre-existing macular oedema, severity of diabetic retinopathy and diabetic control are noted to increase the risk of progression of diabetic maculopathy. OCT scan of macula should be used to monitor change in DMO as well as the vitreo-macular interface as it may alter postoperatively (**Level A**).

13.5.1 Earlier studies based on extracapsular cataract extraction reported a high incidence up to 50% of CMO, but provided useful information on risk factors such as concurrent DMO, pre-existing retinopathy and inadequate diabetic control[18] (**Level 2**).

13.5.2 The postoperative cystoid macular oedema may occur more frequently in diabetic patients[19]. OCT provides a useful tool to assess macular thickness increases in diabetic patients post operatively. OCT identified post -operative macular oedema in 22% diabetic patients[20]. The increased risk of inflammation in this population reflects this increased incidence of CMO. With the advent of phacoemulsification, the risk of post op CMO has steadily declined[21].

13.5.3 CMO responds well to periocular and intraocular steroids in addition to nonsteroidal anti-inflammatory agents[22,23]. In cases of post-operative cystoid macular oedema nonsteroidal anti-inflammatory drops should be tried first but a fluorescein angiogram should be obtained to exclude diabetic macular oedema (**Level A**).

13.5.4 In CMO cases not responsive to topical NSAIDs, intra/periocular steroid injections should be considered. Where FFA indicates DMO, appropriate treatment for DMO should be considered. (**Level A**).

13.5.5 Increasingly intra-vitreal pharmacological agents are used for persistent diabetic macular oedema that may coexist with cataract. At the conclusion of cataract procedure intra vitreal steroid injection or anti VEGF injection may be given (**Level A**). (see Section 11)

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SECTION 14: COMMISSIONING FOR DIABETIC RETINOPATHY

14.1 INTRODUCTION:

This commissioning guidance is based on good practice principles to deliver high quality integrated care and consists of:

- A description of the key features of high quality diabetes and eye care.

- A high level intervention map. This intervention map describes the key high level actions or interventions (both clinical and administrative) diabetes and eye *services*should undertake in order to provide the most efficient and effective care, from admission to discharge (or death) from the service. It is not intended to be a care pathway or clinical protocol, rather it describes how a true 'diabetes without walls' service should operate going across the current sectors of health care. The intervention map may describe current service models or it may describe what should ideally be provided by diabetes and eye services.

- A diabetes and eye services contracting framework that brings together all the key standards of quality and policy relating to diabetes and eye care. It is <u>not</u> designed to replace the Standard NHS Contracts as many of the legal and contractual requirements have already been identified in this set of documents. Rather, it is intended to form the basis of a discussion or development of diabetes and eye services between commissioners and providers from which a contract for services can then be agreed.

- A template service specification for diabetes and eye services that forms part of schedule 2 of the Standard NHS Contract covering the key headings required of a specification. It is recommended that the commissioner checks which mandatory headings are required for each type of care as specified by the Standard NHS Contracts.

14.2 FEATURES OF DIABETIC EYE SERVICES

High quality diabetic eye services should have: (**Level B**)

- systems to manage the call and recall of people with diabetes who require regular retinopathy screening
- a process to screen for diabetic eye disease, e.g. retinopathy, maculopathy and cataracts
- a process to screen for diabetic eye disease for women with diabetes, including those with gestational diabetes
- a specialist service to treat diabetic eye disease
- regular monitoring of people with diabetes who have had treatment of their retinopathy.

In addition, the services should:

- be developed in a coordinated way, taking full account of the responsibilities of other agencies in providing comprehensive care (as set out in *National Standards, Local Action*[1]) and involving users
- be commissioned jointly by health and social care based on a joint health needs assessment which meets the specific needs of the local population, using a holistic approach as described by the generic choice model for the management of long term conditions[2]
- provide effective and safe care to people with diabetes in a range of settings including the patient's home, according to recognized standards including the Diabetes NSF[3]
- take into account the emotional, psychological and mental wellbeing of the patient[4]
- take into account race and inequalities with respect to access to care
- ensure that services are responsive and accessible to people with learning disabilities[5]
- have effective clinical networks with clear clinical leadership across the boundaries of care which clearly identify the role and responsibilities of each member of the diabetes healthcare team
- ensure that there are a wide range of options available to people with diabetes to support self-management and individual preferences
- take into account services provided by social care and the voluntary sector
- provide patient/carer/family education on diabetes not only at diagnosis but also during continuing management at every stage of care
- provide education on diabetes management to other staff and organizations that support people with diabetes
- have a workforce that has the appropriate training, updating, skills and competencies in the management of people with diabetes
- provide multidisciplinary care that manages the transition between children and adult services and adult and older peoples' services
- have integrated information systems that record individual needs including emotional, social, educational, economic and biomedical information which permit multidisciplinary care across service boundaries and support care planning[6]
- produce information on the outcomes of diabetes care including contributing to national data collections and audits
- have adequate governance arrangements, e.g. local mortality and morbidity meetings on diabetes care to learn from errors and improve patient safety
- take account of patient experience, including Patient Reported Outcome Measures, in the development and monitoring of service delivery actively[7].
- monitor the uptake of services, responding to non-attendees and monitoring complaints and untoward incidents.

14.3 RESOURCE REQUIREMENTS IN CONTEMPORARY DIABETIC EYE DISEASE SERVICE DELIVERY

14.3.1 Personnel

The contemporary management of diabetic eye disease requires teamwork with the retinal specialist leading each team. The most important aspect of diabetic eye disease management is the prompt and correct diagnosis of the condition, especially regarding the retinal involvement due to diabetes. This means that there should be an effective retinopathy screening service to detect retinopathy in the community, and trained personnel who would decide which patients need referral to the eye hospital for further management., It is crucial that there be well defined pathways for patients to access care services in the hospital after being referred by screening for retinopathy in the community. The ENSPDR has refined the referral pathway recently introducing virtual triage set up for hospital referrals. Furthermore, the management of particular patients may change from time to time, including switching from one treatment to another, or multi-modality treatment. To provide the service, greater personnel resources are required. **(Level B)**

- Ideally, a maximum of ten to twelve patients should be seen per clinic, i.e. not more than 20-24 patients for a 2-session day. There shoud be appropriate adjustment in clinic bookings for trainees and their supervising ophthalmologists.
- The following minimum service team would be required (for each clinical session) for a population of 300,000:
- 2x doctors (one consultant with retinal expertise and one non-consultant)
- 2x trained nurses
- 1 x ophthalmic photographer/technician
- 1 x healthcare assistant
- 1 x administrative coordinator
- 1 x data collection and management support staff
- 1x eye clinic liaison officer (ECLO)

14.3.2 Lead Clinician

The team should be led by a consultant ophthalmologist with retinal sub-specialty expertise who runs dedicated diabetic retinal clinics, and has experience in the management of diabetic eye disease. The lead clinician for diabetic retinopathy in hospital should oversee clinic set up, appropriate team selection and dlegation of work based on skills and expertise of team members,

The decision to treat or not to treat must be made or reviewed, by the medical retinal expert. It is essential that the treatments (laser/injections/surgical) must be undertaken by skilled ophthalmologists with a high level of retinal expertise. The treatments (laser/injections/surgical) are potentially blinding and medical intervention may be

needed in event of complications arising from treatment itself. The ophthalmic surgeon delivering such treatments need to have appropriate technical skills for these interventions(laser/injections) as well as experiences in assessing and adjusting treatment response and side effects of these treatments, based on clinical assessments and investigations. (**Level A**).

14.3.3 Lasers

Laser treatments to the retina form a large part of the case load in a diabetic retinal clinic. Patients would need additional clinic appointments to monitor response to treatments, and frequently they may require multiple episodes of laser treatment to preserve vision. The clinic will need different types of lasers (Diode/Argon) as well as doctors appropriately trained in the use of these lasers. (**Level A)**

14.3.4 Injections

Intravitreal injections of steroids and anti VEGF agents are increasingly being used in the treatment of diabetic retinopathy. It is recommended that the injections are performed by skilled ophthalmologists who would be familiar with and capable of treating the rare but serious complications that can arise from such injections including the ability to manage an anterior chamber paracentesis (the release of aqueous humour from the anterior chamber) which may need to be done in an emergency if the intraocular pressure becomes elevated after the injection and occludes the central retinal artery. (**Level A)** In practice this will mean that these injections will need to be performed by experienced ophthalmologists.

- The use of non-medical staff for injections has been discussed recently, however, the RCOphth guidance recommends that intra-vitreal injections be performed by ophthalmologists[8]. In a recent statement the college has reiterated that, where circumstances and facilities allow, the injection should be given by a specialist doctor trained in the procedure. However in view of increasing pressure on the eye departments, the college considers it reasonable for non-medical Health Care Professionals (HCPs) to administer anti-VEGF agents subject to certain stipulations[9]. (**Level B**)

14.3.5 Vitreoretinal Surgical Services

The diabetic retinal service should have access to vitreoretinal surgical services as these may be needed from time to time to effectively manage diabetic retinopathy not responding to medical/laser treatments.

14.3.6 Coordinator and administrative staff

Administrative staffs are responsible for scheduling new and follow up appointments for patients attending the diabetic retinopathy clinics. As the number of patients will increase over current levels, and required appointments will be more frequent, with increasing numbers of diabetic people the amount of coordination required will be

significant. The coordinator will oversee the patient appointment system, the coordination of theatre or clean procedures room used for injections, as well as secretarial communications. An efficient service also requires good liaison with the hospital pharmacy over the supply of drugs. Data capture and management personnel are important for internal and external audits, as well as resource management.

14.3.7 Ophthalmic Nurses

Nurses should be trained to use ETDRS (LogMAR) visual acuity charts. Nurses will be required to provide, in addition to their normal roles in clinics, cannulation, injections for fluorescein and indocyanine green angiography, counselling, and patient preparation for treatments including intravitreal injections. They will oversee patient recovery. Data capture and quality of life questionnaire completion may also be required. These duties will be undertaken with the assistance of healthcare assistants. The nursing staff will liaise with the hospital pharmacy over drugs required for the service.

14.3.8 Photographers/Ophthalmic Imaging Technicians

The ophthalmic photographer or trained ophthalmic imaging technician will be responsible for the acquisition, storage, and management of fundus photographs and angiography, as well as OCTs.

14.3.9 ECLO

The eye clinic liaison officer will provide the vital link between diabetic retinopathy treatment, and rehabilitation (LVA) and support (social) services and allow better integration of care. Patients who do not respond to treatment need direction to appropriate low vision services. The ECLO, where available, should ensure smooth transition from healthcare to social care. In hospitals without an ECLO, effective measures need to be in place to ensure that patients are directed to available support at a time of their choice. Specialists need to ensure that they offer patients the option of registration as visually impaired or severely visually impaired as soon as patients reach the thresholds for registration. Whilst registration remains a crucial gateway to support (low vision rehabilitation, provision vision devices, counselling, benefits etc.), it is important to encourage eye health professionals to raise awareness of available support services even before patients reach the level of registration in order to maximize the chances of patients adjusting to their sight loss with minimal trauma.

14.4 EDUCATION AND TRAINING

Staff in all hospitals participating in the diabetic eye service will require additional specialised training. In particular this training would include OCT scan interpretation, and injection technique. In addition, team members who have not undertaken these treatments will need to be trained in the techniques and logistics of running such services.

14.5 CAPITAL INVESTMENT

14.5.1 Injection Room

It is essential to give intravitreal injections in a clean room or in theatre. However, it would be more cost effective and convenient to use a dedicated clean room in the outpatients department. Special clean room facilities for intravitreal injections need to be created in units where such facilities do not exist at present. The clean room should be separate from the consulting room. The specifications of a clean room are detailed in the RCOphth IVT Procedure Guidelines[8]. The room needs to be adequately equipped, and approved by the hospital Microbiology, and Health and Safety teams. The details of such specifications should be discussed with the local health and safety representative. Any room where minor operations take place is suitable as long as infected cases are excluded.

14.5.2 Surgical Equipment and Consumables

IVT surgical injection packs will be required for each injection as per the IVT Guidelines (minimum: eyelid speculum, calliper, forceps) and surgical drape. Gowning is not mandatory. However, it is recommended that masks should be worn when IVTs are administeredbecause of the proximity of the surgeons face to the operation field, and because it allows the surgeon to continue verbal communications with the patient while maintaining a sterile field. Sterile surgical gloves must be worn after thorough hand washing.

14.5.3 Retinal Imaging

Retinal imaging services will need to be enhanced at all units providing diabetic eye services. The minimum equipment required to provide a contemporary diabetic retinopathy service are a digital fluorescein angiography (FFA) and optical coherent tomography (OCT): OCT 3 or a later version. It should be possible to transmit images from the peripheral units to each network centre. It is expected that all patients with diabetic eye disease will require refraction Log MAR visual acuities, FFA and OCT atcommencement of treatment. Subsequent follow up may require monthly OCTs, and FFA when indicated.

Section 14 references:

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5. http://www.diabetes.nhs.uk/commissioning_resource/step_3_service_improvement/

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SECTION 15: RESEARCH

Until recently the standard of care for DMO was focal or grid laser photocoagulation. The ETDRS trial which was undertaken in the 1980's confirmed the benefit of laser for DMO. In this trial the 3 year rate of moderate loss of vision (defined as a loss of 15 letters or 3 lines on the ETDRS chart) decreased by 50%. Furthermore, the incidence of clinically significant macular oedema decreased from 74% at baseline to 24% in 3 years. Of those who had a visual acuity worse than Snellen 20/40, 17% of treated eyes experienced moderate visual gain. Nonetheless in the majority of persons with DMO laser does not improve vision. Thus there was a major unmet need in terms of better treatments for DMO.

The pathogenesis of diabetic retinopathy (DR) is complex but there are compelling reasons to believe that many of the manifestations of the condition occur as a result of inappropriate production of growth factors. The biochemical perturbations in diabetes from hyperglycemia results in a hypoxia which has been shown to drive the excess production of various growth factors. The microangiopathy seen in DR is not unlike that of other conditions where there is an excess of vascular endothelial growth factor (VEGF) production. VEGF is a potent angiogenic molecule that also increases vaso permeability dramatically. VEGF induces changes in the proteins that regulate the tight junctions between retinal vascular endothelial cells, making them leaky. Thus the exudation of serous fluid, lipid and whole blood from the retinal microvasculature leading to the clinical picture of dot and blot haemorrhages and lipid exudates is consistent with a pathological over expression of VEGF. In addition VEGF can also compromise the tight junctions between the retinal pigment epithelial cells representing a further mechanism for loss of integrity of the blood-retinal barrier.

In recent years the understanding that inappropriate VEGF production is involved in neovascular pathology in the eye notably in PDR and exudative age-related macular degeneration, has led to a new generation of therapeutics with development of inhibitors of this molecule specifically designed for intraocular administration. Such anti VEGF therapies have been successfully demonstrated to ameliorate the exudative manifestations in AMD with preservation of vision. This approach has now been logically extended to the treatment of diabetic macular oedema as VEGF is again a key driver in the pathogenesis of the exudative manifestations of this disorder.

A systematic Cochrane review of all DMO trials that had been published by 2009 noted that although comparisons tended to favour antiangiogenic therapy over laser, there was insufficient high quality evidence supporting the use of the former either in single or multiple doses as these studies were mainly conducted in the short term (Parravano M, Cochrane Rev. October 2009). However many of the larger trials have since come to fruition. In particular the diabetic retinopathy clinical research network (DRCR net) are reporting longer term findings. DRCR net had initiated a series of trials to meet the challenge of establishing the role of biologicals such as monoclonal antibodies or other neutralising molecules that act on VEGF or its receptor in the management of DMO. In addition DRCR net trials also sought to establish the role of anti inflammatory agents in the repertoire of treatments because of the knowledge that inflammation too plays a role in diabetic microangiopathy, and

because of the reports from numerous small uncontrolled studies of a beneficial effect of steroids in DMO. These trials include:

- Laser photocoagulation versus intravitreal triamcinolone acetonie (IVTA) in DMO. This was a multicentre, randomized controlled clinical trial to investigate the efficacy and safety of 1 or 4 mg of IVTA versus laser. At 4 months there were gains in visual acuity associated with decreased retinal thickness. However by two years these benefits were lost and patients who received laser had a better mean VA and fewer complications (DRCR net Ophthalmology 2008;115:1447-49). By year 3, 24% and 37% of the 1 and 4 mg steroid group respectively had improvements of more than 10 letters of acuity compared with 44% of patients in the laser group.

- The ranibizumab + laser photocoagulation (prompt or deferred) versus triamcinolone + prompt laser in DMO study. This was a 4 arm trial which randomised participants to 4mg triamcinolone combined with prompt laser, 0.5 mg ranibizumab combined with prompt laser, 0.5 mg ranibizumab combined with deferred laser versus laser plus a sham procedure mimicking an intravitreal drug delivery. Ranibizumab treatment resulted in a significant improvement in best corrected visual acuity compared with sham plus laser. Approximately 50% of persons treated with ranibizumab had a gain of 10 letters compared with 28% of those treated with laser only. Eyes treated with triamcinolone plus prompt laser, showed an initial improvement in acuity similar to that observed with ranibizumab but this benefit was lost by one year. Subgroup analysis showed that eyes that were psudeophakic at baseline showed an 8 letter mean improvement which was similar to that observed with ranibizumab. At one year, eyes that received either ranibizumab or triamcinolone were less likely to show progression of retinopathy, exhibit vitreal haemorrhage or require pan retinal photocoagulation compared to eyes that received laser and sham therapy (DRCR, Ophthalmology, 2010;117:1064-77)

- A series of clinical trials on ranibizumab have been undertaken by industry. The small 10 patient phase 1, READ-1 study reported highly encouraging findings in 2006 (Chun DW, Ophthalmmology 2006, 113:1706-12), and revealed marked reductions in macular thickness on OCT which was accompanied by a mean improvement of visual acuity by some 10 letters. In addition the importance of VEGF as a critical growth factor stimulus in the pathogenesis of DMO was shown by this study (Nguyen et al. Am J Ophthalmol 2006,;142:961-9). The subsequent Phase II, Read-2 study also in DMO of 126 patients randomised to focal grid laser only, versus 0.5 mg ranibizumab only versus combined ranibizumab 0.g mg plus laser. At 6 months this study found small differences in favour of ranibizumab monotherapy compared to laser monotherapy or combined ranibizumab plus laser. Decreases in retinal thickness in OCT were concordant with the changes in visual acuity (Nguyen et al Ophthalmology 2009; 116:2175-81).

These trials were followed by several industry sponsored phase 2/3 (RESOLVE) and phase 3 studies (RESTORE) and the DRCR net trials.

RESOLVE was a multicentre study comparing two doses of ranibizumab (0.3 and 0.5mg) versus no treatment in patients with centre involving DMO. Rescue therapy with laser photocoagulation was permitted if certain criteria were met. Also the volume of drug injected could be doubled if the retinal thickness at the month 1 visit was > 300 µm or if the 50 µl volume was in use and at any visit after month 1 the retinal thickness was > 225 µm and any reduction in retinal oedema was less than 50 µm from the previous visit. The mean visual acuity was found to be improved by 10 letters on pooling the two ranibizumab arms compared to a mean fall of 1.4 letters in the control arm. Likewise the central retinal thickness dropped by a mean of 194 µm in the treatment arms compared with control where the drop in retinal thickness was around 48 µm.

The RESTORE trial was a study of monthly ranibizumab 0.5 mg as monotherapy or combined with laser photocoagulation. In this trial 345 patients were randomised to ranibizumab 0.5 mg plus sham laser, ranibizumab 0.5 mg plus active laser, sham ranibizumab + active laser. The primary outcome was the mean change in best corrected visual acuity with secondary outcomes including time course of vision change, reduction in retinal thickness and self reported visual functioning. At one year, the change in mean visual acuity favoured ranibizumab plus sham laser and ranibizumab plus active laser arms (6 letters) compared to the laser monotherapy arm (0.8 letters). Over one-third of patients in the ranibizumab arms gained 10 letters of visual acuity compared with 15% of the laser treatment arm. The reduction in central retinal thickness in the ranibizumab arms was roughly twice that observed with the laser arm. There were also significant improvements in the general vision, near and distance activities subscales of the NEIVFQ a visual functioning and health related quality of life instrument. Approximately 20% of eyes improved by 15 letters or more at one year. Interestingly when Ranibizumab was used in neovascular AMD nearly double this proportion of eyes improved by 15 letters raising intriguing questions on the reasons for this disparity. In terms of the baseline characteristics of the enrolled patients the BCVA letter score had to lie between 78 and 39. For neovascular AMD trials the BCVA limits were 73 and 23 (i.e. the RESTORE study allowed participants with better BCVA and the lower limit of vision was also cut off at a better level). Limiting study entry to eyes with BCVA of 39 or better at the lower range also probably prevented inclusion of eyes with severe irreversible macular damage and hence should have resulted in better outcomes. On comparison with the DRCR net trial which permitted a lower level of acuity (23 letters) at study entry around 30% of eyes showed a 15 letter gain. A subgroup analysis segregating participants by VA into 3 groups > 73 letters, 61 to 73 letters and < 60 letters found least improvement in the best baseline acuity group supporting the view that allowing participants with better BCVA to enter the study limited the amount of improvement that could occur. Surprisingly the best outcomes for both ranibizumab and laser were in the worst acuity groups. Statistically significant reductions in central retinal thickness was achieved in all arms of the study. The most impressive falls were noted in both the ranibizumab and the sole triamcinolone arms.

Adverse events were closely monitored using the antiplatelet collaborative trial criteria and the arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhages were distributed evenly across all groups.

Two other phase 3 trials multicentre, randomized, sham controlled trials in patients with DMO are the RISE and RIDE studies. Recruited patients were randomised to sham, ranibizumab 0.3 or 0.5 mg. The proportion of ranibizumab treated patients who gained 15 letters was more than double that of sham treated patients in both trials (Genentech http://www.gene.com).

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