VISUAL DISABILITY IN DIABETIC EYE DISEASE AND ITS REHABILITATION

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Declaration

I, Hannah Dunbar, confirm that the work presented in this thesis is my own. Where information has been derived form other sources, I confirm that this has been indicated in the thesis.

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Abstract

Objectives:

To determine the effects of diabetic eye disease (DED) on multiple aspects of visual function and self-reported visual ability.

To conduct a randomised controlled trial (RCT) determining the effectiveness of low vision rehabilitation in those with DED.

Methods:

100 participants with DED completed a comprehensive visual function assessment and completed the Activity Inventory (AI). The AI, scored using Rasch analysis, provided a measure of visual ability (logits). Univariate and multivariate regression examined the relationship between disease severity, visual function and visual ability.

Participants were randomised to immediate (within 2 weeks of enrolment) or delayed (3 months after enrolment) intervention. The intervention was a hospital based low vision clinic appointment. The AI was repeated 3 and 6 months after enrolment. Primary outcome was the difference in visual ability between those receiving immediate intervention and those on a waiting list (no intervention control) 3 months after enrolment. Secondary outcomes were the difference in visual ability between those receiving immediate intervention and those receiving delayed intervention 6 months after enrolment and 3 months after intervention (delayed intervention control). Subgroup analyses examined whether severity, visual acuity or scotoma size influenced intervention outcome.

Results:

Disease severity and visual function were significantly associated with visual ability. Severity was not independently related to visual ability following adjustment for visual function. Stepwise regression revealed that a single measure of acuity explained 38% of the variance in visual ability ($p < 0.001$). No significant difference between intervention groups existed 3 or 6 months after enrolment or 3 months after intervention. Those with reduced acuity or central scotoma receiving delayed intervention improved between 0.42 and 0.56 logits more than those receiving immediate intervention 6 months after intervention ($p = 0.02$).

Conclusions:

Although explaining less than half the variance, a measure of acuity provided the best prediction of visual ability in DED. No overall effect of low vision rehabilitation was found. Exploratory subgroup analyses revealed visual ability improvements equivalent to between a 3 - 4 line acuity increase in those with reduced acuity or central scotoma receiving delayed intervention, indicating the need for further investigation of the effectiveness of low vision intervention in these patients.

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Study team

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Chapter 1 – Introduction

1.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a group of metabolic disorders characterised by a sustained hyperglycaemic state secondary to a lack, or diminished efficacy, of endogenous insulin. Two main types of diabetes exist, Type 1 and Type 2. Type 1 typically develops between the ages of 10 and 20 years and is characterised by little or no insulin production. Type 2 frequently develops between the ages of 50 and 70 and is caused by resistance to the effects of insulin despite its normal production.

2.6 million people in the United Kingdom (UK) are known to be affected by the disease[1] with an additional 400,000 expected to be diagnosed between 2010 and 2030[2]. According to World Health Organisation definitions, an additional fifth of the elderly population in the UK are thought to have undiagnosed diabetes or impaired fasting glucose[3]. The rising prevalence of diabetes will ensure it remains a major health and economic problem in the UK[4].

1.1.1 Management of DM

Management of DM aims to establish a normal, or near normal blood glucose concentration. Glucose in the blood stream adheres to haemoglobin molecules within red blood cells to form Haemoglobin A1c (HbA1c). Red blood cells live for approximately 8 – 12 weeks before being replaced; therefore measuring HbA1c concentration indicates the average amount of glucose in the blood over the past

8 – 12 weeks. In those without DM, HbA1c varies between 3.5 – 5.5%. The National Institute for Clinical Excellence (NICE) recommends a HbA1c of less than 7.5% in Type 1 and 6.5% in type 2 DM to protect against long-term complications[5, 6]. A brief summary of treatment options is given below. More detailed information can be found in the appropriate NICE guidelines[5, 6].

Patients with type 1 or 2 DM are prescribed a healthy balanced diet, encouraging high fibre, low glycaemic index sources of carbohydrates and limiting the intake of simple sugars, saturated and trans fatty acids in a bid to reduce HbA1c levels. If blood pressure remains consistently higher than 140/80 mmHg (or 130/80 mmHg if eye, kidney or cerebrovascular damage is present), antihypertensive medication is prescribed.

Those with type 1 DM are placed on an individualised regime of insulin treatment. This can involve single or multiple daily injections, or continuous subcutaneous insulin infusions (insulin pump therapy).

In type 2 DM, if HbA1c levels are not sufficiently controlled with diet management and blood pressure control, oral glucose-lowering treatments are prescribed; Metformin in the first instance with sulphonylureas as second line treatment. Treatment response is assessed by monitoring HbA1c levels. As endogenous insulin production declines, the required dose will increase. If HbA1c levels rise above 7.5%, insulin injections are considered.

1.1.2 Complications of DM

Failure to consistently control HbA1c levels can lead to multiple complications, including foot and leg ulcers, renal and ocular complications, heart disease, stroke and peripheral vascular disease. Ultimately DM causes significant morbidity and mortality[7, 8].

1.2 Ocular complications of DM

The ocular complications of DM are wide reaching, affecting the external ocular surface[9], iris[10], lens[11] and retina. This study focuses on retinal changes described as diabetic retinopathy or diabetic maculopathy when occurring within the macular region, which we refer to as diabetic eye disease (DED).

1.2.1 Diabetic retinopathy

Diabetic retinopathy is the leading cause of registrable sight impairment in the working population of the UK[12]. Recent figures from the Certifications Office indicate it has been responsible for roughly 1,700 new registrations each year between 2007 and 2009[13]. It is clinically thought of as a microvascular disorder, with features of both microvascular occlusion and leakage. However, microvascular complications occur in tandem with degenerative changes in the transparent neural retina[14, 15], as has been demonstrated electrophysiologically[16, 17] and psychophysically[18, 19].

Diabetic retinopathy is classified as non-proliferative or proliferative according to ophthalmoscopically visible changes. Microanuerysms, intraretinal haemorrhage,

venous beading, capillary loss and intraretinal mircovascular abnormalities (IRMA) characterise non-proliferative disease[20].

Proliferative disease occurs in response to microvascular occlusion. Capillary loss leads to the upregulation of growth factors such as vascular endothelial growth factor (VEGF) promoting the growth of abnormal blood vessels on the optic nerve and/or retina. Rupture of these vessels results in vitreous haemorrhage and possible fibrovascular tissue formation, which in turn can cause a tractional vitreous detachment[20]. 6.6% of those with non proliferative disease are expected to progress to proliferative disease after 10 years[20].

A UK wide study in 1998 showed baseline diabetic retinopathy, defined as at least microaneurysms in one eye, was present in 39% of males and 35% of females with DM [21]. More severe retinopathy (cotton wool spots or IRMA) existed in 8% of men and 4% of women with DM [21], mirroring more recent findings in the United States where 8% of all those with DM over the age of 40 had advanced vision threatening retinopathy[22].

Extensive costs are associated with visual impairment derived from DED. A report for the Guide Dogs for the Blind Association in 2003 put the lifetime cost of a person with diabetic retinopathy to the UK Government at £237,000, almost 50% of which was attributable to productivity losses due to visual impairment[23].

1.2.2 Diabetic maculopathy

Diabetic maculopathy can broadly be described as oedema involving the macula with or without hard exudates, with or without the presence of ischaemia. It is

classified according to the underlying pathological process at play into 4 types as shown in table 1.1.

Focal	defined area of oedema associated with clusters of microaneurysms or dilated retinal capillaries
Diffuse	diffuse area of oedema
Ischaemic	capillary closure involving the macula
Mixed	combination of all types

Table 1.1. Classifications of diabetic maculopathy

Diabetic macular oedema is a significant risk factor for the development of visual loss[24]. Its associated health and social care costs in England for the year 2010 were estimated at £116 million[25]. This was not inclusive of societal costs, such as productivity losses and informal care.

1.2.3 Treatment options

Since the 1970s, the main treatment modality for both proliferative retinopathy and maculopathy has been laser photocoagulation. Presently Argon Laser is the most commonly used. Its use aims to prevent further visual loss rather than restore vision, by inducing regression of abnormal blood vessels and reducing central macular thickening and preventing further visual loss[20].

Panretinal photocoagulation is indicated for proliferative diabetic retinopathy displaying high risk characteristics defined as new vessels on the optic disc greater than standard photograph 10A (about 1/3 disc area), or any new vessels on the disc with vitreous haemorrhage, or any new vessels elsewhere

with vitreous haemorrhage[26]. This study was based mainly on those with Type 1 DM, however many retinal specialists would treat any new vessels in patients with type 2 DM, as the prognosis is worse (V.C. Chong, Personal communication, 2011).

In line with published literature, the Royal College of Ophthalmologists recommends macular photocoagulation in the presence of sight-threatening diabetic macular oedema[27-35]. Focal maculopathy responds most readily to photocoagulation. Macular photocoagulation has been shown to be effective in slowing the cumulative rate of central visual loss due to macular oedema[27, 36].

Treatment of maculopathy is indicated in the presence of clinically significant macular oedema (CSMO), as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group[37]. Briefly CSMO is indicated by:

1. thickening of the retina at or within 500 microns of the centre of the macula
2. hard exudates at or within 500 microns of the centre of the macula, if associated with thickening of the adjacent retina
3. a zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the centre of the macula

Triamcinolone, an intravitreal steroid injection has been compared to macular photocoagulation for the treatment of CSMO[38]. Though initial results were promising, 2 years after treatment, laser treated eyes had less CSMO and better

acuity. Also, the risk of cataract and elevated intraocular ocular pressure was higher in those treated with triamcinolone[20, 38].

Intravitreal Anti VEGF injections have also been indicated for the treatment of CSMO. Pegaptanib (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin) have been investigated for effectiveness. A phase II trial investigated the safety and efficacy of intravitreal pegaptanib in 172 patients with diabetic macular oedema[39]. Following an average of 5 injections over the course of 30 weeks, 34% of patients treated with 0.3 mg of pegaptanib experienced a gain in visual acuity of 10 letters (equivalent to 0.2 logMAR) compared to 10% of those given sham injection ($p = 0.003$). More recently in a trial comparing the use of intravitreal ranibizumab over standard photocoagulation, 49% of patients treated with ranibizumab gained 10 letters in visual acuity compared to only 28% of those on standard treatment ($p < 0.001$)[20, 40].

1.3 Diabetic retinopathy screening

1.3.1 History of the service

Principles for the screening of human diseases were set out by Wilson and Jungner in 1968[41]. Conditions with a known natural history, where those to be screened can be easily identified and where a cost effective treatment is available are considered ideal candidates for screening services. The first calls for the development of a screening service for diabetic retinopathy in Europe came in 1994 from the St. Vincent Joint Task Force for Diabetes[42]. Several photographic screening and optometry-led services were developed reporting various degrees

of success in the mid 1990s[43-45]. This was followed by calls for the introduction of a national service[46, 47]. The National Screening Committee of the Department of Health responded by proposing a national risk reduction programme[4] and then in late 2001 the National Service Framework for Diabetes was published, including specific requirements for the introduction of a national screening programme for diabetic retinopathy in England and Wales[48]. As digital retinal photography facilitates external quality assurance checks, the framework suggested the National Health Service (NHS) invest in this form of screening. In fact, retinal photography with mydriasis has been shown to be the most effective screening modality for diabetic retinopathy[46, 49, 50]. In 2003, Harding and colleagues proposed a protocol for grading diabetic retinopathy, specifically designed for inclusion in a national guideline on screening for England and Wales[51].

1.3.2 UK National Grading Protocol

The proposed protocol, the National Grading Protocol (NGP) for Diabetic Retinopathy[51], was the consensus protocol recommended by the Royal College of Ophthalmologists in 2005[45]. Currently clinics in England use the English National Screening Programme Grading Protocol[52], which is based on Harding's model.

The NGP makes the distinction between retinopathy and maculopathy, grading each separately according to retinal signs and under certain circumstances, visual acuity. There are 4 retinopathy levels: R0 corresponding to no retinopathy, R1 to mild to moderate non-proliferative retinopathy, R2 to severe non-proliferative retinopathy and R3 to proliferative retinopathy. Maculopathy is represented by M1 (where M0 represents no maculopathy). Treatment with laser

photocoagulation is indicated by the letter P, preceded by M or R to denote whether macular (focal) or pan retinal (scatter) respectively. Table 1.2 displays the grading protocol in further detail.

R1	Mild to moderate non-proliferative (previously background)	Microaneurysm(s) Retinal haemorrhage(s) ± exudate
R2	Severe-non proliferative retinopathy (previously pre-proliferative)	Venous beading Venous looping or reduplication Intraretinal microvascular abnormality Multiple deep, round or blot haemorrhages Cotton wool spots
R3	Proliferative retinopathy	New vessels on disc New vessels elsewhere Preretinal or vitreous haemorrhage Preretinal fibrosis ± tractional retinal detachment
M1	Maculopathy	Exudate within 1 DD of the centre of the fovea Circinate of group of exudates within the macula Retinal thickening within 1 DD of the centre of the fovea Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea if associated with a best VA of ≤ 6/12
P1	Photocoagulation	Focal (macular) or Grid (pan retinal)

Table 1.2. NGP grades and diagnoses (adapted from Harding et. al., 2003). DD = disc diameter.

The grading procedure has 2 potential photographic steps and slit lamp biomicroscopy for those with unobtainable or ungradable images. If the primary images are graded either R0 or R1, no further action is taken with patients invited back for routine annual screening. Secondary images are taken in the remainder of cases. R2 or M1 cases are referred to the hospital eye service (HES), whereas R3 cases are fast tracked to the HES.

Graders can be either trained, non-clinicians or clinicians such as general practitioners (GPs) or optometrists. Screening service locations include optometry practices, community hospitals, GP practices and mobile units. Patients seen within the HES are also diagnosed according to the NGP.

1.4 DED and vision

1.4.1 Effects on visual function

DED affects multiple facets of vision. Previous studies indicate that increasing severity of retinopathy is associated with reduced visual acuity[24, 53, 54]. In fact, nearly one in thirty people with type 1 DM and 1.6% of those with type 2 DM have visual acuity of less than 6/60[55, 56].

Increasing severity of retinopathy has been shown to be associated with reduced contrast sensitivity and colour vision deficits[54, 57]. Indeed deficits in contrast sensitivity[54, 58], colour vision[19, 59-61] and central retinal function[62, 63] have been demonstrated in persons with diabetes before the onset of ophthalmoscopically visible retinopathy. It has been suggested that colour vision deficits are primarily due to accelerated lens yellowing rather than neuronal or microvascular changes, as hue discrimination in pseudophakic diabetic patients and age similar normals was not statistically different[64].

Visual field defects are present in those with advanced disease[65], with some suggesting visual field measurements may be of more use than visual acuity alone when assessing functional loss in diabetic retinopathy[53]. For example, patients

receiving pan retinal photocoagulation for vitreous haemorrhage, tractional retinal detachment or a combination of both, with a mean visual acuity was 0.2 logMAR (6/9.5), on average lost 71% of their central visual field[66], with only 20% retaining adequate visual field to satisfy Driver and Vehicle Licensing Agency (DVLA) driving standards[67].

Diabetic macular oedema has also been associated with reduced central field function and unsteady fixation[68-70]. However central, stable fixation despite the presence of macular oedema has been observed[71]. Unsteady fixation has been shown to negatively impact on reading ability in patients with macular degeneration[72].

1.4.2 Assessing the impact of DED

It has been argued that visual function measures, in particular visual acuity, may not accurately reflect the true extent of a visual impairment or how it impacts on day to day life[73-77]. Review papers by Fenwick[78] and Sharma[79] highlight a substantial amount of evidence revealing the negative impact of diabetic retinopathy, macular oedema and visual impairment on the patient.

DED is associated with significantly reduced health related quality of life (HRQoL)[78, 80-83], the reduction more pronounced following progression to the second eye[80]. The negative impact of DED on vision related quality of life (VRQoL), a component of HRQoL, has also been described[35, 84, 85]. VFQoL is a multifaceted concept incorporating not only vision related ability to complete everyday tasks (visual ability), but symptoms, emotional well-being, social relationships and vision related concerns[78, 86].

Visual ability reduces with increasing severity of DED, particularly when sight-threatening stages are reached[87]. Visual ability can be defined within the context of the World Health Organisation International Classification of Functioning, Disability and Health (WHO ICF)[88]. Within the WHO ICF, difficulty executing tasks or actions is termed 'activity limitation' whereas problems experienced in involvement in life situation are termed 'participation restrictions'. As such, visual ability is a vision related activity limitation according to the WHO ICF. Vision related activity limitation has been highlighted as an important quality of life domain in patients with diabetic retinopathy in a recent qualitative study indentifying content for a diabetic retinopathy specific quality of life item bank[89].

Visual acuity appears to make a unique significant contribution to VRQoL, independent of DED severity. A population based cohort study of 602 persons with type 1 DM followed up for 14 years showed that both severity of retinopathy and visual acuity were independently associated with poorer VRQoL as captured by the National Eye Institute Visual Function Questionnaire (NEI-VFQ)[35, 90]. 471 of these participants were followed up for a further 10 years[84]. No significant correlation between severity and NEI-VFQ score was found over this period, rather the most significant factor associated with reduced VRQoL was a loss of 3 lines of logMAR visual acuity, particularly in subscales such as general vision, mental health and driving.

Certainly visual acuity may not be the only visual function measure making a unique contribution, but to date the link between multiple measures of visual function and self reported visual ability has not been fully established.

Cusick and colleagues examined the association between 3 visual function measures (visual acuity, contrast sensitivity and central field function) and NEI-VFQ near and distance subscale scores[85]. Both near and distance subscales were independently associated with visual acuity following adjustment for mental health, demographic variables and treatment history. Near subscale score was also independently related to contrast sensitivity and central field function, though distance scores were not. Unfortunately 44% and 41% of subjects had missing contrast sensitivity and central field data respectively. Further investigation is clearly needed to evaluate the contribution of other aspects of visual function on visual ability in DED.

The impact of undergoing photocoagulation should also be considered, though it may depend upon whether a person is receiving follow up or first time treatment. A pronounced reduction in quality of life has been demonstrated in patients receiving their first treatment[91], however over subsequent treatment sessions, vision related quality of life has been seen to improve, despite a very limited change in visual acuity[75].

In addition, a substantial social and emotional impact has been described[92, 93], related to vision loss[94-97], fear associated with treatment[98] and the stresses these issues place on personal and family life[99, 100]. Moreover, a considerable impact stems from the underlying diagnosis of DM[101].

1.4.3 Patient reported outcome measures in healthcare

Patient reported outcome measures (PROMs) are used in many areas of healthcare including physiotherapy[102], psychiatry[103] and within different

ophthalmological disciplines such as glaucoma[104], refractive surgery[105] and low vision rehabilitation[106, 107]. Their use has risen dramatically in recent decades[86]. Currently over 100 vision related PROMs are available (K. Pesudovs, Personal communication, 2012). By eliciting reports directly from patients, often in the form of questionnaires (also referred to as instruments), they provide a subjective measure of health status.

In recent years the number of PROMs developed for those with visual impairment has increased. A review paper in 2001 identified 13 such instruments[108]. 31 were reviewed in a similar paper in 2004, however substantial variation in the psychometric quality of instruments was demonstrated[109]. Researchers therefore need to exercise care in the choice of an appropriate PROM[110].

Many instruments use raw scores (summed totals of numeric values assigned to questionnaire responses) as measurements[111-113], the disadvantages of which have been much discussed[114, 115]. Raw scores are derived from ordinal response data and as such cannot be treated as continuous, interval measurements.
The NEI-VFQ, a widely used PROM, utilises this scoring method. The NEI-VFQ is a 51 item VRQoL questionnaire, covering 13 separate subscales (general health, general vision, ocular pain, near vision, distance vision, vision specific social functioning, vision specific mental functioning, expectations for visual function, dependency due to vision, driving, peripheral vision and colour vision), each scored on a 0 – 100 raw score scale[111, 116]. A shorter 25 item version was subsequently developed[90]. Though a subset of 17 NEI-VFQ items has been shown to produce a valid interval scale[117], Langelaan and colleagues, in a study of working age adults attending a low vision rehabilitation service, used the Rasch

Model to determine that NEI-VFQ-25 responses do not represent an interval scale[118].

The Rasch model[119] can be used to transforms raw scores, creating abstract, equal-interval scales. Chapter 4 of this thesis provides a detailed description of the Rasch Model and its uses, but briefly, the Rasch model can be employed in the development of a PROM ensuring data collected can be successfully Rasch analysed to produce true interval measurements. PROMs developed in this manner are considered to be of high quality[114]. In addition, existing PROMs, not developed on this basis have been successfully modified based on the outcomes of Rasch analysis. The Activity Inventory (AI)[120] and the Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ 48)[121, 122] are examples of PROMs that have been validated with Rasch analysis. The Impact of Visual Impairment Instrument (IVI)[123] and the Visual Function 14 (VF-14)[124] are examples of instruments that have been modified and revalidated on the basis of Rasch analysis[125, 126].

None of these instruments were developed specifically for those with DED, however patients with DM were included in the samples on which they were developed and validated[78]. A diabetic retinopathy specific quality of life instrument, the Retinopathy Dependent Quality of Life (RETDQoL), has however been developed and validated by researchers at the Royal Holloway University of London[127, 128]. The RetDQoL includes 26 items covering self-care ability, functional ability, family and working life and emotional well being, plus 2 overview items referring to 'present QoL' and 'retinopathy-specific QoL'. The validation process of the RetDQoL suggested visual acuity, macular oedema and

diabetic retinopathy were significantly associated with a detrimental impact on quality of life. Significantly lower scores were reported in those with more severe retinopathy (proliferative versus moderate or severe non-proliferative). Responses to the overview items support the existence of a diabetic retinopathy specific impact on quality of life over and above general quality of life, demonstrating that relying on generic measures when investigating condition specific quality of life may over estimated quality of life in these patients. However, the RetDQoL has some noteworthy limitations. It was initially based on 2 older instruments, the Audit of Diabetes Dependent Quality of life (ADDQoL)[129] and the Macular Disease Dependent Quality of Life MacDQoL[130] measures. These instruments were validated according to Classical Test Theory (CTT), which as will be described further in chapter 4, makes a number of inappropriate assumptions regarding response data. Furthermore, its responsiveness as an outcome measure in low vision rehabilitation studies is limited as many of its items cannot likely be expected to vary with low vision intervention, for example items such as 'other people's reactions', 'physical appearance', 'feelings about the past' and 'close personal relationship'. To date, a rigorously designed, well-validated quality of life instrument, able to assess DM specific quality of life is lacking[78].

1.5 DED and low vision rehabilitation services

1.5.1 Low vision rehabilitation services

No international consensus on the definition of low vision rehabilitation exists[131]. Substantive differences between services are present. Professional input can

come from a variety of individuals: optometrists, ophthalmologists, occupational therapists and rehabilitation officers to name a few. Services are provided in both in and out patient settings[132, 133]. Additionally, specific provision of eccentric viewing training, orientation and mobility support, device training and emotional support have also been described[106, 131, 134, 135]. Aids may be provided at no cost or at a fee and can range from simple optical aids to sophisticated electronic aids. The majority of low vision rehabilitation in the UK occurs within the NHS hospital eye service[136].

1.5.1.1 NHS low vision clinics

Recommended standards for NHS low vision services have been published by the NHS Low Vision Working Group[137]. The NHS model is an out-patient, primarily optometrist led service with no provision for eccentric viewing training or orientation and mobility support. Referrals to Moorfields Eye Hospital low vision clinic are based on a best-corrected visual acuity of 6/12 or less and/or significant field loss in common with other services[138, 139]. A history is taken by the optometrist to establish the goals of the patient. This covers daily living activities, living arrangements, mobility, recreation and social activities and employment and education where necessary. Patients are refracted, determining optimal distance and near spectacle prescription. Potentially appropriate distance and near optical low vision aids are demonstrated to the patient. A joint decision is made regarding which devices should be dispensed. Specific device training is not routinely offered, over and above that which takes place within the assessment, however the majority of devices dispensed to new referrals are relatively simple illuminated hand and stand magnifiers[140]. Assessments and

optical magnifiers are provided through state funding, at no charge to the patient. Electronic aids are not provided, but are available for demonstration purposes.

Optometrists signpost charitable and government agencies capable of providing additional information on a range of topics from adaptive technologies, employment, education and leisure activities. Information regarding 'Access to Work' (AtW) is also provided. AtW is a government scheme providing advice and practical support to disabled individuals either in, or seeking employment. It can provide assistance in a number of ways including adaptations to premises or equipment, adaptive software and electronic magnifiers, support workers, travel to and from work and awareness training for colleagues.

An Eye Care Liaison Officer (ECLO) works in tandem with the Moorfields Eye Hospital low vision clinic. Patients seeking further advice on living with sight loss, maintaining independence, education, employment, housing and leisure can be referred directly to the ECLO. Referrals for counseling and emotional support can also be made via the ECLO.

The ECLO works closely with the Certificate of Visual Impairment (CVI) team. Patients who meet the criteria for 'sight impaired' or 'severely sight impaired' registration (determined by their consultant ophthalmologist) are referred to the CVI team who discuss the registration process with the patient, listening to and addressing any concerns. They also signpost social services and provide guidance on financial benefits patients may be able to apply for once registered.

Patients who do not meet registration criteria, but who may benefit from additional support (such as mobility training) can be referred to social services by an optometrist, by completing a 'Referral of Visual Impairment' (RVI) form and sending this, with the patient's consent, to their local social services department.

1.5.2 The diabetic low vision patient

Diabetic patients are thought to present a unique set of challenges to the low vision practitioner due to the early onset and fluctuating nature of vision loss, the specific visual demands of disease management and associated multisystem losses[141]. In addition, visual impairment occurring in middle age may be more debilitating than that occurring in later life[142].

Speculation exists as to whether this represents a unique disease specific pattern of disability due to the interaction between the pathological process responsible for vision loss and the extra daily duties a person with DM contends with (administration of medication, measurement of blood glucose levels, skin and foot care and maintenance of a healthy diet)[143].

Further, more visual problems and greater disruption to functional activities have been reported in those with a diabetic visual impairment compared to those with other common ocular conditions[111, 144].

Moorfields Eye Hospital houses the largest low vision clinic in the UK. Departmental figures show that 8% of patients attending the clinic have a primary diagnosis of DED[140], a figure similar to that reported recently by the Greater Baltimore Medical Centre[145]. Whether this small proportion reflects the

percentage of patients eligible for referral, poor attendance of those referred or under referral is not clear.

Poor attendance of those with diabetic retinopathy was observed in a study of access and utilisation of a new low vision service in Australia in 2008. Only one third of referred patients with diabetic retinopathy attended the service in contrast to 80% of those with age-related macular degeneration who were referred[146].

Previous literature supports the possibility of under referral contributing to the low number of patients with DED attending low vision services. Referral may be overlooked until active treatment, often necessary in DED, has been suspended as has been reported by focus groups previously[147]. Active treatment is certainly a recognised barrier to the registration process in the UK[148, 149]. Additionally, referral may not be instigated until visual acuity is reduced to a greater degree than 6/12[150]. The visual fluctuations common in DM may compound this further. Moreover, clinicians and patients alike may prioritise appointments related to other, potentially life threatening complications of DM.

The predicted rise in the diabetic population, together with deficits in visual function and the apparent under representation of these patients in low vision clinics suggests provision of services may need to be reviewed. To date, no randomised controlled trials (RCT) investigating the effectiveness of low vision intervention in this growing group have been published, which may in itself represent a further barrier to referral.

1.5.3 Visual rehabilitation in RCTs

RCTs are generally accepted as providing the highest standard of evidence for interventional studies[151]. Surprisingly few RCTs investigating low vision rehabilitation have been conducted and of those that have, none have specifically looked at the effectiveness of low vision interventions in persons with DED. A recent systematic review of low vision service provision found only 7 RCTs in the literature, highlighting the need for more high quality evidence in this field.[152] An additional RCT has since been identified[107]. The interventions trialed varied substantially. Many were quite unlike low vision services offered in this country, including educational interventions[153, 154], a vision self management model[155], a family based intervention[156] and home based rehabilitation[157]. Of those similar, results were mixed[106, 107, 131].

Pearce and colleagues reported on the efficacy of an extra device training session in addition to a conventional hospital low vision clinic appointment[107], using the AI[120] as their primary outcome measure. This masked RCT concluded that an additional device handling session conferred no further benefit over that of a standard low vision clinic appointment (shown to be 0.64 logits, equivalent to just over a 5 line improvement in LogMAR visual acuity[117]) 3 months after intervention. It was speculated that the simple nature of the devices provided negated the need for supplementary training.

Reeves and colleagues reported on a large RCT comparing a conventional NHS hospital low vision assessment to an enhanced service and an extended service controlling for the extra contact time in participants with age related macular degeneration[131, 158]. VRQoL captured by the Vision Quality of Life Core Measure

(VCM1)[159] was recorded at baseline and 1 year after intervention. Results indicated that the enhanced service was no more effective than the conventional. In fact, VCM1 scores described a small but significant decline in VRQoL over the 1 year follow up period of the trial. High self reported usage of low vision aids (94% of participants reported using at least 1 low vision aid at the end of the trial) did not translate into improved quality of life.

These results may reflect the significant reductions in visual acuity and contrast sensitivity encountered by participants over the same period. As the effect of low vision rehabilitation has been shown to decline significantly between 3 and 12 months post intervention[132], any gains made immediately after intervention may have been hidden by virtue of the length of the follow up period. In addition, the VCM1 pertains to psychological aspects of visual impairment, issues that the intervention does not specifically attempt to address. Furthermore VCM1 responses were summary scored. The problem with this approach has been discussed above.

Finally, the Veteran's Administration in the US developed an extensive outpatients low vision rehabilitation programme for veterans with moderate to severe vision loss from macular diseases and conducted an RCT to evaluate its effectiveness (LOVIT)[106, 133].

Participants with a range of macular conditions were randomised to intervention or waiting list control. Diabetic macular oedema was not within in the inclusion criteria. The intervention included an optometry assessment providing refraction and prescription of appropriate devices; 5 weekly 2 hour sessions of low vision

therapy, providing device training, eccentric viewing training and counseling; and a 1 hour home visit. Following each therapy session, participants completed homework. On average participants spent 10.46 hours with a low vision therapist and 17.08 hours on homework tasks. All participants were provided with electronic magnifiers and stand magnifiers in addition to other devices. For example, 81% received a monocular telescope, 86% received a pocket magnifier, 83% were provided with a reading stand and 86% with glare control filters. The self-reported reading ability of participants receiving intervention increased significantly by 2.06 logits compared to a decrease of 0.37 logits in the control group.

Substantial differences in study design make useful comparison of these RCTs difficult. Though Pearce and Reeves conducted their RCTs with the NHS low vision service, noteworthy differences in design existed. For example, Pearce and colleagues recruited patients with a range of ocular conditions (including 15% with diabetic retinopathy) and administered follow up questionnaires at 1 and 3 months. Reeves studies patients with AMD only and followed patients up for 1 year. Furthermore, the 'enhancements' in each study were quite different; an additional 1 hour session in the low vision clinic versus up to three 2 hour home visits over a six month period.

LOVITs results are unlikely to be generalisable beyond the specific population in which it was conducted. The intervention is only accessible by veterans and the study population was almost exclusively male. Unlike private low vision clinics in the US, the VA provides all devices and training at no cost to the veteran. Though NHS low vision services are accessible to all and provide low vision aids at no

cost, complex devices such as electronic aids, extensive training and home visits are not provided.

1.6 Conclusion

With the number of diabetes diagnoses increasing and current treatment aiming to prevent rather than reverse visual loss, we can expect greater need for visual rehabilitation services in the future. Indeed, recent figures from the Certifications Office highlighted roughly 1,700 new 'sight impaired' registrations in England each year between 2007 and 2009 due to DED, a potentially preventable cause of sight loss[13].

As described in section 1.4.1, it is clear that DED results in deterioration of many aspects of visual function. What remains unclear is how these multiple deficits impact on the visual ability of a person with DED. Where multiple measures of visual function have been examined in relation to self-reported visual ability[85], questionnaires developed and validated using CTT have been used. Problems with this methodology are discussed in chapter 4. A comprehensive study of multiple aspects of visual function in relation to patient reported visual ability is lacking.

Furthermore, as highlighted in section 1.5.3, not only is there a general lack of high quality evidence of the effectiveness of low vision services, there has never been an RCT investigating the effectiveness of low vision rehabilitation in patients with DED. A review of existing literature specifically states the need for further evidence within specific populations including working age groups[152]. Of the 2

NHS based RCTs previously published[107, 131] only 15% of participants in one study had a primary diagnosis of DED.

Given this, the unique challenges faced by visually impaired diabetic patients, the question over possible poor referral rates and the inevitable rise in the number of people developing sight loss from DED, there is a clear need for an RCT investigating the effectiveness of low vision rehabilitation in those with DED.

1.7 Proposed aims and hypotheses

This thesis contains the following two projects, designed to address the concerns raised in the previous section.

Project 1 – Fundamental research on the impact of DED

- Aim 1 – To explore the impact of disease severity on visual function
- Aim 2 – To explore the impact of disease severity on visual ability
- Hypothesis – The reduction in visual ability associated with increasing disease severity is explained by visual function deficits
- Exploratory analysis – Which visual function variables provide the best assessment of visual ability?

Project 2 – RCT investigating the effectiveness of an NHS low vision clinic appointment.

- Hypothesis – An NHS hospital based low vision clinic assessment results in increased visual ability in patients with DED

- Exploratory analysis – Do the factors associated with visual ability in project 1, influence the outcome of a low vision clinic appointment?

Chapter 2- Methodology: Fundamental research on the impact of diabetic eye disease

2.1 Patients

Patients were recruited from medical retina clinics at Moorfields Eye Hospital and participated in both projects. Potential participants were identified by an ophthalmologist at their routine clinic appointment.

2.1.1 Inclusion and exclusion criteria

Participants were recruited using the following criterion:

- People with diabetes mellitus attending Moorfields medical retina clinics, with diabetic eye disease diagnosed by an ophthalmologist

Participants were excluded according to the following criteria;

- people under the age of 18;
- people not fluent in English;
- people with serious hearing impairment;
- people with concomitant eye disease other than mild cataract (determined by reviewing individual hospital notes and on recommendation of referring ophthalmologist);
- those who had previously attended a low vision clinic;
- those with poor mobility or in poor general health;
- people who were hospital inpatients, living in nursing homes or who were otherwise non-independent.

2.1.2 Informed consent

Those expressing an interest in taking part were referred to the research optometrist (HD) who verbally described the project, provided a patient information sheet (see Appendix I) detailing study involvement and answered any subsequent questions. Patients still keen to take part were contacted by telephone up to one week later to confirm their interest. Appointments were booked for all those still interested at which time informed consent was taken by HD.

Patients signed a standard consent form (Appendix I). As part of the consent process, participants were asked whether they agreed to their GP being informed of their study involvement. A standard letter was posted to their GP if appropriate (see Appendix I). The study conformed to the Declaration of Helsinki.

2.1.3 Disease severity groups

Ophthalmologists at Moorfields Eye Hospital medical retina clinics use the English National Screening Programme Grading Protocol (NGP) for Diabetic Retinopathy as described in Chapter 1[51]. Diagnoses are made for each eye separately and recorded in the patient's record.

Briefly, as described in the previous chapter, the protocol grades retinopathy and maculopathy according to retinal signs and, under certain circumstances, visual acuity. NGP retinopathy level R1 corresponds to mild to moderate non-proliferative retinopathy, R2 to severe non-proliferative retinopathy and R3 to proliferative retinopathy. Maculopathy is defined as clinical signs within one disc

diameter of the centre of the fovea and is denoted as M1 (where M0 represents no maculopathy). Treatment with laser photocoagulation is indicated by the letter P, preceded by M or R to denote whether macular (focal) or pan retinal (scatter) respectively. Table 1.2 in chapter 1 gives full definitions of the NGP categories.

Disease status of recruited patients was determined by reviewing hospital notes following their most recent clinic visit. Participants were recruited to the following groups based on the NGP diagnosis of their better eye:

1. Mild/moderate non-proliferative retinopathy without maculopathy: R1
2. Severe non-proliferative retinopathy without maculopathy: R2
3. Severe non-proliferative retinopathy with maculopathy: R2 + M1/MP
4. Proliferative retinopathy with/without maculopathy: R3/RP ± M1/MP

The better eye was defined as the eye with the less severe diagnosis. Where the diagnoses were the same, the better eye was that with better visual acuity. If visual acuity was equal, the participant's dominant eye for aiming was chosen. This was attained by asking the participant to look at a spot target across the room and with their arm outstretched to position their index finger in front of the spot. The eyes were then covered in turn and the participant reported whether the spot was still covered. The open eye for which the spot was still covered was designated the aiming dominant eye. In a small number of cases, participants reported that they could not cover the spot (i.e., neither eye was obviously dominant). If this was the case the participant chose the eye they felt was their most dominant.

2.2 Baseline visual function assessment

All participants completed a visual function assessment designed to describe multiple aspects of visual function. Measurements were taken binocularly where possible with the exception of contrast sensitivity, which was recorded in the better eye. Where binocular measurements were not possible, the better eye was used. All participants performed the following visual function tests. Tests were performed by HD, a qualified optometrist. The order of testing was not randomised. All data were recorded on purpose made case report forms. Copies of these are provided in Appendix II.

2.2.1 Refraction

Spectacle prescription was determined by refraction, performed according to ETDRS protocols using ETDRS distance viewing charts at 4 metres (m). Briefly, the most positive or least negative spherical and least negative cylindrical lens consistent with best correct visual acuity (VA) was used. Full aperture trial lenses were used.

2.2.2 Distance acuity

Habitual (pre-refraction, wearing any previously prescribed glasses or unaided as appropriate) and corrected (post-refraction, wearing the prescription determined by refraction) distance acuity was assessed using an internally illuminated ETDRS chart (Lighthouse International, New York) at 4m with room lights extinguished. A different chart was used on each occasion.

Letter by letter scoring was employed in accordance with the method described by Ferris[160]. Briefly, the number of correctly read letters was recorded. Participants were encouraged to continue reading or guessing until a full line (5 letters) was read incorrectly to ensure threshold was reached. This score was converted to the logarithm of the Minimum Angle of Resolution (logMAR) VA as follows:

(Number of letters read at 4m + 30) x 0.02

If less than 20 letters were read correctly from 4m the test distance was reduced to 1m, with +0.75DS added to the eye being tested to correct for the reduced distance. Participants attempted to read the first 6 lines of the chart (first 30 letters only). Again the number of correctly read letters was recorded. In this instance, logMAR VA was calculated as follows:

(Number of letters read at 4m + number of letter read at 1 m) x 0.02

If this was not possible, participants were asked to differentiate between horizontal and vertical hand movements at 50cm, recording 'Hand movements' if this was possible. Where this was not possible, 'Perception of light' or 'no perception of light' was recorded, depending on whether the participant could identify the room lights being turned on and off.

This protocol is consistent with previously published methodologies[161-163].

2.2.3 Contrast sensitivity

Contrast sensitivity was assessed using the Pelli-Robson chart at 1 metre under the recommended luminance level of ~ 85 cd m^{-2}[164]. The chart comprises 16 triplets of letters arranged in 8 rows of two triplets, each subtending 2.8° at the test distance. The letters within each triplet have equal contrast. Contrast between triplets, reading from left to right and on successive lines, decreases by a constant factor of 0.15 log units. Contrast between the first and last triplet ranges from 100% to 0.6%. Participants, wearing full refraction for a test distance of 1 metre, were encouraged to read letters until 2 or more letters in any triplet were read incorrectly. Contrast sensitivity was calculated as follows:

(Number of letters read correctly – 3) x 0.05

2.2.4 Habitual near acuity

Habitual near acuity was assessed using the Bailey-Lovie Reading Chart[165]. The chart comprises 16 lines of between 2 and 6 words of varying length. Words have no obvious semantic relationships, therefore eliminating contextual cues[165]. Print size ranges from N80 to N2 (or 1.6 – 0.0 Log MAR when viewed from a distance of 25cm). Participants were asked to read the chart binocularly from their habitual working distance wearing any habitual reading correction. Habitual reading acuity was recorded as the physical size of the smallest line read with no more than one error. LogMAR notation was not used, as it is dependent upon the working distance employed.

2.2.5 Reading performance

Reading acuity alone does not adequately describe a person's reading performance[166]. Therefore participants completed 2 functional reading tests, assessing habitual and corrected reading performance.

2.2.5.1 Habitual reading performance

The International Reading Speed Test (IReST) was used to determine habitual reading speed[166]. The test comprises 10 extended passages, 830 +/- 2 characters (approximately 160 words) in length that have comparable linguistic complexity.

The texts were printed in two sizes, 9 and 18 point (approximately N5 and N10), Times Roman font (referred to here as large and small for simplicity). Two passages, one large and one small, were selected at random from a possible 10. Participants viewing binocularly, read each aloud from their habitual working distance wearing any habitual reading prescription. The time taken in seconds for each paragraph was measured. Both large and small habitual reading speed, accounting for errors, in words per minute (wpm) were recorded using the formula:

$$\frac{\text{(Number of words read correctly x 60)}}{\text{Time taken (seconds)}}$$

2.2.5.2 Corrected reading performance

The MNREAD test (Regents of the University of Minnesota, Minneapolis), a continuous text reading acuity test, was used to assess corrected reading performance[167]. The test comprises 2 cards, each one with 19 sentences ranging

from 1.3 to -0.5 logMAR from a distance of 40cm. Each sentence is 60 characters long (including a space between each word and at the end of each line), printed over three lines with even right and left margins. The test measures reading acuity, peak reading speed and critical print size.

Participants viewed one randomly selected chart binocularly from a distance of 40cm wearing optimum spectacle correction (+2.50DS addition). Sentences were revealed one at a time, starting with the largest. Participants read the sentence aloud and the time taken, in seconds, to read the sentence and any errors made were recorded. Progressively smaller sentences were revealed until no words of the sentence could be read in the first 30 seconds of testing. Corrected reading speed in words per minute (wpm) for each print size was calculated based on the number of words read correctly, with the fastest speed recorded as corrected peak reading speed.

Corrected reading acuity (in LogMAR) was calculated using the formula:

1.4 – 0.1(number of sentences attempted) + 0.01(number of errors made)

Corrected critical print size, the smallest print size that supports the peak reading speed, was also recorded. This was defined as the smallest print size read at a speed within 10% of the average of the fastest 3 reading speeds, as recommended by Patel[168].

Where participants were unable to read even the largest sentence from 40cm, the chart was moved to 25cm. Spectacle correction was adjusted accordingly

(+4.00DS addition). This increases the effective print size by 0.3 logMAR (range 1.6 to -0.2 logMAR).

2.2.6 Colour vision

As the study aim was to determine acquired change in function (rather than congenital colour vision abnormality) that accompany diabetic eye disease[169, 170], the Lanthony desaturated panel D-15 test (D-15ds) was used[171, 172]. The D-15ds was developed to examine chromatic discrimination loss accompanying eye disease and allows the evaluation of even mild acquired defects[172, 173]. It has also been shown to be valid in the presence of moderate visual acuity loss, up to 6/30[172] and sensitive enough to detect subtle colour deficits in young persons with type 1 diabetes and normal acuity[174].

The D-15ds is analogous in design to the D-15 panel, comprising caps of the same hues, but reduced chroma (4.2 versus 2) and increased value (5 versus 8), i.e. they look paler and lighter than their D-15 counterparts, making the D-15ds the more demanding test[172].

Participants completed the test binocularly whilst wearing their habitual near correction. The test was administered at a working distance of 50cm, on a black surface illuminated by a CIE illuminant C light source (Richmond Flat Tray Tru-Daylight Illuminator: 6700 Kelvin), consistent with the manufacturer's instructions.

The 16 caps are numbered from 0 (the reference cap) to 15. Prior to testing, caps numbered 1 through 15 were randomly arranged on the testing tray with the

reference cap placed to one side. Participants were instructed to select the cap (from the remaining 15 caps) most closely matching the colour of the reference cap and place it beside the reference cap. From the remaining caps they next selected that which most closely matched the colour of the previously selected cap and so on until all caps were placed in sequence. No time limit was enforced and no practice session was given.

The sequence of arranged cap numbers is recorded and plotted on a circular score chart, with a line drawn from the reference cap through the number sequence generated by the cap arrangement as shown in figure 2.1. Perfect cap arrangement produces a circular recording. Errors in arrangement result in the line crossing the circle. The direction of these crossings is compared to the defect specific confusion axes on the chart, giving an indication of the type of defect experienced by the participant.

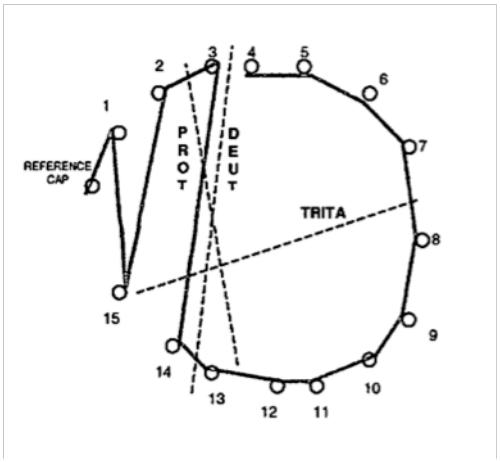

Figure 2.1. A score chart showing the following cap arrangement - reference cap, 1, 15, 2, 3, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4. The errors shown run parallel to the deutan confusion axis.

This method of analysis does not produce a numeric score suitable for statistical analysis[175], however several authors have developed ways of quantitatively scoring the results of the D-15 and D-15ds[175, 176]. The test was scored using the

Confusion Index (C-Index) and Selectivity Index (S-Index) as described by Vingrys and King-Smith[176], using colour differences scores for desaturated caps published by Geller[177]. The C-Index quantifies the degree of colour loss relative to perfect cap arrangement. The S-Index quantifies the amount of polarity in a cap arrangement. All measures were calculated using web-based automated scoring software (http://www.torok.info/colorvision/d15.htm) developed by Béla Török.

2.2.7 Peripheral visual fields

Binocular testing is thought to provide the best representation of visual function and disability related to visual field changes[178]. Participants completed a Binocular Esterman visual field examination on the Humphrey Visual Fields Analyser (HFA, Carl Zeiss Meditec Inc, USA). This test has been used widely in the study of visual function in glaucoma[179-181].

The test was carried out in a darkened room without spectacle correction. 120 points are examined with a 10dB white Goldman III stimulus using a suprathreshold approach. Test points extend up to 160° horizontally, 50° below and 30° above fixation. Test locations are biased towards central and inferior visual field, as these are thought to be the most functionally significant areas[178]. Each location is initially tested once. Missed points are re-examined once and deemed unseen if they are missed twice. Reliability is monitored automatically by false positive and false negative responses. Plots with false negative or false positive rates greater than 33% were considered unreliable. Fixation cannot be reliably monitored in binocular mode. The Esterman efficiency score (percentage of points seen) was used as a measure of peripheral visual field function.

2.2.8 MP-1 Microperimeter

Microperimetry and fixation assessment was performed using the MP-1 Microperimeter (Nidek, Italy). The MP-1, as shown in figure 2.2, comprises an infrared fundus camera that allows video fundus imaging and a liquid crystal display (LCD) to present stimuli. Retinal position is monitored throughout the examination, allowing stimuli positions to be adjusted for any retinal movement.

Both pupils were dilated with 1 drop of 1% tropicamide. If sufficient dilation was not achieved after 20 minutes, a second drop was instilled. Tests were performed on the better eye, as binocular recordings are not possible. The fellow eye was occluded.

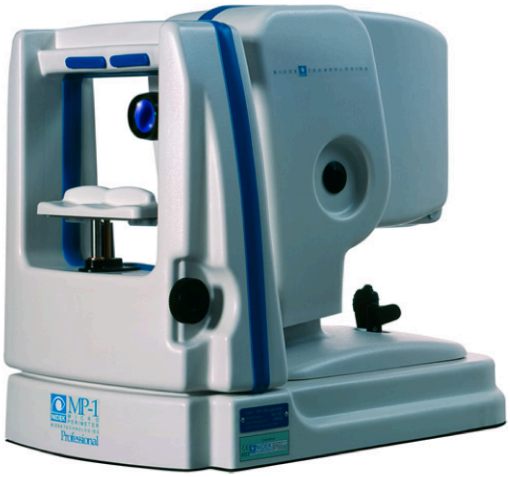

Figure 2.2. The MP-1 from Nidek Technologies (Italy), comprising an infrared fundus camera and an LCD display.

2.2.8.1 Fixation stability

The MP-1 was used to assess fixation stability. Fixation stability measurements have traditionally been performed using the Scanning Laser Ophthalmoscope (SLO)[182-184]. Agreement of fixation stability measurements derived from each instrument had not been demonstrated at the time of study design. Therefore a

pilot study was performed to ascertain whether fixation measurements from the MP-1 were comparable to those from the Rodenstock SLO-101. This experiment is described in the following chapter.

Fixation stability was assessed by asking participants to look steadily at a 2° red cross in the centre of the LCD screen whilst positioned on the chin rest with their head resting against the brow bar. The size of the cross was increased if a participant's VA prohibited its detection. An infrared fundus image was captured by the instrument's camera and a reference area of high contrast retinal features selected. During the examination, inbuilt software (MP-1 SW 1.7) tracked this reference area at a frequency of 25 Hz. If tracking of the real time image failed, co ordinates were not generated until tracking resumed. The retinal image was tracked until 30 seconds of data were generated. These data were exported for offline analysis. Bivariate contour ellipse area (BCEA) values were calculated and recorded as described in chapter 3.

2.2.8.2 Microperimetry

Microperimetry was performed using a 10-2 stimulus pattern. This pattern comprises 68 points with horizontal and vertical separation of 1° in the 10° of visual field surrounding fixation. Stimuli were of Goldman III size and were presented for 200ms whilst participants fixated a central 2° red cross. Threshold, in decibels (dB), at each point was determined using a 4-2 staircase method with an initial stimulus intensity of 10dB (12.7cd/m^2)

A colour coded sensitivity map, as shown in figure 2.3, was generated by the MP-1 software, displaying the sensitivity of the retina at each location tested. Locations

with high retinal sensitivity are represented by cool colours and those with low sensitivity by warm colours.

A local defect map, as shown in figure 2.4, displaying the difference in dB between absolute thresholds and age-corrected normal values at each test point was also generated. It uses a similar colour-coding scheme, classifying test locations as 'normal', 'suspect', 'relative scotoma' or 'absolute scotoma'. Negative values represent points with lower than normal sensitivity and positive value show locations with higher than normal sensitivity.

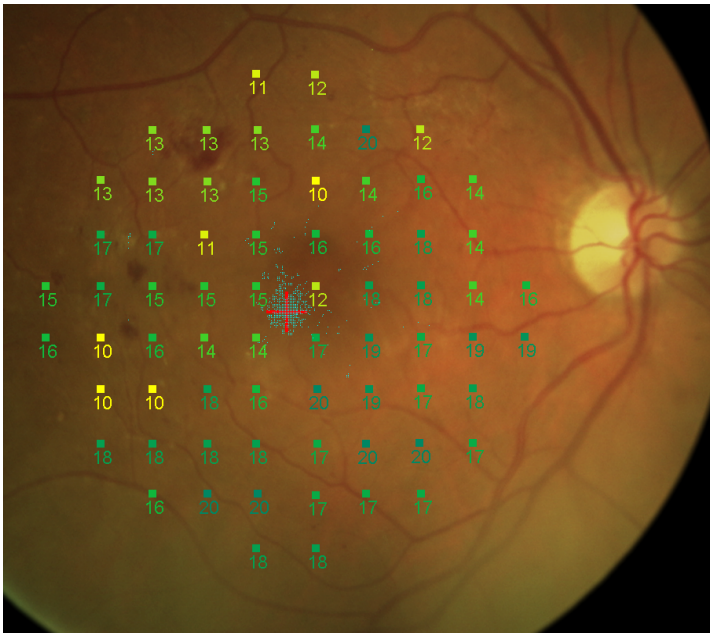

Figure 2.3. Retinal sensitivity map. A colour coded map displaying the 68 stimuli positions and their associated sensitivities overlaid on a retinal image. Locations with high retinal sensitivity are represented by cool colours. Low sensitivities are represented by warm colours. The threshold value, in dB, is shown directly below the coloured point.

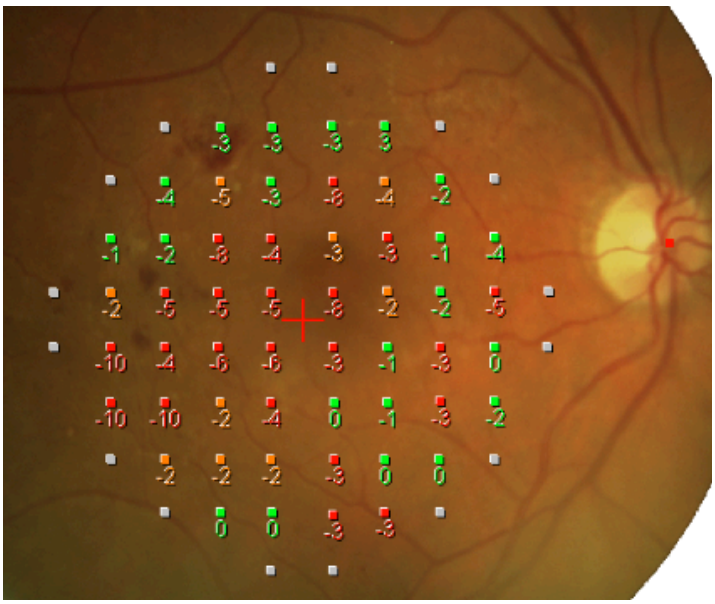

Figure 2.4. Local defect map. A colour coded map displaying the difference in dB between absolute thresholds and age-corrected normal values at each test point. Negative values represent points with lower than normal sensitivity. Positive values represent points with higher than normal sensitivity.

Mean sensitivity (of all tested points) and mean defect (of all tested points) was recorded for all participants. In addition, central mean sensitivity (average of the central 16 points) and paracentral mean sensitivity (average of all points excluding the central 16), as described by Chen were also recorded[185]. Lastly, scotoma size was defined as the number of relative and absolute points within each plot.

2.3 Summary of visual function variables

The baseline visual function assessment gave rise to 18 variables (table 2.1), referred to in this thesis collectively as 'visual function variables'.

Visual function variables	Measurement units
Habitual distance acuity	LogMAR
Corrected distance acuity	LogMAR
Contrast sensitivity	Log units
Habitual near acuity	N notation
Habitual large reading speed	wpm
Habitual small reading speed	wpm
Corrected reading acuity	LogMAR
Corrected peak reading speed	wpm
Corrected critical print size	LogMAR
Confusion Index	Ratio value
Selectivity Index	Ratio value
Esterman efficiency score	%
Mean sensitivity	dB
Mean defect	dB
Central mean sensitivity	dB
Paracentral mean sensitivity	dB
Scotoma size	Number of points
Log BCEA	Log min arc^2

Table 2.1. Summary of the 18 visual function variables recorded at the baseline visual function assessment. LogMAR = logarithm of the minimum angle of resolution, wpm = words per minute, % = percentage, dB = decibels, BCEA = bivariate contour ellipse area, Log min arc^2 = logarithm of minutes of arc squared.

2.4 Demographic and clinical variables

Demographic (sex, age, ethnicity (according to ethnic groups used in the UK census)) and clinical information (type of diabetes, duration of diabetes and duration of diabetic eye disease) were recorded from patient's hospital notes. Where details were missing from notes, information was verbally provided by the participant.

2.5 Visual ability evaluation

Within one week of the baseline assessment, a trained research assistant (HR) contacted participants by phone to administer the Activity Inventory (AI)[186]. A copy of the AI and the administration instructions used is provided in Appendix III. The AI is a well validated, Rasch analysed, patient reported outcome measure (PROM), previously validated for telephone administration[187]. Before completing the AI, participants were instructed on how to answer the questionnaire with a practice question asked to verify understanding.

The AI examines 50 goals divided into 3 objectives: social functioning, recreation and daily living. Examples of goals include reading the newspaper, entertaining guests and dressing oneself. Respondents first rated the importance of each goal with 4 possible responses ranging from 'not important' to 'very important'. Goals rated 'not important' were skipped, but for all other goals the participant was asked to rate its difficulty on a 5 point scale ranging from 'not difficult' to 'impossible without help'. Administration of the AI took between 15 and 30 minutes.

The difficulty responses were Rasch analysed to produce a continuous measure of visual ability, which we refer to here as the AI score. A detailed description of the Rasch analysis procedure and validation of our specific method of analysis is given in chapter 4.

2.6 Data input and storage

Three separate password protected databases were designed in Microsoft Office Access (Version 7.4): the first for confidential patient details including demographic and clinical data, the second for anonymised baseline visual function data, and the third for anonymised AI response data. AI response data entry was single entry. 10% of data were retrospectively selected at random using a random number generator and double entered to check accuracy of data input.

On completion of data collection, data were exported to 2 statistical packages, JMP (version 9, SAS Institute Inc. NC, USA) and SPSS (Version 19, SPSS Inc., Il., USA). In each programme, a data table was produced containing all demographic, clinical, visual function and visual ability data.

2.7 Analysis plan

Univariate analyses were performed in JMP. Multivariate analyses were performed in SPSS. Results were considered significant if $p < 0.05$.

The distributions of all demographic, clinical, visual function and visual ability variables were examined for normality using the Shapiro Wilk W test and transformations made where appropriate.

2.7.1 Aim 1 – To explore the impact of disease severity on visual function

Univariate analyses were used to investigate the influence of demographic (sex, age at recruitment) and clinical variables (type of diabetes, duration of diabetes and duration of diabetic eye disease) on each visual function variable in turn. Regression analysis was used for continuous variables and ANOVA for categorical variables.

Associations between each visual function variable and disease severity were examined by Analysis of Covariance (ANCOVA), adjusting for the demographic and clinical variables described above.

2.7.2 Aim 2 – To explore the impact of disease severity on visual ability

Univariate analyses were used to investigate the influence of demographic and clinical variables on AI score using regression analysis for continuous demographic variables and ANOVA for categorical demographic variables.

Associations between visual ability and severity were examined by ANCOVA, adjusting demographic and clinical variables.

2.7.3 Hypothesis – The reduction in visual ability associated with increasing disease severity is explained by visual deficits

Multiple regression techniques were employed to establish whether the reduction in visual ability associated with disease severity was explained fully by the associated reduction in visual function. These techniques are described more fully in chapter 5.

Chapter 3 – Comparison of the Rodenstock Scanning Laser Ophthalmoscope and Nidek MP-1 in the assessment of fixation stability

3.1 Introduction

For many years fixation stability has been measured with the Scanning Laser Ophthalmoscope (SLO, Rodenstock, Germany). Since its introduction in the early 1980s, it has been used in numerous studies of fixation[69, 70, 77, 182-184, 188, 189], and has proved particularly useful in the examination of fixation in those with eye disease[69, 70, 72, 77, 182, 184, 188, 190]. Though the instrument was not specifically designed to measure fixation, different methods have been described to allow its quantification[69, 184, 188, 190]. One established method follows that first described by Steinman, whereby the position of each fixation point is plotted on Cartesian axes and the elliptical area encompassing a given percentage of points is calculated[191]. This bivariate contour ellipse area (BCEA) presents a value of fixation stability, with smaller values indicating more stable fixation.

The SLO is no longer commercially available and as such is increasingly difficult to service and repair. In recent years, new instruments have been developed with the capacity to assess fixation: the MP-1 Microperimeter (Nidek, Italy), the SLO/OCT (Optos, USA) and the MAIA Microperimeter (Centrevue, Italy).
The MP-1 offers classification of fixation stability based on the system described by Fujii and colleagues, whereby fixation is termed 'stable' if more than 75% of

fixation points fall within a 2° diameter circle centred on the gravitational centre of all fixation points, as 'relatively unstable' if fewer than 75% of fixation points fall within a 2° circle but more than 75% are located within a 4° diameter circle, and as 'unstable' if fewer than 75% of all fixation points fall within a 4° diameter circle[192]. The lack of scientific foundation to this classification has been criticised in the literature[193, 194]. It fails to allow for the elliptical nature of fixational eye movements[194, 195], or the multimodal patterns of fixation often seen in those with macular disease[194, 196-198]. The Fujii system is reductionist, condensing large amounts of information to a broad classification, losing measurement precision. For example, a significant functional difference exists between someone who maintains 75% of fixations within 0.5° and someone who maintains 75% of fixation between 2°, yet they would both be deemed to have 'stable' fixation[194].

It is possible however to extract raw fixation data from the MP-1, thus allowing fixation points to be plotted and characterised by a BCEA value as described above. A lack of correlation between reading speed and fixation stability as classified by the inbuilt MP-1 strategy has been previously been demonstrated, whereas quantifying fixation by calculating a BCEA yielded a stronger correlation[194]. Additionally, as a continuous measurement, BCEA values can be subjected to more powerful statistical techniques than the ordinal categories offered by Fujii. Therefore, BCEA measurement is the preferred method of fixation stability assessment in this detailed study of visual function in persons with diabetic eye disease.

This laboratory is fortunate to have an SLO and MP-1 available, each having previously been used in the study of fixation[194, 199]. It was anticipated that the

baseline visual function testing phase of this PhD study would last between 12 and 18 months. It was imperative that any instrumentation used would remain operational throughout this period. Due to the lack of technical support for the SLO, it was felt the MP-1 would be more reliable. However no comparison of BCEA values derived from the SLO and MP-1 had been published at the outset of this PhD. Therefore in order to validate the use of the MP-1 over the SLO, a preliminary experiment was conducted comparing BCEA values from each instrument in those with normal sight and diabetic maculopathy, in order to determine whether BCEA values derived from the MP-1 can be considered comparable to those from the SLO[200].

This work has been published in Investigative Ophthalmology and Vision Science (Appendix IV).

3.2 Methods

Participants were recruited into two groups: patients with diabetic maculopathy and normally sighted volunteers. Patients were recruited from medical retina clinics at Moorfields Eye Hospital, London. All had been diagnosed with Type 1 or Type 2 Diabetes Mellitus for at least 1 year and had recently been diagnosed with diabetic maculopathy according to the National Grading Protocol (NGP) of at least grade M1. This is defined as having one or more of the following features: exudates within 1 disc diameter (DD) of the centre of the fovea; circinate or group of exudates within the macula; retinal thickening within 1DD of the centre of the fovea; any microaneurysm or haemorrhage within 1 DD of the centre of the fovea

only if associated with a best VA of ≤ 6/12[51]. Normally sighted volunteers were all hospital staff.

Written informed consent was obtained from all participants once an explanation of the nature and possible consequences of the study had been explained. The research was approved by the Moorfields and Whittington research ethics committee and conformed to the Declaration of Helsinki.

3.2.1 Fixation stability measurement

Fixation stability was recorded for each individual on both instruments in a counterbalanced order. All measurements were taken from the better eye with the fellow eye occluded whilst the head was stabilised between a chin and forehead rest. The same researcher (HD) operated both instruments.

3.2.1.1 Scanning Laser Ophthalmoscope

The SLO consists of a helium-neon laser of wavelength 632.8 nm which produces the stimuli and an infrared laser of 780 nm that simultaneously images the fundus using a confocal principle [201]. Images were captured on a professional digital video recorder at a resolution of 768 x 576 pixels, (JVC model BR-DV600E, Japan) and frequency of 12.5 hertz (Hz).

Software provided with the SLO (scotometry module, Rodenstock, Germany) was used to produce a 1° red cross fixation target. Subjects were asked to view the centre of the cross until 10 seconds of relatively blink free data were obtained. The digital video recorder simultaneously recorded fundus images throughout.

Video images were digitised using a frame grabber (Orion Frame Grabber, Matrox, Montreal, Canada) and retinal position was retrospectively analysed using software developed in-house. The software automatically tracked fundus features within a delineated square of predetermined location on the retinal image at 12.5 Hz, producing x and y co ordinates of its position in pixels. If tracking was lost, the square jumped to the extremity of the image and unrealistic co ordinate values were produced. Any such co ordinates were manually deleted, with complete trials being discarded if more than 20% of co ordinates were deleted for this reason.

The SLO was calibrated to quantify the amount of retinal movement shown in the captured fundus image. A semi-silvered mirror was placed in front of the SLO allowing external targets to be viewed on the same visual axis as the SLO. Two cross targets of known horizontal separation were placed on the wall parallel to the observer's line of sight. The distance between the targets and the semi-silvered mirror was recorded and therefore the angular separation of the crosses could be calculated. An observer with normal vision was instructed to look steadily at one target for 10 s and then switch to the second target for a further 10 s. Fundus images were simultaneously recorded. The position of a retinal landmark was tracked, recording eye position in two dimensional pixel coordinates. The horizontal movement of the retinal image between the two positions in image pixels was determined and used in a simple transformation with the angular separation of the two crosses to describe the retinal motion seen on SLO recording in terms of visual angle. The resultant conversion factor; 1 pixel : 2.6 min arc was used in all SLO BCEA calculations. As pixels within the central 5°

of the SLO screen have been shown to be square with respect to the retina[202], this conversion factor is applicable in both the horizontal and vertical plane.

3.2.1.2 MP-1 Microperimeter

The MP-1 comprises an infrared fundus camera and a liquid crystal display (LCD) that presents stimuli to the observer.

A 1° red cross was displayed on the centre of the LCD screen and subjects were asked to view the centre of the cross. Fixation measurement was performed using the techniques recommended by Nidek. First a reference image of the fundus was captured and a reference area of high contrast retinal features selected. During the examination, inbuilt software (MP-1 SW 1.7) tracked this reference area, calculating any shift in its position between the reference image and subsequent frames within the image at a frequency of 25 Hz, producing x and y co ordinates of retinal position in degrees of visual angle. If tracking of the real time image failed, co ordinates were not generated until tracking resumed. Nidek calculates the degree to pixel ratio of each individual instrument, found to be 1 : 15.714 at the most recent service. Ten seconds of tracked data were collected and exported for off-line analysis.

3.2.2 BCEA calculation

The BCEA encompassing 68% of fixations was calculated using the formula:

$$BCEA = 2.28\pi\sigma_H\sigma_V(1-\rho^2)^{1/2}$$

where σ_H and σ_V are the standard deviations of fixation position in the horizontal and vertical meridia respectively and ρ is the product-moment correlation of these two components[191]. BCEA values in minutes of arc squared were normalised with a log transform.

3.2.3 Data analysis

BCEA values from participants in each group were analysed separately. The correlation between BCEA values from each instrument was calculated using orthogonal regression[203], a least squares techniques that fits a straight line allowing for error in both the x and y variable. Agreement between values was also assessed using the techniques described by Bland and Altman, whereby the difference between the two measurements is plotted against their mean, revealing the magnitude of any difference between measurements[204].

3.3 Results

37 participants were recruited. The 16 normally sighted volunteers (6 male and 10 female, age range 21 to 41 years) had visual acuity of 0.0 logMAR (6/6) or better. The 21 (14 male and 7 female, age range 24 to 77 yrs) subjects with diabetic maculopathy had a median visual acuity of 0.2 logMAR (6/9) and interquartile range (IQR) of 0.1 – 0.3 logMAR (6/7.5 – 6/12). All participants had a refractive error of between -6 and +4 DS spherical equivalent.

Complete data were obtained from 28 subjects (14 in each group). The 9 cases with incomplete data all arose from technical problems with the SLO; 4 cases of

He-Ne laser failure and 5 cases where tracking software failed to track recorded images accurately. Analysis was carried out on complete data only.

3.3.1 Normally sighted volunteers

Median BCEA value for SLO was 201 min arc^2 (IQR 80 – 415) and for MP-1 was 303 min arc^2 (IQR 173 – 541). Mean log BCEA value for SLO was 2.26 log minarc^2 (range 1.51 – 2.91, standard deviation (SD) 0.44) and for MP-1 was 2.51 log minarc^2 (range 2.05 – 3.21, SD 0.30). Figure 3.1 shows SLO versus MP-1 log BCEA values. A weak correlation was found (r=0.33) but this was not significant (p > 0.05).

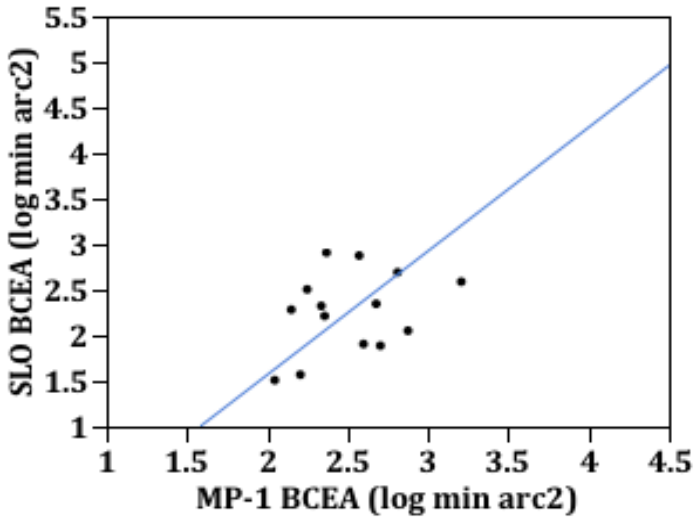

Figure 3.1 SLO versus MP-1 log BCEA values for subjects with normal vision. The orthogonal regression line is shown.

On average SLO log BCEA values were smaller than their MP-1 counterparts by 0.25 log minarc^2, the difference failing to reach significance (matched pairs; p=0.06). This is shown graphically in figure 3.2 with the difference between values from both instruments plotted against their mean. The solid horizontal

line represents the mean difference and the dashed lines ± 1.96 SD around the mean.

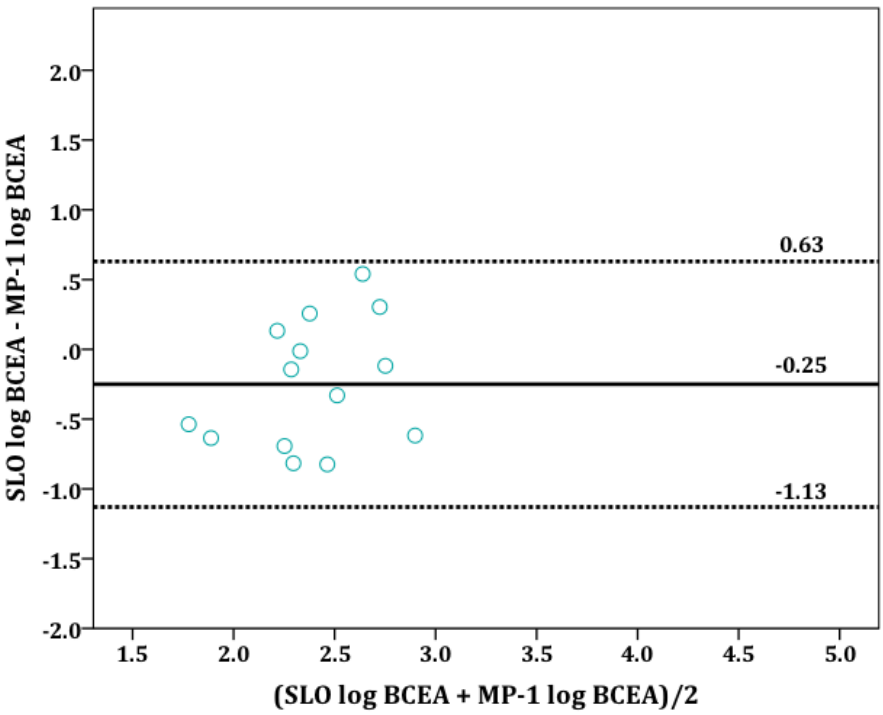

Figure 3.2 Difference between SLO and MP-1 log BCEA values plotted against their mean for subjects with normal vision. Solid horizontal line = mean difference between 2 values. Dashed lines = ± 1.96 SD around the mean.

3.3.2 Diabetic maculopathy subjects

Median BCEA value for SLO was 453 min arc^2 (IQR 359 – 2770) and for MP-1 was 615 min arc^2 (IQR 209 – 2350). Mean log BCEA value for SLO was 2.90 log minarc^2 (range 2.03 – 4.05, SD 0.60) whilst for the MP-1 was 2.94 log minarc^2 (range 1.90 – 5.44, SD 0.88). A slightly stronger correlation was seen between the two sets of values (r=0.42) as shown in figure 3.3, but again this did not reach significance ($p > 0.05$).

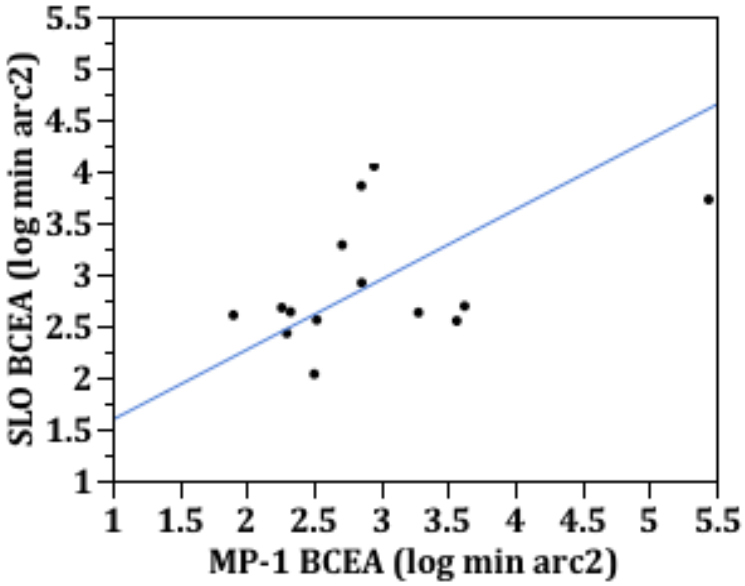

Figure 3.3 SLO versus MP-1 log BCEA values for subjects with diabetic maculopathy. The orthogonal regression line is shown.

On average MP-1 and SLO log BCEA values were very similar, with SLO only slightly smaller by 0.04 log minarc^2. This small difference was not significant (matched pairs; $p = 0.88$). Figure 3.4 shows this graphically.

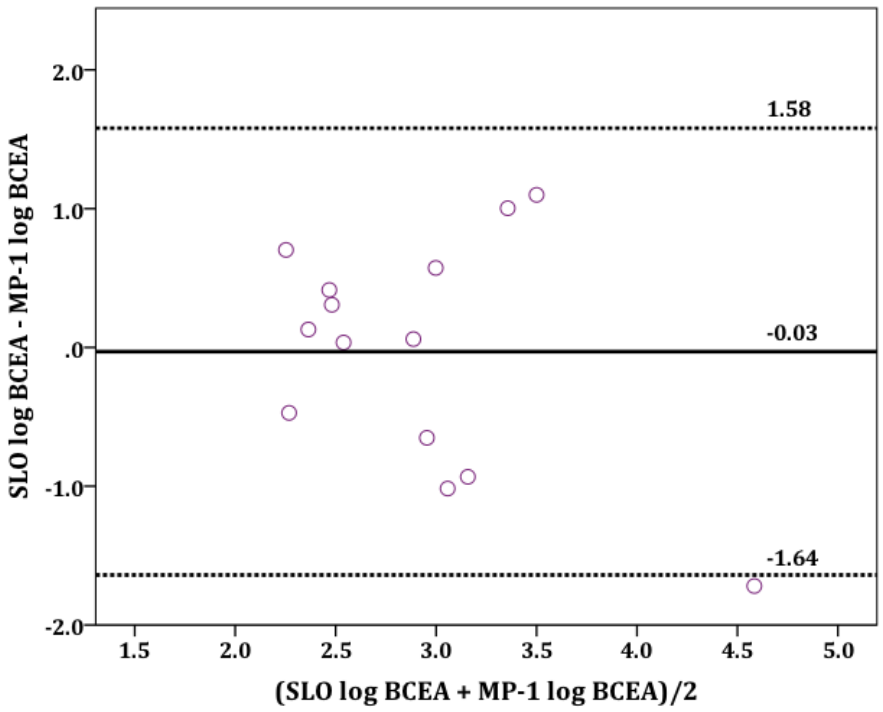

Figure 3.4 Difference between SLO and MP-1 log BCEA values plotted against their mean for subjects with diabetic maculopathy. Solid horizontal line = mean difference between 2 values. Dashed lines: = ± 1.96 SD around the mean.

3.4 Discussion

On average, no significant difference in SLO and MP-1 BCEA values existed in those with normal vision or diabetic maculopathy. The correlation between BCEA values from the two instruments was weak in both study groups, though slightly stronger over the larger range values recorded in those with diabetic maculopathy, likely due to the extended range of measurements obtained.

Moderate agreement has previously been reported between SLO and MP-1 fixation assessments in eyes with retinal disease, though the means of quantifying fixation differed significantly from our method[205]. MP-1 fixation was classified by the inbuilt system described above[192], whilst SLO fixation was deemed 'stable' if the standard deviation of fixation points around the mean fixation point was less

then 0.6°; 'relatively unstable' if the standard deviation was between 0.6° and 1.2° and 'unstable' if greater than 1.2°. Agreement between methods was determined using Cohen's κ coefficient. Additionally fixation was assessed during microperimetric examination, compared to our isolated fixation task. Earlier work by the same author noted steadier fixation during an isolated task than during microperimetry[188].

A significant correlation between MP-1 and SLO fixation assessments in patients with macular disorders has also been observed, however again the quantification method differed considerably between each instrument. MP-1 fixation was quantified by 'mean extent'; that is double the square root of the product of the x and y degree positions of fixation points, whilst SLO fixation was calculated as the percentage of fixation points within the central 2° on SLO measurement[206].

Due to notable differences in outcome measure, the findings from these studies cannot be directly compared to the results presented here.

3.5 Conclusion

As fixation stability is of more interest clinically in those with macular pathology, we were encouraged to find such small differences between values in those with diabetic maculopathy.

The assumption that the MP-1 would be operationally more reliable was confirmed, with all 9 cases of incomplete data arising from technical problems with the SLO. In contrast the MP-1 was operational throughout.

The similarity between BCEA values, together with the consistent and reliable operation of the MP-1 support its use as a valid alternative to the Rodenstock SLO in the assessment of fixation. Therefore all fixation examinations in the baseline visual function assessment described in chapter 2 were performed using the Nidek MP-1.

Chapter 4 – Development of the Activity Inventory and Rasch analysis of response data

As described in chapter 2, all participants completed the Activity Inventory (AI)[120]. This chapter provides a more complete description of the AI and the rationale for its selection as the primary outcome measure in this study. Additionally, a description of the analysis techniques employed in the conversion of qualitative response data to a continuous measure of visual ability is provided.

4.1 Primary outcome measure selection

As introduced in Chapter 1, many vision related patient reported outcome measures (PROMs) exist. Consequently, care needs to be exercised in the selection of the most appropriate PROM for a given study[110].

PROMs have been developed for different target populations including those with cataract[124, 207], age related macular degeneration[208], retinitis pigmentosa[209, 210], Graves' Ophthalmopathy[211] and visually impaired patients[111, 122, 123, 159]. Additionally, they attempt to measure various constructs including vision related quality of life[111], restriction of participation in daily activities[123], visual functioning[122] and visual ability[120]. As low vision rehabilitation aims to improve a person's ability to perform vision related tasks[152], only the use of a visual ability or visual functioning questionnaire was considered for this study.

Furthermore, substantial variation in the psychometric quality of available PROMs has been demonstrated[109], with many instruments treating raw scores as interval measurements. Employing Rasch analysis in the development of a PROM promotes high psychometric quality[114].

Therefore based on the selection guide published by Pesudovs and colleagues[110], consideration was given to PROMs developed for a visually impaired population, measuring visual ability or visual functioning, developed using Rasch techniques. Of those, only the AI had previously been validated for use in a diabetic population[143]. Additionally, the AI has been successfully used in study of an National Health Service (NHS) low vision clinic appointment[107]. Therefore it was deemed the most appropriate instrument available at the time of study design.

4.2 The Activity Inventory

The AI is an adaptive visual ability questionnaire. Its development can be traced back to the 1990s when Massof proposed a systems model for low vision rehabilitation[212, 213]. A hierarchical structure, the Activity Breakdown Structure (ABS) was identified to describe the activities that constitute an individual's life state. These activities were divided into the objectives they serve. Objectives were subdivided into particular goals that must be achieved in order to reach each an objective. Furthermore, each goal was subdivided into a series of tasks that must be performed in order to achieve each goal. For example, the goal of 'cooking daily meals' would come under the objective 'daily living activities'. A number of tasks may have to be accomplished in order to cook a meal, such as

'read a recipe', 'chop food' or 'set oven dial'. The ABS structure can be applied to the World Health Organisation International Classification of Functioning, Disability and Health[88]. Difficulty completing goals is analogous with WHO ICF 'activity limitation' whereas problems achieving objectives is analogous with 'participation limitation'[120]. Tasks are not specifically represented within the WHO ICF.

Relevant objectives, goals and tasks were determined by a retrospective chart review of more than 3,200 patients[213]. Twenty-four frequently cited activities were identified and classified as goals under 3 objectives: daily living, social functioning and recreation. In addition, more than 200 activities were identified and classified as tasks underpinning these goals. An early version of the instrument was produced and administered to 445 low vision patients in a pilot study[213]. Throughout the study, participants were asked to indentify any additional relevant activities not already included. Participants were asked to rate the importance of each goal under an objective. Importance response ratings ranged from (0) 'not important', (1) 'slightly important', (2) 'somewhat important', (3) 'moderately important', (4) 'very important' to (5) 'extremely important'. Any goal with an importance rating greater than 0 was further rated according to its difficulty. Difficulty response ratings ranged from (0) 'not difficult', (1) 'slightly difficult', (2) 'somewhat difficult', (3) 'moderately difficult', (4) 'very difficult', (5) 'extremely difficult or impossible'. If a goal's difficulty rating was greater than 0, participants also rated the difficulty of the tasks serving said goal in the same manner. In this sense, the AI is an adaptive questionnaire; participants rate the importance of each goal, but only the difficulty of those goals

important to them and the difficulty of those tasks serving goals that are at least somewhat difficult.

Rasch analysis, discussed below was used to convert categorical responses to an interval measurement visual ability scale. The instrument was subsequently modified to incorporate 50 goals (459 tasks) and was validated on a group of 1,880 consecutively recruited low vision patients[186]. To date, Massof and colleagues have administered the AI to over 3,500 visually impaired patients (R.W. Massof, Personal communication, June 2011).

The AI can be administered to goal level only (asking only about the importance and difficulty of goals) or to task level (additionally asking about the difficulty of tasks related to difficult goals). Agreement between visual ability measures derived from goal and task level versions of the AI has been shown[186].

4.3 The Rasch model

The Rasch model, developed by Georg Rasch in the 1950s, is a stochastic model that describes the transformation of ordinal data into interval measures and tests the extent to which the data fit the model[115, 119, 214]. Initially developed to deal with dichotomous data (i.e. yes/no), it was later extended to incorporate polytomous data, such as that gathered by rating scale questionnaires[215, 216].

The Rasch model, when used to analyse response data from visual ability questionnaires, provides estimates of the visual ability of a person (person measure) and the visual ability required to complete a task (item measure).

Person and item measures are not directly observed and as such are said to be 'latent'. Latent traits are inferred from observations of manifest behaviour, like assigning a response category to a particular goal in the AI[217].

4.4 Response categories

Items within a visual ability questionnaire typically have a standard format with a question (item) and a range of possible responses on a Likert scale[218], for example:

How **important** is it for you to (enter a given goal)?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How **difficult** is it for you to (enter a given goal)?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

As shown above, responses often have numbers assigned to each category. These numbers simply represent the ordinal categories represented in the rating scale; they do not represent measurements on an interval scale[115]. Investigators however sometimes treat them as such, computing the average or sum of these numerals, or raw scores as a 'measurement' of the trait under scrutiny. In fact, most VRQoL questionnaires were initially developed on this premise, using the principals of Classical Test Theory (CTT)[219] to validate the measures produced[108, 109].

However, CTT makes some inappropriate assumptions. It treats raw scores as interval measures, rather than the ordinal values and assumes that all items are equally difficult[220]. These issues can be addressed by the application of Rasch analysis.

4.5 Interval values

On an interval scale, the difference between 4 and 6 is the same as the difference between 98 and 100. The assignment of consecutive numbers to response categories, as shown above, gives a false impression of interval scaling[221]. For example, using them in arithmetic operations assumes that the difference between (0) 'not difficult' and (1) 'slightly difficult' is exactly equal to the difference between (3) 'very difficult' and (4) 'impossible'. Furthermore, that the ability required to report (1) 'slight difficulty' with a goal is exactly half that required to report (2) 'moderate difficulty' and exactly one fifth of that required to report that a goal is (5) 'impossible'. This does not seem reasonable.

At the turn of the 20th century, Thorndike demonstrated mathematically [221, 222] that the difference between one rating category and the next does not always reflect an equal change in the underlying construct of interest.

4.6 Hierarchical structure

Summing item raw scores assumes all items are equally difficult[223, 224]. This assumed equal difficulty of items is practically counterintuitive. Completion of

some items requires more visual ability than completion of others. Sewing is inherently more visually demanding than watching television, yet if a person reports (1) slight difficulty with each, summing these raw scores gives equal credit to both items. Additionally, different items will be relevant to different people. Using raw scores, a person who deemed only easy items important because they had giving up trying to do more difficult items due to their vision, could in theory receive the same total raw score as someone who deemed only difficult items important, yet they would receive the same visual ability score.

These examples demonstrate that ordering items according to the sum of the difficulty raw scores given by each person does not guarantee that items will be ordered according to their difficulty, or that person will be ordered by their ability; hence the scale described by the items does not have a hierarchical structure.

4.7 Rasch analysis

4.7.1 Estimation of measures

Rasch analysis estimates person measures independently of the selection of items responded to and item measures independently of the sample of people who attempted the item[214]. It also provides estimates of the average threshold functional reserve required for each response category[214]. Functional reserve refers to the difference between the ability of the person and the ability required to respond with a given category[217].

Interval measures are achieved using a logarithmic transformation[214]. The probability of completing an item is divided by the probability of not completing it, giving an odds ratio between 0 and positive infinity. Applying a logarithmic transformation to this ratio provides a log odds or logit value, extending the possible range of values from minus infinity to positive infinity[214, 221]. Therefore, logit values increase linearly with the underlying construct, ensuring differences are meaningful across the whole of the range[221].

4.7.2 Precision of measures

Rasch analysis produces measures of item and person reliability and separation. Person reliability reflects the portion of variance observed in person measures that is attributable to true differences between persons and not due to errors in estimation. Similarly, item reliability represents the portion of variance observed in item measures that is attributable to true differences between items. Reliability improves as the value approaches 1[217].

Separation (also referred to as the G coefficient) reflects the precision with which true variability in the persons or items is sampled by the test [110, 214]. It is expressed as the ratio of the true standard deviation (SD) to standard error (SE) of person or item measures. Separation has practical value in that it can be used to calculate the number of statistically distinct strata into which the measures can be divided[217]. Based on the premise that the range of item measures is ±2 SDs wide and a statum is 3 SEs wide, if the range of item measures is 4G SEs wide, then there are (4G+1)/3 statistically distinct strata[216]. The same is true of person measures. Therefore the larger the separation, the more strata measures can be divided into and the more we can separate items on the basis of their difficulty

and people on the basis of their ability. Separation greater than 2 suggests measures are significantly different across the measurement distribution[110, 214].

4.7.3 Validity of measures

The Rasch model assumes unidimensional measurement[217, 221]. Rasch analysis tests the degree to which responses fit the ideal of a unidimensional construct[214]. Fit statistics are produced which reflect differences between the responses obtained and those expected by the model, with respect to person, item and category threshold measures.

These differences, or residuals are squared. The mean of the squared residuals, standardised by their variance is used to calculate 2 fit statistics: the 'Information weighted fit statistic ' or Infit MNSQ and the 'Outlier sensitive fit statistic' or Outfit mean square (MNSQ)[214, 217]. Outfit and Infit MNSQ values are produced for every person, item and category threshold measure. A person fit statistic refers to the fit of that person's responses to the model. An item fit statistic refers to the fit of responses given to that item to the model. A category fit statistic refers to the fit of responses of a given category to the model.

Infit and outfit statistics adopt slightly different techniques for assessing model fit. Infit gives more weight to the responses of persons whose ability is close to the item measure (or items close to the person measure) as a person whose ability is closer to the item's difficulty should give a more sensitive insight into that item's performance. The Outfit is not weighted, and therefore is more sensitive to influence of outlying scores. Therefore analysts routinely pay more attention to Infit scores [214]. Aberrant Infit scores usually cause more concern.

The expected value of both Outfit and Infit MNSQ is 1, ranging from 0 to positive infinity. Positive values indicate that the variance of actual responses is greater than that expected by the model. Negative values indicate that the variance of actual responses is less than that expected by the model[214]. Practically, the percentage unexpected variance can be calculated as

(Fit statistic value – 1) x 100

where a positive value indicates x% more unexpected variance in the actual responses and a negative values indicates x% less unexpected variance in the actual responses[214].

Interpretation of fit statistics relies on an understanding of the context within which the measurements were made and as such Wright and Linacre offer guidelines on acceptable ranges of values within specific contexts[214, 225]. Values between 0.6 and 1.4 are deemed acceptable in rating scale surveys.

The extent to which responses produce a unidimensional measurement is examined by Principal Component Analysis (PCA) of model residuals. The amount of raw variance explained by the measures and the amount explained if responses had exactly matched the expectations of the Rasch model are calculated. Rasch PCA looks for patterns within the residuals that do not fit with Rasch expectations, demonstrating contrasts between opposing factors rather than loadings on one factor[226]. If the eigenvalue of the first contrast within the residuals is greater than 2, a second dimension may be present[226]. Massof published results of PCA on the AI responses of 1880 low vision patients and

demonstrated that the first principle component accounted for 78% of the variance, however the first contrast had an eigenvalue of 3.9. Massof argues that visual ability measured by the AI has a composite nature incorporating a reading and mobility dimension, however visual ability can be regarded as a single theoretically constructed variable as the reading and mobility domains load equally on the first principle component[120, 227]. PCA on responses to the baseline administration of the AI in this study explained 58% of the variance. The first contrast had an eigenvalue of 2.9.

4.7.4 Rating scales

The quality of data obtained is greatly influenced by the construction of the rating scale used[228]. Respondents are confined to the rating categories available. The extent to which these categories allow effective communication of a person's feelings, directly influences the quality of measures produced[214]. As such, the facility of rating categories to produce meaningful, interpretable measures should be tested empirically[214].

To this end, Rasch analysis provides a series of statistics that can be used to determine whether each category has been selected enough times to provide stable measures, whether the category responses adequately fit the expectations of the model and whether the rating scale has a hierarchical structure[214].

The number of respondents choosing a particular category, summed across all items is given as the observed count. A minimum of 10 responses per category is required to produce a stable, reliable measure[214]. The distribution of responses can also be examined, with regular distributions being preferable[214].

Fit statistics are also used to assess the quality of the rating scales[214]. Infit and Outfit MNSQ values are produced for each rating category. A value greater than 2 is indicative that the given category introduces noise into the measurement procedure[214, 229].

Step measures and category threshold measures parameterise the relationship between 2 adjacent categories[230]. The Andrich rating scale model [215], an extension of the Rasch model used to deal with polytomous responses, dictates that threshold category measures are identical across all items. These thresholds should increase monotonically with the response categories, indicating that the rating scale is hierarchical[214]. Where this is not the case, the response scale is considered disordered[214, 230]. Additionally, the distance between adjacent step measures should be sufficient to indicate that each category defines a distinct portion of the variable[214]. It has been suggested that the distance between step measures should be between 1.4 and 5 logits[231].

The performance of rating scales can be examined graphically by plotting the probability of selecting a given category as a function of functional reserve. These category probability curves should demonstrate that for all values of functional reserve, one category is the most probable response[214]. Where rating categories are not performing adequately, adjacent categories may be collapsed in order to improve rating scale functioning, providing it is done in a meaningful manner[214]. The effect of collapsing categories on observed counts, step measures and category probability curves should be examined to ensure that the resultant scale functions more appropriately[214].

4.8 Rasch analysis of AI responses from this trial

The precision of estimates is reflected by their SE, derived from the number of items responded to and the number people responding to items. Larger sample sizes produce item and person measures with greater precision[217]. Item measures calculated using our sample of 100 participants are unlikely to be precise. As the AI is an adaptive questionnaire, the number of persons responding to each item will vary considerably. In fact, the median number of people responding to individual items was 65 (interquartile range 36 – 88). Therefore the precision of item estimates from our sample may be questionable.

Massof, using Rasch analysis has calibrated the item and category threshold measures for the current AI using his sample of 3,500 plus patients. The measures from this sample will be more consistent and precise than those calculated using the responses from the participants of this study. Massof suggested that his calibrated Rasch estimated measures could be employed in the analysis of response data from the present study (R.W. Massof, Personal communication, June 2011). If anchored in this way, person measures generated from the response data collected in this study will be placed along the same scale as the item measures defined by his sample of 3,500 plus patients.

To date, these item and category threshold measures have not been validated in UK patients. The ABS, on which the AI was developed, is culture-specific and should be validated within each social framework it is applied[212]. Therefore, item and category threshold measures defined in a United States (US) based sample may not be valid for our UK group. Furthermore, the two groups vary

significantly with regard to the cause of visual impairment. The US sample was a heterogeneous group of patients with a range of ocular conditions. Our UK sample has diabetic eye disease, no other significant ocular co-morbidities and was on average younger. The AI has been validated on patients with diabetic retinopathy previously, but again this was a US based sample[143].

In addition, Massof previously reported the use of some response categories was unreliable for some subjects[186]. The first version of the AI had 6 difficulty ratings described above[213]. The most current version, used in this study has 5 response categories[120]. Responses range from 'not difficult', 'slightly difficult', 'moderately difficult', 'very difficult' to 'impossible'. The current category threshold measures used by Massof collapses response categories 'slightly difficult' and 'moderately difficult', in order to improve the reliability of the response categories. Effectively, data are analysed as though only 4 response categories were used: 'not difficult', 'slightly or moderately difficult', 'very difficult' and 'impossible'.

To improve the precision of our person measures and the performance of the rating scale, we propose anchoring our data to Massof's item and category threshold measures; justifiable only if we can validate their use within our UK sample. Therefore person and item measures generated using Massof's calibrations will be compared to those generated with our data. The effect of collapsing response categories as suggested by Massof will also be investigated, as there is no guarantee that UK participants interpret and use the ratings scale in a similar fashion to those from the US.

4.9 Validation of Massof anchoring

All person and item measures were produced by Rasch analysis using the Andrich rating scale model[215]. Commercially available Rasch analysis software, Winsteps, (Version 3.72.0; Chicago, Il) was used. An unconditional maximum likelihood estimation routine was employed[226].

Response data from the baseline administration of the AI were used. Response categories were recoded so that 0 – 4 represented 'impossible' to 'not difficult' rather that not 'difficult' to 'impossible' so that person and item measures would reflect visual ability rather than difficulty (higher values equate to higher ability).

Data from 100 participants and 50 items were analysed. In the interests of clarity we will refer to measures generated with Massof's calibrations as 'anchored values' and those generated exclusively with our data as 'unanchored values'. All unanchored and anchored person measures are provided in Appendix V (table 1). All unanchored and anchored item measures are provided in Appendix VI (table 2).

4.9.1 Response category thresholds

Category observed counts, category measures, category fit statistics and step measures were calculated using both unanchored and anchored data. Category probability functions were also produced for both sets of data, displaying the probability of using each difficulty rating (category probability) as a function of the difference between person measure and item measure (functional reserve).

4.9.1.1 Unanchored response category analysis

Table 4.1 displays category observed counts, category measures, Infit and Outfit MNSQ fit statistics and step measures for the original 5 difficulty ratings in the AI. Recoded responses were used by Winsteps to provide ability rather than difficulty estimates.

AI response	Recoded response	Observed count	Category measure	Infit MNSQ	Outfit MNSQ	Step measure
0	4	1764	(2.52)	1.03	1.03	1.09
1	3	476	1.09	0.98	0.63	0.67
2	2	347	0.07	1.09	1.27	-0.36
3	1	182	-1.06	0.87	1.16	-1.40
4	0	94	(-2.71)	1.22	1.88	none

Table 4.1 Unanchored analysis. Observed count refers to the number of times each response was used across all items. Category measure is the Rasch estimated average functional reserve for a given rating. Measures in parentheses are 0.25 logits from the estimated extreme values. True category measures for extreme ratings are infinite. Infit and Outfit MNSQ values reflect how well each response category structure fits with Rasch model expectations. Step measure gives the functional reserve value (logits) at which the probability of responding with said rating is equal to the probability of responding with the next lower rating.

Figure 4.1 shows the category probability functions for each category rating.

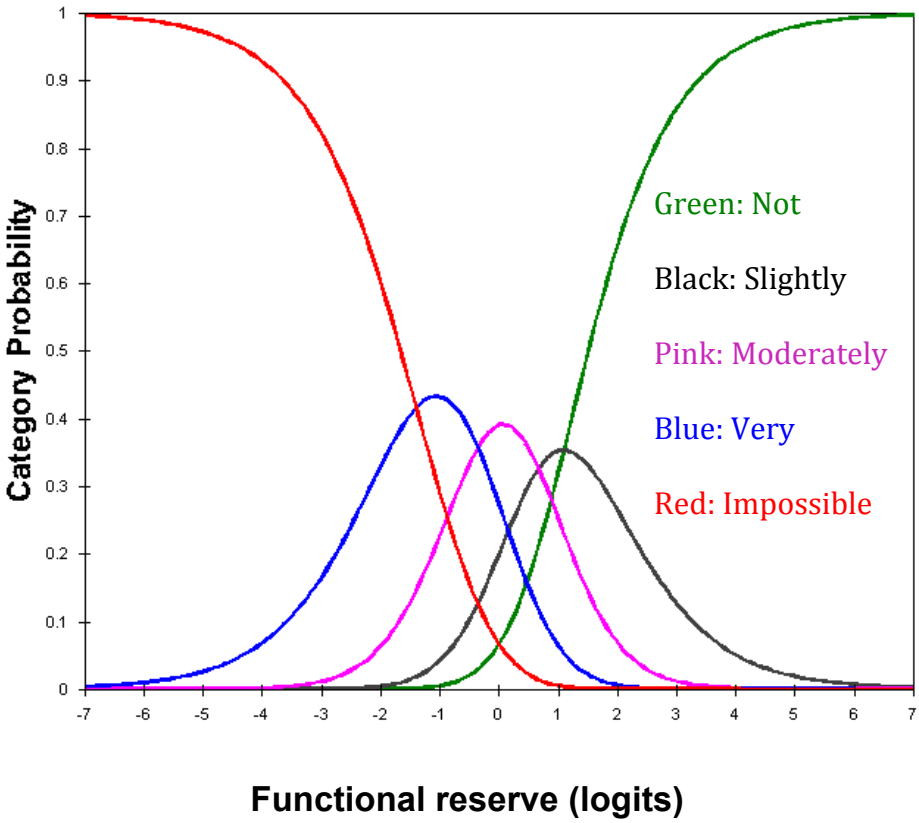

Figure 4.1. Category probability function for each rating as a function of person measure relative to item difficulty (functional reserve).

The green curve on the right represents the rating 'not difficult', black; 'slightly difficult', pink; 'moderate difficult', blue; 'very difficult' and red; 'impossible'. If each rating were being used appropriately, then for each position along the x-axis, the probability of one category would be greater than all the others. If this were the case, each of the curves would have a unique peak. Figure 4.1 illustrates that though each curve has a portion of the axis for which it is the most probable response, the peak for 'slightly difficult' (black) is somewhat obscured by the neighbouring ratings.

If ratings were being used appropriately, category and step measures would decrease with each more difficult rating. Table 4.1 shows this is the case. However, separate examination of the average person measure of those responding with each category across all items, revealed that for 10 items (20%),

the average person measure of those responding 'slightly difficult' was lower than those responding 'moderately difficult'. This suggests, that in line with the results of Massof, our sample of respondents found it difficult to accurately discriminate between the ratings of 'slightly' and 'moderately difficulty'.

4.9.1.2 Anchored response category analysis

The analysis was repeated using the anchored calibrations, collapsing the 'slightly difficult' and 'moderately difficult' categories into one. Table 4.2 displays category observed counts, category measures, Infit and Outfit MNSQ fit statistics for the collapsed category ratings. The step measures, shown in bold are those defined by the anchored values. Again, recoded responses were used.

AI response	Recoded response	Observed count	Category measure	Infit MNSQ	Outfit MNSQ	**Step measure**
0	4	1764	(2.31)	0.98	1.02	**1.04**
1+2	3	823	0.59	1.07	0.91	**-0.26**
3	2	182	-0.67	0.93	1.19	**-0.78**
4	1	94	(-2.19)	1.05	1.81	**none**

Table 4.2 Anchored analysis. Step measure in bold are those defined by the anchored values. A description of all terms is provided in the footnote accompanying table 4.1.

Figure 4.2 displays the anchored category probability functions. Collapsing categories 'slightly difficult' and 'moderately difficult' resulted in a more defined peak for each individual category. For each position along the x-axis, the probability of one category is greater than all the others. The average person measures of those who responded to each category across all items revealed the reduced scale was appropriately used for all but 3 items. This indicates that the reduced rating scale functions in a more appropriate manner.

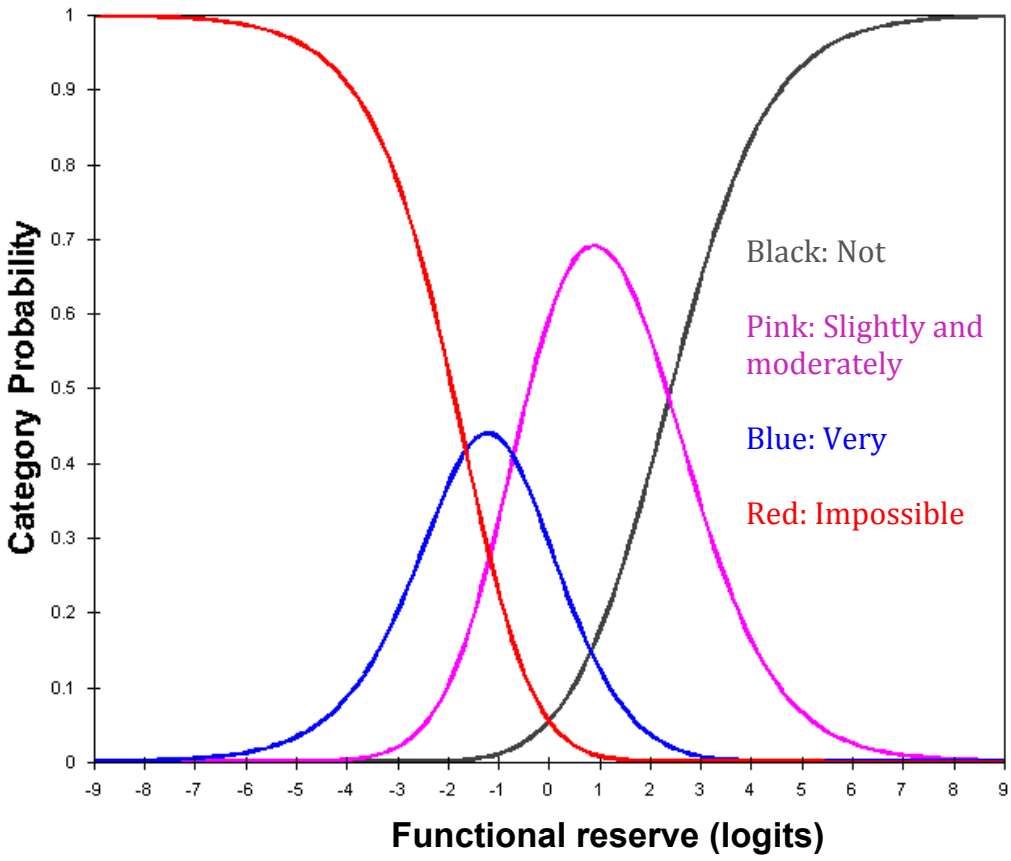

Figure 4.2. Category probability function derived from anchored analysis for each category rating as a function of person measure relative to item difficulty (functional reserve). Slightly and moderately difficult categories have been collapsed to one.

Therefore, is seems likely that US and UK based subjects interpret the response ratings in a similar way and that the most appropriate rating categories are 'not difficulty', 'slightly or moderately difficult', 'very difficult' and 'impossible'.

4.9.2 Correlation of person measures

Item and person measures were generated using both anchored and unanchored values. As both sets of values are random variables, orthogonal regression was performed. Orthogonal regression allows for variability in both the x and y variable, minimising the perpendicular distances between each point and the line

of fit. Figure 4.3 shows orthogonal regression of the anchored and unanchored person measures. Person measures from each data set were highly correlated (r = 0.99, p < 0.05).

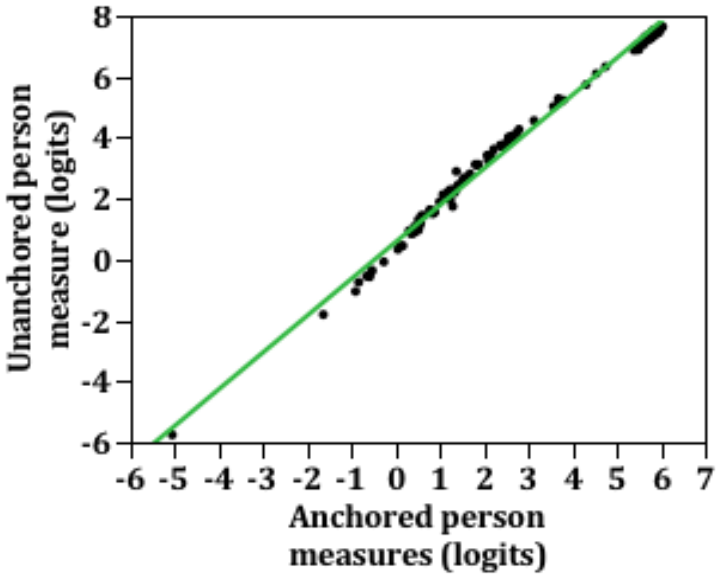

Figure 4.3. Orthogonal regression of unanchored and anchored person measures of all 100 participants (Intercept = 0.57, slope = 1.21, r = 0.99, p < 0.05).

4.9.3 Correlation of item measures

Figure 4.4 shows orthogonal regression of the anchored and unanchored item measures. Though correlation between values was high (r=0.80, p > 0.05), an obvious outlier was present (top right corner of the plot).

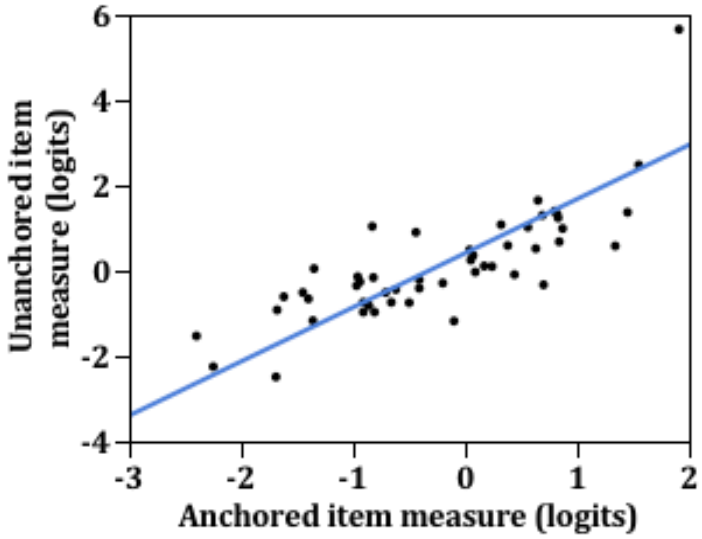

Figure 4.4. Orthogonal regression of the unanchored and anchored item measures of all 50 items (Intercept = 0.41, slope = 1.27, r = 0.80, $p < 0.05$).

The outlier corresponds to the item 'How important/difficult is it for you to go hunting or shooting?'. Only 2 participants reported this item important. This can most likely be explained by the difference in gun licensing laws between the US and UK. As described earlier, measures produced for items responded to by a small number of respondents are likely to be imprecise. The SE of the item measure for 'hunting or shooting' in the unanchored analysis was 1.92, much larger than the mean SE value was 0.28 (standard deviation 0.27).

Therefore, the analysis was repeated, removing this item. The results are shown in figure 4.5.

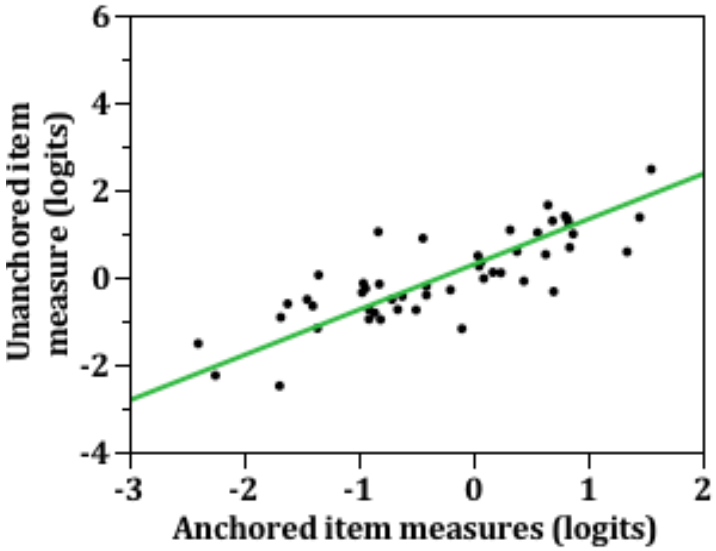

Figure 4.5. Orthogonal regression of the unanchored and anchored item measures of 49 items (hunting or shooting removed) (Intercept = 0.29, slope = 1.04, r = 0.81, $p < 0.05$).

Figure 4.5 shows orthogonal regression between the remaining 49 anchored and unanchored item measures (excluding hunting and shooting). Correlation was essentially unchanged at 0.81 ($p < 0.05$). However as the intercept of the regression line was closer to 0 at 0.29 and the slope was closer to 1 at 1.04, the relationship between the anchored and unanchored values was closer to 1:1. Hence, removal of 'hunting or shooting' item improved agreement. Removal of additional items did not increase agreement further.

4.9.4 Reliability and separation measures

As discussed above, Rasch analysis produces measures of reliability and separation. Reliability and separation for person and item measures were compared between those produced using unanchored values, anchored values from all items (50 item analysis) and anchored values from all items except 'hunting or shooting' (49 item analysis). The values are shown in table 4.3. An unanchored analysis of all items except 'hunting and shooting' is also displayed for comparison.

	Person Separation	Person Reliability	Item Separation	Item Reliability
50 item unanchored analysis	2.21	0.83	1.97	0.80
49 item unanchored analysis	2.21	0.83	1.94	0.79
50 item anchored analysis	2.17	0.83	1.46	0.68
49 item anchored analysis	2.17	0.82	2.18	0.83

Table 4.3. Separation and reliability of person and item measures produced by analysis of 50 unanchored items, 49 unanchored items (excluding hunting or shooting), 50 anchored items and 49 anchored items (excluding hunting or shooting).

Though the unanchored analyses produced satisfactory person separation and reliability values, item separation did not reach the recommended value of 2[110, 214].

Person separation and reliability changed little when anchored values were used. Item separation and reliability values considerably reduced with anchoring, however removal of 'hunting or shooting' improved both beyond that initially found in the unanchored analyses. In fact, item separation only exceeded 2 in the 49 item analysis. This further supports removal of this item from our analysis.

We offer the high correlation of unanchored and anchored person and item measures, improved item separation and improved category functioning as strong evidence in favour of anchoring item and category threshold measures to those proposed by Massof, with the exception of removing the item 'hunting or shooting'.

4.10 Analysing follow up data

As will be described in chapter 7, the AI was administered on three occasions: at month 0, 3 and 6. Two methods of analysing follow up data have been proposed by Wright[232]. Data can be racked whereby person measures are held constant, forcing all change into the item measure. Alternatively data can be stacked where items measures are held constant, forcing all change into the person measure. These techniques were compared in a study investigating the use of the Veteran Affairs Low Vision Visual Functioning Questionnaire (LV VFQ-48) as an outcome measure[121]. Data before and after low vision rehabilitation were analysed by both techniques separately. As item measures did not alter significantly following rehabilitation, data were stacked to examine the change in person measures following rehabilitation.

By anchoring pre and post intervention item measures to Massof's values, we used a modified version of the stacked method, forcing all change into the person measure. True stacking would derive item measures from all person responses across all administrations of the AI. Anchored values would not be used.

4.11 Summary of Rasch analysis procedure

The following summarises the analysis procedure for AI goal level response data in the present study:

- Difficulty ratings (response categories) were reordered so that 0 – 4 represented 'impossible' to 'not difficult' rather than 'not difficult' to 'impossible' meaning that

person logit scores (person measures) and the logits required to complete a goal (item measures) would reflect visual ability rather than difficulty

- Item and category threshold measures were anchored to those defined by Massof's calibrations. As such, Rasch analysis was conducted as though our sample of 100 participants estimated the ability required to complete each item (item measure) and the ability required to report each individual difficulty rating (category threshold ratings) identically to Massof's sample
- Data for the item 'hunting or shooting' were excluded from all analyses
- Follow up data were 'stacked'. This assumed the ability required for each item (item measure) remained constant at each administrations of the AI. Therefore any change in difficult ratings reported across the 3 administrations of the AI represented changing ability of the person (person measure)

Chapter 5: Results: Fundamental research on the impact of diabetic eye disease

This chapter describes the results of project 1, a fundamental study of the impact of diabetic eye disease (DED) on visual function and its relationships with disease severity and visual ability.

5.1 Recruitment

Recruitment commenced in June 2009 and was completed in February 2011. 256 patients were assessed for eligibility, of whom 156 were excluded. Reasons for exclusion were declining (103 patients); wanting to take part but being unable, for example living too far from the hospital (16 patients), and being ineligible (37). Reasons for ineligibility are shown in table 5.1.

Reason for ineligibility	Number of patients
Non fluency in English	20
Concomitant eye condition	8
Hearing impairment	3
Non-independence	3
Previous attendance at low vision clinic	2
Poor mobility	1

Table 5.1. Summary of reasons for ineligibility.

100 patients were recruited following informed consent. The overall acceptance rate, calculated from all those eligible, was 46%.

5.2 Data cleaning

Data were examined for errors before being analysed. Initially, frequency histograms for each variable were examined for obvious errors. Any outlying data were checked against source data on case report forms and amended where necessary. Additionally Mahalanobis distances were calculated for all participants, using all continuous variables as predictors. Mahalanobis distances measure the distance of cases (in this case participant measurements) from the mean of the selected variables. Distances higher than the average for the sample may indicate the presence of potential data entry errors. A scatterplot displaying distances for each participant was produced. Source data for those with outlier values were compared to data within the JMP data table. Errors were amended where necessary. The data table was then locked to prevent future errors. A copy of the data table was also made in SPSS.

5.3 Baseline participant characteristics

5.3.1 Demographic and clinical characteristics

Participants were predominantly male (male: 62, female: 38) with type 2 diabetes (Type 1: 28, Type 2: 72). Mean age was 57 years (range: standard deviation (SD), 26 – 83: 12). Just over half were White European (55%). Median time since diagnosis was 21 years (Interquartile range (IQR)): 12-30), with diabetic eye disease being present for a median of 5 years (IQR: 3 – 10). Demographic and clinical data are summarised in table 5.2. Full details are provided in appendix VII (table 3).

Participant characteristics	Data
Sex Male : Female	62 : 38
Age Mean ± SD (years)	56.7 ± 12.0
Ethnicity White : Black : Asian : Chinese	55 : 33 : 11 : 1
Type of diabetes 1 : 2 ratio	28 : 72
Duration of diabetes Median (IQR) years	20.0 (12.0 - 29.8)
Duration of diabetic eye disease Median (IQR) years	5.0 (3.0 – 10)

Table 5.2. Demographic and clinical characteristics of recruited participants. SD = standard deviation, IQR = interquartile range.

The full range of English National Screening Programme Grading Protocol (NGP) diagnoses were represented, splitting participants into 4 disease severity groups as shown in table 5.3

Severity group	NGP diagnosis	Number of participants	Total number of participants in severity group
1	R1	25	25
2	R2	21	21
3	R2 + M1 R2 + MP	5 13	18
4	R3 R3 + MP R3P R3P + M1 R3P +MP	8 2 14 3 9	36

Table 5.3. Number of participants within each severity group broken down by NGP diagnosis. NGP = English National Screening Programme Screening Protocol. R1 = Mild to moderate non-proliferative, R2 = Severe-non proliferative retinopathy, R3 = Proliferative retinopathy, R3P = Laser treated proliferative retinopathy, M1 = Maculopathy, MP = Laser treated maculopathy.

5.3.2 Baseline visual function data

All participants attended a baseline visual function assessment as described in Chapter 2. Median time between initial clinic visit and visual assessment was 9 days (IQR 6-20). Assessments lasted between 120 – 150 minutes. Contrast

sensitivity and MP-1 measurements were performed monocularly on the better eye as defined in section 2.1.3 of Chapter 2. All other measurements were recorded binocularly.

A summary of visual function data are shown in table 5.4. Full details are provided in appendix VII (table 4). The Shapiro Wilk W test was used to test whether variables were normally distributed. Normality was rejected where data significantly differed from the normal distribution, at the $p < 0.05$ level. The majority of variables were not normally distributed and were summarised by their median and IQR. Distributions approximating a normal distribution were defined by mean ± SD and range. Bivariate contour ellipse area (BCEA) measures were normalised with a log transformation.

Visual function measure	N=	Median / Mean ± SD*	IQR / Range*
Habitual distance acuity (LogMAR)	100	0.10	0 – 0.24
Corrected distance acuity (LogMAR)	100	0.04	-0.08 – 0.18
Contrast sensitivity (Log units)	100	1.40	1.26 – 1.55
Habitual near acuity (N)	100	N5	N4 – N8
Habitual large reading speed (wpm)	97	143 ± 55*	0 – 264*
Habitual small reading speed (wpm)	97	124 ± 61*	0 – 249*
Corrected reading acuity (LogMAR)	97	0.06	-0.04 – 0.16
Corrected peak reading speed (wpm)	97	216 ± 62*	65 – 433*
Corrected critical print size (LogMAR)	97	0.60	0.40 – 0.60
Confusion Index	100	1.69	1.13 – 2.69
Selectivity Index	100	1.97	1.56 – 2.60
Esterman efficiency score (%)	98	99	94 – 100
Mean sensitivity (dB)	83	16.04	13.37 – 17.69
Mean defect (dB)	83	-3.30	-5.70 – -1.60
Central mean sensitivity (dB)	83	16.31	13.50 – 18.38
Paracentral mean sensitivity (dB)	83	15.87	13.35 – 17.46
Scotoma size (Number of points)	83	25	12 - 45
Log BCEA (Log min arc^2)	92	2.90 ± 0.45*	1.79 – 4.31*

Table 5.4. Distribution of visual function measures. * denotes normally distributed variables. N = sample size, SD = standard deviation, IQR = interquartile range, LogMAR = Logarithm of minimum angle of resolution, wpm = words per minute, dB = Decibels, min arc = minutes of arc.

5.3.3 Baseline visual ability data

Responses to the baseline administration of the Activity Inventory (AI) were Rasch analysed using Winsteps® (Version 3.72.0, Winsteps® Rasch Management Computer Software, Beaverton, Oregon, USA) as described in Chapter 4. This produced a baseline AI score for each participant, giving a measure of visual ability in logits. Median AI score was 1.64 logits (IQR: 0.60 – 3.75). Higher values represent higher ability. To demonstrate the range of potential values obtainable, the AI score of a person reporting every item 'not difficult' would be 6.27 logits, whereas that of someone reporting every item 'impossible to do without someone else's help' would be -6.61 logits. Baseline AI scores for all participants are provided in Appendix VII (table 5).

5.4 Missing data

Full data were collected on 79 participants. Of the 21 participants with missing data, 1 failed to complete 2 assessments (microperimetry and binocular esterman) and 20 failed to complete 1 assessment (3 reading performance measures, 16 microperimetry and 1 Binocular Esterman).

Difficulties in conducting microperimetry were primarily due to participant tiredness (n= 9) or image tracking difficulties (n=6). On 2 occasions MP-1 data could not be collected because of MP-1 technical problems and one participant did not want to be dilated. As microperimetry was the only examination requiring dilation, it was conducted last. If patients reported tiredness, a second visit to complete data collection was offered, but was declined on all occasions. Ocular media disturbances interfered with the infrared tracking system of the MP-1 in the remainder of cases.

Demographic, visual function and visual ability data of those with missing data were compared to those with full data. Fisher's Exact test was used for categorical variables and analysis of variance (ANOVA) for continuous variables.

Those with missing data were on average 7 years older ($p = 0.03$). No other significant differences between demographic variables were observed. Multiple measures of visual function were worse in those with missing data. Habitual and corrected distance acuity ($p = < 0.001$), contrast sensitivity ($p < 0.001$), reading performance ($p < 0.001 – 0.04$), colour vision ($p = 0.01$) and peripheral fields ($p < 0.001$) were all significantly reduced compared to those

with full data. Baseline AI score was also significantly worse by an average of 1.49 logits (p = 0.006).

5.5 Aim 1 – To explore the impact of disease severity on visual function

5.5.1 Demographic and clinical effects on visual function variables

As shown in table 5.5, the majority of visual function measures declined with age and were worse in type 2 diabetes. Duration of diabetic eye disease was associated only with MP-1 mean sensitivity, paracentral mean sensitivity and Esterman efficiency score. Esterman efficiency score was also related to duration of diabetes.

Visual function measure	Significantly related clinical variables
Habitual distance acuity (LogMAR)	Age r = 0.33, p = < 0.001 DM type r = 0.27, p = 0.007, type 2 worse
Corrected distance acuity (LogMAR)	Age r = 0.37, p = < 0.001 DM type r = 0.24, p = 0.01, type 2 worse
Contrast sensitivity (Log units)	Age r = 0.24, p = 0.02
Habitual near acuity (N)	Age r = 0.38, p = < 0.001 DM type r = 0.35, p = < 0.001, type 2 worse
Habitual large reading speed (wpm)	Age r = -0.34, p = < 0.001 DM type r = 0.41, p = < 0.001, type 2 slower
Habitual small reading speed (wpm)	Age r = -0.41, p = < 0.001 DM type r = 0.45, p = < 0.001, type 2 slower
Corrected reading acuity (LogMAR)	Age r = 0.28, p = 0.005
Corrected peak reading speed (wpm)	Age r = -0.37, p = < 0.001
Corrected critical print size (LogMAR)	Age r = 0.24, p = 0.02 DM type r = 0.20, p = 0.05, type 2 worse
Confusion Index	Age r = 0.31, p = 0.002 DM type r = 0.35, p = < 0.001, type 2 worse
Selectivity Index	Age r = 0.30, p = 0.002 DM type r = 0.27, p = 0.007, type 2 worse
Esterman efficiency score (%)	Duration of DM r = -0.20, p = 0.04 Duration of DED r = -0.30, p = 0.002
Mean sensitivity (dB)	Age r = -0.27, p = 0.01 Years since DED r = -0.23, p = 0.04
Mean defect (dB)	Age r = -0.28, p = 0.01
Central mean sensitivity (dB)	Age r = -0.28, p = 0.01
Paracentral mean sensitivity (dB)	Age r = -0.27, p = 0.01 Duration of DED r = -0.25, p = 0.02
Scotoma size (Number of points)	Age r = 0.09, p = 0.008
Log BCEA (Log min arc^2)	None

Table 5.5. Influence of demographic variables on visual function measures. DM = diabetes, DED = diabetic eye disease, r = correlation coefficient.

5.5.2 Relationship between severity and visual function

The relationship between severity group and visual function was examined graphically. The median and IQR (or mean ± 2 standard deviations where appropriate) of each visual function variable were plotted for those in each severity group. This is shown in figures 5.1 to 5.4.

Analysis of Covariance (ANCOVA) was used to examine the impact of severity group on each visual function measure in turn. All analyses were additionally adjusted for age, sex, type of diabetes, duration of DM and duration of DED.

To determine if a monotonic trend existed, contrasts between group 1 and 2, 2 and 3 and 3 and 4 were made. Significant contrasts are indicated with asterisks on graphs 5.1 to 5.4 (* = $p < 0.05$, ** = $p < 0.01$).

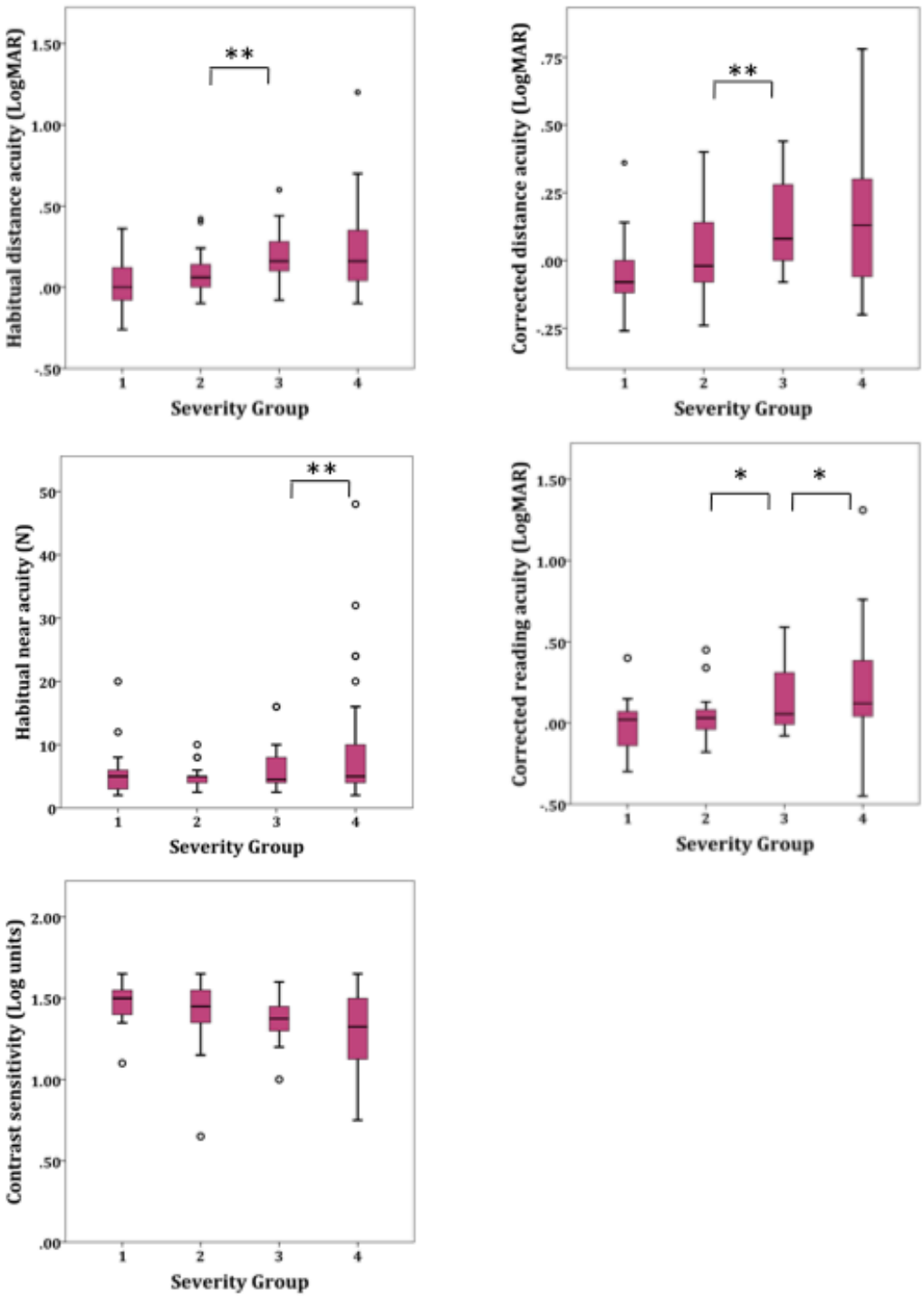

Figure 5.1. Boxplots plots displaying the distribution of habitual and corrected distance acuity, habitual near acuity, habitual reading acuity and corrected contrast sensitivity in each severity group. Median, 25th and 75th (IQR) represented by the box, whiskers show the range. Outlying data points lying more than 1.5 x IQR beyond the 25th or 75th percentile are shown as open circles.

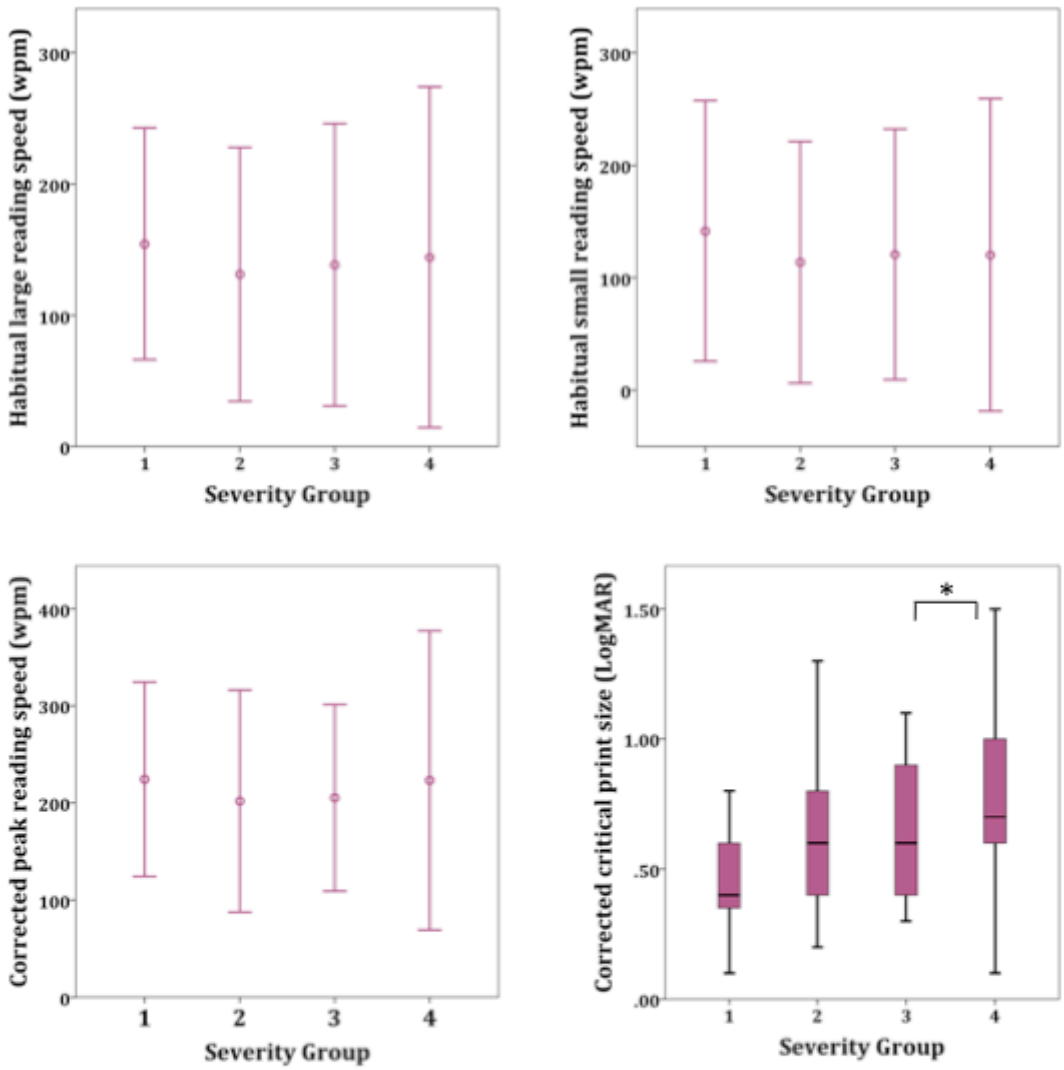

Figure 5.2. Means plot displaying the distribution of habitual large and small reading speed, corrected peak reading speed in those from each severity group. The mean value (open circles), ± 2 standard deviations (vertical lines) are shown. Boxplots displaying the distribution of corrected critical print size in those from each severity group. Median, 25th and 75th (IQR) are represented by the box, whiskers show the range. Outlying data points lying more than 1.5 x IQR beyond the 25th or 75th percentile are shown as open circles.

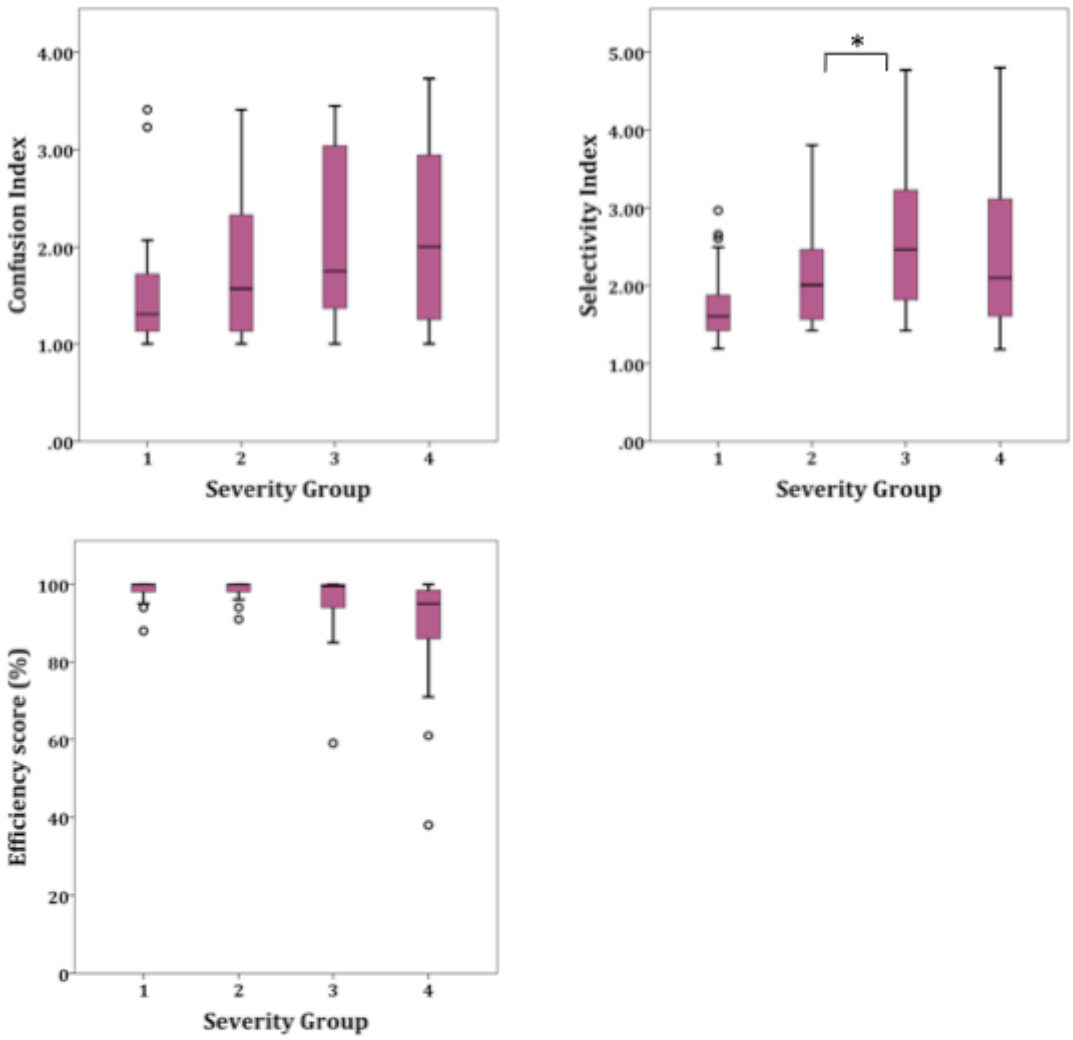

Figure 5.3. Boxplots displaying the distribution of confusion index and selectivity index in those from each severity group. Median, 25th and 75th (IQR) are represented by the box, whiskers show the range. Outlying data points lying more than 1.5 x IQR beyond the 25th or 75th percentile are shown as open circles. Boxplots displaying the distribution of Esterman efficiency score in those from each severity group. Median, 25th and 75th (IQR) are represented by the box, whiskers show the range. Outlying data points lying more than 1.5 x IQR beyond the 25th or 75th percentile are shown as open circles.

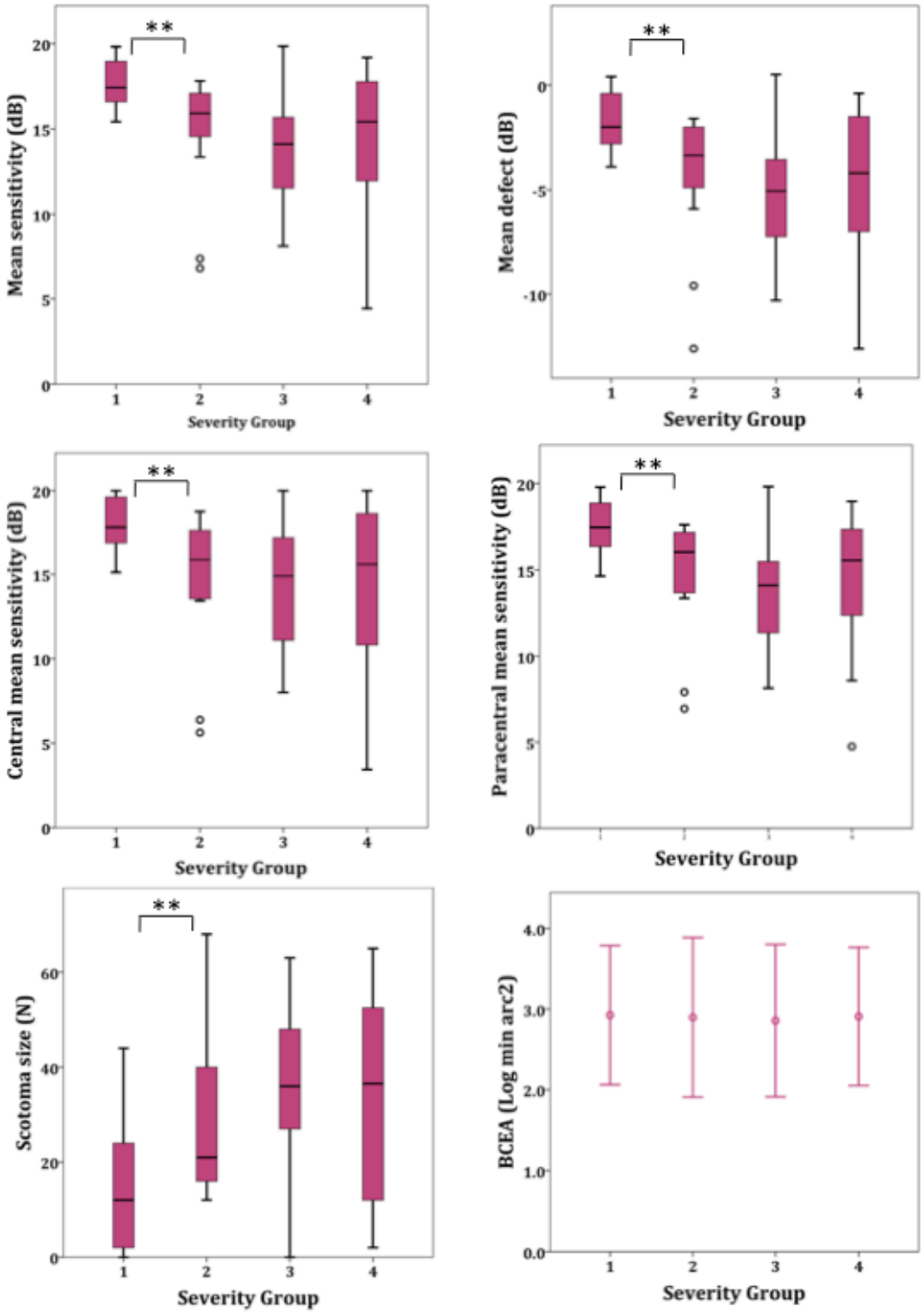

Figure 5.4. Boxplots displaying the distribution of mean sensitivity, mean defect, central mean sensitivity, paracentral mean sensitivity and scotoma size in those from each severity group. Median, 25th and 75th (IQR) are represented by the box, whiskers show the range. Outlying data points lying more than 1.5 x IQR beyond the 25th or 75th percentile are shown as open circles. Figure 5.18. Means plot displaying the distribution of bivariate contour ellipse area (BCEA) in those from each severity group. The mean value (open circles), ± 2 standard deviations (vertical lines) are shown.

All visual function variables except fixation stability were associated with severity group once adjusted for age, sex, type of diabetes, duration of diabetes and duration of DED ($r^2 = 0.24 – 0.47$, $p \leq 0.002$).

No visual function variables decreased monotonically with severity groups, though some significant contrasts were revealed. Microperimetry variables were significantly worse in group 2 compared to group 1. Habitual distance acuity, corrected distance acuity and selectivity index were significantly worse in group 3 compared to group 2. Habitual near acuity and corrected critical print size were significantly worse in group 4 compared to group 3.

The closest thing to a monotonic trend was observed for corrected reading acuity where group 3 was significantly worse than group 2 and group 4 was significantly worse than group 3. Results are shown in table 5.6.

Visual function measure	r^2	Overall p	Group contrasts		
			1 - 2	2 – 3	3 - 4
Habitual distance acuity (LogMAR)	0.40	< 0.001	N.S.	0.009	N.S
Corrected distance acuity (LogMAR)	0.47	< 0.001	N.S.	0.007	N.S.
Contrast sensitivity (Log units)	0.30	< 0.001	N.S.	N.S.	N.S.
Habitual near acuity (N)	0.27	< 0.001	N.S.	N.S.	0.001
Habitual large reading speed (wpm)	0.24	0.002	N.S.	N.S.	N.S.
Habitual small reading speed (wpm)	0.34	< 0.001	N.S.	N.S.	N.S.
Corrected reading acuity (LogMAR)	0.36	< 0.001	N.S.	0.03	0.04
Corrected peak reading speed (wpm)	0.24	0.001	N.S.	N.S.	N.S.
Corrected critical print size (LogMAR)	0.31	< 0.001	N.S.	N.S.	0.04
Confusion Index	0.35	< 0.001	N.S.	N.S.	N.S.
Selectivity Index	0.29	< 0.001	N.S.	0.03	N.S.
Estermand efficiency score (%)	0.25	0.001	N.S.	N.S.	N.S.
Mean sensitivity (dB)	0.42	< 0.001	0.004	N.S.	N.S.
Mean defect (dB)	0.42	< 0.001	0.003	N.S.	N.S.
Central mean sensitivity (dB)	0.37	< 0.001	0.01	N.S.	N.S.
Paracentral mean sensitivity (dB)	0.42	< 0.001	0.004	N.S.	N.S.
Scotoma size (Number of points)	0.42	< 0.001	0.002	N.S.	N.S.
Log BCEA (Log min arc^2)	0.08	N.S.			

Table 5.6. Results of ANCOVA between visual function measures and severity group controlled for age, sex, type of diabetes, duration of DM and duration of diabetic eye disease. r = correlation coefficient, N.S. = Not significant.

5.6 Aim 2 – To explore the impact of disease severity on visual ability

5.6.1 Demographic and clinical effects on baseline AI score

Univariate analyses were used to investigate the influence of demographic and clinical variables on AI score. Continuous variables were examined using regression analysis. ANOVA was used for categorical variables. No significant effects were observed ($p = 0.09 – 0.80$).

5.6.2 Relationship between baseline AI score and severity group

The relationship between baseline AI score and severity groupings was first examined graphically (figure 5.5). Mean baseline AI score and 95% CIs were plotted for those in each severity group. The numerical values are given in table 5.7.

Analysis of Covariance (ANCOVA) was used to examine the impact of severity group on AI score, adjusted for age, sex, type of diabetes, duration of DM and duration of DED.

Contrasts between group 1 and 2, 2 and 3 and 3 and 4 were made. Significant contrasts are indicated with asterisks on graph 5.5 (* = $p < 0.05$, ** = $p < 0.01$).

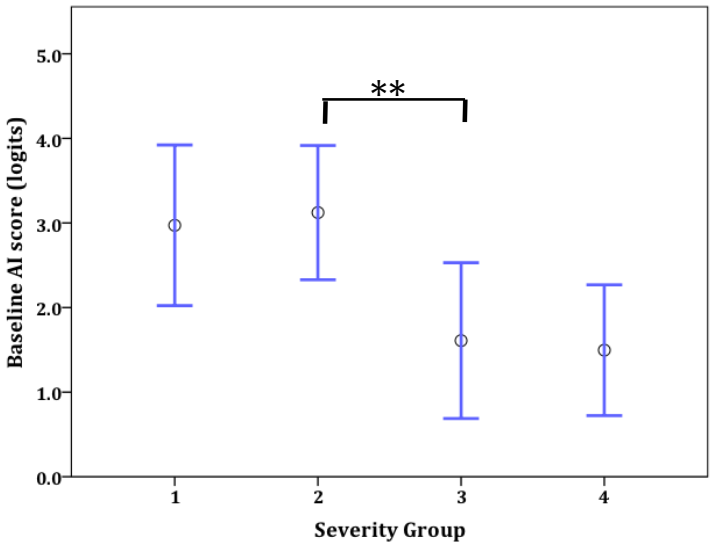

Figure 5.5. Mean baseline AI score and 95% confidence intervals for each severity group.

Severity group	Number of participants	Mean baseline AI score (95% CI)
1	25	2.97 (2.02, 3.92)
2	21	3.12 (2.32, 3.92)
3	18	1.61 (0.69, 2.53)
4	36	1.50 (0.72, 2.27)

Table 5.7. Mean baseline AI score across severity groups. All values in logits. CI = confidence interval.

Baseline AI score was significantly associated with severity group ($r^2 = 0.27$, $p = < 0.001$), with scores in group 3 significantly worse than group 2 ($p = 0.005$). No other contrasts were significant.

As described in section 5.4 of this chapter, 21 participants have at least one missing visual function data point. Data were not missing at random, with baseline AI scores significantly worse for those with missing data (difference in means 1.49 logits, $p = 0.006$). Therefore, the above analysis was repeated excluding all those with missing data to confirm a similar trend in baseline AI score across severity groups. The results are shown in table 5.8 and graphically

in figure 5.6. Significant contrasts are indicated with asterisks (* = p < 0.05, ** = p < 0.01).

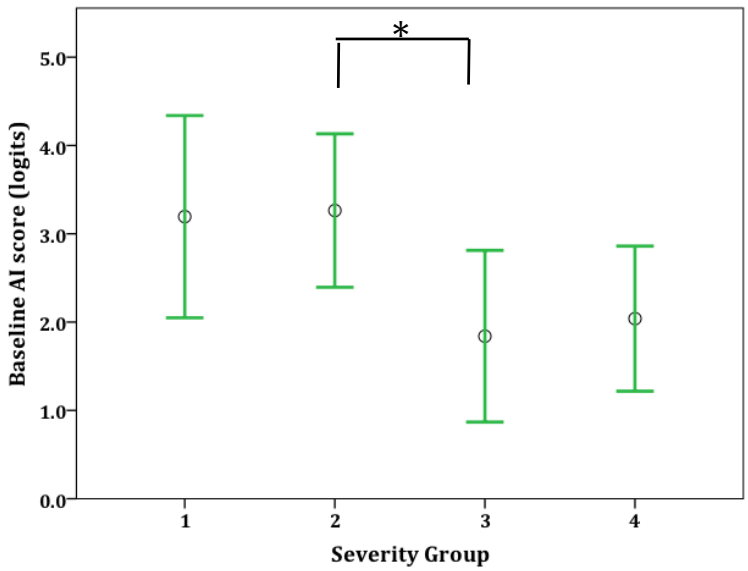

Figure 5.6. Mean baseline AI score and 95% confidence intervals for each severity group (excluding those with at least 1 missing visual function data point).

Severity group	Number of participants	Mean baseline AI score (95% CI)
1	19	3.19 (2.05, 4.34)
2	17	3.26 (2.39, 4.13)
3	16	1.84 (0.87, 2.81)
4	27	2.03 (1.21, 2.86)

Table 5.8. Mean baseline AI score and 95% confidence intervals for each severity group (excluding those with at least 1 missing visual function data point).

In this reduced sample, the association between baseline AI score and severity group failed to reach significance (r = 0.18, p = 0.08), however scores in group 3 were still significantly worse than group 2 (p = 0.02). No other contrasts were significant.

As group 4 includes participants with and without maculopathy, further analyses were undertaken to determine whether a further significant decline in visual ability between group 3 and 4 was obscured by the effect of those participants

without maculopathy on group 4. Therefore, severity groups were recoded and reordered as shown below, separating those with maculopathy from those without. Briefly, groups 1, 2 + 3 contain participants with increasingly severe retinopathy but no maculopathy and groups 4 + 5 contain participants with severe non-proliferative retinopathy with maculopathy and proliferative retinopathy with maculopathy respectively. Contrasts between recoded groups 2 + 3, 3 + 4 and 4 + 5 were reexamined.

Recorded severity groups were as follows:

1. Mild/moderate non-proliferative retinopathy without maculopathy: R1
2. Severe non-proliferative retinopathy without maculopathy: R2
3. Proliferative retinopathy without maculopathy: R3/RP
4. Severe non-proliferative retinopathy with maculopathy: R2 + M1/MP
5. Proliferative retinopathy with maculopathy: R3/RP + M1/MP

Figure 5.7 shows mean baseline AI score and 95% confidence intervals of participants within each modified severity group. Significant contrasts are indicated with asterisks (* = $p < 0.05$, ** = $p < 0.01$). The numerical values are given in table 5.9.

Figure 5.7 shows that those with maculopathy had the worst mean AI scores. A significant association existed between baseline AI score and recoded severity group ($r^2 = 0.13$, $p = 0.01$) however the only significant contrast was that between group 2 and group 3 ($p = 0.04$).

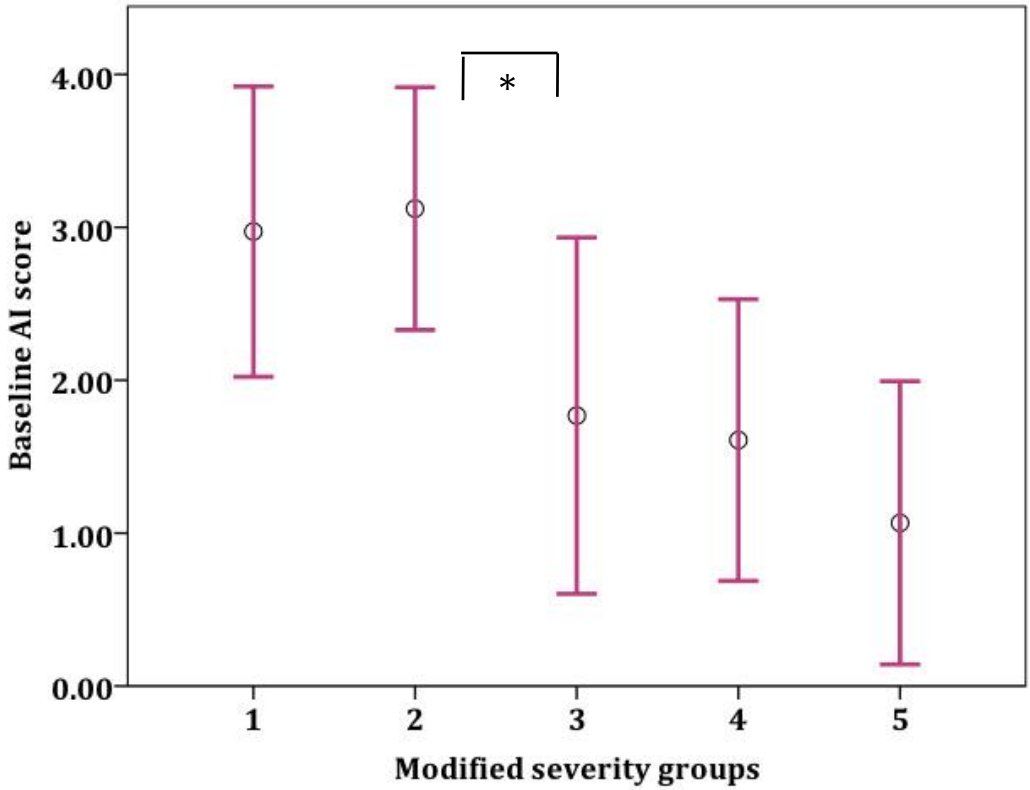

Figure 5.7. Mean baseline AI score and 95% confidence intervals for each severity group.

Modified severity group	Number of participants	Mean baseline AI score (95% CI)
1	25	2.97 (2.02, 3.92)
2	21	3.12 (2.32, 3.92)
3	18	1.77 (0.87, 2.66)
4	22	1.61 (0.69, 2.53)
5	14	1.07 (-0.06, 2.19)

Table 5.9. Mean baseline AI score across severity groups. All values in logits. CI = confidence interval.

5.7 Hypothesis – The reduction in visual ability associated with increasing disease severity is explained by visual function deficits

5.7.1 Relationship between baseline AI score and visual function

The correlation between each visual function measure and baseline AI score was first examined graphically. As shown in figures 5.8 to 5.11, scatterplots of baseline AI score against each visual function measure were constructed.

Pearson's correlation coefficients (r) were calculated for each visual function variable and AI. However as the majority of visual function variables were not normally distributed, Spearman's rank order correlations (ρ) were also calculated for comparison. Moderate significant correlations between baseline AI score and all visual function measures except log BCEA were observed. The r and ρ values between each visual function measure and baseline AI score are shown in table 5.10.

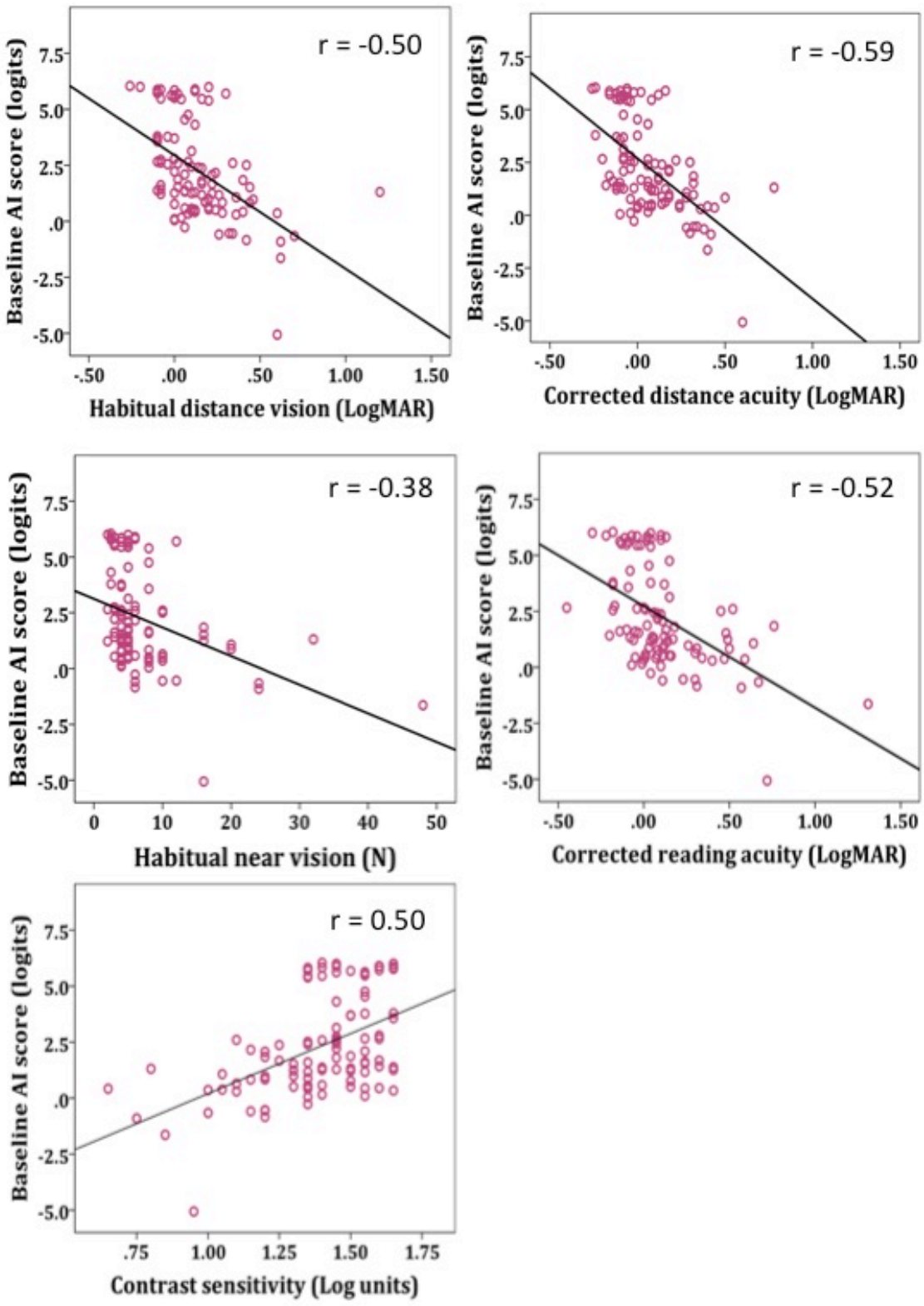

Figure 5.8. Scatterplots displaying the relationships between habitual distance acuity, corrected distance acuity, habitual near vision, corrected reading acuity and corrected contrast sensitivity and baseline AI score. r = Pearson correlation coefficient.

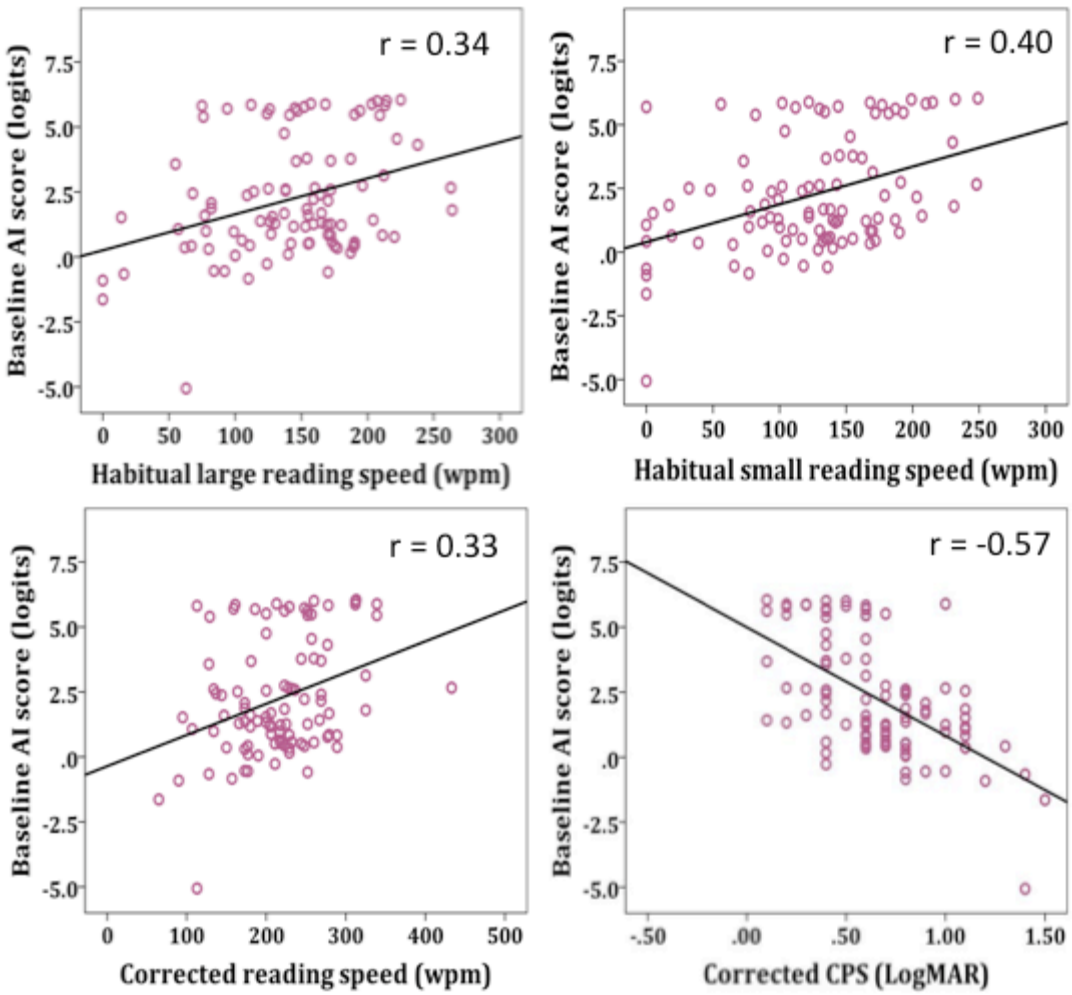

Figure 5.9. Scatterplots displaying the relationships between habitual large reading speed, habitual small reading speed, corrected reading speed and corrected critical print size (CPS) and baseline AI score. r = Pearson correlation coefficient.

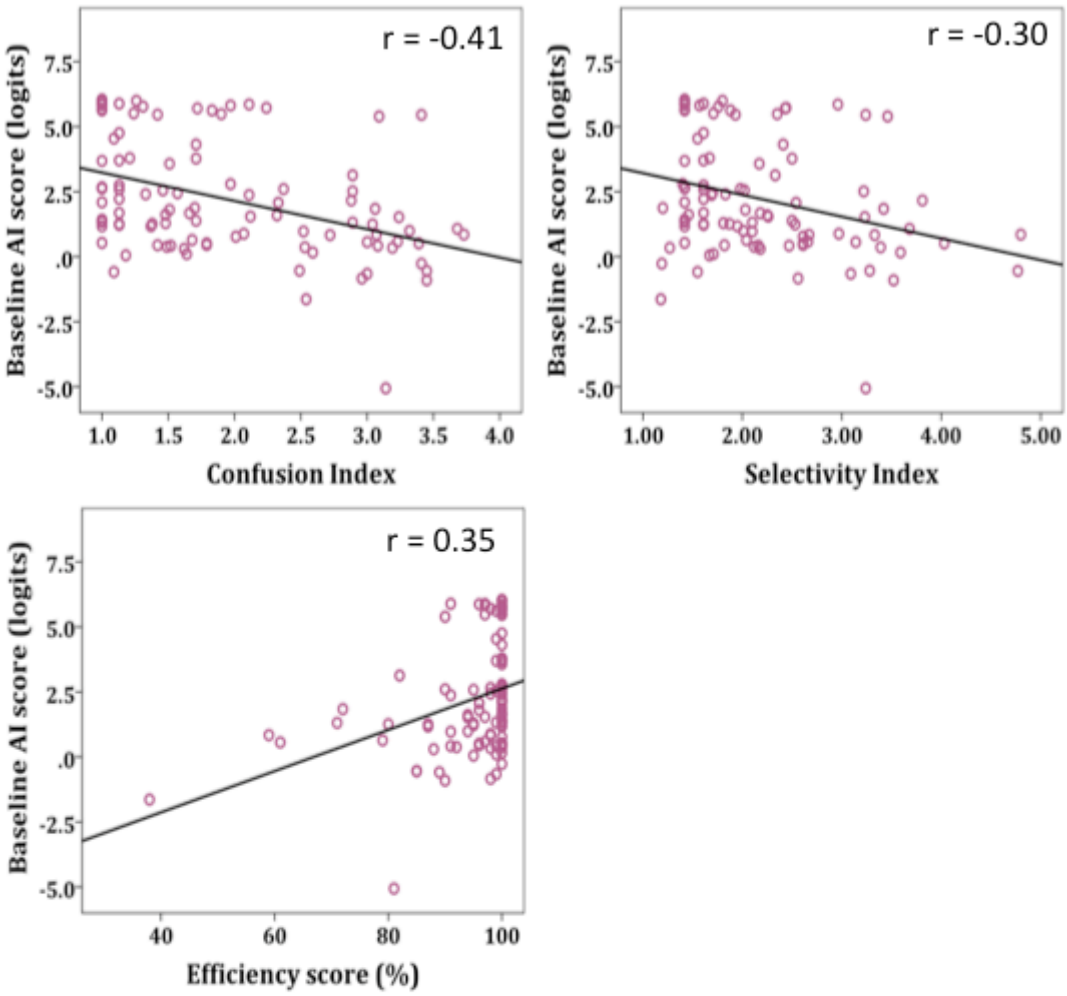

Figure 5.10. Scatterplots displaying the relationships between confusion index, selectivity index and Esterman efficiency score and baseline AI score. r = Pearson correlation coefficient.

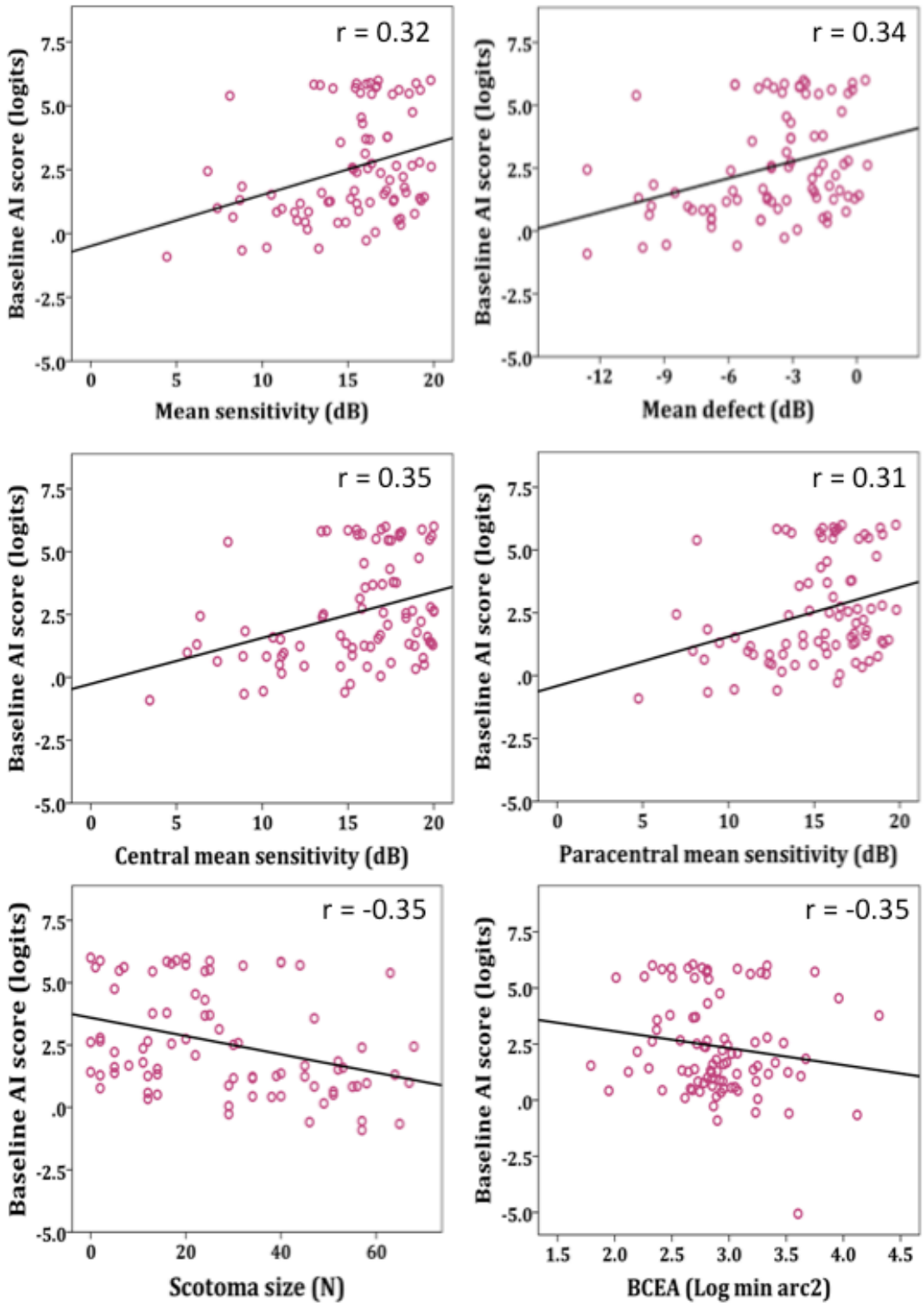

Figure 5.11. Scatterplots displaying the relationships between mean sensitivity, mean defect, central mean sensitivity, paracentral mean sensitivity, scotoma size and log BCEA and baseline AI score. r = Pearson correlation coefficient.

Visual function measure	Correlation with baseline AI			
	Pearson r	**p value**	**Spearman ρ**	**p value**
Habitual distance acuity (LogMAR)	-0.50	<0.001	-0.52	<0.001
Corrected distance acuity (LogMAR)	-0.59	<0.001	-0.59	<0.001
Contrast sensitivity (Log units)	0.51	<0.001	0.51	<0.001
Habitual near acuity (N)	-0.38	<0.001	-0.40	<0.001
Habitual large reading speed (wpm)	0.34	<0.001	0.29	0.003
Habitual small reading speed (wpm)	0.40	<0.001	0.37	<0.001
Corrected reading acuity (LogMAR)	-0.52	<0.001	-0.52	<0.001
Corrected peak reading speed (wpm)	0.33	<0.001	0.30	0.003
Corrected critical print size (LogMAR)	-0.57	<0.001	-0.55	<0.001
Confusion Index	-0.41	<0.001	-0.44	<0.001
Selectivity Index	-0.30	0.002	-0.33	<0.001
Esterman efficiency score (%)	0.35	<0.001	0.38	<0.001
Mean sensitivity (dB)	0.32	0.003	0.33	0.002
Mean defect (dB)	0.34	0.002	0.35	0.001
Central mean sensitivity (dB)	0.35	0.001	0.36	0.001
Paracentral mean sensitivity (dB)	0.31	0.004	0.31	0.004
Scotoma size (Number of points)	-0.35	0.001	-0.37	0.001
Log BCEA (Log min arc^2)	-0.15	N.S.	-0.18	N.S.

Table 5.10. Pearson's correlation coefficients (r) and Spearman's rank order correlations (ρ) between each visual function measure and baseline AI score. N.S. = not significant.

5.7.2 Multivariate regression models

Multivariate regression was used to determine whether disease severity groups were associated with baseline AI score, independently of visual function.

As multicollinearity between independent variables in a multivariate regression model can compromise the accuracy of its output[233], correlation coefficients between all visual function measures were systematically examined to determine potential variables for model entry. A full correlation matrix is shown in table 5.11.

FIX	**SS**	**PMS**	**CMS**	**MD**	**MS**	**EES**	**SI**	**CI**	**CPS**	**CRS**	**CRA**	**HSS**	**HLS**	**HNA**	**CCS**	**CDA**	**HDA**
0.26	0.64	-0.65	-0.69	-0.67	-0.67	-0.47	0.42	0.55	0.77	-0.47	0.86	-0.66	-0.55	0.79	-0.82	0.93	
0.29	0.69	-0.68	-0.72	-0.71	-0.70	-0.48	0.50	0.57	0.77	-0.42	0.81	-0.61	-0.47	0.73	-0.84		
-0.25	-0.69	0.70	0.74	0.71	0.72	0.48	-0.42	-0.55	-0.67	0.37	-0.76	0.60	0.50	0.72			
0.34	0.59	-0.59	-0.61	-0.61	-0.61	-0.48	0.42	0.57	0.64	-0.60	0.82	-0.77	-0.69				
-0.18	-0.50	0.54	0.52	0.54	0.54	0.22	-0.23	-0.39	-0.49	0.87	-0.53	0.88					
-0.34	-0.59	0.60	0.60	0.62	0.61	0.29	-0.32	-0.45	-0.59	0.81	-0.66						
0.41	0.58	-0.61	-0.62	-0.62	-0.62	-0.59	0.40	0.54	0.76	-0.49							
-0.23	-0.41	0.46	0.44	0.46	0.47	0.21	-0.15	-0.31	-0.42								
0.35	0.47	-0.44	-0.44	-0.46	-0.46	-0.36	0.33	0.42									
0.21	0.44	-0.43	-0.53	-0.47	-0.47	-0.34	0.76										
0.18	0.42	-0.40	-0.46	-0.45	-0.43	-0.13											
-0.11	-0.35	0.48	0.45	0.44	0.48												
-0.19	-0.91	0.99	0.97	0.99													
-0.21	-0.94	0.98	0.97														
-0.17	-0.91	0.94															
-0.18	-0.91																
0.17																	

HDA	Habitual distance acuity
CDA	Corrected distance acuity
CCS	Corrected contrast sensitivity
HNA	Habitual near acuity
HLS	Habitual large reading speed
HSS	Habitual small reading speed
CRA	Corrected reading acuity
CRS	Corrected peak reading speed
CPS	Corrected critical print size
CI	Confusion Index
SI	Selectivity Index
EES	Esterman efficiency score
MS	Mean sensitivity
MD	Mean defect
CMS	Central mean sensitivity
PMS	Paracentral mean sensitivity
SS	Scotoma size
FIX	log BCEA

Table 5.11. Correlation coefficients (r) for all visual function variables.

Highly correlated variables, capturing the same aspect of vision were grouped together. Seven groups were considered: acuity, contrast sensitivity, reading speed, colour vision, peripheral fields, central visual field function and fixation stability. The variables within each group are given in table 5.12.

Aspect of vision group	Visual function variables
Acuity	Habitual distance acuity Corrected distance acuity Habitual near acuity Corrected reading vision Corrected critical print size
Contrast sensitivity	Corrected contrast sensitivity
Reading speed	Habitual large reading speed Habitual small reading speed Corrected peak reading speed
Colour vision	C-Index S Index
Peripheral visual fields	Esterman efficiency score
Central visual field function	Mean sensitivity Mean defect Central mean sensitivity Paracentral mean sensitivity Scotoma size
Fixation stability	Log BCEA

Table 5.12. Visual function variables grouped according to the aspect of vision to which they pertain.

As variables within each group were highly correlated, the variable with the highest univariate correlation with AI was chosen to represent each particular aspect of vision. The resultant 7 variables were: corrected distance acuity, contrast sensitivity, habitual small reading speed, C-Index, Esterman efficiency score, central mean sensitivity and log BCEA.

Seven separate multivariate regression models were constructed examining the association between baseline AI and severity controlling for each of the resulting variables in turn. All models (and subsequent models in this section) were adjusted for age, sex, type of disease, duration of diabetes and duration of diabetic eye disease. Results are displayed in table 5.13. The results of the ANCOVA analysis examining the relationship between baseline AI score and severity described in section 5.6.2 is given for comparison.

Model	**Overall r^2**	**Overall p value**	**Severity p value**	**Visual function p value**
Severity	0.27	< 0.001		
Severity Corrected distance acuity	0.41	< 0.001	N.S.	< 0.001
Severity Corrected contrast sensitivity	0.37	< 0.001	0.03	< 0.001
Severity Habitual small reading speed	0.33	< 0.001	0.002	0.007
Severity Confusion Index	0.31	< 0.001	0.009	0.02
Severity Esterman efficiency score	0.30	< 0.001	0.01	0.02
Severity Central mean sensitivity	0.23	< 0.001	0.05	0.04
Severity log BCEA	0.27	0.002	< 0.001	N.S.

Table 5.13. Results of multivariate regression models investigating the link between AI and severity, controlling for visual function variables in turn. N.S. = not significant.

All visual function variables except log BCEA were associated with AI, independently of severity. No association between AI and severity existed once corrected distance acuity had been controlled for.

A further multivariate regression model was constructed examining the influence of severity on baseline AI whilst controlling for multiple visual function variables. All visual function variables independently associated with baseline AI (in the previous models) were considered potential covariates for this model. A reduced correlation matrix, containing correlations between these potential covariates is shown in table 5.14.

	CDA					
CCS	-0.84	**CCS**				
HSS	-0.61	0.61	**HSS**			
CI	0.57	-0.55	-0.46	**CI**		
EES	-0.48	0.48	0.32	-0.33	**ESS**	
CMS	-0.77	0.78	0.70	-0.57	0.50	**CMS**

CDA Corrected distance acuity
CCS Corrected contrast sensitivity
HSS Habitual small reading speed
CI Confusion Index
EES Esterman efficiency score
CMS Central mean sensitivity

Table 5.14. Correlation matrix showing the correlation coefficients (r) between the 6 visual function variables independently associated with baseline AI.

Corrected distance acuity and corrected contrast sensitivity were highly correlated (r = -0.84), exceeding the limit for collinearity advised by Field[234] and as such only corrected distance vision was included in the final model.

A multivariate regression model was constructed as shown in table 5.15. All predictors entered simultaneously. Adjustment was made for demographic and clinical data as described above.

Dependent variable	Independent variables
Baseline AI score	Severity group
	Corrected distance acuity
	Habitual small reading speed
	Confusion index
	Esterman efficiency score
	Central mean sensitivity

Table 5.15. Variables entered into multivariate linear regression model.

The model accounted for 34% of the variance in baseline AI score ($p = 0.005$). Adjusted r^2 values, which give an indication of how well the model is expected to perform in the general population, was 0.21 suggesting this model would predict 13% less variance in the general population. Severity was not independently associated with baseline AI score when multiple aspects of visual function were accounted for. However, corrected visual acuity was independently associated with baseline AI score ($p = 0.01$). Model estimates, scaled estimates and Variance Inflation Factor (VIF) values are shown in table 5.16.

Independent variables	Estimate	Standard error	Scaled estimates	p value	VIF
Constant	-0.76	4.36		0.86	
Severity group	-0.16	0.25	-0.07	0.62	2.06
Corrected distance acuity	**-5.56**	**2.12**	**-0.42**	**0.01**	**2.63**
Habitual small reading speed	0.00	0.00	0.04	0.80	1.99
Confusion Index	-0.52	0.33	-0.21	0.12	1.72
Central mean sensitivity	-0.07	0.09	-0.13	0.42	2.64
Esterman efficiency score	0.05	0.04	0.16	0.23	1.75

Table 5.16. Results of multivariate regression model adjusted for age, sex, type of diabetes, duration of diabetes and duration of diabetic eye disease shown in table 5.10. VIF = Variation Inflation Factor. Significant variables shown in bold.

The model was repeated replacing corrected visual acuity with corrected contrast sensitivity, to determine whether choice of either substantially affected the model outcome. This model accounted for less overall variance in AI (31%, p = 0.001), and corrected contrast sensitivity was not an independent predictor of AI.

5.7.3 Model validity

Variation Inflation Factor (VIF) values were calculated to determine whether multicollinearity of independent variables was present. VIF values exceeding 5 are suggestive of collinearity[235]. As shown in table 5.16, all VIF values were sufficiently low, indicating no major multicollinearity.

Multivariate regression models are based on assumptions of normality, linearity and homoscedasticity of residuals[233]. A normal probability plot of residuals was produced to assess residual normality. Standardised residuals were plotted against predicted values to evaluate linearity and homoscadasticity of residual. These plots are shown in figures 5.12 and 5.13 respectively.

Figure 5.12 suggests model residuals approximate a normal distribution as data points approximately follow the identity line. The random scatter of data points around the Y = 0 line in figure 5.13 suggests the assumptions of homoscedasticity and linearity of residuals were met.

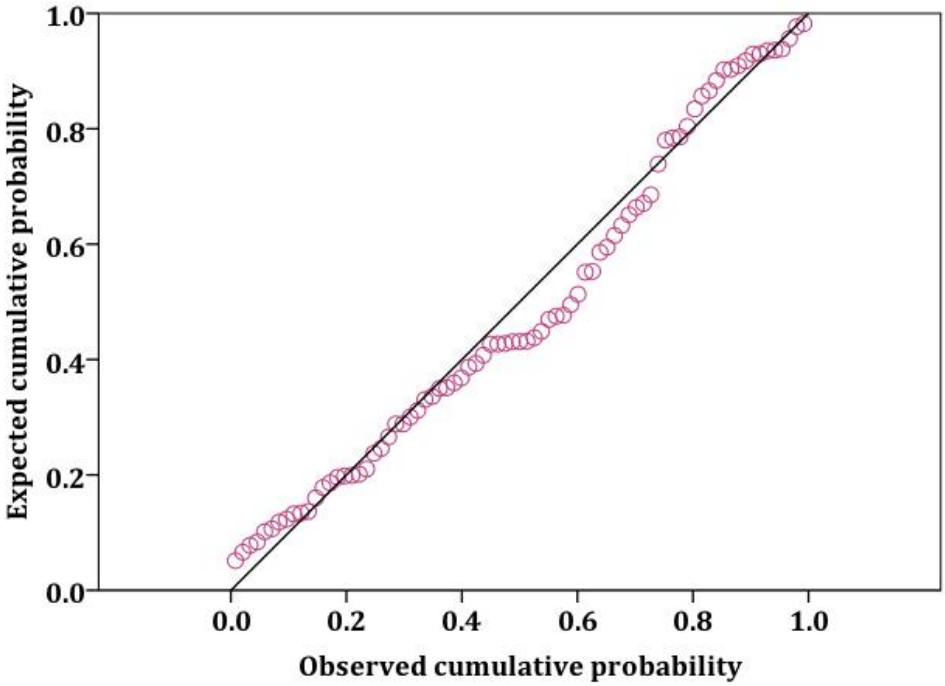

Figure 5.12. Normal probability plot of model residuals. The points follow the identity line suggesting model residuals approximate a normal distribution.

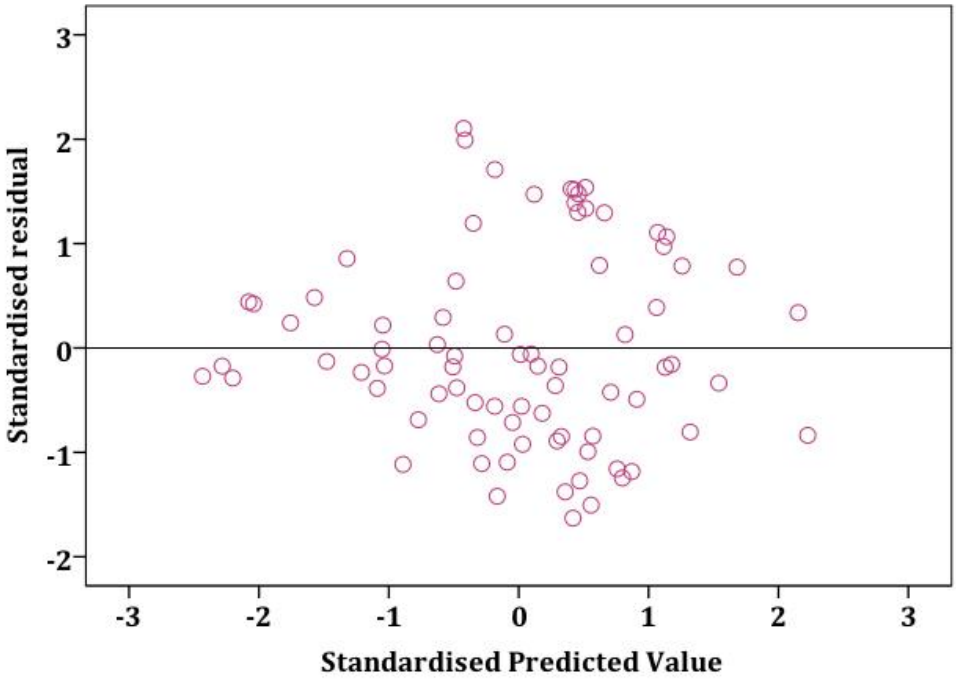

Figure 5.13. Scatterplot of standardised model residuals against predicted values. Random scatter of points around the y = 0 line suggests the assumptions of homoscedasticity and linearity of residuals were met.

5.7.4 Influence of missing data

As mentioned in section 5.4, 21 participants had at least one missing data point. The model described above used listwise deletion, excluding those with missing data on any variables entered. Therefore the above results were drawn from a sample of 79 people.

The majority of cases excluded (17/21) did not have a central mean sensitivity measurement (CMS). In order to test the above model on a larger sample (n=95), it was reconstructed removing this variable. As shown in table 5.15, CMS was not a significant predictor in the previous model and had the lowest scaled estimate of all visual function variables. Pairwise deletion, which includes all available data and does not eliminate cases, was also considered. By necessity, resultant model

estimates are based on different sample sizes. This approach has been criticised for producing erroneous results and was therefore not used[236].

Table 5.17 gives the results of this reconstructed model. Overall the model accounted for 45% of the variance in baseline AI score ($p < 0.001$). Adjusted r^2 was 0.38, indicating this model is more generalisable to wider population. Severity variables were not independently related to baseline AI score. Of the visual function variables entered, corrected distance acuity was an independent predictor of baseline AI ($p < 0.001$). Model estimates, scaled estimates and VIF values are shown in tables 5.17.

	Estimate	Standard error	Scaled estimates	p value	VIF
Constant	0.20	2.82		0.94	1.04
Severity group	-0.10	0.20	-0.05	0.62	1.78
Corrected distance acuity	**-5.98**	**1.58**	**-0.49**	**<0.001**	**2.57**
Habitual small reading speed	0.00	0.00	0.02	0.85	1.90
Confusion Index	-0.36	0.30	-0.13	0.23	1.78
Esterman efficiency score	0.03	0.02	0.13	0.20	1.44

Table 5.17. Results of reconstructed multivariate regression model adjusted for age, sex, type of diabetes, duration of diabetes and duration of diabetic eye disease. VIF = Variation Inflation Factor. Significant variables shown in bold.

VIF values were sufficiently low for all predictors, indicating no serious multicollinearity. Model residuals approximated a normal distribution and the

assumptions of linearity and homoscedasticity were met, as shown graphically in figure 5.14 and 5.15 respectively.

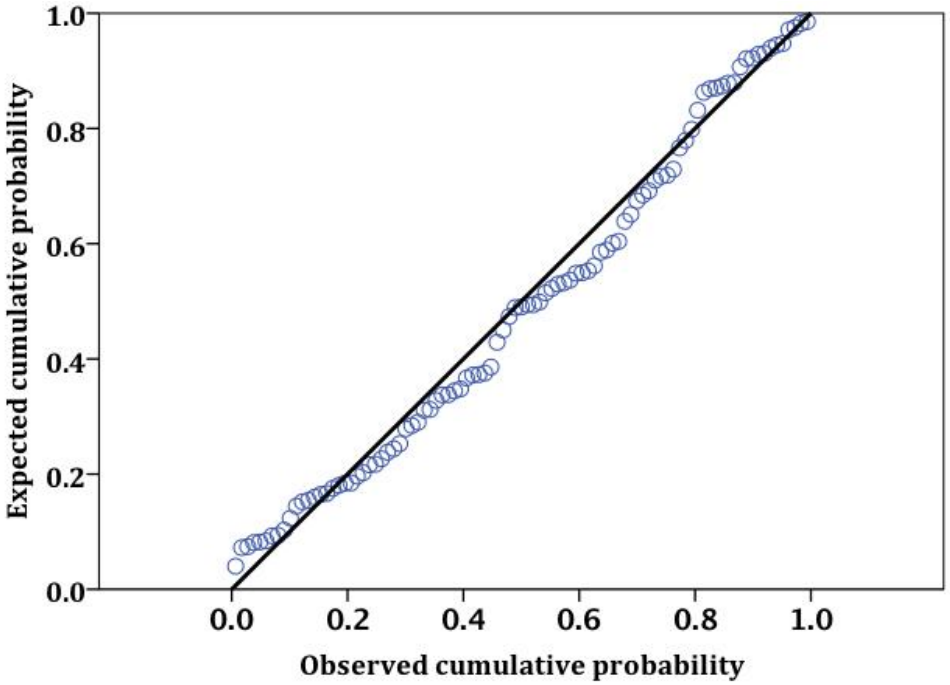

Figure 5.14. Normal probability plot of reconstructed model residuals. The points follow the identity line suggesting model residuals approximate a normal distribution.

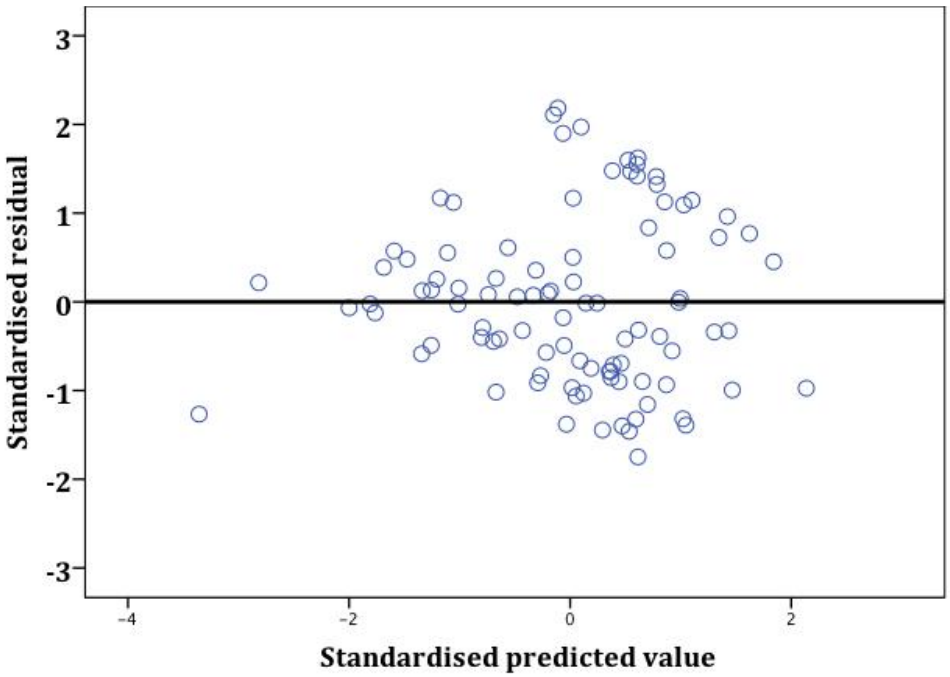

Figure 5.15. Scatterplot of standardised residuals against predicted values from the reconstructed model. Random scatter of points around the y = 0 line suggests the assumptions of homoscedasticity and linearity of residuals were met.

5.8 Exploratory analysis – Which visual function variables provide the best estimate of baseline AI score?

5.8.1 Stepwise regression model

Multivariate stepwise regression was used to establish those visual function variables that best predict baseline AI score. Initially a forward method was specified, though backwards and mixed (labeled 'stepwise' in SPSS) models were also constructed. A p value stopping rule was employed, with entrance criteria at 0.05 and exit at 0.10. Table 5.18 shows those variables entered into the model. Adjustment was made for demographic and clinical data as described above.

Dependent variable	Independent variables
Baseline AI score (logits)	Corrected distance acuity
	Habitual small reading speed
	Confusion Index
	Esterman efficiency score

Table 5.18. Variables entered into multivariate stepwise model.

In order to construct the model on the largest data set possible, CMS was not used as a predictor for the same reasons expressed in section 5.7.4. Model validity was assessed by the methods described in section 5.7.3. The same results were produced when variables were entered in a forwards, backwards and mixed manner. Corrected visual acuity predicted visual ability to an r^2 value of 0.38 ($p < 0.001$). No other visual function variables made a significant independent contribution to the variance in baseline AI. Table 5.19 shows the r^2 value, adjusted r^2 and significance level.

Step	Variable	r^2	Adjusted r^2	p value
1	Corrected distance acuity	0.38	0.37	< 0.001

Table 5.19. Results of multivariate stepwise model as described in table 5.14.

The 0.01 difference in r^2 and adjusted r^2 indicates this model would predict 1% less variance in visual ability if applied to the wider population.

5.8.2 Stepwise model validity

Figure 5.16 suggests model residuals approximate a normal distribution and figure 5.17 indicated linearity and homoscadasticity of model residuals.

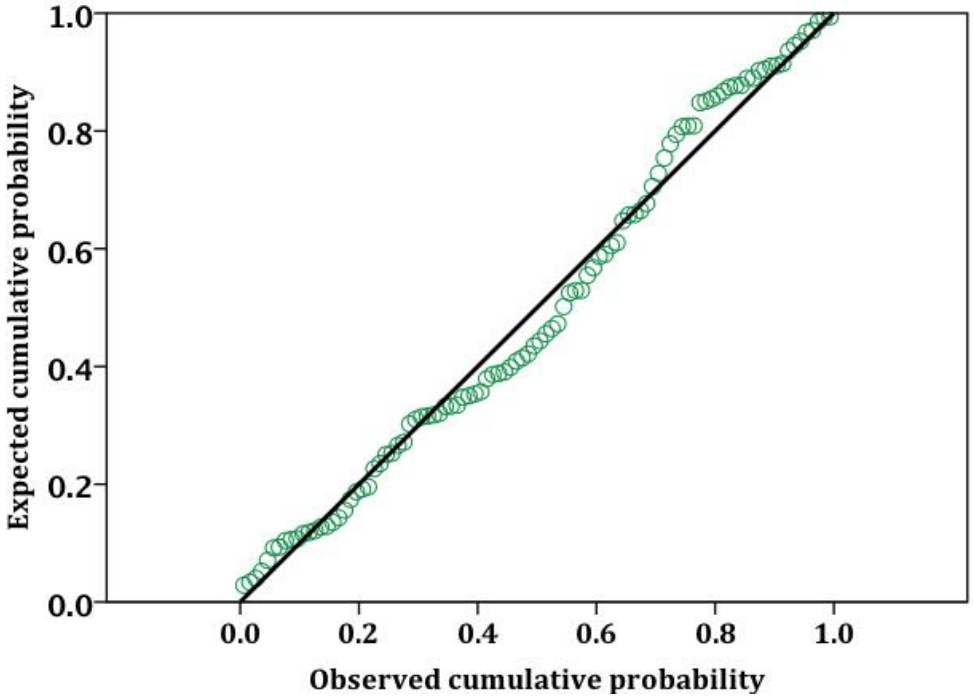

Figure 5.16 Normal probability plot of multivariate stepwise model residuals. The points follow the identity line suggesting model residuals approximate a normal distribution.

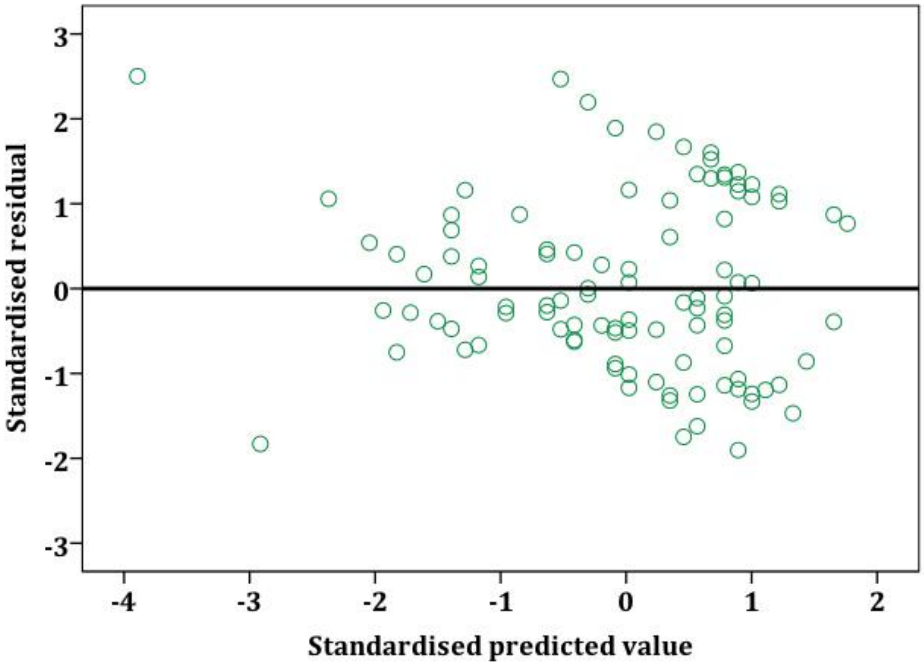

Figure 5.17 Scatterplot of standardised residuals against predicted values from the multivariate stepwise model. Random scatter of points around the y = 0 line suggests the assumptions of homoscedasticity and linearity of residuals were met.

5.9 Summary of results

In the present study, all visual function variables except fixation stability were significantly associated with disease severity. The distribution of log BCEA values reported here, closely matched those observed in patients with diabetic maculopathy presented in chapter 3 (2.90 ± 0.45 versus 2.94 ± 0.88).

A monotonic relationship between severity group and visual function was not demonstrated. As described in section 2.1.3, each severity group captures increasingly severe NGP diagnoses, however groups 3 and 4 include multiple diagnoses. Therefore this conclusion cannot legitimately be extrapolated to NGP steps. Furthermore, the lack of a significant trend may also reflect the small sample sizes within each severity group.

Results suggest that self-reported visual ability declines with increasing severity. Visual ability was significantly worse in those with severe non-proliferative retinopathy with maculopathy compared to severe non-proliferative retinopathy without maculopathy. Potentially the addition of maculopathy may be responsible for this significant reduction. Indeed it has been speculated that patients with type 2 diabetes and macular oedema experience significantly worse vision related quality of life than type 1 patients with diabetic retinopathy[237].

Recoding of severity groups, separating those with and without maculopathy demonstrated that lowest visual ability was indeed found in those with maculopathy

(proliferative retinopathy with maculopathy: 1.07 logits, followed by severe non-proliferative retinopathy with maculopathy: 1.61 logits). However the only significant break in the function between adjacent severity groups occurred between those with severe non-proliferative retinopathy without maculopathy (3.12 logits) and proliferative retinopathy without maculopathy (1.77 logits).

As all visual function measures except fixation stability displayed statistically significant univariate correlations with visual ability, multivariate techniques were used to explore the possibility that a combination of visual function measures provide the best prediction of visual ability. However, a single measure of corrected acuity alone provided the best prediction, explaining 38% of the visual ability.

Chapters 7, 8 and 9 describe the methods and results of an RCT investigating the effectiveness of a hospital based low vision clinic appointment in patients with DED. As described in the Introduction, factors associated with visual ability in the current chapter were explored for their influence on the outcome of a low vision clinic appointment.

On the basis of the results described above, subgroups were defined on the basis of severity group, scotoma size and corrected distance acuity.

Scotoma size, defined as the number of relative or absolute scotoma points within 10° of fixation was used as a surrogate for maculopathy as lowest visual ability

scores were found in those with maculopathy irrespective of their underlying level of retinopathy .

Chapter 6 – Discussion: Fundamental research on the impact of diabetic eye disease

The results presented thus far provide a comprehensive assessment of visual function in a large sample of participants with a wide range of DED severity levels. Additionally, the impact of multiple functional deficits and severity on self-reported visual ability has been explored using a Rasch validated instrument.

Though reduced visual function in DED has been presented previously, in the main, studies have focused on only one or a limited number of visual function measures[18, 24, 53, 54, 61, 68, 76, 80, 81, 84, 169, 174, 237-243], included a limited range of disease severity stages[18, 54, 68, 174, 241, 242] or have not employed patient reported outcomes measures (PROMs)[18, 24, 53, 54, 61, 68, 76, 169, 174, 239-242]. Where PROMs have been employed, scores have often been based on summing Likert responses, treating ordinal data as interval measures[35, 80, 81, 84, 85, 237, 243, 244]. Lamoureux and colleaugues used Rasch scaled measures of vision specific functioning in an investigation of the impact of diabetic retinopathy, however visual acuity was the only visual function measure included[87].

6.1 Recruited participants

The majority of participants were male with type 2 diabetes. The average age of participants was 56.7 years, similar to that reported in other studies of diabetic patients[85, 87, 143, 245]. 75% had a longstanding diagnosis of diabetes of more than 12

years, having been diagnosed with DED more than 3 years earlier. A wide spread of severity levels was represented, favouring those with proliferative retinopathy (36%) and mild to moderate non-proliferative retinopathy (25%). 32% had either current macular oedema or previously treated maculopathy.

Substantial variation in the visual status of participants with DED was observed, due to the wide eligibility criteria employed. However, the participants in the current study are broadly representative of those with diabetic eye disease in other studies of DED.

With median values of 0.04 logMAR and 1.4 logunits, corrected distance acuity and contrast sensitivity were better than that recorded in a study of disability related to diabetic retinopathy (median 0.3 logMAR and 1.25 logunits respectively)[246]. However Cusick and colleagues, in a study of central visual function in people with diabetes and a range of severities found very similar acuity levels (mean 0.1 logMAR, 13% worse than 0.3 logMAR). Contrast sensitivity on the other hand was better, with only 23% of patients having a contrast sensitivity of less than 1.5 log units compared to a value of 63% in the present study[85].

Variation in self-reported visual functioning measures of diabetic patients has also been observed in previous works. Median visual ability of participants in the current study was 1.64 logits, considerably higher than that found by Ahamdian and Massof (mean 0.55 logits)[143], yet less than that encountered in the Malay Eye Study (mean 3.24 logits)[87]. Median values were not presented in either instance.

This disparity may reflect differences between the samples from which these values were drawn. For example, 100% of Ahmadian and Massof's participants had diabetic eye disease (DED) and the majority had visual acuity between 6/9 and 6/48 (20/32 and 20/160). Only 23% of participants within the Malay Eye Study had diabetic retinopathy and 93% had visual acuity better than 0.3 logMAR (6/12). Furthermore, whereas Ahmadian and Massof employed the goal level AI, the Malay Eye Study utilised the VF-11[126], a Rasch modified version of the VF-14[124]. However, the VF-14 and AI have previously been shown to provide estimates of the same visual ability variable (Pearson correlation between person measures from the AI and VF-14 was 0.86)[120]. To date, no comparison of person measures from the VF-11 and AI has been published.

6.2 Fundamental research on the impact of diabetic eye disease

Chapter 5 presents the results of the first comprehensive study of visual function in DED and its relationship with disease severity and self reported visual ability.

6.2.1 Aim 1 – To explore the impact of disease severity on visual function

The results presented in section 5.5 suggest visual function decreases with increasing severity, however a monotonic trend with severity was not observed.

All visual function variables except fixation stability were associated with severity group once adjusted for age, sex, type of diabetes, duration of diabetes and duration

of DED (r^2 = 0.24 – 0.47, p ≤ 0.002). Similar relationships have previously been presented for visual acuity[24, 53, 54], contrast sensitivity[54], colour vision[54, 57] visual fields[53] and retinal microperimetry[63]. Fixation stability and reading performance measures do not appear to have been investigated previously for their association with disease severity in DED.

Given that the majority of diabetic patients retain central, stable fixation in the presence of maculopathy[63, 247], the lack of relationship between severity and fixation stability may not be surprising. However, fixation stability in patients with diabetic maculopathy has previously been shown to be worse than normal controls[69]. Data were reanalysed, comparing log BCEA values in those patients with macular involvement (n = 28) and those without (n = 64). Mean log BCEA values differed by 0.06 log min arc^2 between the 2 patient groups. This was not statistically significant (p = 0.57).

Of the visual function variables considered in this study, strongest associations with severity groups were observed for corrected distance acuity (r^2 = 0.47, p < 0.001) and MP-1 microperimetry measures: mean sensitivity (r^2 = 0.42, p < 0.001), mean defect (r^2 = 0.42, p < 0.001) and paracentral mean sensitivity (r^2 = 0.42, p < 0.001).

These results contradict those of Bengtsson who reported disease severity correlated more strongly with visual fields than logMAR visual acuity[53]. This may reflect differences in both the method of assessment (Humphrey VFA, 24-2 Swedish Interactive Threshold Algorithms (SITA) Standard White on White perimetry) and

the disease severity classification methods (11 steps of the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale[248]) employed.

Similar microperimetry measurements in diabetic patients without retinopathy have been considered by Verma and colleagues, who reported significantly lower mean sensitivity in the absence of retinopathy than in age matched normal controls[62]. Furthermore, Nittala and colleagues recently examined retinal sensitivity with the MP-1 in patients with increasingly severe diagnoses ranging from mild non-proliferative, moderate non-proliferative, severe non-proliferative and proliferative retinopathy[63]. Severity group was significantly associated with decreasing mean retinal sensitivity, however between groups comparisons were not reported.

An additional reading measure, reading index has been defined in the literature. Originally defined as reading speed divided by reading acuity[249], it has been latterly used to express reading speed divided by of critical print size[250] and has been shown to be a useful predictor of self-reported performance on vision dependent daily living tasks and visual ability[249, 250]. Proponents of the measure point to the inability of critical print size to distinguish those who read quickly at their critical print size from those who read slowly at their critical print size. However, to the person reading at their most fluent level, speed may be trivial if they are able to comprehend the text.

Reading index was calculated retrospectively by dividing corrected peak reading speed by corrected critical print size. Though significantly related to severity

grouping ($r^2 = 0.24$, $p = 0.001$), the strength of the association was less than that for critical print size.

Duration of diabetes did not appear to have a significant impact on visual function. Of the 18 visual function measures in this study, only efficiency score was significantly related (see table 5.5). This is consistent with previous findings of non-significant relationships between visual acuity, contrast sensitivity, central fields, fixation stability and duration of diabetes[54, 68, 251]. Findings are mixed with regard to colour vision; it is inversely related to duration of disease in some studies[19, 54, 174, 252], but not in others[59, 170].

6.2.2 Aim 2 – To explore the impact of disease severity on visual ability

The results presented in section 5.6 suggest visual ability decreases with increasing severity. A moderate association with severity was observed ($r^2 = 0.27$, $p < 0.001$). A monotonic relationship between visual ability and severity was not observed, though visual ability scores in group 3 were significantly lower than in group 2.

A fundamental difference in the composition of groups 3 and 4 compared to the remaining two groups is the inclusion of participants with maculopathy, either active or treated. In fact, visual ability in those with maculopathy was 1.37 logits, compared to 2.63 in those without ($p = 0.008$).

Analysis separating those with and without maculopathy suggested the presence of maculopathy alone did not account for the significant difference between group 2

and 3 despite those with maculopathy having the lowest visual ability scores, as those with proliferative disease also had significantly reduced visual ability.

This break roughly dichotomises participants into those who may need treatment and those who may not. Quality of life has been shown to decline following first time laser photocoagulation[91], however vision related quality of life (VRQoL) improves over subsequent treatments[75]. Improved VRQoL has also been reported following vitrectomy for proliferative retinopthy[253]. Therefore it is not possible to attribute the break in the function entirely to the fear of treatment. Certainly it seems likely that the presence of maculopathy contributes to declining visual ability.

These findings mirror those of Lamoureux and colleagues who found that patients with sight threatening retinopathy (defined as severe non-proliferative retinopathy, proliferative retinopathy or clinically significant macular oedema) or proliferative retinopathy were significantly more likely to report difficulty with vision related daily activities[87]. In fact, persons with vision threatening retinopathy were up to 6 times more likely to report poor functioning when compared to those with less severe disease (odds ratio (OR): 6.14, 95% CI: 2.22, 16.96), the value rising to up to 12 times when those with proliferative disease were considered (OD: 12.07, 95% CI: 2.41, 60.40).

6.2.3 Hypothesis – The reduction in visual ability associated with increasing disease severity is explained by visual function deficits

All visual function measures, except log BCEA, displayed moderate significant univariate correlations with visual ability ($r = -0.59$ to 0.30, $p = 0.002$ to < 0.001).

As participants respond to patient reported outcome measures (PROMs) from the standpoint of their everyday vision, it seems reasonable to expect that habitual measures of visual function offer more useful predictions of visual ability than their corrected counterparts. Contrary to this, strongest univariate correlations were observed for corrected distance acuity ($r = -0.59$), corrected critical print size ($r = -0.57$) and corrected reading acuity ($r = -0.52$), with their habitual counterparts displaying weaker associations (habitual distance acuity: $r = -0.50$; corrected near acuity: $r = -0.42$). This may reflect a learning effect due to the order of testing, as habitual measures were undertaken before corrected.

This is consistent with earlier findings; corrected visual acuity displayed a much strong correlation ($r = -0.42$, $p < 0.05$) with self reported visual specific functioning than that observed for presenting acuity ($r = -0.19$, $p < 0.05$) in a study of the impact of diabetic retinopathy[87].

Multivariate regression techniques were employed to ascertain whether severity groups were independently associated with visual ability following adjustment for visual function measures. The 18 visual function variables examined were condensed to 7 variables; corrected distance acuity, contrast sensitivity, habitual

small reading speed, C-Index, Esterman efficiency score, central mean sensitivity and log BCEA. These 7 variables were selected as the optimal set of measures that would describe all aspects of visual function measured, whilst minimising potential multicollinearity.

Models examining the relationship between visual ability and severity plus 1 visual function measure at a time explained between 23 and 41% of the variance of visual ability. All visual function variables except fixation stability made an independent contribution to the variance accounted for. Severity remained an independent predictor in all models, except in that containing corrected distance acuity.

A further model, including all severity and visual function variables except fixation stability accounted for 34% of the variance in visual ability (adjusted $r^2 = 0.21$). Severity did not make an independent contribution; rather corrected visual acuity was the only significant predictor.

Due to the inclusion of central mean sensitivity, this model included data from 79 participants only. A further model was constructed, excluding central mean sensitivity and therefore including data on 95 participants, the results of which also indicated that disease severity group did not produce an independent influence on visual ability.

The combination of the remaining visual function variables and severity groups accounted for more variance in visual ability ($r^2 = 0.45$, $p < 0.001$), with an improved

adjusted r^2 of 0.40. Again, corrected visual acuity was the only independent predictor of visual ability.

The increased r^2 (and adjusted r^2) likely reflects the wider range of visual ability and visual function measures included in the model. The assumptions of normality, linearity and homoscedasticity of residuals were adequately met in each version of the model and no significant multicollinearity was observed.

Significant association between disease severity and self-report measures of health and vision related quality of life have been reported elsewhere[80, 81]. However, in agreement with the recent findings of Hirai[84] and Cusick[85], these results support the hypothesis that disease severity per se does not influence self reported visual ability, but rather the reduction in visual acuity that occurs as severity increases, negatively impact on the person's perception of their visual ability.

Currently, patient reported outcome instruments are not employed routinely in ophthalmology and optometry care in the UK. There has however been a shift of focus in research literature over the last decades, concentrating heavily on such measures[114]. It would be useful for clinicians to know which visual function test or combination of tests provide the closest approximation of self reported visual ability.

6.2.4 Exploratory analysis - Which visual function variables provide the best estimate of visual ability?

Many authors have argued that reliance on visual acuity alone underestimates the true extent of a person's visual disability[73-77]. However, despite employing an extensive range of visual function measures, we could not account for any significant additional variance in visual ability beyond that captured by corrected measure of acuity. Of the visual function variables considered, corrected distance acuity alone accounted for 38% of the variance of visual ability. Although a comprehensive battery of visual function tests was employed, it is possible that associations between other measures not included here may augment this finding.

Recently, an extensive battery of visual function tests was examined for their association with visual ability measurements captured with the Activity Inventory in 100 patients attending a low vision clinic[250]. Tests included distance acuity, reading performance, contrast sensitivity, binocular static threshold central visual fields and stereopsis. The study also examined the effect of psychosocial factors on responses; this will be discussed later in the chapter.

Mean goal level visual ability was 1.98 logits, comparable to that observed in the current study (median: 1.64 logits), however visual function was poorer (mean distance acuity = 0.84 logMAR, mean contrast sensitivity = 1.10 logunits, mean reading acuity = 0.81 logMAR). Despite this, correlations between visual ability and visual function measures were strikingly similar (distance acuity r = -0.60 versus r =

-0.59: with contrast sensitivity r = 0.53 versus r = 0.51: with reading acuity r = -0.64 versus r = -0.52).

Multiple regression indentified that a trio of distance acuity, reading index and mean sensitivity within a ring extending between 10° and 30° of fixation (termed outer ring) explained 53% of the variance of goal level visual ability, with distance acuity displaying the strongest association (distance acuity: $r^2 = 0.41$, reading index: $r^2 = 0.07$, 10° - 30° field: $r^2 = 0.05$).

Visual field measures used in the present study differ considerably from those employed above. Of the 2 perimetric tests performed, neither focused on the outer ring as described above. MP-1 microperimetry assessment examined the central 10° of fixation. Though paracentral mean sensitivity was calculated, it refers to the area between 4° and 10° from fixation which is considerably smaller and more centrally located. Furthermore, paracentral mean sensitivity was obtained for 83 participants only.

Binocular Esterman visual field testing covers an area 160° wide, extending 50° below and 30° above fixation, however as a suprathreshold test it lacks the sensitivity of the threshold testing employed in the above study. Additionally, 42% of participants had full peripheral fields as quantified by a perfect efficiency score of 100, with a further 41% scoring 90 or more. Therefore, if an association between peripheral fields and visual ability existed, it is unlikely that efficiency score would be sensitive enough to tease it out.

Excluding the variance attributed by the outer ring measure and reading index, these results approximate those obtained in our sample of diabetic patients, further supporting the conclusion of Ahmadian and Massof that visual impairment experienced by those with diabetic retinopathy is a result of the end impact of the disease on visual function rather than representing a condition specific pattern of disability[143].

A sizable proportion (62%) of unexplained variance still remains. Though consistent with other findings[250], it is possible that additional measures of visual function will provide further explanation. As mentioned above, stereopsis has been examined but proved not to be a significant predictor, however only 8 participants had measureable stereopsis[250].

Disability glare, the reduction of visual acuity or contrast sensitivity as a result of forward intraocular light scatter[254], has been reported in patients with DED, often more pronounced following laser photocoagulation treatment[255]. Debate exists as to the effectiveness of glare tests in the assessment of real world vision[256], though adverse affects of glare on driving performance have been demonstrated[257, 258]. The capacity of glare tests to predict self-reported symptoms has been found to be lacking in studies predominantly focused on patients with cataract[259-262]. However, Rubin and colleagues demonstrated glare sensitivity measured using the Brightness Acuity Tester (BAT; Mentor, Norwell, MA) represented an individual underlying component of self-reported visual disability, independent of the contribution of visual acuity, contrast sensitivity, stereoacuity and central visual field function[263]. It

is therefore possible that employing a glare sensitivity measure may have allowed explanation of unique variance in visual ability.

Furthermore, measurements of dark adaptation may also have influenced results as Henson and North found slower dark adaptation times and higher than expected absolute thresholds in 35 patients with DED, that were not related to disease severity[264].

Other tests of visual function have been previously described: Useful Field of View (UFOV)[265], dark adapted perimetry[266, 267] and microperimetry[268], though they have not been used in the examination of visual function in DED.

6.3 Factors influencing patient reported outcome measures

Recent evidence suggests that non-visual and psychosocial measures influence patient responses to self-report measures[250, 269]. As referred to previously, responses to the AI have been examined to establish the influence of psychosocial factors on visual ability[250].

A combination of visual function variables and psychosocial factors accounted for 69% of the variance of visual ability, of which 16% was unique variance attributed to psychosocial factors and a further 17% was shared with visual function[250]. Specifically, acceptance and self worth and depression were independently related to visual ability.

Existing evidence supports the hypothesis that psychosocial factors may influence the responses of persons with DED. Though it has been speculated that the combination of diabetes and visual impairment may accentuate mental health issues in patients with DED[92], the impact related to the underlying chronic condition from which these patients suffer should also be considered.

As Rubin states[101]:

> *'The psychosocial toll of living with diabetes is a heavy one….. Patients must deal with their diabetes all day, every day, making countless decisions in an often futile effort to approximate the non-diabetic metabolic state.'*

Many people with diabetes find keeping up with their treatment regimes tough, regardless of whether it involves dietary manipulation only or multiple daily doses of medication and glucose monitoring checks[270]. The extra stress and anxiety of dealing with diabetes and its effects on everyday issues can be detrimental to disease management[271] and therefore metabolic control, increasing the likelihood of long-term complications[270]. The occurrence of complications in itself can lead to increased stress, further raising the risk of psychological disorders such as depression and as such patients can easily become trapped in a vicious cycle[270]. Meta analysis has shown that a diagnosis of diabetes doubles the odds of co-morbid depression[272], which has been linked to worsening retinopathy status[273]. In a separate meta analysis, a consistent significant relationship was demonstrated between depressive symptoms and diabetic retinopathy[274].

Aside from depressive symptoms, other emotional reactions to diabetic retinopathy have been described including anxiety[94, 98, 270], emotional instability and low self-esteem[99], distress[99, 275], stress[96, 99] and fear[276]. It would appear that the emotional impact of diabetic retinopathy is not constrained to depressive symptoms, rather a range of emotional reactions may be involved[92].

Depressive symptoms have been shown to increase in the two years following a diagnosis of proliferative diabetic retinopathy, regardless of the extent of the associated visual impairment and irrespective of whether vision was recovered[96, 101]. In addition, it has been suggested that the fluctuating nature of vision in diabetes can present a greater psychosocial burden than that of complete vision loss[96, 275], indicating that any link with visual acuity may be a complex one.

An investigation of psychosocial adjustment to proliferative diabetic retinopathy demonstrated a significant psychosocial burden despite relatively mild visual impairment (mean acuity 20/25 or 6/7.5)[95]. Using the Psychosocial Adjustment to Illness Scale (PAIS)[277], a self report measure assessing the impact of medical illness on psychosocial functioning, Wulsin demonstrated that patients with proliferative disease reported significantly worse adjustment than diabetic patients without retinopathy. Greatest difficulties were reported in relation to vocational functioning, domestic roles, extended family relationships and social environment[95]. Furthermore, a significant correlation between visual acuity and PAIS scores existed; those with worse visual acuity exhibited more adjustment problems. The authors specifically highlight the need for further prospective studies investigating the

effectiveness of interventions aimed at reducing the psychosocial implications of progressive vision loss in DED[95].

Though Tabrett and Latham found no association between the AI responses of low vision clinic patients and social support and personality[250], these factors have previously be shown to influence health related quality of life (HRQoL) and mental health in diabetic patients[101].

Personality traits and coping strategies had a greater influence on HRQoL than the presence of other diabetic complications[278]. Peyrot and Rubin showed that people who believed they could effectively control their diabetes were less depressed and anxious than those who believed that their control was more a matter of chance[279]. Higher diabetes related social support was correlated with better HRQoL scores in patients with type 1 diabetes[280], and associated with better social functioning in patients receiving intensive insulin treatment[281].

Other non-visual factors have been described for their association with DED. Negative effects of DED on social and recreational activities have been described in numerous qualitative studies. Driving cessation[100, 127] has been cited as a barrier to a fulfilling social life, leading to increased social isolation and difficulty maintaining social interactions[92]. Withdrawal from social and recreational activities has also been reported, some using this as a protective mechanism to avoid the reality of their limitations[282]. Problems recognising faces[100] and feelings of being a burden to

others[282] caused anxiety around meeting new people and in the maintenance of existing relationships[92].

In the current study, items under the 'Social Activities' and 'Recreation' objectives of the AI would be expected to capture the visual related component of these difficulties. However difficulties in other domains of life, not specifically addressed by the AI have been described, namely family life and employment. Responses under each objective were not analysed separately as they do not represent independent domains[187].

Increased tension, anxiety and stress around family relationships have been reported due to the inevitable lifestyle changes brought about by both diabetes and diabetic retinopathy[92, 100, 127, 270]. Close personal relationships are also at risk, with visual impairment in diabetes cited as the predominant factor in marriage breakdown[99]. In fact, divorce rates were higher in diabetic patients with vision loss compared to those without vision loss[99]. These issues do not have an obvious visual component, however the associated emotions and worries experienced may contribute to AI variance in the manner that depressive symptoms have been shown to[250].

Issues around employment have also been raised. Focus groups of patients with sight threatening or proliferative retinopathy felt their vision problems greatly impaired their working life[127, 282], whereas those with less severe disease felt this not to be the case[100]. However over half the population of the latter study were retired. Patients with diabetic retinopathy were more often unable to work than diabetic

patients without retinopathy[283]. Given that diabetic retinopathy is the leading cause of registrable sight impairment in working age groups[12], visual difficulties encountered during or in the search for employment, together with thoughts and feelings around these issues need to be addressed in an attempt to measure visual ability in working diabetic patients. Indeed the development of a vocational objective within the AI has been alluded to by the authors, but to date this has not been published[187].

This omission may account for a proportion of the unexplained variance in our sample, as 78 of the 100 participants in this study were less than 65 years old.

Given published evidence, it seems likely that inclusion of specific measures of the psychosocial burden of DED and diabetes may have facilitated the explanation of a larger proportion of the variance of visual ability in the present study.

6.4 Study limitations

Full visual function data were collected on 79% of participants. Of the 18 variables assessed, 6 had data on all 100 participants and 12 had data on at least 95%.

The majority of missing data points were related to measurements derived from the MP-1 assessments (6 variables). Two main problems were encountered. Several participants opted out of the assessments due to tiredness. As dilation was required, it was necessary to perform assessment once all other visual function measures had

been attempted. In addition, inability to track the infrared fundus image was encountered on several occasions. This may suggest that reliance on ophthalmologists grading of lens opacities was not sensitive enough to exclude those with visually significant cataract. However, even in instances of mild cataract, tracking may have proved difficult because unlike in age related macular degeneration, a diabetic retinopathy fundus often does not have a prominent high contrast area to track such as a disciform scar.

Use of a new instrument, the MAIA microperimeter (Centrevue S.p.A., Padova, Italy), which was not available at the outset of this study, may have avoided both of these issues. Employing a line scanning laser ophthalmoscope system rather than an infrared camera, the fundus images produced are of superior quality. Also, with a minimum required pupil diameter of 2.5mm, dilation is rarely required, cutting the overall visual function assessment time by at least 20 minutes and allowing microperimetry to be carried out at any stage of the assessment.

Data were not missing at random; those with missing data were significantly older, with worse visual function and visual ability measures. Attempts were made to account for this by running analyses on those with full data only and after exclusion of those with missing data with respect to investigating the relationship between visual ability and disease severity and in multivariate regression models examining the effect of multiple visual function variables and severity on visual ability. In either case, the trend of results was the same whether those with missing data were excluded or not.

In the case of the multivariate regression model, inclusion of the majority of participants with missing data (n=95) by excluding central mean sensitivity from the model accounted for more of the variance in visual ability (from 34% to 45%). As those with missing data had significantly worse visual function and visual ability, this likely reflects stronger correlations over the larger range of abilities and function included. This step also reduced the difference between r^2 and adjusted r^2 values from 0.13 to 0.07, indicating increased generalisability of results to the wider population.

Caution should be exercised in the interpretation of the relationships between the severity groups presented here. The severity groups used were defined by the study team and were designed to reflect increasingly severe disease. In retrospect, they have a number of limitations, which may have contributed to the failure to find significant monotonic trends between severity and visual function or visual ability.

Groups 3 and 4 combine multiple National Grading Protocol (NGP) steps. Group 3, 'Severe non-proliferative with macular involvement' includes those with current maculopathy and previously treated maculopathy. Group 4, 'Proliferative retinopathy' includes those with active proliferative disease and those with previously treated proliferative disease who may or may not have current maculopathy or previously treated maculopathy.

The wide range of diagnoses included in group 4, in particular the inclusion of persons both with and without maculopathy, reflects the broad spread of visual

function measurements obtained within the group, particularly for distance acuity, contrast sensitivity, reading measures, Esterman efficiency score, and microperimetry measures as demonstrated in figures 5.1 to 5.4. Those without maculopathy accounted for 69% of group four (25/36) and retained very good visual function (median visual acuity: 0.07 log MAR, IQR: -0.11 to 0.17; median contrast sensitivity: 1.43 log units, IQR: 1.19 to 1.55). Though data were analysed accounting for heterogeneity within group 4, power was lost due to the reduction in numbers within each group.

Additionally, the group definitions did not allow the inclusion of patients with mild to moderate non-proliferative retinopathy with macular involvement. This resulted in a number of potential recruits being ineligible. Maculopathy can occur at any stage of the condition[284] and as such group definitions should have allowed for this.

Furthermore, as visual function declines prior to the presentation of DED[19, 54, 58-62], inclusion of diabetic patients without DED would have facilitated a more detailed examination of link between severity and visual function measures.

Diabetic control was not monitored throughout this study. Numerous studies have investigated the link between HbA1c and visual function. With the exception of contrast sensitivity[76, 174], the evidence favours the conclusion that visual acuity, colour vision, visual fields and fixation stability are not significantly associated with HbA1c levels[19, 59, 68, 169, 174, 238, 285, 286]. It is therefore unlikely that lack of monitoring substantially affected the results presented here.

6.5 Summary of main findings

These findings describe the impact of DED on a comprehensive range of visual functions and patient reported visual ability.

Increasing severity of DED impacts negatively on visual function, though a monotonic trend was not observed.

Increasing severity also negatively impacts on patient reported visual ability. Although a monotonic trend was not demonstrated, visual ability was significantly lower in those with severe non-proliferative retinopathy with maculopathy compared to those with severe non-proliferative retinopathy without maculopathy.

The reduction in visual ability experienced can be explained by the reduced visual function that accompanies increasing severity. Disease severity does not make a unique contribution to visual ability. The best prediction of visual ability is provided by a single binocular best-corrected measure of acuity, explaining 38% of the variance.

Numerous psychosocial factors influence quality of life in diabetes and DED[92, 101]. Indeed psychosocial factors have previously been shown to correlate with PROMs, independently of visual function correlates[250, 269]. It would seem likely therefore that psychosocial factors might explain additional variance in visual ability.

6.6 Implications of findings

It has often been proposed that visual acuity alone does not capture the true extent of a person's visual impairment[73, 75-77]. A corrected measure of acuity may provide the closest approximation of visual ability in patients with DED. It should be stressed that the measure of acuity used, 'corrected distance acuity' refers to a binocular measurement, following accurate refraction, employing letter by letter scoring, on a logMAR chart. Standardisation of the method of measurement may be in part responsible for the strength of the relationship. A simple habitual Snellen measurement, often performed by ophthalmic staff prior to an ophthalmology clinic appointment, may not yield a similar association.

We speculated that a low vision clinic appointment may be more beneficial to those with reduced visual ability. On the basis of these findings, participants with more severe disease, maculopathy or reduced visual acuity may be the best candidates for low vision intervention.

As such, 3 subgroups analyses were planned to investigate this based on

- Disease severity group
- Corrected distance acuity
- Scotoma size

Scotoma size, defined as the number of relative or absolute scotoma points within the central 10° of fixation, was chosen over other microperimetry variables as

although the Nidek MP-1 is not widely used, scotoma size can be assessed with other perimetry instruments.

Chapter 7- RCT Methodology: Effectiveness of a hospital based low vision clinic appointment

7.1 Participants

Following all baseline examinations as described in chapter 2, all participants were enrolled into a randomised controlled trial (RCT) investigating the effectiveness of low vision intervention in those with diabetic eye disease. The RCT had two arms: immediate intervention (intervention within 2 weeks of enrolment) and delayed intervention (intervention 3 months after enrolment).

7.2 Randomisation

Participants were allocated by minimisation to one of two arms; immediate or delayed intervention. The minimisation procedure incorporated 4 weighted factors: corrected distance acuity (weighted 4), disease severity grouping (weighted 3), age (weighted 2) and sex (weighted 1), using 'Minim', a freely available minimisation programme available from www.sghms.ac.uk/depts/phs/guide/randser.htm. Access to the procedure was held by a statistician in the Research and Development department of Moorfields Eye Hospital.

Reduced visual acuity has been associated with reduced health and vision related quality of life in many studies[35, 243, 287-290]. An association between disease severity

and health-related quality of life has also been described; however the effect of severity appears an indirect one mediated by reduced visual acuity as severity increases[81]. Therefore, visual acuity was given more weight in the minimisation procedure.

A visual acuity cut off of 0.2 LogMAR was chosen as evidence suggests that even a mild restriction in visual acuity can impact negatively on quality of life[243, 290]. Specifically a 10 letter drop in LogMAR acuity (equivalent to 2 lines) produced significantly reduced NEI-VFQ scores in patients with diabetic retinopathy[243].

Conflicting opinions exist on whether age or sex is significantly correlated with health related vision quality of life measures. Chia reported slightly poorer SF-36 scores for females than males and a strong negative correlation between age and SF-36 scores[287]. However more recently in a longitudinal study of people with diabetic retinopathy no significant association between NEIVFQ-25 scores and either age or sex was found[243]. This apparent ambiguity reflects the decision to give age and sex lower weights in our minimisation procedure.

7.3 Intervention schedule

Those on the immediate intervention arm received intervention within 2 weeks of enrolment. Three months after enrolment, HR contacted all participants by telephone and asked them to repeat the AI. Those on the delayed intervention arm were scheduled to receive intervention within the next week. Six months after

enrolment all participants were contacted again to complete the final AI. The anticipated flow of participants through both intervention arms of the RCT is shown in figure 7.1, using the CONSORT template[291].

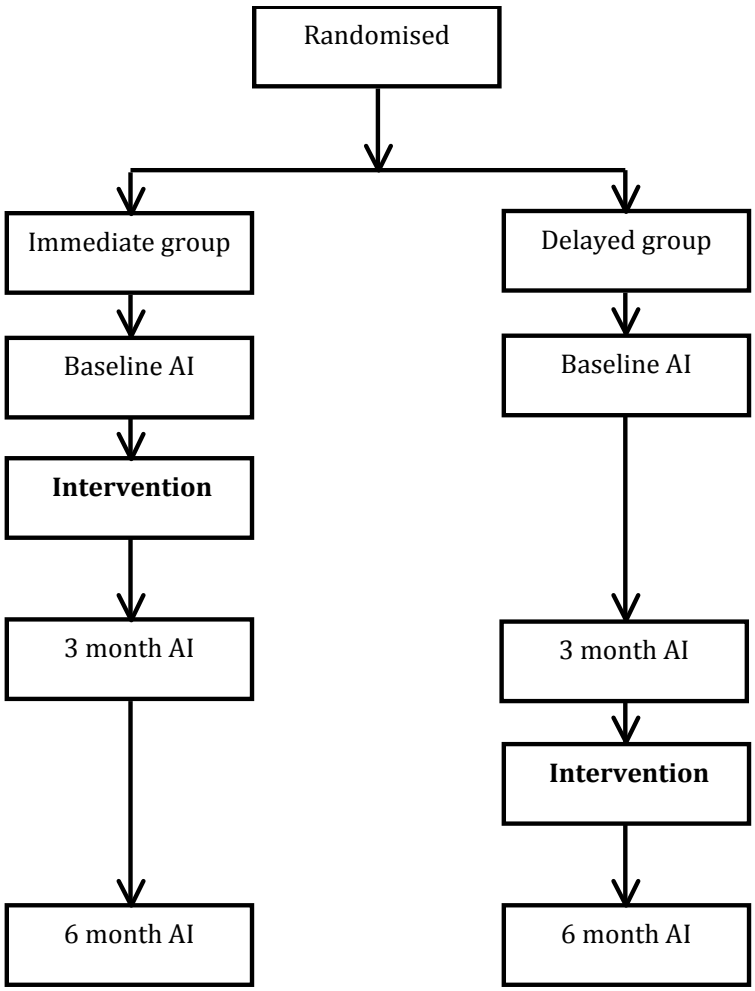

Figure 7.1 Anticipated flow of participants through both intervention arms of the RCT, AI = Activity Inventory.

7.4 Masking procedure and evaluation of success

HR was masked to the randomisation procedure and reminded participants not to reveal information regarding their allocation at the beginning of each administration of the AI. Any inadvertent masking violations were recorded and reported in

accordance with the CONSORT Statement[291]. On completion of the AI, HR guessed the allocation of participants, in order to evaluate the success of the masking procedure. Study design dictated that neither the participants nor optometrist responsible for administering the intervention could be masked.

7.5 Record of changes in management

At each administration of the AI, participants were asked whether there had been any change in the medical management of their diabetes, whether they had received additional laser photocoagulation and whether they had experienced any significant changes in their general health since the previous administration. Any changes were recorded as dichotomous yes/no variables.

7.6 Intervention

The intervention was a low vision assessment (LVA), conforming to the standard care provided to all low vision patients at Moorfields Eye Hospital and was consistent with previously published standards[158]. The assessment included:

- Assessing patient's understanding of their eye condition
- Discussing needs/visual requirements and setting initial goals
- Assessing distance and near acuity
- Determining appropriate levels of magnification

- Demonstrating selected low vision aids based on the results of the vision assessment and patient goals
- Determining visual aids to be prescribed and reviewing use and handling
- Discussing lighting and other methods of enhancing vision as appropriate
- Demonstrating electronic magnifiers where appropriate
- Discussing availability of other applicable services (e.g. social services, charitable organisations)
- Dispensing prescribed low vision aids on loan
- Arranging follow-ups as necessary

The same experienced low vision optometrist (HD) conducted all LVAs. Participants were deemed to have received the intervention even if low vision aids were not required.

7.7 Sample size

The software package PS for Windows (Version 2.1.31) was used to calculate the minimum number of participants required to detect a clinically significant difference in outcome measure, (difference in AI score at 3 months, between intervention groups)[292]. Calculation was based on detecting a 0.7 logit difference following rehabilitation, consistent with previous publications[107]. Standard deviation of the AI score was estimated at 1.0 logits (based on previously published data from AI questionnaires administered to Moorfields' low vision patients)[107]. Type I error rate (alpha) was set at 0.05 (two-tailed). For a power of 0.90 a minimum of 44 patients

per group was required. To allow for participant dropout, 50 participants were recruited onto each arm.

7.8 Data input and storage

Two of the databases described in section 2.6 were used for RCT data entry. 3 and 6 month AI response data were added to the anonymised AI database and intervention assignment was added to the patient details database.

The JMP (version 9, SAS Institute Inc. NC, USA) data table, also referred to in section 2.6 was updated to include all AI follow up data and intervention assignment once all data were collected.

7.9 Analysis plan

All analyses were carried out in JMP (version 9, SAS Institute Inc. NC, USA). Data were analysed using the intent to treat principle. Results were considered significant if $p < 0.05$. Analysis of covariance was used to determine the following primary and secondary outcomes.

7.9.1 Primary outcome

The primary outcome was the difference in AI score (adjusted for baseline AI score) 3 months after enrolment between those who received immediate intervention and those on a waiting list (control).

7.9.2 Secondary outcomes

Two secondary outcomes were defined. First, the difference in AI score (adjusted for baseline AI score) 6 months after enrolment between those who received immediate intervention and those who received delayed intervention (control).

Second, the difference in AI score (adjusted for baseline AI score) 3 months after intervention was delivered between those who received immediate intervention and those who received delayed intervention (control), i.e. at 3 months in the immediate group and 6 months in the delayed group.

This required the formation of 2 further variables: 'before intervention' and 'after intervention'. Before intervention records AI score immediately before intervention (month 0 AI score in the immediate group and month 3 AI score in the delayed group). 'After intervention' records AI score 3 months after intervention (month 3 AI score in the immediate group and month 6 AI score in the delayed intervention group).

Models were adjusted for the factors on which minimisation took place (as recommended by Taves[293]). Further sensitivity analyses were performed by

constructing an additional model adjusted for minimised factors plus 3 additional factors shown to be related to reduced quality of life[91, 101, 271]:

1) change in general health,
2) change in medical management of diabetes, and
3) the occurrence of additional laser photocoagulation throughout the time period in question

As described in section 6.6 of the previous chapter, exploratory subgroup analyses were conducted to investigate whether change in AI score following intervention was related to disease severity group, corrected distance acuity or scotoma size. As recommended by Altman, an interaction test was used to test whether the difference between results from sub groups was statistically different from zero[294].

The influence of corrected distance acuity was investigated by dividing participants into sub groups according to whether their baseline acuity fell above or below a threshold. The difference in mean change in AI score between arms within these groups was calculated as described above. As referrals to Moorfields Eye Hospital are currently made when vision drops below 6/12, a threshold of 0.3 LogMAR (6/12) was initially used. Sequentially lower thresholds (better acuity) were used to establish the level of corrected distance acuity at which patients may benefit from a referral for low vision services.

In order to investigate the influence of scotoma size, participants were again dichotomised according to scotoma size. The difference in mean change in AI score between arms within the 2 groups was calculated as above. Initially a threshold of 25 points was used. As the median value when all participants were considered, 25 points was chosen to ensure the largest possible sample size in each of the 2 subgroups.

As the number of participants within each subgroup was small, these analyses lacked sufficient power to provide definitive results and therefore were considered exploratory only.

7.10 Clinical trial administration

7.10.1 Ethical approval

Full ethical approval was granted by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (REC) (approval number 08/H0716/70). The study conformed to the tenets of the declaration of Helsinki.

7.10.2 Clinical trial registration

The trial was registered on a publically available trials database (http://www.controlled-trials.com/ISRCTN91672999).

7.10.3 Trial steering committee

In accordance with the CONSORT Statement[291], a trial steering committee was set up at the outset of the study to oversee and guide the management of the trial. The committee comprised an external chairperson, statistician, consultant ophthalmologist, patient representative and the study team. The committee met twice yearly to discuss management of the trial, recruitment progress, data collection and storage and subsequent dissemination of results.

Committee members
Tom Margrain – External chairperson, Cardiff University
Catey Bunce – Chief statistician, Moorfields Eye Hospital
Catherine Egan – Consultant ophthalmologist, Moorfields Eye Hospital
Sheila Burston – Patient representative

Chapter 8 – RCT Results: Effectiveness of a hospital based low vision clinic appointment

This chapter describes the results of the randomisd controlled trial (RCT) investigating the effectiveness of a hospital based low vision clinic appointment.

8.1 Trial participants

All 100 participants described in section 5.3 continued into this experiment.

8.1.1 Minimisation results

The minimisation procedure assigned 49 participants to immediate intervention and 51 to delayed (control). The intervention groups were well balanced for visual acuity (VA), disease severity, age and sex. Table 8.1 demonstrates the allocation of participants between intervention groups for each minimised factor.

	Immediate intervention n=49				**Delayed intervention n=51**			
Visual acuity	≤ 0.2 LogMAR n = 39		> 0.2 LogMAR n = 10		≤ 0.2 LogMAR n = 38		> 0.2 LogMAR n = 13	
Disease severity	1 n = 12	2 n = 10	3 n = 9	4 n = 18	1 n = 13	2 n = 11	3 n = 9	4 n = 18
Age	≤ 50 yrs n = 12		> 50 yrs n = 37		≤ 50 yrs n = 14		> 50 yrs n = 37	
Sex	Male n = 31		Female n = 18		Male n = 31		Female n = 20	

Table 8.1. Summary of minimisation results. Balance was achieved between intervention groups on visual acuity, disease severity, age and sex.

8.1.2 Balance of intervention groups

Aside from the factors on which minimisation was conducted, balance was achieved on participant characteristics and baseline visual function measures as demonstrated in table 8.2.

Baseline characteristics	Immediate n=49	Delayed n=51
Sex male : female	31 : 18	31 : 20
Age mean (range) years	58 (36 – 83)	56 (26 – 83)
Diabetes type 1 : 2	12 : 37	16 : 35
Duration of diabetes median (IQR) years	19 (12 – 30)	20 (12 – 27)
Duration of diabetic eye disease median (IQR) years	5 (4 – 10)	5 (3 – 9)
Disease severity groups 1 : 2 : 3 : 4	12 : 10 : 9 : 18	13 : 11 : 9 : 18
Corrected distance acuity median (IQR) LogMAR	0.00 (-0.08 – 0.18)	0.06 (-0.08 – 0.18)
Contrast sensitivity median (IQR) Log units	1.45 (1.30 – 1.55)	1.40 (1.25 – 1.55)
Corrected reading acuity mean (SD) LogMAR	0.11 (0.25)	0.11 (0.27)
Confusion index median (IQR)	1.72 (1.16 – 2.80)	1.64 (1.13 – 2.59)
Efficiency score median (IQR) %	98 (92 – 100)	99 (95 – 100)
Mean sensitivity median (IQR) dB	15.7 (13.1 – 17.3)	16.1 (13.7 – 18.0)
Scotoma size median (IQR) Number of points	41 (23 – 71)	35 (13 – 59)
Log BCEA mean (SD) log min arc^2	2.90 (0.54)	2.86 (0.33)
Baseline AI score median (IQR)	1.61 (0.65 – 3.63)	1.67 (0.58 – 4.75)

Table 8.2. Baseline demographic and visual function characteristics of those in each intervention group. IQR = interquartile range; SD = standard deviation, BCEA = bivariate contour ellipse area, AI = Activity Inventory.

8.1.3 Participant follow-up and missing data

Of the 100 participants who enrolled, 92 completed the study: 45 in the immediate arm and 47 in the delayed arm. Figure 8.1 shows recruitment and retention of participants throughout the study. Four participants withdrew from each arm. The reasons for withdrawal are specified in table 8.3.

Reason for trial withdrawal	Number of participants withdrawn from	
	Immediate arm	Delayed arm
Lost to follow up	1	1
Deceased	1	1
Illness	1	1
Withdrew without reason	1	1

Table 8.3. Summary of participant withdrawals per intervention arm.

Demographic, disease history and baseline visual function data from participants who withdrew were compared to data from those who completed the trial. Fisher's Exact Test was used for categorical data and analysis of variance (ANOVA) for continuous variables.

Participants who withdrew did not differ significantly from those who did not on sex, age, diabetes type, years since diagnosis of diabetes and years since diagnosis of diabetic eye disease ($p = 0.10 – 0.83$). Neither did they differ significantly on corrected distance acuity ($p = 0.41$), contrast sensitivity ($p = 0.37$) or baseline AI score ($p = 0.40$). These results suggest that participant withdrawals were at random.

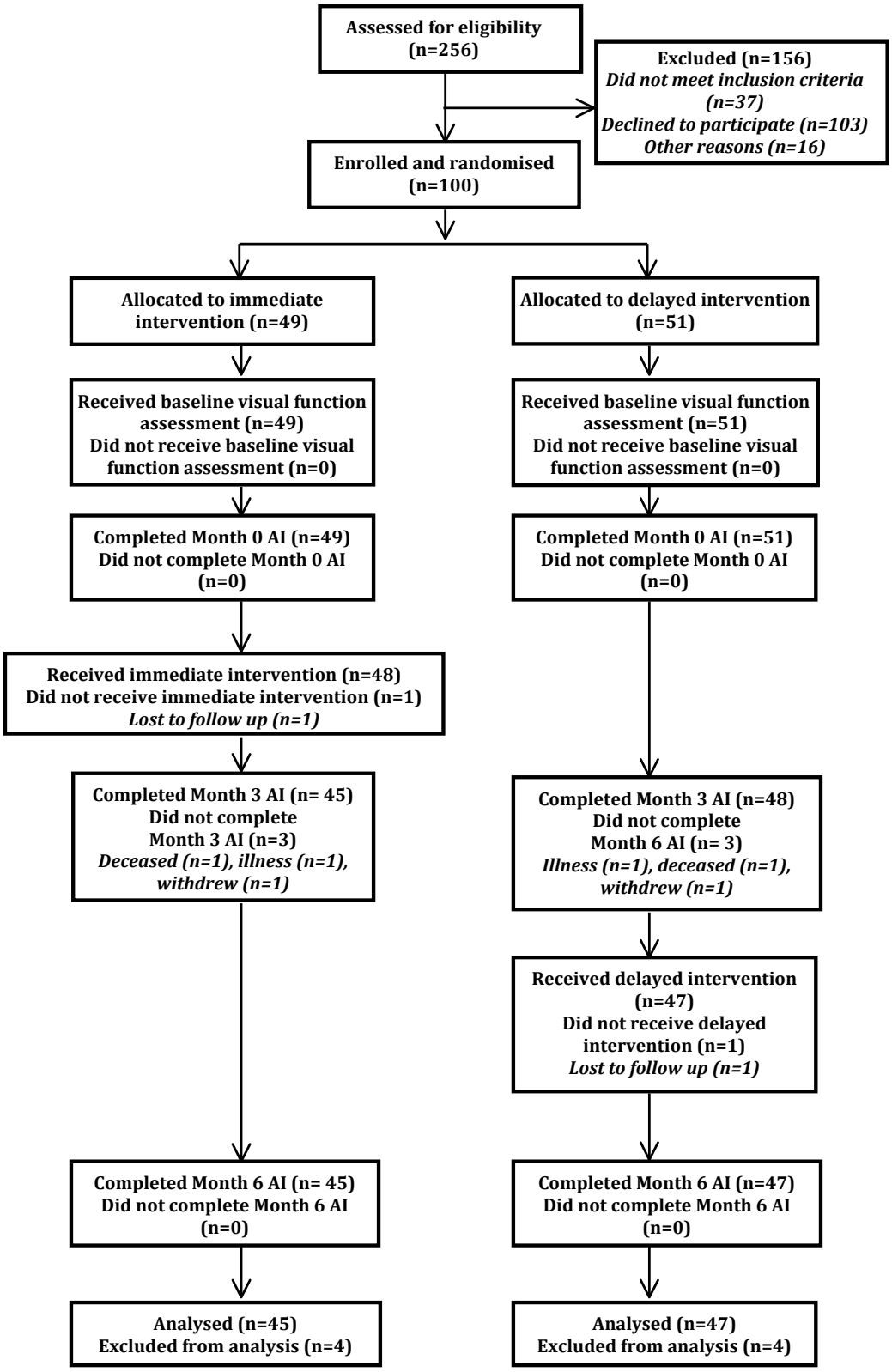

Figure 8.1. Flowchart of participant recruitment and retention. Italicised script describes the reasons for withdrawal.

Data from 45 participants in the immediate group and 47 participants in the delayed group were analysed, meeting the sample size requirement of 44 per arm. As intention to treat analysis is only possible when data sets are complete[295], trial data were analysed on an all available cases basis.

8.1.4 Trial timings

The day of randomisation was defined as day 0. Baseline AI was scheduled between day 1 and 7 (week 1), immediate low vision assessment (LVA) between day 8 and 14 (week 2), month 3 AI between day 78 and 84 (week 11), delayed LVA between day 85 and 91 (week 12) and month 6 AI between day 168 and 182 (weeks 24 – 26). Scheduled and actual timings are shown in table 8.4.

Trial step	Scheduled timing (days)	Median (IQR) day of occurrence
AI 0	1 – 7	4 (2 – 6)
Immediate LVA	8 – 14	13 (10 – 15)
AI 3	78 – 84	81 (79 – 84)
Delayed AI	85 – 91	90 (87 – 94)
AI 6	168 – 182	173 (169 – 179)

Table 8.4. Scheduled and actual day of occurrence of each administration of the AI and each LVA . AI = Activity Inventory, LVA = low vision assessment.

91% of month 0, 90% of month 3 and 88% of month 6 AI administrations occurred on time. For those participants who completed the trial, 73% of immediate LVAs occurred on time with the remaining 27% occurring within the following week. 72% of delayed LVAs occurred on time, 17% within the following week, 6% within the next 2 weeks and 1 delayed LVA was 19 days late.

8.2 Data input and storage

Responses from the Activity Inventory (AI) were recorded at month 0 (baseline), month 3 and month 6 and entered by a trained research assistant (HR) into a password protected database designed in Microsoft Office Access (Version 7.4). Data input was initially single entry. Input accuracy was assessed by re-entering 10% of data, selected at random. Double entered data was 100% accurate; therefore no further steps were taken. Winsteps (version 3.72.0; Chicago, Il.) was used to Rasch analyse all ordinal response data in accordance with the method described in Chapter 4.

8.3 Success of masking

HR was masked to the intervention allocation and conducted all AI telephone interviews. 18 (6%) inadvertent masking violations were recorded throughout the 285 telephone interviews (100 at month 0 + 93 at month 3+ 92 at month 6). HR correctly guessed participant allocation 56% of the time, a value consistent with chance.

8.4 Summary of intervention received

27 participants reported no visual problems. When this was encountered, a full refraction and visual assessment was still carried out and spectacles updated where

appropriate. Current diabetic control and risk factors for disease progression were discussed with all participants regardless of their symptoms, with advice given where appropriate. Participants were referred back to their general practitioner if they had queries of a medical nature.

The remaining participants reported a range of visual difficulties, with reading difficulties being the most commonly described, both prolonged reading and spot tasks such as reading price labels, medication and appliance controls. Participants also reported difficulty seeing faces, reading signage when using public transport, problems with glare and seeing in low light levels and visual disturbances linked to their diabetic control.

33 participants were prescribed new spectacles: 8 had both distance and near correction, 3 had distance correction only and 22 had near correction only.
27 participants (12 in the immediate group and 15 in the delayed) were prescribed at least 1 low vision aid. 41 aids were prescribed in total ranging from simple high reading adds, non-illuminated stand magnifiers, illuminated hand and stand magnifiers and distance binoculars and monoculars. Near aids were prescribed more often than distance aids (8 distance, 33 near). Mean corrected visual acuity of those receiving aids was 0.26 logMAR. Information was also provided on a number of different topics, or example computer accessibility and adaptive software, task lighting and use of contrast, glare control techniques, DVLA visual requirements, Access to Work, availability of large print reading materials, NHS stop smoking

service and sight impairment registration. A full description of aids and spectacles dispensed is given in appendix VII (table 6).

8.5 Summary of pre and post intervention data

A summary of the unadjusted AI scores in each intervention group at month 0, 3 and 6 is shown in table 8.5. Both median and mean values are given; medians as the data were not normally distributed and means to facilitate comparison with other studies. AI scores for all participants at months 0, 3 and 6 are provided in Appendix VII (table 5).

AI score	Visual ability (logits) Immediate n=45		Visual ability (logits) Delayed n=47	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
0 months after enrolment	1.87 (0.80 –1.87)	2.11 (2.22)	1.67 (0.64 – 5.45)	2.44 (2.21)
3 months after enrolment	1.80 (0.87 – 4.58)	2.39 (2.21)	2.15 (0.65 – 4.68)	2.56 (2.19)
6 months after enrolment	2.23 (0.52 – 4.51)	2.52 (2.24)	3.13 (1.15 – 5.48)	3.03 (2.20)

Table 8.5. Median and mean AI score at each administration of the AI for both intervention groups. AI = Activity Inventory, IQR = interquartile range, SD = standard deviation.

Further analyses rely on parametric tests and for this reason mean values will be reported in subsequent sections. Figure 8.2 shows mean AI score and 95% confidence intervals (CI) for each intervention group at month 0, 3 and 6.

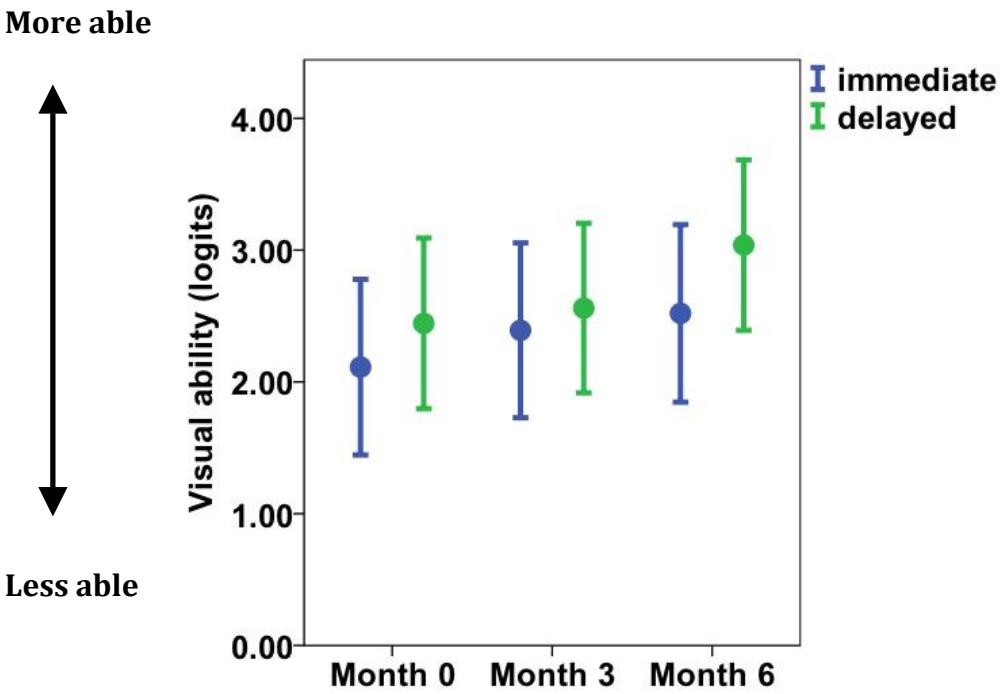

Figure 8.2. Plot displaying mean AI score (filled circles) with 95% confidence intervals at month 0, 3 and 6 per intervention group. Immediate group represented in blue, delayed in green.

AI scores adjusted for baseline AI (and the 4 factors on which minimisation took place) were calculated for each group at month 0, 3 and 6. A summary is given in table 8.6.

	Immediate AI scores (logits)		Delayed AI scores (logits)	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Month 0	2.11 (2.22)		2.44 (2.21)	
Month 3	2.39 (2.21)	2.33 (1.88)	2.56 (2.19)	2.24 (1.92)
Month 6	2.52 (2.24)	2.90 (2.21)	3.03 (2.20)	3.12 (2.19)

Table 8.6. Unadjusted mean AI scores (standard deviation) per intervention group 0, 3 and 6 from enrolment. Adjusted mean AI scores (standard deviation) adjusted for month 0 AI and the factors on which minimisation took place. All values in logits. AI = Activity Inventory.

8.6 Primary outcome – Adjusted difference in AI score between intervention groups 3 months after enrolment

Difference in AI scores between intervention groups 3 months after enrolment was assessed by analysis of covariance (ANCOVA) adjusting for month 0 AI score and the factors on which minimisation took place as shown in table 8.7. For simplicity, 'difference in AI scores adjusted for month 0 AI score and minimising factors' has been abbreviated to 'adjusted difference'.

ANCOVA, has two additional assumptions in addition to those made by ANOVA[234]:

1) Independence of covariates and independent variable

2) Homogeneity of regression slopes

The allocation of participants to intervention group according to the minimisation procedure ensured that the covariates (as shown in table 8.7) were independent of the independent variable.

All models constructed in the primary and secondary analyses included an interaction term, crossing month 0 AI score and intervention group. The interaction was not significant in any model, confirmed homogeneity of regression slopes (p = 0.26 – 0.94).

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Dependent variable	Independent variable	Co-variates
Month 3 AI score	Intervention group	Month 0 AI
		Binocular corrected visual acuity
		Severity group
		Age
		Sex
		Month 0 AI x Intervention group

Table 8.7. Variables used in ANCOVA investigating the adjusted difference between intervention groups after 3 months.

A positive adjusted difference indicates that the immediate group improved more (on average) than the delayed group. A negative value indicates that the delayed group improved more (on average) than the immediate group.

Three months after enrolment, the adjusted difference between intervention groups was +0.05 logits (95% confidence interval (CI): -0.18, +0.28). This difference was not statistically significant (p = 0.67).

8.6.1 Sensitivity analysis

In order to test the robustness of the covariates chosen, a further analysis was performed adjusting for change in medical management of diabetes; change in general health and receipt of additional laser photocoagulation.

Results of each of this analysis were essentially identical to that of the primary analysis (shown in table 8.8). Therefore all subsequent analyses were conducted adjusting for the factors included in the minimisation procedure and month 0 AI score only (as in table 8.7, excluding interaction term).

Outcome	Adjusted difference in AI score (95% CI)	p value
Primary outcome*		
• 3 months after enrolment	+0.05 (-0.18, +0.28)	0.67
Additionally adjusted analysis✣		
• 3 months after enrolment	+0.05 (-0.19, +0.29)	0.68

Table 8.8. Sensitivity analyses results. * adjusted for minimised factors, ✣ adjusted for minimised factors plus change in diabetic medication, change in general health and additional photocoagulation. Adjusted difference in AI score is expressed in logits. AI = Activity Inventory. CI = confidence interval.

8.7 Secondary outcomes

8.7.1 Adjusted difference in AI score between intervention groups 6 months after enrolment

Adjusted difference in AI score between intervention groups was -0.11 logits (95% CI: -0.37, +0.15). This difference was not statistically significant (p = 0.40). These results are summarized in table 8.9.

8.7.2 Adjusted difference in AI scores between intervention groups 3 months after intervention

To compare intervention groups 3 months after intervention, the model was adjusted for 'before intervention' AI score (as described in Chapter 7) as opposed to month 0 AI score as in the previous two models.

Adjusted difference in AI score between intervention groups 3 months after intervention was -0.15 logits (95% CI: -0.41, +0.11). This difference was not statistically significant (p = 0.25). These results are summarized in table 8.9.

Outcome	Adjusted difference in AI score (95% CI)	p value
Primary outcome		
• 3 months after enrolment	+0.05 (-0.18, +0.28)	0.67
Secondary outcomes		
• 6 months after enrolment	-0.11 (-0.37, +0.15)	0.40
• 3 months after intervention	-0.15 (-0.41, +0.11)	0.25

Table 8.9. Results of primary and secondary analyses. Adjusted difference in AI score expressed in logits. AI = Activity Inventory. CI = confidence interval.

8.8 Exploratory analyses

Three planned exploratory subgroup analyses were carried out, partitioning participants into subgroups according to:

- Disease severity group
- Baseline binocular corrected visual acuity
- Scotoma size

8.8.1 Subgroups analyses by disease severity group

As increasing disease severity is related to worsening visual ability, it was hypothesis that those with more severe disease would stand to gain more from the intervention.

Participants were divided into four subgroups according to their severity group (defined in section 2.1.3). Adjusted difference in AI score between intervention groups within each severity subgroup was examined 3 months after enrolment, 6 months after enrolment and 3 months after intervention using the methods described above.

The result obtained in severity subgroup 1 was compared in turn to the results obtained in subgroups 2, 3, and 4 using an interaction test[294]. A significant finding suggests the difference between the two results is significantly different to zero.

As severity group was included in the minimisation procedure, the number of participants in each intervention group was balanced within each severity subgroup. Data is displayed in table 8.10.

Severity subgroup	Total n=	Immediate n=	Delayed n=
1	23	11	12
2	19	9	10
3	15	8	7
4	35	17	18

Table 8.10. Distribution of participants between intervention groups per disease severity subgroup.

Across all comparisons, no significant adjusted differences in AI scores between interventions groups were found. Additionally, the difference between the result in severity subgroup 1 and all other subgroups was not significantly different to 0. A full description of these results is shown in tables 8.11 A, B and C. Table A shows adjusted differences in AI scores 3 months after enrolment, table B; 6 months after enrolment and table C; 3 months after intervention.

A

3 months after enrolment			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference compared to group 1**	**Interaction test p value**
1	-0.29 (-0.76, +0.18)		
2	+0.15 (-0.53, +0.83)	+0.44	0.21
3	+0.04 (-0.84, +0.92)	+0.33	0.31
4	-0.07 (-0.40, 0.27)	+0.22	0.29

B

6 months after enrolment			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference compared to group 1**	**Interaction test p value**
1	-0.40 (-0.92, +0.12)		
2	+0.16 (-0.67, +0.99)	+0.56	0.18
3	-0.36 (-1.57, +0.85)	+0.04	0.40
4	-0.02 (-0.37, +0.33)	+0.38	0.18

C

3 months after intervention			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference compared to group 1**	**Interaction test p value**
1	-0.43 (-0.93, +0.06)		
2	-0.25 (-1.29, +0.78)	+0.18	0.38
3	-0.37 (-1.60, +0.86)	+0.06	0.40
4	-0.22 (-0.49, +0.04)	+0.21	0.29

Table 8.11. A, B, C. Results of severity subgroup analyses. Table A gives adjusted differences in AI score between intervention groups 3 months after enrolment, table B, 6 months after enrolment and table C, 3 months after intervention (values in table C adjusted for before intervention AI score). Adjusted differences and difference compared to group 1 are expressed in logits. Difference compared to group 1 was calculated by subtracting the result from subgroup 1 from the result found in each of the subsequent subgroups. CI = confidence interval.

A graphical representation of these results is shown in figure 8.3. The adjusted difference in AI score with 95% confidence intervals is shown for each severity subgroup. The horizontal line represents no adjusted difference in AI score between intervention groups.

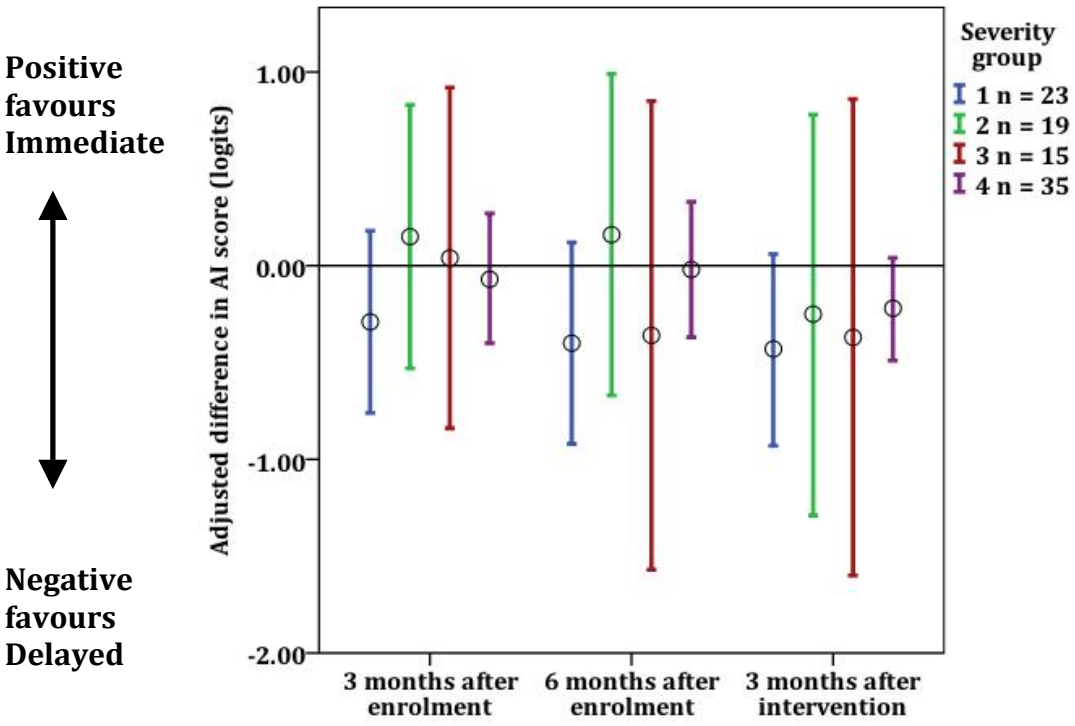

Figure 8.3. Plot displaying adjusted difference in AI score between intervention groups (open circle) and 95% confidence interval for each severity subgroup 3 months after enrolment, 6 month after enrolment and 3 months after intervention. The horizontal line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

As the results in section 5.6.2 indicated that a significant difference in baseline visual ability exists between group 2 and 3, a further analyses was carried out combining group 1 + 2 into one subgroup and groups 3 + 4 into a second subgroup.

Across all comparisons, no significant adjusted differences in AI scores between interventions groups were found. Additionally, the differences between results from each group at each time point were not significantly different to 0. These results are shown in tables 8.12 A, B and C. Table A shows adjusted difference in AI scores 3 months after enrolment, table B; 6 months after enrolment and table C; 3 months after intervention.

A

3 months after enrolment			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference between subgroups**	**Interaction test p value**
1+2	0.06 (-0.24, 0.35)	-0.04	0.39
3+4	0.09 (-0.24, 0.42)		

B

6 months after enrolment			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference between subgroups**	**Interaction test p value**
1+2	-0.06 (-0.52, 0.39)	+0.01	0.40
3+4	-0.07 (-0.42, 0.28)		

C

3 months after intervention			
Severity subgroup	**Adjusted difference in AI score (95% CI)**	**Difference between subgroups**	**Interaction test p value**
1+2	-0.20 (-0.65, 0.25)	-0.10	0.37
3+4	-0.10 (-0.46, 0.26)		

Table 8.12. A, B, C. Results of severity subgroup analyses comparing groups 1+2 to 3+4. Table A gives adjusted differences in AI score between intervention groups 3 months after enrolment, table B, 6 months after enrolment and table C, 3 months after intervention (values in table C adjusted for before intervention AI score). Adjusted differences and difference compared to group 1 are expressed in logits.

A graphical representation of these results is shown in figure 8.4. The adjusted difference in AI score with 95% confidence intervals is shown for each severity subgroup. The horizontal line represents no adjusted difference in AI score between intervention groups.

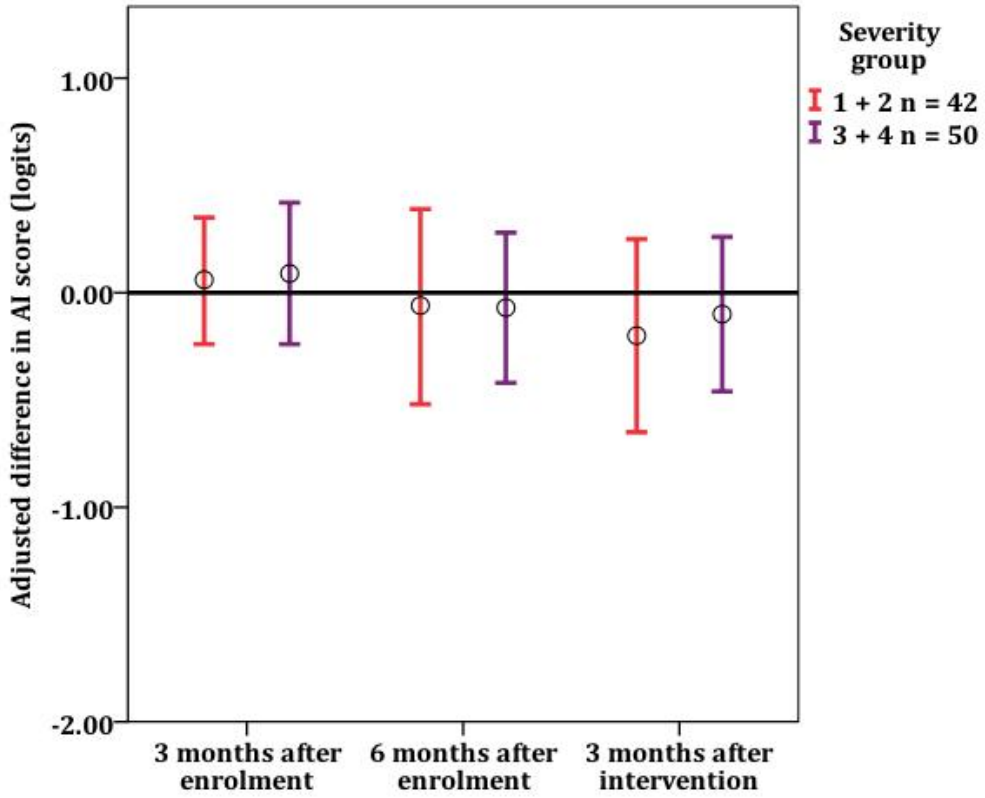

Figure 8.4. Plot displaying adjusted difference in AI score between intervention groups (open circle) and 95% confidence interval for combined severity subgroups (1+2 and 3+4) 3 months after enrolment, 6 month after enrolment and 3 months after intervention. The horizontal line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

8.8.2 Subgroup analyses by visual acuity

As demonstrated in chapter 5, a corrected measure of acuity was the single best predictor of visual ability from a comprehensive range of visual function tests. Therefore it was hypothesis that those with reduced acuity would stand to gain more from the intervention.

In order to investigate the influence of baseline visual acuity on the effectiveness of low vision intervention, participants were split into subgroups according to their baseline binocular corrected distance visual acuity.

Participants were divided into 2 subgroups according to whether their binocular corrected distance acuity at baseline was better than 0.3 LogMAR, or 0.3 LogMAR or poorer. The adjusted difference in AI score between intervention groups was calculated for each visual acuity subgroup. To examine whether results within each subgroup differed, an interaction test was used to test the null hypothesis that the difference between the two results was zero.

This procedure was repeated for 4 threshold values:

1. ≥ 0.3 LogMAR versus < 0.3 LogMAR
2. ≥ 0.2 LogMAR versus < 0.2 LogMAR
3. ≥ 0.1 LogMAR versus < 0.1 LogMAR
4. ≥ 0.0 LogMAR versus < 0.0 LogMAR

Participants in all visual acuity subgroups were well balanced across intervention groups (table 8.12).

Visual acuity threshold	Visual acuity subgroup	Total n=	Immediate n=	Delayed n=
1	≥ 0.3 logMAR	13	6	7
	< 0.3 logMAR	79	39	40
2	≥ 0.2 logMAR	19	9	10
	< 0.2 logMAR	73	36	37
3	≥ 0.1 logMAR	34	17	17
	< 0.1 logMAR	58	28	30
4	≥ 0.0 logMAR	51	25	26
	< 0.0 logMAR	41	20	21

Table 8.12. Distribution of participants within visual acuity subgroups. Participants within each visual acuity subgroup were balanced between intervention groups.

The adjusted difference in AI for each group, dichotomised by each visual acuity criterion, is shown in tables 8.13 – 8.16. These data are also shown graphical in figures 8.5 to 8.8. In the interests of clarity, ≥ has been substituted for 'worse than' and < for 'better than'.

	VA worse than 0.3 LogMAR	VA better than 0.3 LogMAR	2 - 1	Interaction test p value
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)		
3 months after enrolment	-0.18 (+1.21, -0.84)	0.03 (-0.22, +0.28)	+0.21	0.34
6 months after enrolment	-1.06 (-2.49, +0.38)	-0.07 (-0.33, +0.19)	+0.99	0.07
3 months after intervention	-0.88 (-2.20, +0.44)	-0.09 (-0.35, +0.18)	+0.79	0.11

Table 8.13. Summary of visual acuity subgroup analyses examining those with visual acuity worse than 0.3 LogMAR and those with visual acuity better than 0.3 LogMAR. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. VA = visual acuity, CI = 95% confidence interval. All values (except p values) are in logits.

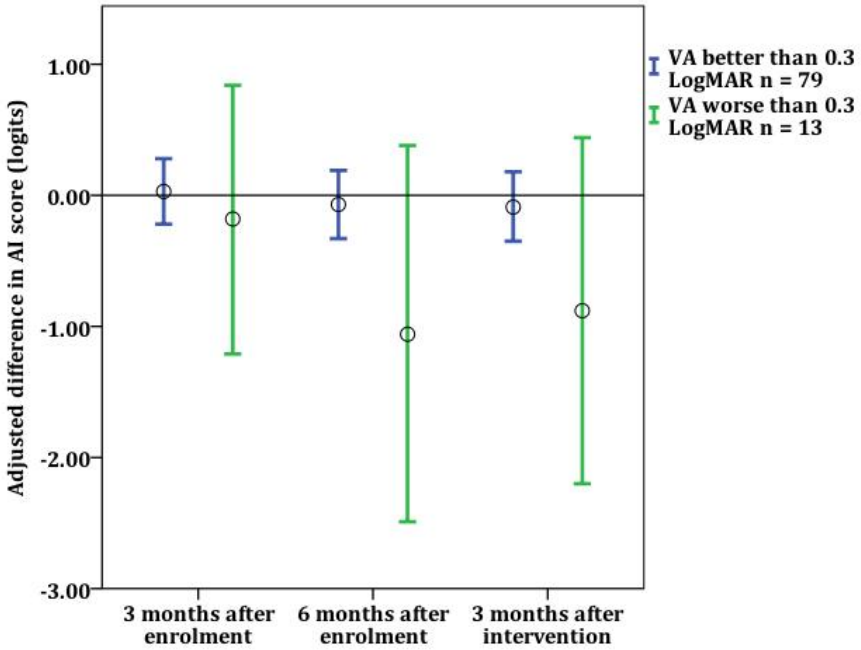

Figure 8.5. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with visual acuity worse than 0.3 LogMAR (green) and those with visual acuity better than 0.3 LogMAR (blue). The horizontal black line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

	VA worse than 0.2 LogMAR	VA better than 0.2 LogMAR	2 - 1	Interaction test p value
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)		
3 months after enrolment	-0.43 (-1.04, +0.19)	+0.07 (-0.19, +0.34)	+0.50	0.11
6 months after enrolment	-0.53 (-1.28, +0.22)	-0.04 (-0.32, +0.24)	+0.49	0.16
3 months after intervention	-0.46 (-1.24, +0.32)	-0.09 (-0.37, +0.20)	+0.37	0.25

Table 8.14. Summary of visual acuity subgroup analyses examining those with visual acuity worse than 0.2 LogMAR and those with visual acuity better than 0.2 LogMAR. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. VA = visual acuity, CI = 95% confidence interval. All values (except p values) are in logits.

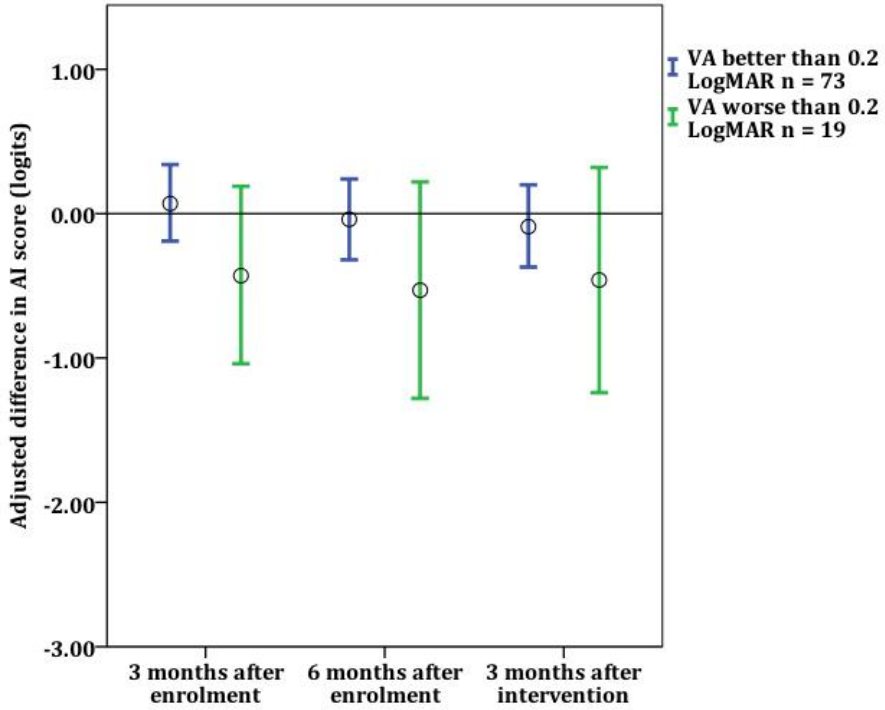

Figure 8.6. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with visual acuity worse than 0.2 LogMAR (green) and those with visual acuity better than 0.2 LogMAR (blue). The horizontal black line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

	VA worse than 0.1 LogMAR	VA better than 0.1 LogMAR	2 - 1	Interaction test p value
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)		
3 months after enrolment	-0.11 (-0.39, +0.17)	0.05 (-0.27, 0.37)	+0.16	0.30
6 months after enrolment	-0.44 (-0.82, -0.06*)	-0.05 (-0.38, +0.29)	+0.39	0.11
3 months after intervention	-0.49 (-0.85, -0.13*)	-0.09 (-0.42, +0.24)	+0.40	0.09

Table 8.15. Summary of visual acuity subgroup analyses examining those with visual acuity worse than 0.1 LogMAR and those with visual acuity better than 0.1 LogMAR. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. VA = visual acuity, CI = 95% confidence interval, * significant at p < 0.05. All values (except p values) are in logits.

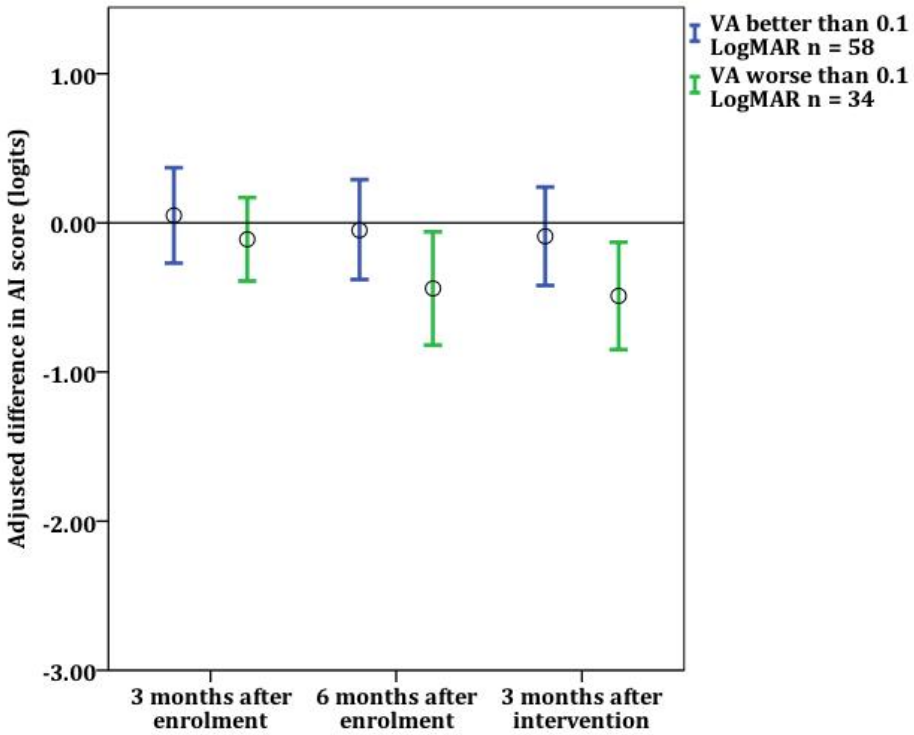

Figure 8.7. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with visual acuity worse than 0.1 LogMAR (green) and those with visual acuity better than 0.1 LogMAR (blue). The horizontal black line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

	VA worse than 0.0 LogMAR	VA better than 0.0 LogMAR	2 - 1	Interaction test p value
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)		
3 months after enrolment	-0.10 (-0.37, +0.18)	+0.06 (-0.33, +0.45)	+0.15	0.33
6 months after enrolment	-0.42 (-0.77, -0.07*)	+0.09 (-0.25, +0.43)	+0.51	0.04*
3 months after intervention	-0.39 (-0.75, -0.03*)	-0.05 (-0.42, +0.31)	+0.34	0.16

Table 8.16. Summary of visual acuity subgroup analyses examining those with visual acuity worse than 0.0 LogMAR and those with visual acuity better than 0.0 LogMAR. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. VA = visual acuity, CI = 95% confidence interval, * significant at p < 0.05. All values (except p values) are in logits.

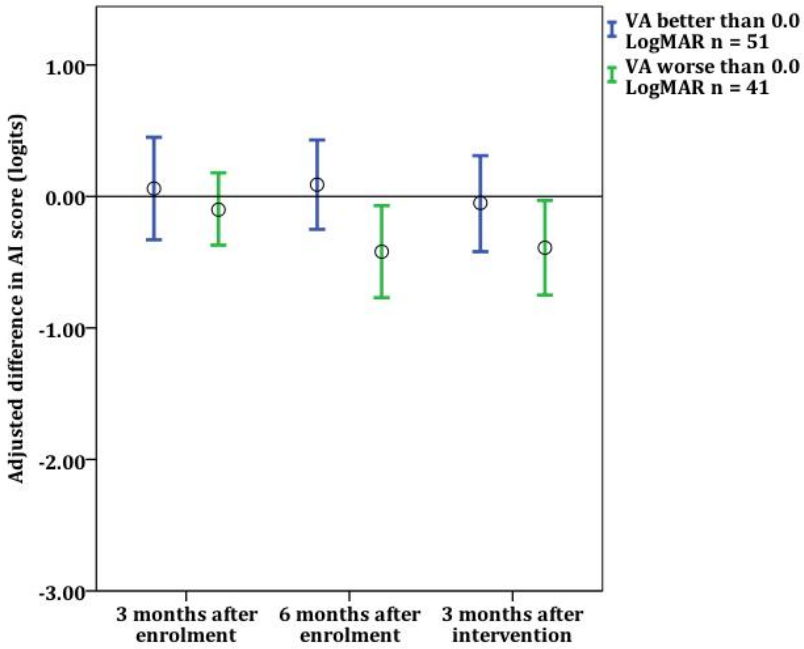

Figure 8.8. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with visual acuity worse than 0.1 LogMAR (green) and those with visual acuity better than 0.1 LogMAR (blue). The horizontal black line represents no adjusted difference in AI score between intervention groups. All measurements in logits.

8.8.3 Subgroup analyses by scotoma size

As those with maculopathy had the worst visual ability at baseline, it was hypothesised that those with central scotomas would gain more from the intervention.

In order to investigate the influence of scotoma size on the effectiveness of low vision intervention, participants were split into subgroups according to the size of their scotoma. As discussed in section 2.2.8.2, scotoma size was defined as the number of points classified as relative or absolute scotoma by the Nidek MP-1. 17 participants had missing scotoma size data, 2 of which did not complete the trial. Therefore 77 participants (100-17-6) were analysed in this section.

Three scotoma sizes were tested

1. ≥ 25 points versus < 25 points
2. ≥ 30 points versus < 30 points
3. ≥ 35 points versus < 35 points

Participants in all scotoma size subgroups were reasonably well balanced across intervention groups (table 8.17).

Scotoma size threshold	Scotoma size subgroup	Total n=	Immediate n=	Delayed n=
1	≥ 25 points	40	20	20
	< 25 points	37	18	19
2	≥ 30 points	34	17	17
	< 30 points	43	21	22
3	≥ 35 points	27	15	12
	< 35 points	50	23	27

Table 8.17. Distribution of participants within scotoma size subgroups. Participants within each scotoma size group were reasonably well balanced between intervention groups.

Data for each category is shown in tables 8.18-8.20. These data are also shown graphical in figures 8.9 to 8.11.

	≥ 25 points	< 25 points		
	1 Adjusted difference in AI score (95% CI)	**2 Adjusted difference in AI score (95% CI)**	**2 - 1**	**Interaction test p value**
3 months after enrolment	+0.02 (-0.30, +0.34)	-0.01 (-0.43, +0.41)	-0.03	0.26
6 months after enrolment	-0.21 (-0.62, +0.19)	-0.09 (-0.50, +0.32)	+0.12	0.37
3 months after intervention	-0.27 (-0.72, +0.19)	-0.02 (-0.46, +0.41)	+0.25	0.28

Table 8.18. Summary of scotoma size subgroup analyses examining those with scotoma size ≥ 25 points and those with scotoma size < 25 points. Column '2-1' gives the difference between the results from each subgroup .A p value < 0.05 suggests this difference is significantly different to zero. CI = 95% confidence interval, * significant at p < 0.05. All values (except p values) are in logits.

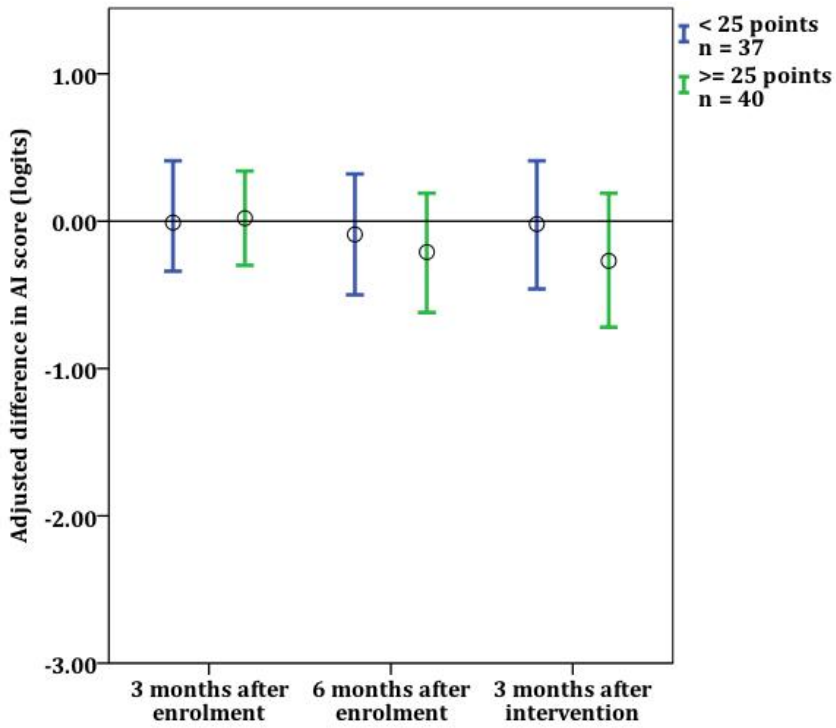

Figure 8.9. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with scotoma size ≥ 25 points (green) and those with scotoma size < 25 points (blue). The horizontal black line represents no adjusted difference AI score between intervention groups.

	≥ 30 points	< 30 points		
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)	2 - 1	Interaction test p value
3 months after enrolment	-0.02 (-0.42, +0.37)	+0.03 (-0.32, 0.38)	+0.05	0.39
6 months after enrolment	-0.34 (-0.83, +0.15)	+0.02 (-0.30, +0.37)	+0.36	0.18
3 months after intervention	-0.39 (-0.95, +0.17)	+0.01 (-0.35, +0.37)	+0.40	0.19

Table 8.19. Summary of scotoma size subgroup analyses examining those with scotoma size ≥ 30 points and those with scotoma size < 30 points. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. CI = 95% confidence interval, * significant at p < 0.05. All values (except p values) are in logits.

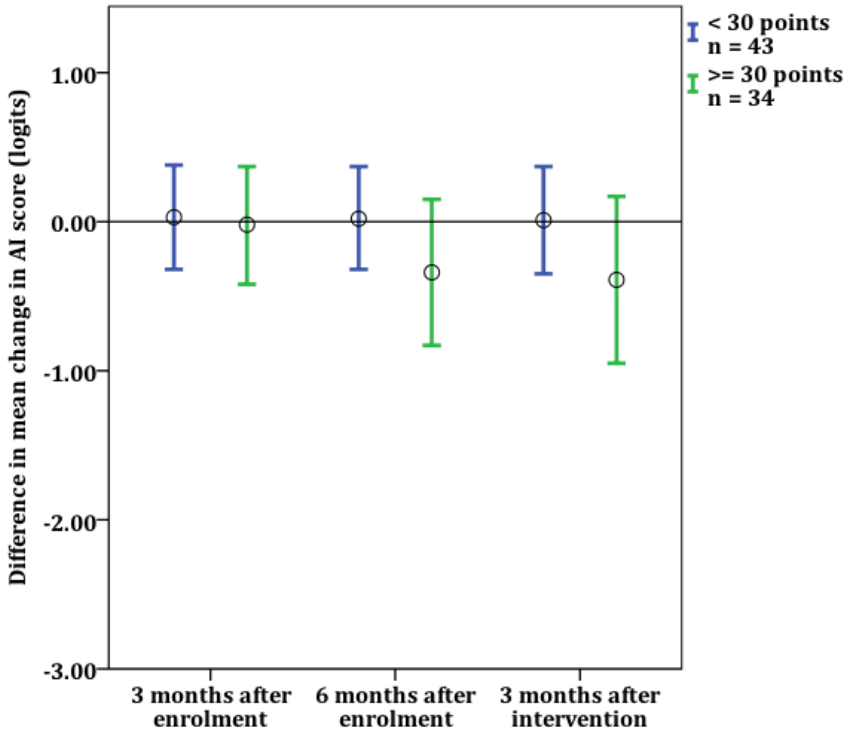

Figure 8.10. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with scotoma size ≥ 30 points (green) and those with scotoma size < 30 points (blue). The horizontal black line represents no adjusted difference AI score between intervention groups.

	≥ 35 points	< 35 points		
	1 Adjusted difference in AI score (95% CI)	2 Adjusted difference in AI score (95% CI)	2 - 1	Interaction test p value
3 months after enrolment	-0.24 (-0.63, +0.15)	0.18 (-0.16, +0.52)	+0.42	0.10
6 months after enrolment	-0.56 (-1.03, -0.08*)	+0.09 (-0.27, +0.44)	+0.65	0.03*
3 months after intervention	-0.60 (-1.13, -0.07*)	+0.04 (-0.33, +0.42)	+0.64	0.04*

Table 8.20. Summary of scotoma size subgroup analyses examining those with scotoma size ≥ 35 points and those with scotoma size < 35 points. Column '2-1' gives the difference between the results from each subgroup. A p value < 0.05 suggests this difference is significantly different to zero. CI = 95% confidence interval, * significant at p < 0.05. All values (except p values) are in logits.

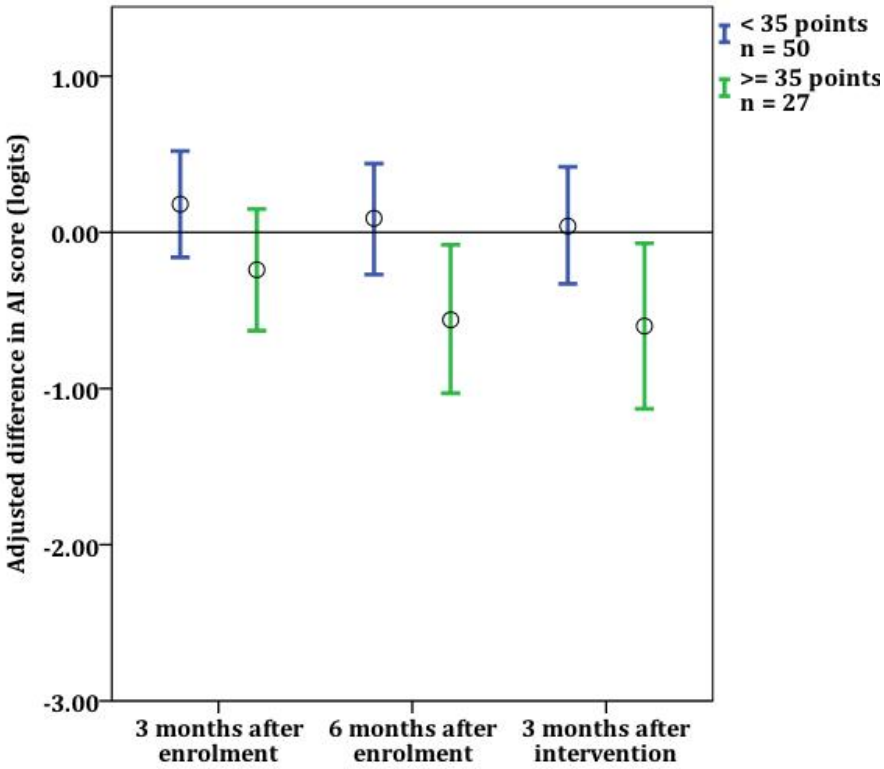

Figure 8.11. Adjusted difference in AI score between intervention groups (open circles) and 95% confidence intervals for those with scotoma size ≥ 35 points (green) and those with scotoma size < 35 points (blue). The horizontal black line represents no adjusted difference AI score between intervention groups.

8.9 Summary of results

The trial was run successfully. Recruitment target was met, significant attrition of participants was avoided, the majority of intervention appointments occurred on time, outcome data were collected on schedule and masking was successful.

Acceptance rate throughout the recruitment period was 46%, comparing favourably to that encountered by Pearce and colleagues (50%)[107], though less well to that experienced by Reeves (86%)[131].

It was anticipated that an immediate hospital based low vision clinic appointment would significantly increase a person's visual ability compared to waiting list control. However primary analysis revealed that the difference in improvement between intervention groups was very small; +0.05 logits in favour of the immediate group, thought to be equivalent to a change of 0.4 lines of logMAR visual acuity[117].

Sensitivity analyses revealed an unchanged result following further adjustment for variables concerning diabetes management, general health and additional photocoagulation. Over the period of the trial, 8 participants had their diabetes medical management changed, 6 reported significant deterioration in their general health and 19 received additional laser treatment. Adjustment for these factors did not alter the primary trial findings. The consistency of the result, irrespective of whether the model was adjusted for minimised factors and baseline AI score only, or additionally adjusted suggests that the model was stable.

Secondary analysis was planned to investigation the sustained effects of low vision intervention by examining the difference between those who received immediate intervention and those who received delayed intervention, 6 months after enrolment. However at this time point, a non-significant difference between intervention groups existed (-0.11 logits, $p = 0.40$).

Further secondary analysis investigated the effect of delaying intervention by examining the difference between those who received immediate intervention and those who received delayed intervention, 3 months after intervention. Again a non-significant difference existed between intervention groups (-0.15 logits, $p = 0.25$).

In the absence of statistically significant results, we cannot suggest that a hospital based low vision appointment is useful for all those with DED.

Exploratory subgroup analyses were performed to determine whether clinical characteristics, determined to be related to baseline visual ability in chapter 5, were related to intervention success. On this basis, subgroups were classified according to disease severity groups defined in section 2.1.3, corrected distance acuity and scotoma size. All subgroup analyses involved very small sample sizes and as such it should be stressed that all subgroup results are considered exploratory only.

No significant difference between intervention groups was found within any disease severity subgroup. As severity was not an independent predictor of baseline visual ability when visual function accounted for (see Chapter 5), this result is perhaps not

unexpected. As significant reduction in visual ability occurred between severity group 2 and 3, two further subgroups were redefined as groups 1 + 2 and 3 + 4, but again no significant difference between intervention groups was observed. However, subgroup analyses did suggest those with reduced visual acuity and those with central field loss may stand to benefit more from a hospital low vision clinic appointment.

One often used criterion for referral to a low vision service is visual acuity worse than or equal to a Snellen distance acuity of 6/12[138, 139]. As 6/12 is the Snellen equivalent of 0.3 logMAR, this was initially selected as the threshold upon which to dichotomise participants according to their corrected distance acuity.

Indeed the largest differences between intervention groups (favouring delayed intervention) were found in participants with visual acuity worse than 0.3 logMAR, 6 months after enrolment and 3 months after intervention; -1.06 logits, 95% CI: -2.49, +0.38, p = 0.11 and -0.88 logits, 95% CI: -2.20, +0.44, p = 0.14 respectively. The large confidence intervals associated with these estimates reflect the small sample size (n = 13) from which they were drawn. Statistical significance was not reached (p = 0.11 and p = 0.14).

Similarly, the difference between these results and those observed in the remaining participants with better visual acuity was large and just failed to reach significance (6 months after enrolment: +0.99 logits, p = 0.07; 3 months after intervention: +0.79, p = 0.11).

In a bid to study larger samples of participants and provide more accurate estimates of the adjusted difference between intervention groups, participants were dichotomised according 3 additional visual acuity levels, i.e. better or worse than 0.2 logMAR, 0.1 logMAR and 0.0 logMAR.

Participants receiving delayed intervention in each of the 'worse than' visual acuity subgroups fared better than their immediate counterparts. Though estimates were smaller, a similar pattern was observed whereby the delayed group improved more on average than the immediate, 6 months after enrolment and 3 months after intervention. In fact, significant improvements in both the worse than 0.1 logMAR (6 months after enrolment: -0.44 logits, 95% CI: -0.82, -0.06, p = 0.02; 3 months after intervention: -0.49 logits, 95% CI: -0.85, -0.13, p = 0.01) and worse than 0.0 logMAR (6 months after enrolment: -0.42 logits, 95% CI: -0.77, -0.07, p = 0.02 and 3 months after intervention: -0.39 logits, 95% CI: -0.75, -0.03, p = 0.04 respectively) subgroups were observed. Though smaller estimates, clinically they are thought to be equivalent to a gain of around 4 lines of logMAR visual acuity[117]. No significant differences were found in those with better visual acuity.

Difference between the results observed in those with worse than 0.0 logMAR acuity and their better seeing counterparts was significantly different from zero 6 months after enrolment (+0.51 logits, p = 0.04).

These results suggest that those with poorer acuity may stand to benefit from delayed intervention. As exploratory analyses, it is not possible to identify a visual

acuity limit beneath which a referral to low vision services should be instigated. These results suggest that even those slightly reduced acuity may experience clinically significant gain in visual ability following a low vision clinic appointment, however a further study of a larger sample of participants with reduced acuity is needed before this can be validated.

Similarly, those with a scotoma size measuring 35 points or more, receiving delayed intervention experienced significant improvements in visual ability 6 months after enrolment (-0.56 logits, 95% CI: -1.03, -0.08, $p = 0.02$) and 3 months after intervention (-0.60 logits, 95% CI: -1.13, -0.07, $p = 0.03$).

Clinically these estimates are thought to equate to around a 5 line improvement in logMAR visual acuity[117]. The difference between these results and those from the remaining participants with smaller scotomas was significantly different from 0 in each case (6 month after enrolment: +0.65 logits, $p = 0.03$ and 3 months after intervention: +0.64 logits, $p = 0.04$).

The similar pattern of results in the both visual acuity and scotoma size subgroups is perhaps not surprising given the high correlation between acuity and scotoma size as measured in project one of this study ($r = 0.69$, $p < 0.001$).

A full discussion of these results, their limitations and clinical implication is provided in the chapter 9.

Chapter 9 – Discussion: Effectiveness of a hospital based low vision clinic appointment

No randomised controlled trial (RCT) exploring the effectiveness of hospital based low vision intervention specifically for those with diabetic eye disease (DED) has been published. In fact, a recent systematic review of effectiveness of low vision service provision highlighted the lack of a strong evidence base displaying effectiveness of low vision intervention in working age groups[152].

9.1 Comparisons with previous work

Results of the current study suggest that a low vision clinic appointment is not effective in all those with DED, but that referral of those diabetic patients with reduced distance acuity or a central scotoma should be considered.

We found no evidence of effectiveness being related to disease severity. These results contradict those of Nilsson, who in a previous uncontrolled study of patients with advanced diabetic retinopathy reported 'dramatic' low vision rehabilitation effects[296]. Study design, intervention and outcomes used differed considerably from those presented here.

In Nilsson's study, participants attended multiple rehabilitation sessions; initially a first 'series' consisting of an average of four 1 hour sessions, followed by additional

'series' where appropriate. Spectacle mounted distance telescopes and near hyperoculars were predominantly issued. Training in the use of devices and residual vision was provided, with specific eccentric viewing training for those with an absolute central scotoma. Access to social workers and vocational rehabilitation authorities was also provided, but no specific information regarding the extent to which this occurred was given.

Focus was placed on significant improvements in distance and near acuity, however acuity gains with magnification are not unexpected. Magnification induced acuity improvements are not indicative of intervention success as they make no comment towards the application of such devices in everyday living situations. Improved ability to read newspapers and watch television was claimed, but the method of assessment before and after intervention was not consistent. Subjectively reported ability was recorded before rehabilitation and objective measures were performed after. It was also stated that participant's capacity for employment was enhanced, but no mention of how this was assessed or who made the assessment was given.

Neither intervention nor contact time was controlled for and as such the effectiveness of the intervention may be overstated. Participants may have experienced 'dramatic' improvements, but the data provided is not sufficient to back up this claim.

As described in the introduction, outcomes of other RCTs of hospital based low vision rehabilitation have been mixed[107, 131]. The 'best' published evidence in support of a

hospital based low vision clinic appointment was presented by Pearce and colleagues[107]. Though not the primary outcome of their RCT, visual ability improved significantly by an average of 0.64 logits, comparable to a 5 line increase in logMAR acuity[117]. Despite a very similar intervention, the results of this trial failed to show a similar effect. Caution should however be exercised in the interpretation of this result, as analysis did not include an untreated control group.

The substantial difference in participant characteristics between each study may contribute to the disparity between results. The current trial focused only on those with DED, rather than a general low vision population. By virtue of their diagnoses, participants on the current trial were substantially younger (57 years versus 73 years). Visual function and visual ability of participants was also considerably better (visual acuity ≈ 6 logMAR lines better, visual ability ≈ 1.3 logits better).

9.2 Summary of subgroup analyses

Though no overall effect of low vision intervention was demonstrated, subgroup analyses suggested that statistically and clinically significant gains were observed in those with poorer visual function.

Sizeable significant gains, between 0.49 and 0.60 logits (thought to be equivalent to the change in visual ability attributable to between a 4 and 5 line improvement in logMAR visual acuity[117]) were seen in those with reduced corrected distance acuity or compromised central fields.

Estimates of the effect of delayed intervention in those with the worst distance acuity (worse than 0.3) were extremely large (-1.06 logits, 6 months after intervention and -0.88 logits, 3 months after intervention), though failed to reach statistical significance (p = 0.11 and p = 0.14). This analysis was hindered by a very small sample size (n=13). Sample size was increased by including those with better distance acuity. This resulted in significant findings, but smaller estimates of the effects of intervention.

In each subgroup analysis, results from participants with poorer visual function were compared to those from participants with better function as recommended by Altman and Bland[294]. A significant finding in one subgroup and not the other is not sufficient evidence of a significant difference between subgroups. Therefore the evidence suggests that those with corrected distance acuity worse than or equal to 0.0 logMAR, or with a central scotoma equating to 35 points of more are most likely to benefit from a hospital based low vision assessment. Had sample size been greater, larger significant effects of intervention may have been observed in those with more reduced distance acuity.

On first glance, the distance acuity cut off seems high, however patients with diabetic retinopathy experiencing a 10 letter drop in visual acuity have been identified as appropriate candidates for clinical intervention previously. In a small longitudinal study (n = 39, mean visual acuity 0.10 logMAR) a 10 letter reduction in visual acuity (2 lines of logMAR) was significantly associated with a reduction in vision related quality of life (VRQoL)[243].

When low vision aids are dispensed, it is hoped that they will improve a person's visual ability by enabling them to perform vision related tasks they were unable to do unaided. However, only 45% of participants within the worse than 0.0 logMAR subgroup and 48% within the more than 35 point scotoma size subgroup received low vision aids. Therefore the improvements in visual ability observed here may reflect factors other than prescription of low vision aids.

Though not the principal aim of low vision intervention, positive effects on psychosocial functioning after low vision assessment have been reported[152, 297, 298]. As discussed in chapter 6, AI visual ability scores are subject to the influence of psychosocial factors, particularly acceptance and self worth and depressive symptoms[250]. Potentially, indirect positive effects on psychosocial factors could translate into improved visual ability score. This suggestion is only speculative as no specific assessments of psychosocial status were made either before or after our intervention.

Surprisingly, intervention appeared to be more effective when delayed for 3 months, suggesting that an adaptation period may be required before the benefits of low vision rehabilitation are realised. There is not a simple explanation as to why this might be the case.

As prescription of low vision aids was not randomised, the distribution of aids between intervention groups was reviewed. Though distributed fairly evenly (12 immediate, 15 delayed), two participants who were prescribed aids did not complete

the trial. As both had been assigned to immediate intervention, the number of aids prescribed between intervention groups differed by 5 (10 immediate, 15 delayed). This small sample may contribute to the apparent outperformance of the immediate group.

These results suggest that a closer look at referral criteria of patients with DED may be warranted. On the basis of evidence presented here, referral should be considered when best-corrected distance acuity falls short of 0.0 logMAR or central scotamas are present in a 10° radius of fixation. However this would need to be confirmed by a larger randomised controlled trial, powered to detect differences between participants with differing acuity levels or scotoma sizes.

9.3 Consideration of trial design

As previously stated, the current trial was successfully managed. However, the rationale underpinning some salient features of trial design deserve further consideration, as do the effects of potential limitations in relation to interpretation of results.

9.3.1 RCT design

Due to the assertion that pragmatically designed trials produce generalisable results more applicable to clinical practice and policy makers[299], a pragmatic approach was adopted wherever practical. Our inclusion criteria were deliberately broad, with

little stipulation made on severity of disease and no exclusion of patients treated with laser photocoagulation.

Consequently the visual function of participants was somewhat better than anticipated. This does not reflect difficulties in recruitment of those with poor visual acuity; rather visual acuity was intentionally omitted from the recruitment criteria. As a secondary issue to that of pragmatism, it was decided not to assume that visual acuity would be the best predictor of success with low vision intervention. Therefore patients with good acuity were included provided they had gradable diabetic retinopathy in their better eye.

As referrals are often made on the basis of visual acuity, this decision also facilitated an exploratory investigation of the acuity level at which referral to a hospital based low vision clinic should be considered. The results from the observational work presented in chapter 5 suggest that a corrected measure of acuity is the single best predictor of visual ability. Corrected acuity may therefore be a useful predictor of those likely to benefit from a low vision clinic appointment. Distance acuity subgroup analyses appear to support this claim. In future studies of low vision intervention it may be useful to exclude those whose corrected distance acuity is better than 0.0 logMAR. Furthermore, inclusion criteria based on distance acuity worse than 6/12 or 6/18 Snellen as employed elsewhere[107, 158], may exclude patients likely to benefit from intervention.

In common with RCTs in this field[107, 133, 158], those with previous experience of low vision rehabilitation were excluded. This could be a potential source of selection bias, as those with previous experience may be those with more severe disease or greater motivation, who stand to gain most from the intervention. If so, this would result in an underestimation of the effect of the intervention.

It is clear that much is still unknown regarding optimal intervention dose, follow-up interval, what constitutes rehabilitation success, and who is most likely to benefit[152]. Though no international consensus on the definition of low vision rehabilitation exists, the National Health Service (NHS) Low Vision Working Group have published recommended standards to which our intervention conformed[137]. Though present results may not be applicable outside the NHS setting, this model of care represents the majority of rehabilitation appointments in the UK[136] and therefore further investigation into its effectiveness is warranted.

The control for the primary analysis in this study was a waiting list (no intervention), as withholding intervention was not considered ethical. Participants in the delayed group were not penalised compared to standard practice, as the 3 month delay was less than the normal waiting list time for a low vision clinic appointment in Moorfields Eye Hospital (MEH) low vision clinic.

Participants were allocated to intervention groups using minimisation, a technique first described by Taves[293]. Minimisation assigns participants to treatment and control groups, whilst minimising differences in the number of participants in each

group and the presence of predetermined prognostic factors between groups. Chance skewing of prognostic factors between treatment groups may result in spurious conclusions[300]. Usually, this is avoided by employing stratified randomisation, where different subgroups are created representing all possible combinations of prognostic factors, with the aim of achieving equal numbers of participants in each subgroup. As the number of prognostic factors increases, so too does the number of subgroups and as such, stratified randomisation is often not appropriate for small studies or studies with more than 2 prognostic variables[293, 301]. Minimisation only seeks to achieve balance on each prognostic variable considered separately and as such can handle more prognostic variables even in studies with relatively few participants. In this instance, with a sample size of 100 and 4 minimisation factors, minimisation was considered to be a more appropriate technique than stratified randomisation.

Though lauded by some for ensuring group balance[302] and for reducing the probability of severe imbalances as compared to randomisation[293], minimisation has been criticised for the lack of complete randomness in its allocation method[303]. Participants are allocated to the group that minimises the existing difference between prognostic factors, therefore the allocation of previous participants influences future allocations. In theory, an investigator with prior knowledge of the participants already enrolled, could potentially determine the allocation of the next participant. Taves and others refute this, as any potential selection bias is excluded if the procedure is controlled by an independent person[304-306]. To protect against

selection bias, our minimisation procedure was set up and controlled exclusively by the Research and Development department at Moorfields Eye Hospital.

The non-random nature of minimisation has implications for subsequent analysis, as tests of statistical inference are based on random assignment to groups. Compensation is achieved by adjusting for the factors on which minimisation was carried out using analysis of covariance[293] and as such this was incorporated into the trial analysis.

Indeed, minimisation produced balanced intervention groups. Tests of statistical significance were not used to examine the balance of intervention groups. Though commonly performed, they are inappropriate in this situation[307-309]. They test the hypothesis that differences between groups are due to chance. When a random procedure has been used to produce groups, any differences are by definition due to chance. Rather, groups were examined on the basis of whether any chance clinically significant difference between groups existed. This was not the case.

Though VRQoL instruments are perhaps better placed to provide a full assessment of the effectiveness of a treatment[86], the main aim of low vision rehabilitation is improvement of a person's functional ability[152] and as such a visual ability questionnaire was employed. Arguably, low vision rehabilitation may also facilitate improved quality of life and psychosocial status[152], but as a hospital based low vision clinic appointment makes no specific attempt to augment either status, it was felt

that a VRQoL instrument would be less sensitive to change following intervention in this trial.

Though designed as both an outcome measure and rehabilitation tool[186], the Activity Inventory (AI) was used solely as an outcome measure. HD did not have access to AI responses prior to providing the low vision clinic appointment. Therefore, the intervention was not tailored around difficulties previously expressed. This reflected current practice as the MEH low vision clinic does not employ standardised questionnaires in its examination of patients; rather optometrists discuss individual's visual requirements and goals at the outset of the examination. Placing emphasis on those difficulties raised by the AI may well promote a positive finding, but the intervention received would not be a true representation of our hospital based low vision clinic. Furthermore, if rehabilitation had been guided by baseline AI responses, fair consideration may not been given to issues such as employment and education, which are not specifically covered by the AI.

The AI was administered by telephone. The validity of this mode of administration has been previously established[187]. It has been suggested that telephone administration techniques are subject to biased responses, such that a respondent may wish to present their current situation in a more positive light. A study comparing 3 administration methods: telephone, in person and postal, in 3 groups of age, sex and visual function match low vision patients, showed that postal administration resulted in significantly lower quality of life scores[310]. The authors speculated that postal administration is the least bias, as without an interviewer,

respondents receive no prompting. Neither will they feel any compulsion to down play their difficulties.

As telephone administration was consistently employed throughout the study, any bias would be expected to uniformly influence each administration. Therefore the trial outcome would not be affected. Furthermore, previous researchers in this laboratory had successfully administered the AI by telephone to 96 participants on 3 separate occasions over a 3 month period[107].

Deteriorating vision over the course of a study may mask potential benefits and as such the interval between delivery of intervention and assessment of outcomes should be given careful consideration[152]. An interval of 2 months has been suggested to negate such problems[310], as progression of visual impairment is unlikely to impact on quality of life scores over this period. However this suggested interval does not address this issue of the most appropriate interval that allows any benefits of the intervention to be realised.

In a recent review of low vision service provision, no relationship between follow up period and effect size was observed, however many of the studies varied substantially on other factors such as type of intervention, dose and outcome measure used[152]. The authors proposed that a follow-up interval of between 2 and 3 months is adequate for any benefit of rehabilitation to be uncovered. By including both a 3 and 6 month follow up, sufficient time for benefits to be uncovered in both intervention groups was given.

9.3.2 Limitations

As described in chapter 8, 8 participants (4 in each arm) did not complete the trial. Despite this, sample size targets were adequately met. Trial withdrawals appeared to be random. Reasons behind withdrawal were evenly distributed between arms. Therefore, the influence of these withdrawals is likely to be minimal.

As mentioned in section 5.4, 17 participants had missing scotoma size data. Though having no effect on the primary and secondary trial results, missing data reduced the number of participants included in the subgroup analyses by scotoma size to 77. Furthermore, as those excluded patients had significantly worse visual function; this may have led to the results being underestimated.

Our recruitment criteria, by excluding those with poor hearing, poor mobility or those in poor health, may have excluded patients likely to be more challenging. This may limit the applicability of the trial results to the wider DM population. These criteria were deemed necessary however as participants needed adequate hearing to complete the AI over the telephone and be able to attend 2 additional hospital visits over and above their routine appointments.

As previously discussed, omission of a visual acuity criterion resulted in participants having better visual function and ability than anticipated. The preponderance of highly visually able individuals enrolled may have masked true effectiveness in those with more limited ability. Highly visually able participants reporting no visual

problems had no potential for improvement following low vision rehabilitation. This was alluded to in the subgroup analyses presented in chapter 8, where participants with better visual function made no significant gains following intervention. In addition to this, the authors of the AI concede that it does not target those with high visual ability sufficiently[120].

Therefore in order to investigate the whether a ceiling effect was responsible for the lack of significant findings, 2 further analyses were retrospectively conducted. First, primary and secondary analyses were repeated after exclusion of all those with a baseline visual ability within 0.5 logits of the ceiling value of 6.04 logits (15 participants). Second, primary and secondary analyses were repeated following removal of all items that had been reported 'not difficult' at baseline. As ability on 'not difficult' items cannot improve, their inclusion may mask improvement experienced on other more difficult items. Furthermore, rehabilitation does not target tasks that are not difficult; therefore it could be considered unreasonable to assess outcomes without allowing for this.

Table 9.1 shows the results of these additional analyses, alongside the original findings of the trial. The pattern of results in each case was similar, with visual ability improving more in the delayed group, however estimates were still small and insignificant. Therefore, a ceiling effect does not fully explain the lack of significant findings.

	Adjusted difference in AI score and 95% CI (logits)		
	3 months after enrolment	**6 months after enrolment**	**3 months after intervention**
Original results	+0.05 (-0.18, +0.28) p = 0.67	-0.11 (-0.37, +0.15) p = 0.40	-0.15 (-0.41, +0.11) p = 0.25
Excluding persons	+0.04 (-0.20, +0.30) p = 0.70	-0.11 (-0.42, +0.19) p = 0.45	-0.11 (-0.41, +0.19) p = 0.47
Excluding items	+0.02 (-0.24, +0.29) p = 0.88	-0.14 (-0.48, +0.20) p = 0.41	-0.22 (-0.55, +0.11) p = 0.20

Table 9.1. Ceiling effect analysis. Summary of original trial results and results of 2 further analyses excluding persons at ceiling and items at ceiling. AI = Activity Inventory, CI = confidence interval.

The AI has a number of limitations that should be stated. As a non-condition specific instrument, the AI may not adequately target the rehabilitative potential of persons with DED, as no attention is given to the regular activities of daily living they encounter due to their condition[143]. Additionally, its failure to sample difficulties related to employment and vocational domains may limit its utility in the current study as does its lack of sufficiently difficult items to adequately target highly able persons[120]. As described in the introduction, a diabetic retinopathy specific quality of life instrument, the Retinopathy Dependent Quality of Life (RETDQoL) was available at the outset of this trail. Due to concerns with its sensitivity to change following low vision intervention, it was not included as an outcome.

The AI was administered to goal level. Within the hierarchical structure of the AI, difficulty accomplishing goals reflects a disability, therefore analysis of goal responses produced a measure a visual ability[187]. However, the AI can be expanded

to cover an additional 459 tasks. Task responses are thought to capture functional limitation[227]. As low vision rehabilitation seeks to improve visual ability, the goal level version of the AI was selected as the measure of choice. It was also substantially quicker to administer.

Though agreement between overall goal and task scores has been shown[120], task level administration allows the examination of 4 specific domains of functional limitation, namely: reading, mobility, visual information and visual motor[227]. As in previous studies[143, 250], it may have been beneficial to utilise the full extent of the AI so that changes within specific domains could have been examined. Indeed, as reading is one of the most frequently reported difficulties of patients with reduced vision and many low vision aids are designed to aid reading[311], the primary outcome measure of the Veterans Affairs Low Vision Intervention Trial (LOVIT) trial[106, 133] was the reading domain of the Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ 48)[122]. Both the recreational and daily living objectives of the AI include reading tasks, however they make up a very small proportion of the total goals included (3 items from a possible 50). Additionally, reading as a leisure activity is embedded in a general item termed leisure entertainment which incorporates watching television, playing cards, doing puzzles and reading books or magazines. As such, the AI at goal level could be considered quite a blunt instrument in relation to change in visual ability related to reading. Therefore using the extended task level version of the AI may have provided a better assessment of change in ability following low vision rehabilitation.

Trial design dictated that HD, responsible for recruitment, baseline assessments and low vision clinic appointments was unmasked. Booking participants directly into the general MEH low vision clinic may have enabled masking, however waiting list times for low vision clinic appointments varied between 4 and 6 months throughout the duration of the trial. Therefore it would not have been possible to schedule immediate appointments in accordance with the trial protocol, without significantly increasing the time taken to complete the trial.

As this represents a potential source of bias, every attempt was made to ensure that HR, responsible of all AI administration remained masked. With only 6% masking violations and a chance likelihood of correctly guessing intervention group allocation, HR was successful masked, however due to the open nature of the trial it was not possible to control for any potential bias stemming from the participant's knowledge of their intervention group allocation.

Early in the trial, HR realised that participants often wanted to ask questions regarding past or future appointments with HD, potentially jeopardizing the masking procedure. At this stage the written script used for AI administration was amended to reinforce the masking procedure. A full copy of this script is included in appendix III.

The sample size calculation was based upon the standard deviation of baseline AI scores (1.0 logits) found in a study of the effectiveness of an extra low vision device training session in a hospital based low vision clinic, using the same outcome

measure[107]. However, due to differences in the baseline characteristics of the study populations in terms of visual function and diagnoses, the standard deviation observed in the current study was considerably higher (2.2 logits). This suggests the power of the current study may be low.

Additionally, the study was powered on the basis of detecting a 0.7 logit difference between intervention groups, based on similar values used in RCTs of low vision rehabilitation[107, 133]. However, extrapolating from the figures provided by Massof and Fletcher[117], this is thought to be equivalent to a gain of 5.8 lines of logMAR visual acuity. The Early Treatment of Diabetic Retinopathy Study (ETDRS) considered laser photocoagulation successful if it prevented a doubling of the visual angle, equivalent to a 3 line drop in ETDRS visual acuity[37]. Using 0.7 logits difference as an indication of clinical significance equates to a Cohen's effect size of 0.7 (difference between intervention group means/standard deviation = 0.7/1.0)[312]. If a low vision assessment made a smaller but clinically significant improvement in AI score, a sample size based on an effect size of 0.7 would not have been large enough to detect it.

Two further limitations related to trial design have been noted. As displayed in figure 7.1, randomisation occurred before the first administration of the AI. Ideally randomisation should have taken place after the baseline outcome measurement had been made, as prior knowledge of intervention group allocation has the potential to bias patient responses to the AI. Unfortunately there is no way of knowing whether this affected the outcome, but it should be noted as a design limitation.

The second limitation relates to one of the planned secondary analyses. The effect of delaying intervention was investigated by examining the difference between intervention groups 3 months after intervention, i.e. 3 months after enrolment in the immediate group and 6 months after enrolment in the delayed group. However within an RCT, intervention groups should vary on intervention only. In the above analysis, intervention groups varied not only on intervention but also on the number of times they have responded to the AI and as such, in the amount of contact they had with the study team. Therefore it cannot be concluded that differences between intervention groups 3 months after intervention related only to the intervention administered.

91 separate tests of significance were carried out within the subgroup analyses presented here. Bonferroni correction was not applied, as in the case of underpowered exploratory analyses, it is considered too conservative[313]. However, the effect of multiple significance testing was considered. Using a $p < 0.05$ significance level, 1 in 20 findings will be significant despite no real effect existing[313]. Therefore in the absence of any true effects, between 4 and 5 results could be expected to yield significant results. Subgroup analyses produced 9 significant findings. Additionally, it is important to stress that these analyses were exploratory only and involved very small sample sizes. Therefore care should be taken in the interpretation of their results.

9.4 Outcome measures in RCTs of low vision intervention

It has been speculated that performance of everyday activities with low vision aids may not be as relevant to quality of life as once assumed[131]. Indeed a recent study reported that magnifier usage measured 1 month after a low vision clinic appointment was not related to 3 patient reported outcome measures (PROMs): the Low Vision Quality of Life (LVQOL)[314], the Adaptation to Age Related Vision Loss (AVL-12)[315] and the Keele Participation Restriction Questionnaire (KAP)[269, 316]. Similarly, low vision aid assisted reading acuity was not a significant predictor of visual ability as captured by the AI[250], however this assessment was made a minimum of 2 weeks after a low vision clinic appointment. It should be noted that neither of these studies were reporting on the effectiveness of low vision services. The short interval between prescription of the low vision aid and measurement of outcomes in both studies may not have allowed sufficient time for full integration of the aid into everyday life.

It is possible that self-report instruments do not fully capture the effects of low vision rehabilitation. As low vision rehabilitation aims to improve a person's functional ability[152], it is assumed that if rehabilitation is successful a person will report less difficulty with everyday tasks and as such higher visual ability will be recorded. However, the successful use of a low vision device in accomplishing a given task will not always result in a patient reporting less difficulty. Clinically, patients often report a task as difficult by virtue of the fact that they have to use a magnifier to accomplish it. Additionally, the use of a magnifier fundamentally alters the task. A

person may read to indulge in quiet reflection and relaxation. The addition of a magnifier may not achieve this, regardless of whether a fluent reading speed is reached or not. This begs the question, what constitutes a successful outcome of low vision rehabilitation?

In recent years, researchers have focused on the assessment of patient reported outcomes[114, 152]. They are thought to provide a measure of effectiveness in the home environment, rather than showing efficacy in a clinic setting. Used as an outcome measure in low vision rehabilitation studies, they ultimately ask patients whether they perceive their situation to be better or different. It is interesting to consider then what constitutes success for the patient; belief that one is better, irrespective of whether enhanced skills can be demonstrated or improved ability demonstrated by improved performance. Assessments of both self-report and performance may help provide the answer. Indeed if the perception of improvement is really the issue, do patients need low vision aids at all or should focus be placed on alternate thinking patterns and coping strategies? This presents an interesting question, which will be discussed later in the chapter.

Consideration of performance based measures of visual ability in tandem with PROMs has been encouraged as a means of bridging the gap between traditional clinic based measures of visual function and self-reported visual ability[246]. The concept of performance measurement is not new and is not a simple issue.

It has been reported that clinical measures of visual function may underestimate true performance at home[152]. In a study of 57 elderly visual impaired patients, 75% could read newspaper sized print in a clinic setting whereas only 39% were able to in their own home[317]. A contradictory finding has also been presented. A subset of 97 patients enrolled in the Salisbury Eye Evaluation Study[318] were examined to establish the correlation between performance on tasks carried out at home and in a clinic setting[319]. Those with habitual vision of 6/12 Snellen or worse performed significantly better at home compared to in the clinic. Contrary to expectations, lighting levels were not associated with reading speed at home. The authors concede that participants may try harder in the presence of an observer grading their performance, though arguably this could be the case in the presence of a clinician. Interestingly, reading speed measured at home was not associated with self-reported reading ability[319].

A study examining performance of 4 common everyday tasks by visually impaired patients (reading a newspaper, reading a medicine label, making change and entering a Personal Identification Number (PIN)), found that patients may over estimate self-reported difficulty compared to actual difficulty reported directly after task completion[320].

This discrepancy may reflect differences between performing a real world task and a simulated version in an experimental setting, as small variations in the task impacted on the relationship between self-report and actual difficulty reported. For example, reading newspaper print from a different publication reduced the amount of

variance in self-reported difficulty accounted for by actual difficulty reported from 46% to 30% when read aloud and from 51% to 24% when read silently. Additionally, measuring performance in an experimental setting neutralises the fear of 'messing up' encountered in real world scenarios.

Dedicated performance based outcome measures have previously been described using observer rating scales[246, 321, 322]. The Melbourne Low Vision Activities of Daily Living Index (MLVAI)[321] is a Rasch validated instrument, designed primarily as a measure of ability to perform activities of daily living, but secondarily as on outcome measure in low vision intervention studies. Its most recent version weights task difficulty by importance[323]. A combination of age, near word acuity, contrast sensitivity and peripheral fields explained 75% of the variance of person measures derived from the MLVAI[324].

More recently, the Assessment of Disability Related to Vision (ADREV) has been validated for use in persons with diabetic retinopathy[246]. Based on a previous Rasch validated instrument, the Assessment of Function Related to Vision (AFREV)[325], the ADREV consists of 9 visually intensive tasks, graded by an observer on a 0 – 7 interval scale determined by Rasch analysis.

A comparison of ADREV total and task scores to clinical measures of visual function and NEIVFQ scores in 91 patients with non-proliferative and proliferative diabetic retinopathy, demonstrated that logMAR visual acuity was significantly related to total score and all task scores except ambulation ($r = -0.40$ to -0.78). Multiple

regression analysis revealed that visual acuity, contrast sensitivity and central fields were each independently related to total ADREV score.

Though NEIVFQ total score was significantly related to ADREV total score (r – 0.50), 'reading in reduced illumination', the only reading task within the ADREV, was not significantly association with NEIVFQ score, or the 'general vision', 'distance activities' or 'near activities' subscale scores. As reading difficulties are of the most commonly cited problems reported by visual impaired patients, the ADREVs usefulness as an outcome measure in a low vision rehabilitation clinical trial may be limited.

Trials measuring self-reported ability and performance in tandem may help establish what constitutes success for the patient. For example, better self-reported measures in the absence of improved performance may suggest that psychosocial interventions have promise in this field. As such, a performance outcome measure would have been a useful addition to the current trial.

9.5 Psychosocial interventions in diabetes and low vision rehabilitation

Psychosocial interventions have been examined in relation to diabetes management [326], depression in diabetes[327] and visual impairment due to diabetic retinopathy[275]. The concept of psychosocial interventions as an adjunct to traditional low vision rehabilitation for those with DED was described in the 1980s and the need for it has been repeated more recently[245].

Bernbaum and colleagues reported outcomes of a 12-week individualised programme in patients with diabetic retinopathy[275]. The programme included diabetes education and self-management sessions, both individual and family counseling sessions, social support and exercise regimes. Psychosocial state was assessed before and after intervention.

29 participants received intervention; 16 had stable vision (12 with complete vision loss and 4 with vision between 20/300 (6/90) and light perception) and 13 were undergoing active treatment and had fluctuating vision ranging from 20/50 (6/15) to light perception. No control group was included in the study. Outcomes in patients with stable and fluctuating vision were analysed separately.

Patients in both groups experienced significant improvements in self-esteem, diabetes self-reliance, depressive symptoms and mental health status, however gains were larger for those in the fluctuating vision group. Whether this was related to the substantial difference in visual acuity between groups or the fact that one group was undergoing active treatment was not investigated. However, as psychosocial problems are greatest in the early, transient stage of vision loss [96, 275], the authors proposed that similar interventions be made available to patients early in the development of visual problems.

The same author subsequently reported on a case series of patients with diabetic retinopathy attending a diabetes education programme specialising in adaptive diabetes devices and techniques, for example syringe magnifiers, syringe loading

devices and speech enabled glucose monitoring systems[328]. Success was simply judged on whether patients could demonstrate proficiency with their adaptive devices. The outcomes of 163 patients were examined, 99 who were 'legally blind' but retained some residual vision and 64 who had complete vision loss. It was concluded that younger patients, with residual vision were significantly more likely to successfully use adaptive devices, however no evidence was presented as to whether the use of these devices translated into better blood glucose monitoring compliance or improved metabolic control. Again, the author proposed that similar interventions should be instigated earlier in the disease process, as this may provide the patient with the confidence to maintain these learned skills if vision subsequently deteriorates.

Rehabilitation strategies incorporating a visual and psychosocial component should be given further consideration. Many questions related to the specific format of the intervention remain; what it should include, who should deliver it, when should it be offered to name a few. Clearly stronger evidence is required in the form of a large randomised controlled trial investigating the effectiveness of such interventions on psychosocial and visual function.

One promising interventional avenue is Cognitive Behavioural Therapy (CBT). Used widely as a treatment for depression, its utility in patients with diabetes has been established[326, 327]. Persons with type 2 diabetes were randomised to either routine diabetes education or routine education with CBT. Ten 1-hour CBT sessions were provided, specifically covering the following,

"1) behavioural strategies to re-involve the patient in pleasurable social activities

2) problem solving procedures to resolve stressful circumstances

3) cognitive techniques to identify distorted or maladaptive thought patterns and replace them with more accurate, adaptive and useful views" [327].

Significantly more participants in the CBT group achieved remission of depressive symptoms compared to those receiving routine diabetes education (70.8% versus 22.2%, $p < 0.001$). Six months after intervention, the difference was smaller, but still significant (58.3% versus 25.9%, $p = 0.03$).

CBT also appeared to have a positive influence of diabetic control, with HbA1c levels significantly lower in the CBT group 6 months after intervention (9.5% versus 10.9%, $p = 0.03$).

As mentioned above, low vision rehabilitation aims to address visual ability, though there may be an indirect link on quality of life and psychosocial factors[152]. For example, a low vision rehabilitation service that made no specific provision for counseling improved 'emotional wellbeing' domain scores on the Impact of Visual Impairment questionnaire more than 'reading and accessing information' scores[125, 139].

The relationship between depression and low vision rehabilitation has been explored previously. Low vision clinical services (assessment of residual vision and prescription of low vision aids), counseling and patients reported use of magnifiers have been identified as significant contributors to a reduction in depressive symptoms[297]. Use of adaptive devices and skills training (orientation and mobility training) were not.

The influence of existing depression on reading rehabilitation success has been demonstrated, with less depressed patients more likely to experience successful outcomes following reading rehabilitation[329]. This may suggest that if rehabilitation strategies incorporating a visual and psychosocial component are to be considered, it may be prudent to address psychosocial difficulties prior to visual function difficulties, as this may ultimately lead to better outcomes.

The use of Problem Solving Therapy (PST) is currently being investigated in visually impaired patients displaying depressive symptoms in a multicentre RCT, the Depression in Visual Impairment Trial (DEPVIT). DEPVIT plans to compare 2 active interventions (PST and a referral to the patient's general practitioner in accordance with the National Institute for Clinical Excellence (NICE) 'step care' recommendations) to a waiting list control in visually impaired adults[330]. Depending on its outcome, this RCT may guide the content and delivery of psychosocial interventions for people with a visual impairment. Due to the additional psychosocial burden of diabetes[92, 94-96], specific interventions should be developed and tested in patients with DED.

9.6 Summary of trial results

No overall effect of low vision rehabilitation on visual ability was found. Visual ability improvements of between 0.49 and 0.6 logits were experienced by those with reduced corrected distance acuity or compromised central visual field function, suggesting these patients may benefit from a low vision clinic appointment. Relying solely on statistically significant results, referral to low vision services should be considered when best-corrected distance acuity is less than 0.0 logMAR or when a central scotoma of 35 points or more is present. However, as subgroups were small and unpowered, it is not useful to draw specific conclusion as to the cut off at which referrals should be made, as larger more clinically significant gains may have been uncovered at different cut off values if sample sizes were larger.

Counterintuitively, the effect of delaying intervention appeared to be beneficial. The reason for this remains elusive. Potentially an adaptation period is required to enable the effects of the intervention to be realised, on the other hand it may be an artefact due to greater numbers of participants in the delayed group receiving a low vision aid.

9.7 Clinical implications

It is clear from these results that a diagnosis of DED does not necessitate a referral to low vision rehabilitation. However current referral criteria may miss patients who could potentially benefit from a hospital based low vision assessment. Certainly,

these results need to be verified by a larger study, powered to detect differences between patients with different levels of corrected distance acuity and varying scotoma sizes.

As microperimetry instruments are not routinely found in hospital eye departments, scotoma size was used over other microperimetry variables, as it can be more easily compared to other perimetric measures. A 10-2 microperimetry exam includes 68 points and covers the area within a 10° radius of fixation. As such, a scotoma covering around half of this area, regardless of the means by which it was assessed may indicate that the patient may benefit from a low vision clinic appointment.

Reliance on visual acuity measurements alone in the assessment of visual function has been criticised previously[73, 75-77], however the current study revealed a corrected measure of acuity to be the single most useful predictor of baseline visual ability explaining 38% of its variance. Further, visual acuity measurements are performed universally in ophthalmology practice and clinicians are already familiar with making referrals based on acuity. Therefore, of all commonly performed visual function tests, an accurate assessment of best-corrected binocular distance acuity may be best placed to identify those diabetic patients likely to benefit from a hospital based low vision assessment.

Chapter 10 – Final conclusions

10.1 Summary of thesis

The work in this thesis represents the most comprehensive study of the impact of diabetic eye disease (DED) on visual function and self-reported visual ability to date. The study benefitted from a large sample of participants representing a range of disease severity levels; from the measurement of multiple aspects of visual function; and from employing Rasch analysis of patient response data. As such, this thesis makes a unique contribution to the field.

Though increasing disease severity impacted on many aspects of visual function, severity was not found to be independently related to visual ability. Instead, visual function deficits were responsible for the reduction in visual ability encountered in more severe disease. From an extensive set of visual function measures, a single measure of best-corrected acuity was the best predictor of visual ability, explaining 38% of the variance. Extra variance could not be explained by the addition of further visual function measures.

This thesis also details the first randomised controlled trial (RCT) investigating the effectiveness of a low vision clinic appointment in persons with DED. Though successfully completed, it is clear from the results that all patients with DED do not benefit from a low vision clinic appointment.

It was speculated in the introduction that the proportion of patients with DED referred to Moorfields Eye Hospital low vision clinics (8%) was low, possibly reflecting under referral. However, based on current referral criteria, this small percentage may represent the proportion of patients who are eligible for referral. An audit of patients attending a mobile digital diabetic screening programme revealed that 9% of patients had a best-corrected visual acuity of 0.3 logMAR or worse[240], not unlike the 13% found in our consecutively recruited sample.

10.2 Clinical implications

A measure of acuity was the most important factor in determining visual ability using our PROM. As such, clinicians should consider whether measurements of contrast sensitivity or colour vision add much to the assessment of people with DED.

However in addition to acuity, central field status assessed by microperimetry may be useful in the identification of those with DED likely to benefit from low vision intervention, particularly if around half the central 10° of fixation is affected.

We speculate that psychosocial factors may help to explain additional variance in visual ability. Clinicians should be conscious of psychosocial factors when assessing people with DED and should consider whether counseling or other psychological interventions may be appropriate. These interventions may improve patients' perceived visual ability.

10.3 Suggestions for future research

A limitation of this study is the relatively good vision of many of the participants. Future studies should investigate the effectiveness of a low vision clinic appointment in patients with poorer visual function. As exploratory subgroup analyses suggested current referral criteria may exclude patients likely to experience improved visual ability following low vision rehabilitation, a further RCT powered to detect differences within visual acuity and scotoma size subgroups is indicated to determine whether amendment of referral criteria is warranted.

A visual acuity inclusion criteria should be employed in future studies. We argue that even patients with corrected distance acuity up to 0.0 logMAR should be included, so that the relative benefits of intervention at varying stages of visual acuity loss can be investigated.

Additionally, a larger prospective study would allow investigation of whether a 3 month adaptation period is in fact required for the benefits of rehabilitation to be realised, or whether this was an artifact of the distribution of low vision aids prescribed in the current study.

A vast body of research supports the view that DED negatively impacts on psychosocial functioning. As such, an assessment of psychosocial outcomes should be included in future trials. Not only would this establish whether low vision

rehabilitation affects psychosocial outcomes in people with DED, but baseline measures may highlight specific areas amenable to psychosocial interventions.

Successful low vision rehabilitation is nebulous concept. Is it defined by perceived improvement or tangibly improved performance? Who should define it; the patient or the clinician? Future work should be directed toward establishing appropriate outcome measures in low vision rehabilitation research. The heavy reliance on PROMs in the assessment of low vision rehabilitation outcomes has left these questions somewhat neglected as PROMS assess perceived change in ability rather than actual enhanced performance. Studies incorporating both PROMs and performance based measures should be encouraged as a means of establishing whether perceive or tangible improvement in visual ability is more important to patients. Performance based measures clearly pose further considerations. For example, which tasks should be assessed, what metric to use (accuracy, time taken, successful completion) and where should assessments take place (at home or in clinic) to name a few.

Not only will this facilitate the development and employment of appropriate outcome measures, ensuring that intervention success can be accurately measured, but it may guide the content of future rehabilitation services.

10.4 Project 1 - Conclusions

Aim 1: To explore the impact of disease severity on visual function

Increasing severity of DED impacts negatively on many aspects of clinically assessed visual function.

Aim 2: To explore the impact of disease severity on visual ability

Increasing severity of DED impacts negatively on visual ability. Poorest visual ability was found in those with maculopathy, however those with proliferative disease only, had significantly worse visual ability that those with severe non-proliferative retinopathy indicating that the threat of treatment may also have a role in the reduced visual ability experienced.

Hypothesis: The reduction in visual ability associated with increasing disease severity is explained by visual function deficits

The reduction in visual ability experienced by those with DED can be explained by the accompanying drop in visual function. Though multiple aspects of function are affected, a single measurement of acuity provides the best prediction of visual ability in patients with DED.

10.5 Project 2 - Conclusions

Hypothesis: An NHS hospital based low vision clinic assessment results in increased visual ability in patients with DED

A low vision clinic appointment does not benefit all those with DED, however exploratory subgroup analyses suggest those with reduced acuity or compromised central field function may experience improved visual ability after rehabilitation. As these analyses were completed on very small sample sizes, this can only be verified by a further RCT.

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List of Appendices

Appendix I - Ethics documents

1. **Consent Form**
2. **Participants Information Sheet**
3. **Letter to General Practitioner**

Moorfields Eye Hospital NHS
NHS Foundation Trust

City Road
London
EC1V 2PD

Tel: 020 7253 3411
www.moorfields.nhs.uk

Centre:
Study Protocol Number:
Patient ID Number (affix label):

CONSENT FORM

Study Title: Visual Disability in Diabetic Eye Disease and its Rehabilitation

Research Team: Professor Gary Rubin, Dr Michael Crossland, Miss Hannah Dunbar

Please initial box

1. I confirm that I have read and understood the information sheet dated 08/08/2008 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from this Hospital and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐

CONSENT FORM (continued)

Study Title: Visual Disability in Diabetic Eye Disease and its Rehabilitation

Research Team: Professor Gary Rubin, Dr Michael Crossland, Miss Hannah Dunbar

Please initial box

4. I give permission for my GP to be informed about my participation in this study. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Patient Name	Signature	Date
_____	_____	_____
Researcher	Signature	Date
_____	_____	_____
Person taking consent (if different from researcher)	Signature	Date

1 copy for patient; 1 for researcher site file; 1 (original) to be kept in medical notes.

Moorfields Eye Hospital NHS
NHS Foundation Trust

City Road
London
EC1V 2PD

Tel: 020 7253 3411
www.moorfields.nhs.uk

Visual disability in diabetic eye disease and its rehabilitation

You are being invited to take part in a research study. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

A lot is unknown about exactly how ocular changes caused by diabetes (Diabetic Eye Disease) affects a persons sight and impacts their day to day life. As the number of people with diabetes continues to increase, it is very important that we fully understand these changes. This study aims to describe the ways in which vision is affected in diabetic eye disease and how useful a Low Vision Assessment is to people with diabetes. This will also help us plan low vision services for future patients with Diabetes. In this study, we will be assessing patients in the Moorfields Low Vision Clinic either within 2 weeks of enrolment into the study, or at 3 months.

Patron: Her Majesty The Queen
Chairman: Rudy Markham
Chief Executive: John Pelly

Why have I been invited?
We are inviting people who have been diagnosed with Diabetic Eye Disease and attend a Moorfields Diabetic Clinic, have no other significant eye condition, are otherwise in good general health and have had no previous low vision appointments.

Do I have to take part?
No, it is up to you whether you want to take part. You do not have to give a reason if you do not want to take part and a decision not to take part will not affect your care at the Hospital.

What will happen to me if I take part?
We will ask you to attend Moorfields Eye Hospital for some vision checks. Our checks will include measuring your vision on a letter chart, checking how well you notice changes between shades of grey and colours, checking the span of your vision and recording the speed at which you read. We will also use an instrument to look at which part of the retina you use to look at different objects and how steady you keep your eyes. To use this instrument we need to put dilating drops into your eyes to enlarge your pupils. These are the same drops routinely used at your diabetic clinic appointments. They may cause blurred vision for 4 – 6 hours and you may be more sensitive to light. You must not drive until the effects of the drops have worn off.

In total these tests should take between 90 minutes and 2 hours. There will be time to stop for breaks if needed. If

you do not feel up to completing all tests in one sitting, we can arrange for a second appointment.

We will pay for your travel expenses and taxi fare if needed.

Following this, you will be allocated to one of 2 groups. The first group will be invited to the Moorfields low vision clinic within 2 weeks and the second group in three months time. During this appointment an Optometrist will assess and help you maximise your vision, issuing spectacles and/or magnifiers if appropriate.

We will contact you by telephone three times, shortly after enrolment, at 3 months and at 6 months to ask you questions about how you are managing with your vision. The phone calls will be at a time convenient to you and will take about 30 minutes.

Your care at Moorfields will not be affected and you should still attend your other appointments as normal.

Will you tell my GP that I am taking part?
We will write to your GP to let him or her know that you are taking part. If you do not wish your GP to be informed of your participation, please let us know.

What are the possible benefits of taking part?
As a participant you will receive a low vision assessment at the Moorfields Low Vision Clinic. You will help us understand the visual changes that can occur through diabetes and help us discover how useful a visit to the Moorfields Low Vision Clinic is for people with Diabetic Eye

Disease. This will enable us to plan this service for future patients.

What if something goes wrong?
The research does not carry any more risks than visiting the hospital in the normal way. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Will my taking part in this study be kept confidential?
All information collected during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The results of the study will be written up as a PhD thesis and be published in a clinical journal. Results will also be presented at international conferences. You will not be identified in any report/publication.

Who is organising and funding the research?
The research is being carried out between the Institute of Ophthalmology (part of University College London) and Moorfields Eye Hospital. It is being supervised by Prof Gary Rubin.

The study is being funded by the charity Fight for Sight.

Who has approved the study?
The study has been approved by the National Hospital for Neurology and Neurosurgery (NHNN) Research Ethics Committee.

Who can I contact for more information?
The research is being organised by Miss Hannah Dunbar, research optometrist. She can be contacted on 020 7608 4047 or h.dunbar@ucl.ac.uk

Moorfields Eye Hospital NHS
NHS Foundation Trust

Date:

Patient label:

City Road
London
EC1V 2PD

Tel: 020 7253 3411
www.moorfields.nhs.uk

Dear Doctor

This letter is to inform you that the above patient has agreed to take part a research project at Moorfields Eye Hospital, London. The project entitled 'Visual disability in diabetic eye disease and its rehabilitation' aims to quantify the effects of diabetic eye disease on multiple aspects of visual performance, relating this to self reported visual disability. We will also determine the efficacy of low vision rehabilitation on people with diabetes by way of a randomised controlled trial of delayed intervention design.

At the outset all patients in the study are asked to attend a baseline vision assessment, where they will complete a series of standard and specialised vision measurements. One week later they will take part in a telephone administered questionnaire which evaluates self reported vision disability. Patients will then be randomised into one of two groups, the intervention group and the delayed intervention group. Within two weeks of their baseline assessment patients in the intervention group will receive a low vision assessment by a qualified optometrist at Moorfields Eye Hospital and will be issued with low vision aids as appropriate. The delayed intervention group will receive the same low vision assessment three months after enrolment in the study. Currently the waiting list time for a Low Vision Assessment at Moorfields is 4 months.

At 3 and 6 months all patients will repeat the vision disability instrument over the telephone. Study involvement will last 6 months.

If you have any questions about this study please do not hesitate to contact me.

With best wishes

Yours sincerely

Hannah Dunbar BSc MCOptom
Research Optometrist

Contact Details
Tel: 020 7608 4047
Email: h.dunbar@ucl.ac.uk

Patron: Her Majesty The Queen
Chairman: Rudy Markham
Chief Executive: John Pelly

Appendix II - Case Report Forms

1. **Subject Characteristics**
2. **Baseline Vision Assessment**
3. **Distance Acuity Score Sheet**
4. **Contrast Sensitivity Score Sheet**
5. **IReST Score Sheet**
6. **MNread Score Sheet**
7. **Desaturated D-15 Assessment**
8. **Minimisation Sheet**

Subject Characteristics

Subject ID:…… **Date:……..**

Subject Initials:……..

Sex:……

Date of Birth:……..

Age:……

Diabetes Type:……..

Duration of Disease:……..

Duration of Eye Disease…….

RE NGP Grade:……..

LE NGP Grade:……..

Better Eye:……..

Disease Severity Group:…….

Intervention Arm:……..

Baseline Vision Assessment

Subject ID:…… **Date:……..**
Subject Initials:……..

Diabetes Type:…….. **Duration of Disease:……..**
Duration of Eye Disease……..

Habitual Distance Vision

Does subject wear Distance Rx? Yes/No (If so record Rx)

R:…….. L:……

Acuity:……..LogMAR Acuity:……..LogMAR

Binocular:……LogMAR

<u>Refraction Result</u> 4m/1m (Delete as appropriate)

R:…….. L:……..……

Letter Score:…….. Letter Score:……..

Acuity:……..LogMAR Acuity:……..LogMAR

Binocular Letter Score:……..

Binocular:……LogMAR

<u>Contrast Sensitivity</u> (at 1m, add +0.75DS)

R:……LogUnits L:……..…LogUnits

Number of Letters:…… Number of Letters:……

Habitual Reading Vision

Does subject use Reading glasses or aid to read? Yes/No
If so record

R:…….. L:……..

Baseline Vision Assessment

Subject ID:…… **Date:……..**
Subject Initials:……..

Bailey Lovie Near Vision

Acuity:……..LogMAR Acuity:……..LogMAR

Binocular Acuity:……..LogMAR WD:……..

IReST (Binocularly)

Large **Small**
Habitual working distance……cm Habitual working distance……cm

Corrected reading speed:……..wpm Corrected reading speed:……..wpm

Potential Reading Vision

MNREAD (Binocularly)

Number of Sentences attempted:…… Add used: u/a/+2.50/+4.00
Working Distance: 40cm/25cm

Number of Errors:……..

Reading Acuity:……LogMAR

Maximum Reading Rate:……wpm

Critical Print Size:……..LogMAR

Baseline Vision Assessment

Subject ID:…… **Date:……..**
Subject Initials:……..

Colour Vision

Desaturated D-15 (Binocularly)

Bowman Classification

Total Error Score (BTES):……..

Colour Confusion Index (CCI)……..

Vingrys & King-Smith Classification

Total Error Score (VTES):…….....

Confusion Angle (CA):……..

Confusion Index (C-Index):……..

Selectivity Index (S-Index):……..

Visual Fields

Binocular Esterman

Esterman Efficiency Score:……..

Microperimetry

R Mean sensitivity:……..(dB)

L Mean Sensitivity:……..(dB)

Fixation Stability

R BCEA:……..min arc ^{2}

L BCEA:……..min arc ^{2}

Distance Acuity Score Sheet

Subject ID:…….. **Date:……..**
Subject Initials……..

Circle letters read correctly at 4m, totalling at the end of each line and end of the column.

Chart One: Right Eye

N C K Z O	☐
R H S D K	☐
D O V H R	☐
C Z R H S	☐
O N H R C	☐
D K S N V	☐
Z S O K N	☐
C K D N R	☐
S R Z K D	☐
H Z O V C	☐
N V D O K	☐
V H C N O	☐
S V H C Z	☐
O Z D V K	☐
Total	☐

Chart Two: Left Eye

D S R K N	☐	**1.00**
C K Z O H	☐	**0.9**
O N R K D	☐	**0.8**
K Z V D C	☐	**0.7**
V S H Z O	☐	**0.6**
H D K C R	☐	**0.5**
C S R H N	☐	**0.4**
S V Z D K	☐	**0.3**
N C V O Z	☐	**0.2**
R H S D V	☐	**0.1**
S N R O H	☐	**0.0**
O D H K R	☐	**-0.1**
Z K C S N	☐	**-0.2**
C R H D V	☐	**-0.3**
Total	☐	

If less than 20 letters read correctly at 4m, move chart to 1m, adding +0.75DS to refraction result.

Chart One: Right Eye

N C K Z O	☐
R H S D K	☐
D O V H R	☐
C Z R H S	☐
O N H R C	☐
D K S N V	☐
Total	☐

Chart Two: Left Eye

D S R K N	☐	**1.6**
C K Z O H	☐	**1.5**
O N R K D	☐	**1.4**
K Z V D C	☐	**1.3**
V S H Z O	☐	**1.2**
H D K C R	☐	**1.1**
Total	☐	

Distance Acuity Score Sheet

Subject ID:…….. **Date:……..**
Subject Initials……..

Total at 4m	☐	**Total at 4m**	☐
If more than 20 add 30 otherwise add 0	☐	**If more than 20 add 30 otherwise add 0**	☐
Total at 1m (if applicable)	☐	**Total at 1m (if applicable)**	☐
Final Letter Score	☐	**Final Letter Score**	☐
LogMAR Acuity	☐	**LogMAR Acuity**	☐
If no letters read at 1m record		If no letters read at 1m record	
Count Fingers	☐	**Count Fingers**	☐
Hand Movements	☐	**Hand Movements**	☐
Perception of Light	☐	**Perception of Light**	☐
No perception of Light	☐	**No perception of Light**	☐

Distance Acuity Score Sheet

Subject ID:…….. **Date:……..**
Subject Initials……..

Chart R: Binocular Acuity

H	**V**	**Z**	**D**	**S**	☐	**1.00**
N	**C**	**V**	**K**	**D**	☐	**0.9**
C	**Z**	**S**	**H**	**N**	☐	**0.8**
O	**N**	**V**	**S**	**R**	☐	**0.7**
K	**D**	**N**	**R**	**O**	☐	**0.6**
Z	**K**	**C**	**S**	**V**	☐	**0.5**
D	**V**	**O**	**H**	**C**	☐	**0.4**
O	**H**	**V**	**C**	**K**	☐	**0.3**
H	**Z**	**C**	**K**	**O**	☐	**0.2**
N	**C**	**K**	**H**	**D**	☐	**0.1**
Z	**H**	**C**	**S**	**R**	☐	**0.0**
S	**Z**	**R**	**D**	**N**	☐	**-0.1**
H	**C**	**D**	**R**	**O**	☐	**-0.2**
R	**D**	**O**	**S**	**N**	☐	**-0.3**

Total ☐

If less than 20 letters read correctly at 4m, move chart to 1m, adding +0.75DS to refraction result.

H	**V**	**Z**	**D**	**S**	☐	**1.6**
N	**C**	**V**	**K**	**D**	☐	**1.5**
C	**Z**	**S**	**H**	**N**	☐	**1.4**
O	**N**	**V**	**S**	**R**	☐	**1.3**
K	**D**	**N**	**R**	**O**	☐	**1.2**
Z	**K**	**C**	**S**	**V**	☐	**1.1**

Total ☐

Distance Acuity Score Sheet

Subject ID:…….. **Date:……..**
Subject Initials……..

Total at 4m	☐
If more than 20 add 30 otherwise add 0	☐
Total at 1m (if applicable)	☐
Final Letter Score	☐
LogMAR Acuity	☐

If no letters read at 1m record as

Count Fingers	☐
Hand Movements	☐
Perception of Light	☐
No perception of Light	☐

Contrast Sensitivity Score Sheet

Subject ID:…….. **Date:……..**
Subject Initials……..

Right Eye

0.00	H	S	Z	D	S	N	0.15
0.30	C	K	R	Z	V	R	0.45
0.60	N	D	C	O	S	K	0.75
0.90	O	Z	K	V	H	Z	1.05
1.20	N	H	O	N	R	D	1.35
1.50	V	R	C	O	V	H	1.65
1.80	C	D	S	N	D	C	1.95
2.10	K	V	H	O	H	R	2.25

Number of letters:……..

R:……..LogUnits

Left Eye

0.00	V	R	S	K	D	R	0.15
0.30	N	H	C	S	O	K	0.45
0.60	S	C	N	O	Z	V	0.75
0.90	C	N	H	Z	O	K	1.05
1.20	N	O	D	V	H	R	1.35
1.50	C	D	N	Z	S	V	1.65
1.80	K	C	H	O	D	K	1.95
2.10	R	S	Z	H	V	R	2.25

Number of letters:……..

R:……..LogUnits

IReST score sheet

All animals that live on other animals face the problem of how to get hold of their prey. Many animals seek and hunt their prey, while others sit still and wait for a harmless victim to come close to them. One widely used way to get food without too much trouble is to build a trap or net. The best known example for animals that catch other animals with the help of a net are spiders. Their sticky nets are spun so fine that they are hard to see, and usually an insect does not notice a net until it has caught itself in it. The spider then only needs to go to the place where the insect is. It is either eaten right on the spot or otherwise it is wrapped in sticky threads for later consumption. Other living things that are stuck on rocks or on the floor of the sea live on tiny animals and plants that they soak in with water.

Patient ID: _____ Date:_____

No Words (Total): 165 Large/Small Text

Distance: _____ Time: _____

No Errors: _____ No words read correctly:_____

Reading Speed::_____

MNread Score sheet

MNREAD ACUITY CHART for 40 cm

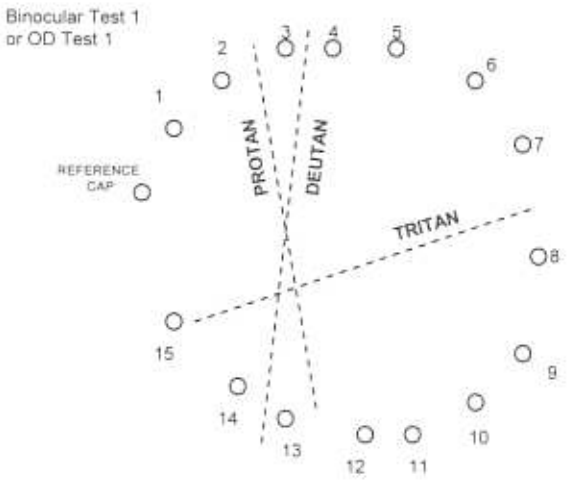
CHART ONE

NAME	DATE
EYE TESTED OU❑ OS❑ OD❑	TEST DISTANCE ❑ 40 cm ❑ OTHER_____

1.3 logMAR 8.0 M 6/120 My father takes me to school every day in his big green car	**0.7 logMAR 2.0 M 6/30** He told a long story about ducks before his son went to bed	**0.1 logMAR 0.50 M 6/8** Our father wants us to wash the clothes before he gets back
1.2 6.3 6/95 Everyone wanted to go outside when the rain finally stopped	**0.6 1.6 6/24** My mother loves to hear the young girls sing in the morning	**0.0 0.40 6/6** They would love to see you during your visit here this week
1.1 5.0 6/75 They were not able to finish playing the game before dinner	**0.5 1.3 6/19** The young boy held his hand high to ask questions in school	**-0.1 0.32 6/5** The teacher showed the children how to draw pretty pictures
1.0 4.0 6/60 My father asked me to help the two men carry the box inside	**0.4 1.0 6/15** My brother wanted a glass of milk with his cake after lunch	**-0.2 0.25 6/4** Nothing could ever be better than a hot fire to warm you up
0.9 3.2 6/48 Three of my friends had never been to a circus before today	**0.3 0.8 6/12** I do not understand why we must leave so early for the play	**-0.3 0.20 6/3** The old man caught a fish here when he went out in his boat
0.8 2.5 6/38 My grandfather has a large garden with fruit and vegetables	**0.2 0.6 6/10** It is more than four hundred miles from my home to the city	**-0.4 0.16 6/2.5** Our mother tells us that we should wear heavy coats outside
		-0.5 0.13 6/2 One of my brothers went with his friend to climb a mountain

Desaturated D-15 Assessment

Subject ID:…… **Date:……..**
Subject Initials:……



Cap Order

Vingrys & King-Smith Classification

Total Error Score (VTES):……..

Confusion Angle (CA):……..

Confusion Index (C-Index):……..

Selectivity Index (S-Index):……..

Minimisation sheet for 'Visual disability in diabetic eye disease and its rehabilitation'

Contact for randomisation: Wen Xing (MEH Research & Development)
Phone: 020 7566 2315 email: wen.xing@moorfields.nhs.uk

Please record the following for each patient

Trial number _____

Date of Randomisation: __ __ / __ __ / 20 __ __

Factors (weight)	**Groups**			
Visual Acuity (4)	≤ 0.2 LogMar	> 0.2 LogMar		
Disease severity* (3)	1	2	3	4
Age (2)	≤ 50 yrs	> 50 yrs		
Sex (1)	Male	Female		
Treatment Allocation	Intervention	Delayed intervention		

Appendix III - Activity Inventory and administration instructions

1. **Activity Inventory Form**
2. **Administration Instructions**

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Social Activities

Social Functions - 1

How important is it for you to attend parties or other functions?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to attend parties or other functions?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Entertain Guests - 2

How important is it for you to entertain guests?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to entertain guests?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Prepare Food for Guests - 3

How important is it for you to cook or bake for social functions; i.e, Christmas and holidays?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to cook or bake for social functions; i.e, Christmas and holidays?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

Dining Out - 4

How important is it for you to dine out?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to dine out?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Spectator Events - 5

How important is it for you to attend plays, concerts, movies, sporting events, etc?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to attend plays, concerts, movies, sporting events, etc?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Attend Meetings - 6

How important is it for you to attend meetings of a club, church, social club, etc.?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to attend meetings of a club, church, social club, etc.?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

Play Games - 7

How important is it for you to play cards, board games, Bingo, or other games?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to play cards, board games, Bingo, or other games?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Perform in Public - 8

How important is it for you to sing in a choir or play an instrument publicly, perform in plays, speak publicly or perform before a group?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to sing in a choir or play an instrument publicly, perform in plays, speak publicly or perform before a group?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Attend Church or House of Worship - 9

How important is it for you to attend church or house of worship services?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to attend church or house of worship services?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Social Dancing - 10

How important is it for you to dance socially?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to dance socially

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Recreation

Leisure Entertainment - 1

How important is it for you to provide yourself with leisure entertainment, such as watch TV, reading books or magazines, playing cards or doing puzzles?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to provide yourself with leisure entertainment, such as watch TV, reading books or magazines, playing cards or doing puzzles?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Exercise - 2

How important is it for you to exercise?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

How difficult is it for you to exercise?

0 Not difficult
1 Slightly difficult
2 Moderately difficuly
3 Very difficult
4 Impossible to do without someone else's help

Sewing or Needlework - 3

How important is it for you to sew or do needlework?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to sew or do needlework?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Knitting or Crocheting - 4

How important is it for you to knit or crochet?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to knit or crochet?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Woodworking - 5

How important is it for you to do woodworking?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory
Subject ID:…… Date:……..
Subject Initials:…….. Follow up:……..

How difficult is it for you to do woodworking?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Metalwork - 6

How important is it for you to do metalwork?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to do metalwork?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Painting or drawing - 7

How important is it for you to paint or draw?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to paint or draw?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Recreational Cooking or Baking - 8

How important is it for you to cook or bake for recreation?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

How difficult is it for you to cook or bake for recreation?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Electrical Work - 9

How important is it for you to do electrical work?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to do electrical work?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Model Building - 10

How important is it for you to build models?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to build models?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Play musical instrument - 11

How important is it for you to play a musical instrument?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory
Subject ID:……. Date:……..
Subject Initials:…….. Follow up:……..

How difficult is it for you to play a musical instrument?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Traveling - 12

How important is it for you to travel?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to travel
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Fishing - 13

How important is it for you to fish?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to fish?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Hunting or Shooting - 14

How important is it for you to go hunting or shooting?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory
Subject ID:……. Date:……..
Subject Initials:…….. Follow up:……..

How difficult is it for you to go hunting or shooting?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Outdoor Activities - 15

How important is it for you to perform outdoor recreational activities; i.e., boating, hiking, fishing, etc.?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to perform outdoor recreational activities; i.e., boating, hiking, fishing, etc.?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Gardening and Lawn Care - 16

How important is it for you to garden for pleasure or work in the garden?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to garden for pleasure or work in the garden?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Play Sports - 17

How important is it for you to play sports; such as, golf, bowling, tennis, etc.?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory
Subject ID:……. Date:……..
Subject Initials:…….. Follow up:……..

How difficult is it for you to play sports; such as, golf, bowling, tennis, etc.?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Leatherwork - 18

How important is it for you to work with leather?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to work with leather?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Computers - 19

How important is it for you to use a computer?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to use a computer?
0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Collections - 20

How important is it for you to collect things; i.e., antiques, stamps, coins, cards, dolls, etc.?
0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory
Subject ID:……. Date:……..
Subject Initials:…….. Follow up:……..

How difficult is it for you to collect things; i.e., antiques, stamps, coins, cards, dolls, etc.?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Read Newspaper - 21

How important is it for you to read the newspaper?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to read the newspaper?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Photography 22

How important is it for you to do photography?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to do photography?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Daily Living

Toileting - 1

How important is it for you to be able to use the toilets in a public place (without anyone else's assistance)?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to use the toilets in a public place without anyone else's assistance?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Personal Hygiene - 2

How important is it for you to take care of yourself; shave, trim nails, apply makeup, etc., without anyone else's assistance?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to take care of yourself shave, trim nails, apply makeup, etc., without anyone else's assistance?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Dressing - 3

How important is it for you to choose your clothes and dress yourself?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

How difficult is it for you to choose your clothes and dress yourself?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Personal Health Care - 4

How important is it for you to take care of your health?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to take care of your health?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Eating - 5

How important is it for you to be able to eat your meals without any assistance?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to be able to eat your meals without any assistance?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Daily Meal Preparation - 6

How important is it for you to be able to prepare your daily meals without anyone else's help?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

How difficult is it for you to be able to prepare your daily meals without anyone else's help?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Household Tasks - 7

How important is it for you to perform household tasks such as cleaning, laundry, or setting a thermostat?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to perform household tasks such as cleaning, laundry or setting a thermostat?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Personal Communication - 8

How important is it for you to recognize people, see expressions, and make contact during personal communications?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to recognize people, see expressions, and make contact during personal communications?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Correspondence - 9

How important is for you to read mail and write letters?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is for you to read mail and write letters?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Follow the News - 10

How important is it for you to follow the news and keep up with current events?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to follow the news and keep up with current events?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Follow A Schedule - 11

How important is it for you to read the time or follow a schedule?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to read the time or follow a schedule?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:……. Date:……..

Subject Initials:…….. Follow up:……..

Manage Finances - 12

How important is it for you to pay bills, balance accounts, or manage personal or household finances?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to pay bills, balance accounts, or manage personal or household finances?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Shopping - 13

How important is it for you to go shopping for food, clothes or other necessities?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to go shopping for food, clothes or other necessities?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Child Care - 14

How important is it for you to care for young children?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to care for young children?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Driving - 15

How important is it for you to be able to drive?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to be able to drive?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Home Care for an Adult - 16

How important is it for you to provide home care for an adult?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to provide home care for an adult

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Pet Care - 17

How important is it for you to provide care for a pet?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to provide care for a pet

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory

Subject ID:…… Date:……..

Subject Initials:…….. Follow up:……..

Phone Use - 18

How important is it for you to be able to use the telephone?

0 Not important
1 Slightly important
2 Moderately important
3 Very important

How difficult is it for you to be able to use the telephone?

0 Not difficult
1 Slightly difficult
2 Moderately difficult
3 Very difficult
4 Impossible to do without someone else's help

Activity Inventory administration instructions

Between 22nd June 2009 and 2nd Feb 2010 the following script was used to instruct participants how to respond to the MAI questionnaire.

> *I would like to ask you some questions about your vision, specifically whether your vision makes it difficult for you to carry out day-to-day tasks. I will ask you about a number of tasks, some of which may not be important to you. In order to find out which tasks are important to you, I will first ask you to rate the importance of the task. If it is a task that you do not do, you should say that it is not important. For example if it is playing the piano and you never have, please say that it is not important. For any task that you do then report as being important, I will ask you to tell me how difficult your vision makes it for you to do that task. This is your best corrected vision, so wearing any glasses, contact lenses or using magnifiers you may need. If you do not understand any questions please let me know. Is this ok?*

As of 3rd February 2010, the script was modified as follows, in order to reinforce the masking procedure of the trial.

> *I would like to ask you some questions about your vision, specifically whether your vision makes it difficult for you to carry out day-to-day tasks. Before we start, could I ask you not to tell me about any past or future appointments you have had on the trial. You may contact Hannah Dunbar if you have any queries.*

I will ask you about a number of tasks, some of which may not be important to you. In order to find out which tasks are important to you, I will first ask you to rate the importance of the task. If it is a task that you do not do, you should say that it is not important. For example if it is playing the piano and you never have, please say that it is not important. For any task that you do then report as being important, I will ask you to tell me how difficult your vision makes it for you to do that task. This is your best corrected vision, so wearing any glasses or contact lenses or using any magnifiers you may need. If you do not understand any questions please let me know. Is this ok?

Also at the end of each administration, the following question will be asked in order to ascertain whether participants have been in receipt of any further interventions.

Have you, since your last visit to Moorfields Eye Hospital had any change in the treatment of your diabetes or treatment to your eyes? This can include any change in your diabetes medication, any laser to your eyes, any visit to another eye department or optician.

Appendix IV - List of presentations and publications

Poster presentations

Association for Research in Vision and Ophthalmology (2009)

- Fixation stability assessment: A comparison between Laser Scanning Ophthalmoscope and a Microperimeter.

Association for Research in Vision and Ophthalmology (2010)

- The relationship between severity of disease and visual ability and function in diabetic eye disease

Oral presentations

First European Congress on Low Vision (2010)

- Effect of Low Vision Rehabilitation on Visual Ability in Diabetic Eye Disease: Methodology

10th International Conference on Low Vision (2011)

- Relationship between visual function and visual ability in Diabetic Eye Disease

Association for Research in Vision and Ophthalmology (2012)

- The Effect of Low Vision Rehabilitation in Diabetic Eye Disease: A Randomised Controlled Trial.

38th Hospital Optometrists Annual Conference (2012)

- The Effect of Low Vision Rehabilitation in Diabetic Eye Disease: A Randomised Controlled Trial.

Awards

Envision Atwell Award for Best Young Investigator in Low Vision (2011)

Publications

Dunbar, H.M.P., Crossland, M.D. and Rubin, G.S. *Fixation Stability: A Comparison between the Nidek MP-1 and Rodenstock Scanning Laser Ophthalmoscope in Persons with and with Diabetic Maculopathy.* Investigative Ophthalmology and Vision Science, 2010. **51**(8): p. 4346 – 4350.

Dunbar, H.M.P., Crossland, M.D., Bunce, C., Egan, C. and Rubin, G.S. *The effect of low vision rehabilitation in diabetic eye disease: a randomised controlled trial protocol.* Ophthalmic and Physiological Optics, 2012. **32**: p. 282 – 293.

Fixation Stability: A Comparison between the Nidek MP-1 and the Rodenstock Scanning Laser Ophthalmoscope in Persons with and without Diabetic Maculopathy

Hannah M. P. Dunbar,[1] *Michael D. Crossland,*[1,2] *and Gary S. Rubin*[1,2]

Purpose. Impaired fixation stability is associated with reduced reading speed. In previous research, fixation stability has been assessed using an infrared eye tracker or a confocal scanning laser ophthalmoscope. The new MP-1 microperimeter from Nidek Technologies (Padova, Italy) provides another option for the assessment of fixation. Here the authors compare fixation stability values measured using the MP-1 microperimeter and the Rodenstock scanning laser ophthalmoscope (SLO; Rodenstock GmbH, Munich, Germany) in persons with and without diabetic maculopathy.

Methods. Sixteen normally sighted volunteers and 21 patients with diabetic maculopathy were recruited. Fixation stability was recorded monocularly on the SLO and the MP-1 in counterbalanced order while participants fixated a red 1° cross. Fixation data collected from each instrument were used to calculate a bivariate contour ellipse area (BCEA) that encompassed 68% of fixation points.

Results. For control subjects, MP-1 BCEA values were larger than SLO by 0.25 log min arc^2, though the difference was small (10%) and of borderline significance (MP-1, 2.51 log min arc^2; SLO, 2.26 log min arc^2; $P = 0.06$). In patients with diabetic maculopathy there was no significant difference between MP-1 and SLO values (MP-1, 2.94 log min arc^2; SLO, 2.90 log min arc^2; $P = 0.88$).

Conclusions. No significant difference was found in BCEA values from the SLO and MP-1 in control subjects and patients with diabetic maculopathy. The authors suggest that the similarity between BCEA values, together with the consistent and reliable operation of the MP-1, make it a useful and viable alternative to the SLO in the assessment of fixation. (*Invest Ophthalmol Vis Sci.* 2010;51:4346–4350) DOI:10.1167/iovs.09-4556

In normal vision, an eye fixating a static target does not remain stationary[1]; it constantly makes small involuntary eye movements such as microsaccades, drifts, and tremors.[2] Elimination of such movements would cause our perception of a stationary target to fade completely[3–6]. However, excessive instability degrades visual resolution[7] and may interfere with the performance of everyday tasks such as reading.[8] Eye conditions affecting central vision are known to impair fixation.[9–14] Therefore, awareness of a patient's ability to fixate is important when considering functional vision.

Although it is no longer commercially available, one well-established instrument in the assessment of fixation is the Rodenstock scanning laser ophthalmoscope (SLO; Rodenstock GmbH, Munich, Germany). Since its introduction in the early 1980s it has been used in numerous studies of fixation[9–11,14–18] and has proven to be particularly useful for the examination of fixation in those with eye disease.[9,11,13–17,19] The instrument was not specifically designed to measure fixation, but different methods have been described that allow its quantification.[11,14,15,19] One established method follows that first described by Steinman, whereby the position of each fixation point is plotted on Cartesian axes and the elliptical area encompassing a given percentage of points is calculated.[20] This bivariate contour ellipse area (BCEA) presents a value of fixation stability, with smaller values indicating more stable fixation.

A new instrument, the Nidek MP-1 microperimeter (Nidek Technologies, Padova, Italy), has been designed with fixation stability assessment capability. It allows fixation to be assessed during a microperimetric examination or as an isolated assessment. The MP-1 offers classification of fixation stability based on the system described by Fujii et al.,[21] whereby fixation is termed *stable* if >75% of fixation points fall within a 2° diameter circle centered on the gravitational center of all fixation points, *relatively unstable* if <75% of fixation points fall within a 2° circle but >75% are located within a 4° diameter circle, and *unstable* if <75% of all fixation points fall within a 4° diameter circle.[21] The lack of scientific foundation to this classification has been criticized in the literature.[22] However, it is possible to extract raw fixation data from the MP-1, thus allowing fixation points to be plotted and characterized by a BCEA value, as described. Recently we published data showing a lack of correlation between reading speed and fixation stability as classified by the inbuilt MP-1 strategy but a stronger correlation between reading performance and fixation quantified by calculating a BCEA.[23]

Because both the SLO and the MP-1 are used in the evaluation of fixation, an understanding of their comparability is vital. Different methods of assessment are known to produce different BCEA values; for example, in healthy young persons, SLO BCEA values are up to 2.25 times smaller than those from a head-mounted eye tracker system.[24] Given that the factors influencing measurement differ between those with steady fixation and those with poor fixation, we feel it important to compare fixation measurements not only in healthy young subjects but also in patients with poorer fixation.

Diabetic eye disease is the leading cause of blindness in the working-age population of the United Kingdom, and the incidence of diabetes mellitus continues to rise in many developed countries.[25–27] Although fixation behavior has been widely

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studied in macular disease,[9,11–13,19,22,23,28] the impact of diabetic maculopathy on fixation stability is less well understood.[14–17,29,30] A better understanding of fixation in the presence of diabetic maculopathy and its impact on visual function is necessary for clinicians involved in the visual rehabilitation of patients and for those responsible for the strategic planning of such services.

Here we evaluated fixation stability in persons with and without diabetic maculopathy using two different instruments, the Rodenstock confocal SLO and the Nidek MP-1 microperimeter.

Methods

Participants were recruited into two groups, patients with diabetic maculopathy and normally sighted volunteers. Patients were recruited from medical retina clinics at Moorfields Eye Hospital in London. All had diagnoses of type 1 or type 2 diabetes mellitus for at least 1 year and had recently diagnosed diabetic maculopathy of at least grade M1 according to the National Grading Protocol for England and Wales. This grade is defined as having one or more of the following features: exudates within 1 disc diameter (DD) of the center of the fovea; circinate or group of exudates within the macula; retinal thickening within 1 DD of the center of the fovea; and any microaneurysm or hemorrhage within 1 DD of the center of the fovea, only if associated with a best visual acuity of ≤6/12.[31] All normally sighted volunteers were hospital staff.

Written informed consent was obtained from all participants once an explanation of the nature and possible consequences of the study had been explained. The research was approved by the Moorfields and Whittington Research Ethics Committee and conformed to the Declaration of Helsinki.

Measurement of Fixation Stability

Fixation stability was recorded for each participant on both instruments in a counterbalanced order. All measurements were taken from the better eye, with the fellow eye occluded while the head was stabilized between a chin and forehead rest. The same researcher (HD) operated both instruments.

Scanning Laser Ophthalmoscope

We used a scanning laser ophthalmoscope (SLO-101; Rodenstock GmbH) consisting of a helium-neon laser of wavelength 632.8 nm that produces the stimuli and an infrared laser of 780 nm that simultaneously images the fundus according to a confocal principle.[32] Images were captured on a professional digital video recorder at a resolution of 768 × 576 pixels (model BR-DV600E; JVC, Yokohama, Japan) and a frequency of 12.5 Hz.

Software provided with the SLO (scotometry module) was used to produce a 1° red cross fixation target. Subjects were asked to view the center of the cross until 10 seconds of relatively blink free data were obtained. The digital video recorder simultaneously recorded fundus images throughout.

Video images were digitized using a frame grabber (Orion Frame Grabber; Matrox, Montreal, Canada) and retinal position was retrospectively analyzed using software developed in house. The software automatically tracked fundus features within a delineated square of predetermined location on the retinal image at 12.5 Hz, producing x and y coordinates of its position in pixels. If tracking was lost, the square jumped to the extremity of the image, and the related coordinates had unrealistic values. Any such coordinates were manually deleted; complete trials were discarded if >20% of coordinates were deleted for this reason.

The SLO was calibrated to quantify the amount of retinal movement shown in the captured fundus image. A semi-silvered mirror was placed in front of the SLO, allowing external targets to be viewed on the same visual axis as the SLO. Two cross fixation targets of known horizontal separation were placed on the wall parallel to the observer's line of sight. The distance between the targets and the semi-silvered mirror was recorded, and, therefore, the angular separation of the crosses could be calculated. The observer was instructed to look steadily at one target for 10 seconds and then switch to the second target for another 10 seconds. Fundus images were simultaneously recorded. The position of a retinal landmark was tracked at a frequency of 12.5 Hz, recording eye position in two-dimensional pixel coordinates. The horizontal movement of the retinal image between the two positions in image pixels was determined and used in a simple transformation, with the angular separation of the two crosses to describe the retinal motion seen on SLO recording in terms of visual angle. The resultant conversion factor, 1 pixel:2.6 min arc, was used in all SLO BCEA calculations. Because pixels within the central 5° of the SLO screen have been shown to be square with respect to the retina,[33] this conversion factor is applicable in both the horizontal and the vertical planes.

MP-1 Microperimeter

The MP-1 microperimeter (Nidek Technologies) was used. This instrument comprises an infrared fundus camera and a liquid crystal display (LCD) that presents stimuli to the observer.

A 1° red cross was displayed on the center of the LCD screen, and subjects were asked to view the center of the cross. Standard fixation measurement was performed using the techniques recommended by Nidek. First, a reference image of the fundus was captured, and a reference area of high-contrast retinal features was selected. During the examination, inbuilt software (MP-1 SW 1.7) tracked this reference area, calculating any shift in its position between the reference image and subsequent frames within the image at a frequency of 25 Hz, producing x and y coordinates of retinal position in degrees of visual angle. If tracking of the real-time image failed, coordinates were not generated until tracking was resumed. Nidek calculates the degree/pixel ratio of each individual instrument, found to be 1:15.714 when recently serviced. The MP-1 reports the total time of a fixation trial and the tracked time; therefore, the amount of time during which tracking fails is known. Ten seconds of tracked data were collected and exported for offline analysis.

BCEA Calculation

The BCEA encompassing 68% of fixations was calculated using the formula

$$\text{BCEA} = 2.28\pi\sigma_H\sigma_V(1 - \rho^2)^{1/2}$$

where σ_H and σ_V are the standard deviations of fixation position in the horizontal and vertical meridia, respectively, and ρ is the product moment correlation of these two components.[20] BCEA values in minutes of arc squared were normalized with a log transform. In addition to correlation, agreement between values from each instrument was assessed using the techniques described by Bland and Altman,[34] whereby the difference between the two measurements is plotted against their mean. This also reveals the magnitude of any difference.

Results

Thirty-seven participants were recruited. The 16 normally sighted volunteers (6 men, 10 women; age range, 21–41 years) had visual acuity of 0.0 logMAR (6/6, 20/20) or better. The 21 (14 men, 7 women; age range, 24–77 years) patients with diabetic maculopathy had visual acuity between 0.8 and 0.0 logMAR (6/38, 20/125 to 6/6, 20/20). All participants had refractive error of between −6 and +4 DS spherical equivalent.

Complete data were obtained from 28 subjects (14 in each group). The nine instances of incomplete data—four instances of He-Ne laser failure and five instances during which tracking

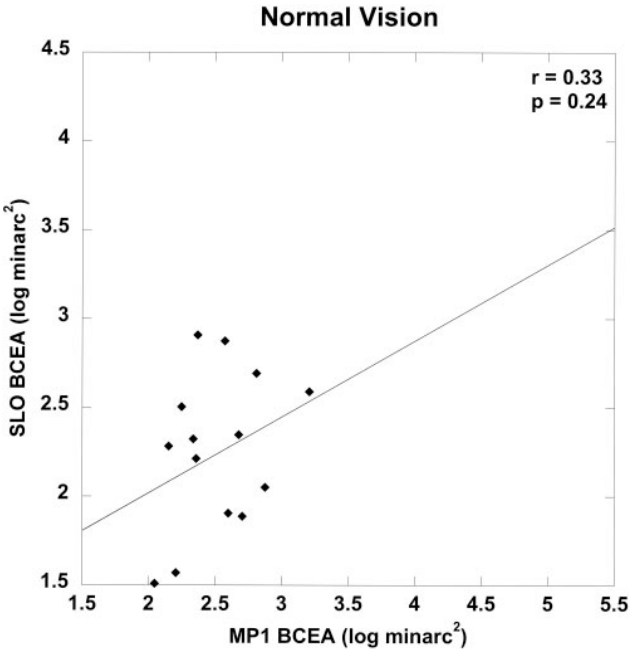

FIGURE 1. SLO BCEA values compared with MP-1 BCEA values for subjects with normal vision. All values are in log minutes of arc squared.

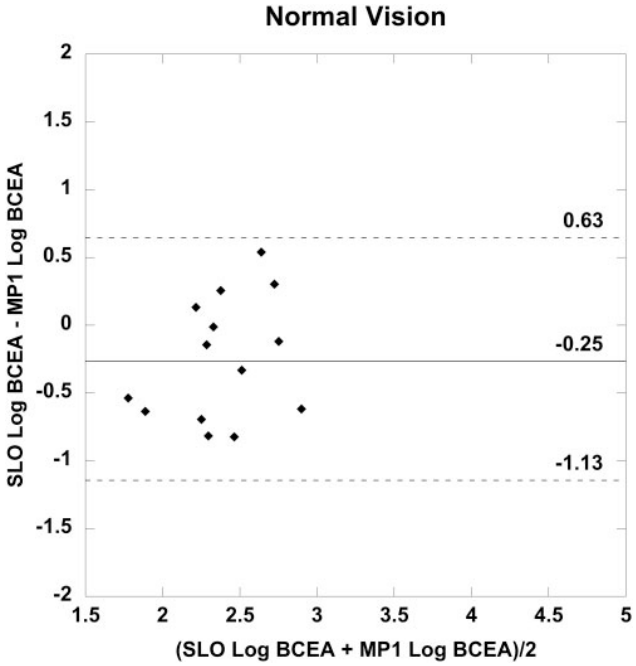

FIGURE 2. Differences between SLO and MP-1 BCEA values are plotted against the mean of the two values for subjects with normal vision. *Solid line*: mean difference between the two values. *Dashed lines*: ±1.96 SD from the mean. All values are in log minutes of arc squared.

software failed to track recorded images accurately—all arose from technical problems with the SLO. Analysis was conducted on complete data only.

Normally Sighted Volunteers

Median BCEA value for SLO was 201 min arc^2 (inter quartile range 80–415) and for MP-1 was 303 min arc^2 (173–541). Mean log BCEA value for SLO was 2.26 log min arc^2 (range, 1.51–2.91; SD, 0.44), and for MP-1 it was 2.51 log min arc^2 (2.05–3.21; SD, 0.30). Figure 1 shows SLO versus MP-1 log BCEA values. A weak linear correlation was found ($r = 0.33$), but this was not significant ($P = 0.24$).

On average, SLO log BCEA values were smaller than their MP-1 counterparts by 0.25 log min arc^2; the difference failed to reach significance (matched pairs; $P = 0.06$). This is shown in Figure 2, with the difference between values from both instruments plotted against their mean. The solid horizontal line represents the mean difference, and the dashed lines represent ±1.96 SD around the mean.

Subjects with Diabetic Maculopathy

The median BCEA value for SLO was 453 min arc^2 (359–2770), and for MP-1 it was 615 min arc^2 (209–2350). Mean log BCEA value for SLO was 2.90 log min arc^2 (range, 2.03–4.05; SD, 0.60), whereas for the MP-1 it was 2.94 log min arc^2 (1.90–5.44; SD, 0.88). A slightly stronger linear correlation was seen between the two sets of values ($r = 0.42$), as shown in Figure 3, but again this did not reach significance ($P = 0.13$).

On average MP-1 and SLO log BCEA values were similar. SLO values were smaller by only 0.03 log min arc^2. This small difference was not significant (matched pairs; $P = 0.88$), as shown in Figure 4.

DISCUSSION

On average, no significant difference in BCEA values between the SLO and the MP-1 was observed in subjects with normal vision and patients with diabetic maculopathy. Somewhat surprisingly, the correlation between BCEA values from the two instruments was weak in both study groups but was slightly stronger over the larger range of BCEA values recorded in patients with diabetic maculopathy.

A previous study reported moderate agreement between SLO and MP-1 fixation assessments in eyes with retinal disease,

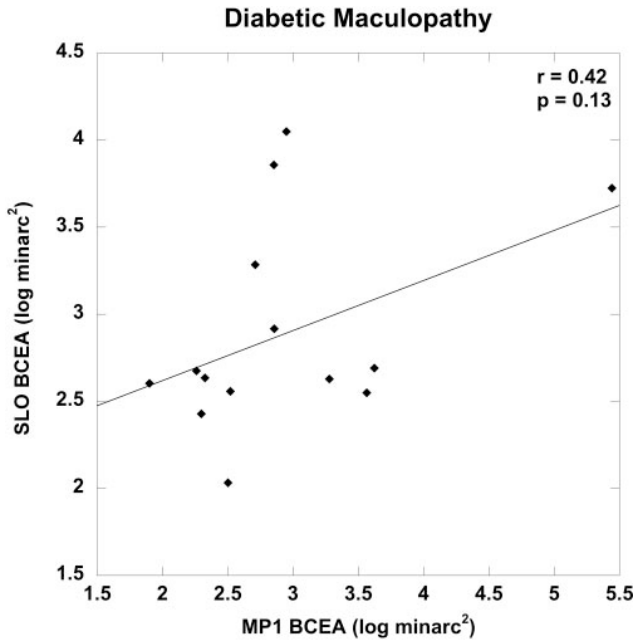

FIGURE 3. SLO BCEA values compared with MP-1 BCEA values for subjects with diabetic maculopathy. All values are in log minutes of arc squared.

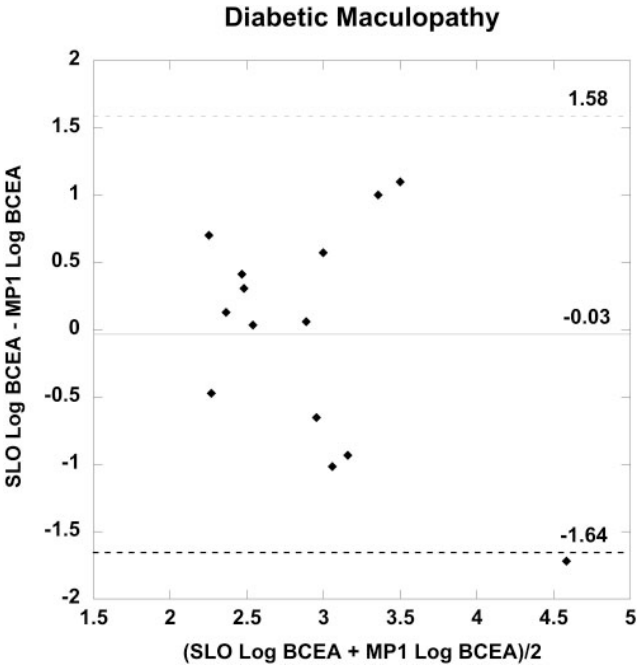

FIGURE 4. Differences between SLO and MP-1 BCEA values plotted against the mean of the two values for subjects with diabetic maculopathy. *Solid line*: mean difference between the two values. *Dashed lines*: ±1.96 SD from the mean. All values are in log minutes of arc squared.

but the means of quantifying fixation differed significantly from our method. Fixation was classified according to the MP-1 classification system described[21] and was compared for agreement using Cohen's κ coefficient. In the case of the SLO data, fixation was stable if the SD of fixation points around the mean fixation point was less then 0.6°, relatively unstable if the SD was between 0.6° and 1.2°, and unstable if the SD was greater than 1.2°.[35] Additionally, fixation was assessed during microperimetric examination compared with our isolated fixation task. Earlier work by the same author noted steadier fixation during an isolated task than during microperimetry.[15]

In contrast to our results, a significant correlation between MP-1 and SLO fixation assessment in patients with macular disorders has been observed; however, the method of quantification differed considerably between each instrument. MP-1 fixation was quantified by mean extent, which is double the square root of the product of the x and y degree positions of fixation points, whereas SLO fixation was calculated as the percentage of fixation points within the central 2° on SLO measurement.[28] Because of notable differences in study design, the findings from these studies cannot be directly compared with our results.

To make direct comparisons between our BCEA measurements and other published values, we examined the standard deviations of fixation points along the horizontal and vertical axes. In normal vision, while fixating a stationary target, fixation points tend to spread out horizontally more than vertically.[10,11,22,36,37] The mean horizontal and vertical SDs of our SLO and MP-1 data from subjects with normal vision conformed to this description, with average horizontal and vertical SDs of 8 min arc and 6 min arc, respectively, on SLO and 9 min arc and 7 min arc, respectively, on MP-1. Our SLO standard deviations fall within the narrow range cited by Culham (4–8 min arc horizontally and 3–7 min arc vertically)[10] and toward the lower ranges quoted by Rohrschneider[11] (8–88 min arc horizontally and 6–65 min arc vertically) and Timberlake[37] (4–38 min arc horizontally and 4–18 min arc vertically). Data published in 2008 reported horizontal and vertical ranges of 4 to 9 min arc and 3 to 6 min arc, respectively, on the MP-1 for 10 experienced observers with normal vision.[22] Although our mean values fall slightly above these top limits, we suggest this to be a consequence of the relative inexperience of our observers.

In those with diabetic maculopathy, the mean horizontal and vertical standard deviations were 29 min arc and 22 min arc, respectively, on SLO and 34 min arc and 59 min arc, respectively, on MP-1. We do not know of any previous studies that have quantified fixation in patients with diabetic maculopathy in terms of BCEA or horizontal and vertical SDs. Our findings agree with the value of 45 min arc given for a standard deviation around a mean fixation point in eyes with clinically significant diabetic macular edema.[15] Fixation characteristics in this patient group are not well defined. One recent study looking at fixation in this population using the MP-1 found stable fixation in more than 70% of eyes,[29] whereas another observed found unstable fixation in most (60%) eyes.[30]

To discover whether the different sampling rates of the two instruments, 12.5 Hz on SLO and 25 Hz on MP-1, should influence the size of the BCEA, we under sampled three MP-1 data files. Every second frame was removed, thereby simulating a sampling rate of 12.5 Hz, equal to that of the SLO. Because nearly equivalent values were found in each case (full data sets: 212, 80 and 514 min arc^2; half data sets: 213, 80 and 528 min arc^2), it is unlikely to be a source of error.

We chose fixation durations of 10 seconds because longer durations of blink-free data are difficult to record. Because previous work revealed no systematic variation over time in BCEAs calculated from the first 10 seconds of each of 8 consecutive minutes of fixation, we believe 10-second fixation trials to be of adequate length for BCEA calculation.[38]

It has been reported that the SLO raster is distorted in a trapezoidal manner such that the raster is 10% larger at the bottom than the top.[39] Misalignment between the infrared imaging system and the LCD screen of the MP-1 has also been described. Spatial alignment errors of 0.5° have been observed between recorded retinal position and the true retinal location stimulated (Woods RL, et al. *IOVS* 2007;48:ARVO E-Abstract 144). Because our subjects viewed a single fixation target in a fixed central position, these distortions are unlikely to meaningfully influence our findings.

In summary, fixation stability values measured using the SLO and the MP-1 did not differ significantly on average. Because fixation stability is of more clinical interest in patients with macular disease, we were encouraged to find such small differences in the values of patients with diabetic maculopathy. As described earlier, the collection of complete data was hampered by persistent technical problems with the SLO. In contrast, the MP-1 was operational throughout. The Rodenstock is no longer commercially available, difficult to maintain, and expensive to service. The MP-1 is backed up by technical and maintenance support from Nidek distributors. We suggest that the similarity found in BCEA values and the consistent and reliable operation of the MP-1 make it a useful and viable alternative to the SLO in the assessment of fixation.

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The effect of low vision rehabilitation in diabetic eye disease: a randomised controlled trial protocol

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Abstract

Purpose: Current research highlights a rising incidence of diabetes and its complications. Diabetic retinopathy is the leading cause of blindness within the working-age population of the United Kingdom. Increasing severity of retinopathy is associated with reduced visual function and participation in daily living. Only 8% of those referred to Moorfields Eye Hospital's low vision clinic have diabetic eye disease, a value less than prevalence figures for diabetes would predict. The lack of evidence for effectiveness of low vision intervention in this patient group could be responsible. Therefore, in line with CONSORT guidance, we present the methodology of the first randomised controlled trial to quantify the effect of low vision rehabilitation on people with diabetic eye disease.

Methods: One hundred participants were recruited into four retinopathy severity groups based on their diagnosis according to the English National Screening Programme Grading Protocol. Participants were randomised to either immediate intervention (1–2 weeks after enrolment) or delayed (control) intervention (3 months after enrolment). Intervention was a standard low vision assessment performed in a hospital clinic. The Activity Inventory (AI), was administered to all participants by telephone within 1 week of enrolment (before any intervention) and repeated at 3 and 6 months.

Results: One hundred participants (Type 1: 28, Type 2: 72; male: 62, female 38) have been recruited. Median habitual distance acuity was 0.19 logMAR (6/9, 20/30), with an interquartile range of 0.06–0.30 logMAR (6/7.5–6/12, 20/25–20/40). AI responses were scored by Rasch analysis, providing a measure of visual ability. Median baseline visual ability was 1.64 logits, with an interquartile range of 0.60–3.75 logits. Difference in mean change in visual ability between intervention groups will be assessed 3 months (primary outcome) and 6 months (secondary outcome) after enrolment.

Conclusions: This is the first randomised controlled trial investigating the effectiveness of low vision rehabilitation for people with diabetic eye disease. With recruitment already complete, it is hoped this work will be the first step in guiding referral criteria for those with diabetic eye disease into the low vision service.

Introduction

Current research highlights a rising incidence of diabetes and its complications.[1,2] The worldwide prevalence is also projected to double between 2000 and 2030, from 171 to 366 million.[3] Within the United Kingdom (UK) an additional 400 000 people are expected to be diagnosed with diabetes between the years 2010 and 2030 taking the 2030 prevalence to just over 2.5 million.[4]

Diabetic retinopathy is the leading cause of blindness in the working-age population of the UK.[5] Previous studies indicate that increasing severity of retinopathy is associated with reduced visual acuity,[6] contrast sensitivity[7] and colour vision.[8,9] Indeed, contrast sensitivity changes can precede acuity loss in the early stages of the disease.[10] Visual field defects are present in those with advanced disease,[11] with some suggesting visual field measurements may be of more use than visual acuity alone when assessing functional loss in diabetic retinopathy.[6] Diabetic macula oedema is a significant risk factor for the development of visual loss.[12] Macular oedema also reduces fixation stability, which is associated with reduced reading ability.[13,14]

Aside from functional deficits, participation in daily activities is detrimentally affected by the presence of diabetic retinopathy,[15] with tasks involving reading print, mobility, work and leisure being particularly affected. Though quality of life also appears to be affected by increasing severity of retinopathy, the effect is thought to be an indirect one, mediated by the reduced visual acuity associated with increasing severity.[16] In a longitudinal study of those with Type 1 diabetes, visual acuity was the most important factor associated with reduced vision-related quality of life scores, however other measures of visual function were not examined.[17]

Moorfields Eye Hospital, London, houses the largest low vision clinic in the UK. Referrals to the clinic are based on a best-corrected visual acuity of 6/12 (20/40) or less and/or significant field loss in common with other UK services.[18] Departmental figures show that only 8% of those attending Moorfields' low vision clinic have a primary diagnosis of diabetic eye disease, very similar to the figure of 9% reported recently from the Greater Baltimore Medical Centre.[19] Whether this reflects poor attendance, under referral of these patients or something else entirely is unclear.

Poor attendance of those with diabetic retinopathy was observed in a study of access and utilisation of a new low vision service in Australia in 2008. Only one-third of referred patients with diabetic retinopathy attended the service in contrast to 80% of those with age-related macular degeneration who were referred.[20]

Previous literature supports the possibility of under referral contributing to the low number of patients with diabetic eye disease attending low vision services. Referral may be overlooked until active treatment, often necessary in diabetic eye disease, has been suspended as has been reported by focus groups previously.[21] Active treatment is certainly a recognised barrier to the registration process in the UK.[22,23]

Additionally, as has also been demonstrated previously, referral may not be instigated until visual acuity is reduced to a greater degree than 6/12 (20/40).[24] The visual fluctuations common in diabetes may compound this further. Moreover, clinicians and patients alike may prioritise appointments related to other, potentially life threatening complications of diabetes.

The predicted rise in the diabetic population together with the reported deficits in both visual function and quality of life, and the apparent under representation of these patients in low vision clinics, suggests provision of services may need to be updated. This can only be achieved if we first establish the effectiveness of the service in this patient group. Therefore we have undertaken the first randomised controlled trial (RCT) examining the effect of low vision intervention in patients with diabetic eye disease. In line with CONSORT guidelines,[25] we present the methodology for this trial.

Methods/Design

Trial objective and design

To determine the effectiveness of standard hospital-based low vision rehabilitation for people with diabetic eye disease, using a delayed intervention RCT.

Participants

Participants were recruited from medical retina clinics at Moorfields Eye Hospital, where patients have been graded according to the English National Screening Programme Grading Protocol (NGP) for Diabetic Retinopathy. The protocol is based on the recommendations of Harding and colleagues.[26] Briefly, it grades retinopathy and maculopathy according to retinal signs and under certain circumstances, visual acuity. NGP retinopathy level R1 corresponds to mild to moderate non-proliferative retinopathy, R2 to severe non-proliferative retinopathy and R3 to proliferative retinopathy. Maculopathy is represented by M1 (where M0 represents no maculopathy). Treatment with laser photocoagulation is indicated by the letter P1, preceded by M or R to denote macular (focal) or pan retinal (scatter) respectively. *Table 1* displays the grading protocol in further detail.

Ophthalmologists within the medical retina clinics were fully briefed on the study protocol by the clinical lead on the study team (CE) and the research optometrist responsible for recruitment (HD). The ophthalmology team identified potential participants according to following criteria.

Inclusion

- patients with Diabetes Mellitus attending Moorfields medical retina clinics; and
- patients with gradable diabetic retinopathy of at least R1 in the better eye.

Table 1. English National Screening Programme grading protocol for diabetic retinopathy (adapted from Harding *et al.*, 2003)

R1	Mild to moderate non-proliferative retinopathy (previously background)	Microaneurysm(s) Retinal haemorrhage(s) ± exudate
R2	Severe non-proliferative retinopathy (previously pre-proliferative)	Venous beading Venous looping or reduplication Intraretinal microvascular abnormality Multiple deep, round or blot haemorrhages Cotton wool spots
R3	Proliferative retinopathy	New vessels on disc New vessels elsewhere Preretinal or vitreous haemorrhage Preretinal fibrosis ± tractional retinal detachment
M1	Maculopathy	Exudate within 1 DD of the centre of the fovea Circinate or group of exudates within the macula Retinal thickening within 1 DD of the centre of the fovea Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best corrected visual acuity of ≤ 6/12
P1	Photocoagulation	Focal (macular) or Scatter (pan retinal)

Exclusion

- patients under the age of 18;
- patients who are not fluent in English;
- patients with serious hearing impairment;
- patients with concomitant eye disease (other than mild cataract);
- patients who have previously attended a low vision clinic;
- patients with poor mobility or in poor general health; and
- patients who are hospital inpatients, live in nursing homes or who are otherwise non-independent.

Those expressing an interest were referred to HD, who verbally described the project, provided a patient information sheet detailing study involvement and answered any subsequent questions. Patients keen to take part were contacted by telephone up to one week later to confirm their interest. Appointments were booked for all those still interested at which time informed consent was taken by HD. Three copies of the consent form were signed by both HD and the participant. One copy was retained by the participant, one by HD and one was placed in the hospital notes.

Disease status of recruited patients was determined by reviewing hospital notes following their clinic visit, allowing participants to be recruited into the following groups based on their recent NGP diagnosis of the better eye:

- Mild to moderate non-proliferative retinopathy without macular involvement: R1.
- Severe non-proliferative retinopathy without macular involvement: R2.
- Severe non-proliferative retinopathy with macular involvement: R2+M1/MP.
- Advanced disease: R3/RP ± M1/MP.

The better eye was defined as the eye with the less severe diagnosis. Where the diagnoses were the same, the better eye was that with better visual acuity. If visual acuity was equal, the participant's dominant eye for aiming was chosen. This was deduced by asking the participant to look at a spot target across the room and with their arm outstretched; position their index finger in front of the spot. The eyes were then covered in turn and the participant reported whether the spot was still covered. The open eye for which the spot was still covered was designated the aiming dominant eye. In a small number of cases, participants reported that they could not cover the spot (i.e. neither eye was obviously dominant). If this was the case the participant chose the eye they felt was their most dominant.

Participant assessment

Following enrolment, participants underwent a visual assessment designed to describe multiple aspects of visual function. Median time between initial clinic visit and visual assessment was 9 days [Inter quartile range (IQR) 6–20]. Examination included refraction, Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity, Pelli-Robson contrast sensitivity[27] and Bailey Lovie near acuity.[28] Central visual field function was also examined using the MP-1 Microperimeter (http://www.nidek.co.uk/html/index.html).

Reading performance measures [MNREAD and the International Reading Speed Test (IReST)],[29,30] Lanthony desaturated panel D-15 test,[31] Binocular Esterman visual fields using the Humphrey Visual Field Analyzer (Humphrey Instruments, http://www.humphrey.com) and MP-1 fixation stability assessments were also carried out as part of a separate study running in tandem with the trial.

Refraction, distance and near visual acuity and contrast sensitivity were measured for each eye, (right eye first) and binocularly using different charts on each occasion. MP-1 measurements were carried out on the better eye only, as binocular testing is not possible. The order of testing was not randomised.

Refraction was performed at 4 m. Briefly, the most positive or least negative spherical and least negative cylindrical lens consistent with best visual acuity was used.

Habitual (wearing any previously prescribed glasses or unaided as appropriate) and corrected (wearing prescription determined by refraction) visual acuity was assessed using an internally illuminated ETDRS chart (Lighthouse International, NY, USA) at 4 m with room lights extinguished. Letter by letter scoring was employed in accordance with the method described by Ferris.[32]

Pelli-Robson contrast sensitivity was measured at 1 m under the recommended luminance level of ~85 cd m^2. Participants wore their full correction with a +1 dioptre addition. The test was scored using the method described by Elliott *et al.*[33]

Habitual near acuity was examined using the Bailey Lovie near vision test. Participants viewed the test at their preferred reading distance wearing their usual near correction. The smallest line read with no more than one error was recorded.

Central visual field function was examined by retinal-specific microperimetry using the MP-1 microperimeter. The MP-1 comprises an infrared fundus camera allowing video fundus imaging and a liquid crystal display (LCD) on which stimuli are presented. Retinal position is monitored throughout the examination, allowing stimuli positions to be adjusted for any retinal movement.

A 10-2 test pattern was used, examining 68 points (1° separation) centred on fixation, in the central 10° of visual field. Goldman III stimuli were presented for 200 ms on the LCD screen whilst participants viewed a central 2° red cross. Threshold sensitivity in decibels (dB) at each point was determined using a 4-2 staircase method with an initial stimulus intensity of 10 dB where 0 dB = 127 cd m^{-2}. Inbuilt software determines the mean sensitivity of all 68 points as well as the difference in dB between measured thresholds and age-corrected normal values at each test location, the average of which is given as the mean defect in dB.

Additionally, test locations are classified as 'normal', 'suspect', 'relative scotoma' or 'absolute scotoma'. The number of relative and absolute points in each plot were summed and expressed as a percentage, which we refer to here as scotoma size.

Within 1 week of the baseline assessment, a trained research assistant contacted participants by phone to administer the Activity Inventory (AI).[34] The AI is a well validated, Rasch analysed patient reported outcome measure (PROM), previously validated for telephone administration.[35]

The AI examines 50 goals split between three objectives: social functioning, recreation and daily living. Examples of goals include reading the newspaper, entertaining guests and dressing oneself. Respondents first rated the importance of each goal with four possible responses ranging from 'not important' to 'very important'. Goals rated 'not important' were skipped, but for all other goals the participant was asked to rate its difficulty on a five point scale ranging from 'not difficult' to 'impossible without help'. The difficulty responses were Rasch analysed to produce a continuous measure of visual ability, which we refer to here as the AI score.

Randomisation

Following the participant assessment, participants were allocated by minimisation to one of two arms; immediate intervention (intervention within 2 weeks of enrolment) and delayed (control) intervention (intervention 3 months after enrolment). The minimisation procedure incorporated four weighted factors: visual acuity (weighted 4), disease severity classification (weighted 3), age (weighted 2) and sex (weighted 1), using 'Minim', a free minimisation programme available from http://www.sghms.ac.uk/depts/phs/guide/randser.htm. Access to the procedure was held by a statistician within the Research and Development department of Moorfields Eye Hospital.

Those on the immediate intervention arm received intervention within 2 weeks of enrolment. Three months after enrolment all participants were contacted and asked to repeat the AI. Those on the delayed (control) intervention arm were scheduled to receive intervention within the next week. six months after enrolment all participants were contacted to complete the final AI.

Before each administration, participants were instructed on how to answer the questionnaire with a practice question asked to verify understanding. The research assistant was masked to the randomisation procedure and reminded participants not to reveal information regarding their allocation. Any inadvertent masking violations were recorded and reported in accordance with the CONSORT Statement.[25] On completion of the questionnaire, the research assistant guessed the allocation of participants, in order to evaluate the success of the masking procedure. Study design dictated that neither the participants nor optometrist responsible for administering the intervention could be masked.

At each administration of the AI, participants were asked whether there had been any change in the medical

management of their diabetes, whether they had received additional laser photocoagulation and whether they had experienced any significant changes in their general health since the previous administration. Any changes were recorded as dichotomous yes/no variables.

Intervention

The intervention was a low vision assessment (LVA), conforming to the standard care provided to all low vision patients at Moorfields Eye Hospital and was consistent with previously published standards.[36] The assessment included:

- assessing patient's understanding of their eye condition;
- discussing needs/visual requirements and setting initial goals;
- assessing distance and near vision;
- determining appropriate levels of magnification;
- demonstrating selected low vision aids based on the results of the vision assessment and patient goals;
- determining visual aids to be prescribed and reviewing use and handling;
- discussing lighting and other methods of enhancing vision as appropriate;
- demonstrating electronic magnifiers where appropriate;
- discussing availability of other applicable services (e.g. social services, charities);
- dispensing prescribed low vision aids on loan;
- arranging follow-ups as necessary.

The same experienced low vision optometrist conducted all LVAs. Participants were deemed to have received the intervention even if no low vision aids were required.

Data analysis

Data will be analysed using the intent to treat principle. However if any participants are lost to follow up and AI data is unobtainable, an available case analysis will be performed. Characteristics of those lost to follow-up will be compared with those not. If significant differences exist, a sensitivity analysis will be performed using imputed data. Difference in mean change in AI score between arms, will be examined by analysis of covariance 3 (primary outcome) and 6 months (secondary outcome) after enrolment. We will also examine whether delaying intervention affects AI score by examining the difference in mean change in AI score between groups 3 months after intervention was delivered, i.e. at 3 months in the intervention group and 6 months in the delayed group (secondary outcome).

Models will be adjusted for prognostic variables used in the minimisation process (as recommended by Taves[37]). Further sensitivity analyses will be performed by constructing two further models; one completely unadjusted model and a second adjusted for minimised factors plus three additional factors: (1) change in general health (2) change in medical management of diabetes and (3) the occurrence of additional laser photocoagulation throughout the time period in question.

Additionally, exploratory sub group analysis will be conducted to investigate whether change in AI score following intervention is related to disease severity group, baseline visual acuity or central visual field function.

In order to investigate the influence of baseline visual acuity, participants will be grouped according to whether their baseline visual acuity falls above or below a threshold. The difference in mean change in AI score between arms within these groups will be calculated as described above. Initially a threshold of 0.3 LogMAR (6/12) will be used. Sequentially lower thresholds (better visual acuity) will be used to establish the level of visual acuity at which patients would benefit from a referral for low vision services.

In order to investigate the influence of central field function, participants will again be dichotomised according to the percentage of relative and absolute points recorded by retinal microperimetry. The difference in mean change in AI score between arms within the two groups will be calculated as above. Initially a threshold of 37% ($\sim$25 points) will be used (the median value when all participants are considered).

As the number of participants within each subgroup will be small, these analyses will lack sufficient power to provide definitive results and will therefore be considered exploratory only.

Data input and storage

Three separate password protected databases were designed in Microsoft Office Access (Version 7.4): the first for confidential patient details and intervention assignment, the second, for anonymised baseline clinical information and the third for anonymised AI response data. AI response data entry was single entry. Ten per cent of data was then selected at random using a random number generator and double entered to check accuracy of data input. Double entered data was 100% accurate and so no further steps were taken.

Sample size

The software package PS for Windows (Version 2.1.31) was used to calculate the minimum number of participants

required to detect a clinically significant difference in outcome measure, (AI score at 3 months).[38] Calculation was based on detecting a 0.7 logit difference following rehabilitation, consistent with previous publications.[39] Standard deviation (S.D.) of the AI score was estimated at 1.0 logits (based on previously published data from AI questionnaires administered to Moorfields' low vision patients[39]). Type I error rate (alpha) was set at 0.05 (two-tailed). For a power of 0.90, a minimum of 44 patients per group is required. To allow for participant dropout, 50 participants will be recruited onto each arm.

Ethics approval

Full ethics approval was granted by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (approval number 08/H0716/70). The study conforms to the tenets of the declaration of Helsinki.

Results

Recruitment

Recruitment took place between June 2009 and February 2011. 256 patients were assessed for eligibility. Of those, 37 were ineligible. Ineligibility was most often due to non-fluency in English (20 patients). A further 16 patients expressed an interest in taking part yet were unable to, for example seven patients reported living too far from the hospital to make extra visits convenient. One hundred and three declined to participate, leaving 100 eligible patients who were enrolled and randomised (an acceptance rate of 46%). Of those, 49 were assigned to the immediate intervention group and 51 to the delayed intervention (control) group. These values (shown in bold) and the structure of study visits are shown in *Figure 1*.

Baseline participant characteristics

Type 2 diabetes was more common (72%) and 62% were male. Mean age was 57 years (range: S.D., 26–83: 12). Median time since diagnosis was 20 years (IQR 12–30) and with diabetic eye disease being present for a median of 5 years (IQR 3–10). Participants were roughly split between the four disease severity groups with 25 in group 1, 21 in group 2, 18 in group 3 and 36 in group 4. Median habitual distance acuity of better eyes was 0.19 logMAR (6/9, 20/30) with an IQR of 0.06–0.3 logMAR (6/7.5–6/12, 20/25–20/40). Median baseline AI score was 1.64 logits, with an IQR of 0.60–3.75 logits. A breakdown of baseline characteristics by intervention group is shown in *Table 2*. The Shapiro–Wilk W test was used to test whether each variable came from a normal distribution. Normality was rejected where $p < 0.05$. Non-normally distributed variables are described by their median and IQR.

The distribution of baseline characteristics between intervention groups was examined for clinically significant differences. All differences were small and deemed to have no clinical significance. The use of statistical significance testing to detect baseline differences between groups is inappropriate.[40–42] When intervention group allocation is determined by a random procedure, any differences are by definition due to chance. In any case, our planned ANCOVA analyses will control for any baseline difference between groups in baseline AI score and the variables on which minimisation took place.

Discussion

More than one in three people with diabetes have some evidence of diabetic retinopathy.[43] Nearly one in thirty people with type I diabetes and 1.6% of those with type II diabetes have visual acuity of <6/60 (20/200).[44,45]

Diabetic patients present a unique set of challenges to the low vision practitioner due to the early onset and fluctuating nature of vision loss, the specific visual demands of disease management and associated multisystem losses.[46] Despite this, there have been no previously published RCTs investigating the effect of low vision intervention in this growing patient group.

Interestingly, the visual acuity of participants in this study is somewhat better than we had anticipated. This does not reflect difficulties in the recruitment of those with poor visual acuity. Visual acuity was intentionally omitted from the recruitment criteria and participants were recruited in a consecutive manner over a period of around 18 months. We chose not to assume that acuity would be the best predictor of success with low vision intervention and so decided to include those with good acuity provided they had gradable diabetic retinopathy in the better eye. Indeed functional deficits in contrast sensitivity,[8,47] colour vision[48–50] and mean retinal sensitivity[51] have been demonstrated in people with diabetes before the onset of ophthalmoscopically visible retinopathy. However, should acuity be a good predictor of success, the data collected will allow us to examine the acuity level associated with success, albeit from an exploratory standpoint.

In additional work running in parallel with this trial we will also be exploring through multiple regression analyses, the association between multiple aspects of visual function and baseline AI score.

RCTs are generally accepted as providing the highest standard of evidence for inteventional studies.[25] Throughout the field of low vision research, there are surprising few RCT investigating low vision rehabilitation and of those published, results are mixed.[39,52,53] Pearce *et al.*[39]

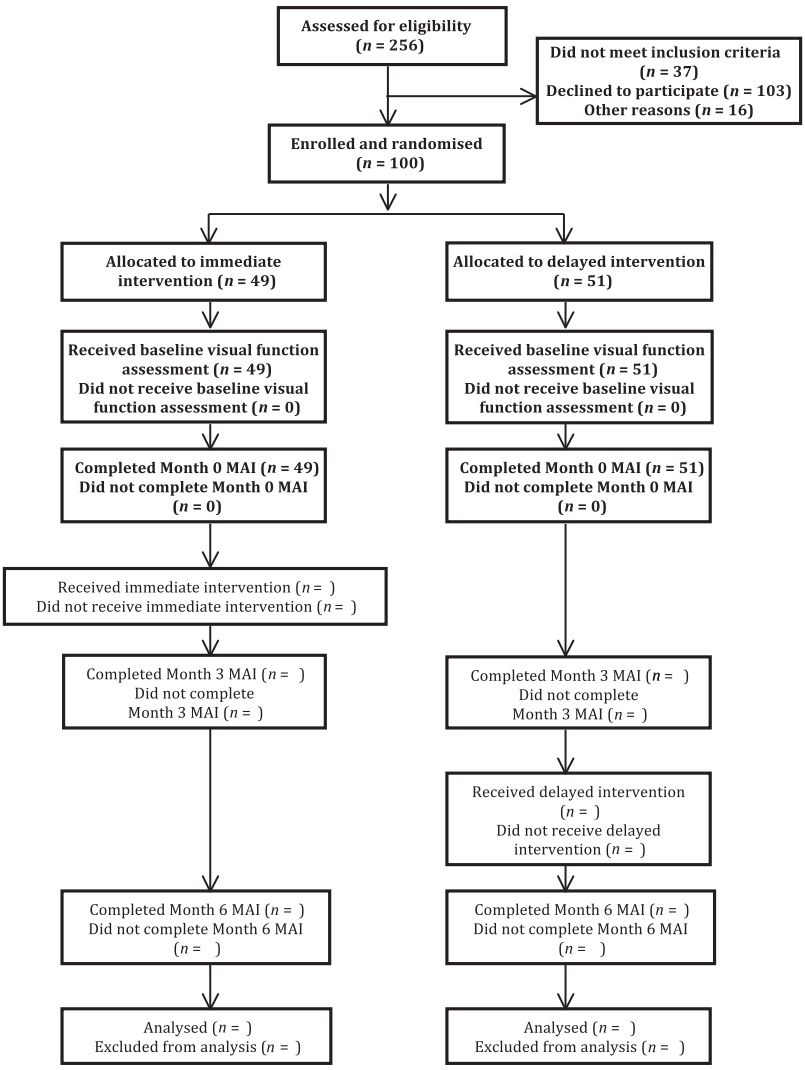

Figure 1. Flowchart describing the trial structure and flow of participants through each stage. Text in bold described participants already recruited.

showed an average 0.64 logits improvement in visual ability as measured by the AI in low vision patients following standard National Health Service (NHS) low vision intervention. However an enhanced service offered no additional benefit. A multicentre RCT investigating the effectiveness of an out-patient low vision rehabilitation programme comprising at least 10 hours of therapy and home visits, revealed an average 2.43 logit improvement in self reported reading ability, whilst those on a waiting list control experienced reduced function.[52] In contrast, Reeves *et al.*[53] reported a small but significant reduction in health and vision specific quality of life over 12 months following conventional and enhanced low vision services.

Randomisation improves the internal validity of a trial. It prevents systematic bias in the allocation of patients to treatment groups,[54] however it does not automatically promote its external validity; the applicability of the results to situations other than the defined circumstances in which a trial was run.[55,56]

Many trials include strict inclusion criteria and have tight control over treatments within trials, but it has been argued that trials undertaken with a more pragmatic approach may produce results that are more applicable in clinical practice and to policy makers.[55] Our inclusion criteria are broad with little stipulation made on the severity of disease and no exclusion of patients treated with laser photocoagulation.

Participants were allocated to intervention groups using minimisation, a technique first described by Taves.[37] Minimisation assigns participants to treatment and control

Table 2. Baseline characteristics by intervention group. Habitual distance acuity, contrast sensitivity and habitual near acuity represent binocular measurements. Mean sensitivity, mean defect and % relative and absolute points were derived from better eye measurements.

Baseline characteristics	Immediate *n* = 49	Delayed *n* = 51
Sex		
Male : female	31 : 18	31 : 20
Age		
Mean (range) years	58 (36–83)	57 (26–83)
Diabetes type		
1 : 2	12 : 37	16 : 35
Duration of diabetes		
Median (IQR) years	19 (12–30)	20 (12–27)
Duration of diabetic eye disease		
Median (IQR) years	5 (4–10)	5 (3–9)
Disease severity groups		
1 : 2 : 3 : 4	12 : 10 : 9 : 18	13 : 11 : 9 : 18
Habitual distance acuity		
Median (IQR) LogMAR	0.10 (0.00–0.25)	0.12 (0.00–0.22)
Habitual near acuity		
Median (IQR) LogMAR	0.4 (0.3–0.4)	0.3 (0.2–0.4)
Contrast sensitivity		
Median (IQR) log units	1.45 (1.30–1.55)	1.40 (1.25–1.55)
Microperimetry sensitivity		
Median (IQR) decibels	15.7 (13.1–17.3)	16.1 (13.8–18.1)
Scotoma size (relative or absolute)		
Median (IQR) % points	41 (23–71)	35 (13–59)
Baseline visual ability		
Median (IQR) logits	1.61 (0.65–3.63)	1.67 (0.58–4.75)

groups, whilst minimising differences in the number of participants in each group and the presence of predetermined prognostic factors between groups. Chance skewing of prognostic factors between treatment groups may result in spurious conclusions.[57] This is usually avoided by using stratified randomisation, where different subgroups are created representing all possible combinations of prognostic factors, with the aim of achieving equal numbers of participants in each subgroup. As the number of prognostic factors increases, so too does the number of subgroups and as such, stratified randomisation is often not appropriate for small studies or studies with more than two prognostic variables.[37,58] Minimisation only seeks to achieve balance on each prognostic variable considered separately and as such can handle more prognostic variables even in studies with relatively few participants. It was considered that with a sample size of 100 and four prognostic factors, minimisation was a more appropriate technique than stratified randomisation.

Though lauded by some for ensuring group balance[59] and for reducing the probability of severe imbalances as compared to randomisation,[37] minimisation has been criticised for the lack of complete randomness in its allocation method.[60] Participants are allocated to the group that minimises the existing difference between prognostic factors, therefore the allocation of previous participants influences future allocations. In theory, an investigator with prior knowledge of the participants already enrolled, could potentially determine the allocation of the next participant. Taves and others refute this, as any potential selection bias is excluded if the procedure is controlled by an independent person.[61–63] To protect against selection bias, our minimisation procedure was set up and controlled exclusively by the Research and Development department at Moorfields Eye Hospital.

The non-random nature of minimisation has implications for subsequent analysis, as tests of statistical inference are based on random assignment to groups. Compensation is achieved by adjusting for the factors on which minimisation was carried out using analysis of covariance.[37] This has been adopted into our analysis plan.

The control for this study was 3 month delayed intervention, as withholding the intervention from half the study population was not considered acceptable. This delay is less than the normal waiting list time for an appointment in the low vision clinic. Therefore our delay did not penalise subjects when compared to standard practice.

No international consensus on the definition of low vision rehabilitation exists. Both in- and out-patient settings have been described.[64,65] Some services have specific provision for eccentric viewing or orientation and mobility training. Aids may be provided at no cost or at a fee and can range from simple optical aids to sophisticated electronic aids. Professional input can come from a variety of individuals: optometrists, ophthalmologists, occupational therapists and rehabilitation officers to name a few. Recommended standards for NHS low vision services have been published by the NHS Low Vision Working Group,[66] to which our intervention conforms. The NHS model is an out-patient, primarily optometrist led service with no provision for eccentric viewing training or orientation and mobility training. All treatment, low vision assessments and optical magnifiers are provided through state funding at no charge to the patient. Electronic aids are not provided, but are available for demonstration purposes.

Though results of this study may not be applicable outside the NHS setting, this model of care represents the majority of rehabilitation appointments in the UK[67] and therefore warrants analysis. Furthermore, a recent systematic review of effectiveness of low vision service provision found only seven RCTs in the literature, highlighting the need for more high quality evidence in our field.[68]

The use of a PROM allows the assessment of effectiveness in everyday life as opposed to measuring performance on a surrogate task in a clinic setting.

In recent years the number of PROMs developed for those with visual impairment has increased. A review paper in 2001 identified 13 such instruments.[69] Thirty one were identified in a similar review in 2004, however substantial variation in the psychometric quality of instruments was demonstrated.[70] Researchers therefore need to exercise care in the choice of an appropriate PROM.

Many instruments use raw scores as measurements,[71–73] the disadvantage of which has been much discussed.[74,75] Briefly, raw scores are derived from ordinal data and as such cannot be treated as continuous measurements. The Rasch model transforms raw data to create abstract, equal-interval scales. Equality of intervals is obtained through log transformation of raw data odds and abstraction is accomplished through probabilistic equations.[76] Instruments developed using Rasch anaylsis are considered to be of the highest quality.[74] As such we considered only Rasch developed questionnaires. We also eliminated those developed for an inappropriate target population (i.e. cataract patients). Of those considered for this study, only the AI has demonstrated sensitivity to change following low vision rehabilitation in the NHS setting[39] and validity in a diabetic population.[77] For these reasons the AI was deemed to be the most appropriate PROM available at the time of study design. The AI however does not assess vocational and education activities. This may be a limitation, as patients may be studying or employed.

As described above, for the purposes of the sample size calculation the S.D. of baseline AI scores was estimated as 1.0 logits. However the true S.D. of our sample was 2.2 logits suggesting our sample sizes are low. This disparity may reflect differences in baseline characteristics of the two study populations in terms of visual acuity and diagnosis and is a limitation of the current study.

Though focusing on the ocular manifestations of diabetes, we are essentially dealing with a systemic condition. Therefore, any change in blood glucose control leading to adjustment of the medical management of the condition or to further health decline throughout the study may mask change attributable to the intervention. Similarly, active treatment of any retinopathy or maculopathy may alter a participant's visual function and hence influence the effectiveness of the intervention. We are therefore collecting data from participants at each administration of the AI, relating to general health and medical and ocular disease management, so that any changes can be adjusted for in the final analysis. Exclusion of these patients would greatly limit the applicability of the results outside the trial setting.

In common with previous RCTs in this field,[36,39,64] those with previous experience of low vision rehabilitation are excluded. This could be a potential source of selection bias, as those with previous experience may be those with more severe disease or greater motivation, who stand to gain most from the intervention. If so, this would result in an underestimation of the effect of the intervention.

In accordance with the CONSORT Statement,[25] a trial steering committee has been set up to oversee and guide the management of the trial. The committee comprises an external chairperson, statistician, consultant ophthalmologist, patient representative and the study team. The committee meets twice yearly to discuss management of the trial, recruitment progress, data collection and storage and subsequent dissemination of results. The trial has also been registered on a publically available trials database (http://www.controlled-trials.com/ISRCTN91672666).

This is the first RCT investigating the effectiveness of standard NHS hospital-based low vision rehabilitation for people with diabetic eye disease. A pragmatic approach has been adopted to increase the applicability of the results beyond that of the trial setting. With recruitment already complete, it is hoped this work will be the first step in guiding referral criteria for those with diabetic eye disease into low vision services.

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Appendix V – Unanchored and anchored person measures

Person ID	Unanchored person measure	Anchored person measure
1	7.34	5.85
2	3.12	1.87
3	6.33	4.75
4	6.1	4.54
5	7.51	5.81
6	5.25	3.77
7	1.5	0.84
8	7.58	5.99
9	0.85	0.34
10	0.94	0.3
11	-0.57	-0.59
12	2.58	1.52
13	1.57	0.85
14	4.06	2.66
15	6.91	5.51
16	7.64	6.04
17	0.44	0.1
18	0.89	0.42
19	7.25	5.77
20	1.89	0.99
21	2.28	1.22
22	-0.08	-0.27
23	1.55	0.88
24	4.01	2.55
25	2.23	1.26
26	4.56	3.13
27	3.1	1.84
28	7.22	5.7
29	5.15	3.7
30	4.02	2.6
31	7.35	5.68
32	1.06	0.45
33	-5.76	-5.06
34	1.58	0.83
35	1.44	0.64
36	4.05	2.62
37	3.44	2.16
38	2.19	1.31
39	0.86	0.38
40	7.39	5.87
41	7.27	5.62
42	7.07	5.62
43	7.45	5.96
44	1.19	0.56
45	-1.05	-0.91
46	2.67	1.59
47	2.02	1.17
48	7.32	5.83
49	-0.35	-0.54
50	2.8	1.67
51	1.94	1.24

Table 1. Unanchored and anchored person measures (in logits) for all participants.

Person ID	Unanchored person measure	Anchored person measure
52	0.94	0.36
53	1.63	0.77
54	3.82	2.51
55	2.81	1.68
56	0.45	0.16
57	2.31	1.36
58	5.23	3.79
59	3.76	2.44
60	3.42	2.07
61	4.15	2.74
62	5.28	3.68
63	3.89	2.58
64	3.62	2.22
65	6.99	5.45
66	-0.75	-0.84
67	3.96	2.65
68	3.25	2.09
69	2.18	1.17
70	2.68	1.54
71	7.03	5.46
72	1.44	0.58
73	-0.4	-0.55
74	0.33	0.05
75	1.04	0.44
76	3.71	2.4
77	2.46	1.42
78	7.22	5.72
79	2.19	1.33
80	5.02	3.57
81	6.87	5.39
82	7.58	6
83	7.53	5.88
84	2.27	1.26
85	3.12	1.8
86	1.08	0.53
87	1.07	0.42
88	-1.81	-1.64
89	1.3	0.51
90	5.74	4.31
91	1.87	0.97
92	2.89	1.37
93	2.37	1.38
94	-0.55	-0.66
95	2.13	1.07
96	1.74	1.29
97	6.88	5.48
98	3.75	2.37
99	4.27	2.79
100	0.96	0.51

Appendix table 1 continued. Unanchored and anchored person measures (in logits) for all participants.

Appendix VI – Unanchored and anchored item measures

Item	Unanchored item measure	Anchored item measure
Parties	-0.82	-0.86
Guests	-0.92	-1.68
Cook	-0.44	-0.62
Dine	-0.21	-0.41
Plays	0.25	0.05
Meetings	-0.51	-0.71
Games	-0.03	0.09
Performance	0.9	-0.44
Church	-0.26	-0.94
Dance	-0.97	-0.91
Leisure	1.04	-0.83
Exercise	-0.66	-1.4
Sew	2.48	1.55
Knit	1.4	0.8
Woodwork	0.99	0.87
Metalwork	1.65	0.65
Paint	0.52	0.63
Bake	-0.41	-0.41
Electrics	1.02	0.56
Models	1.33	0.82
Music	0.59	0.38
Travel	0.1	0.24
Fish	0.36	0.07
Hunt	5.66	1.91
Outdoor	0.49	0.04
Garden	-0.29	-0.2
Sport	1.24	0.83
Leather	-1.18	-0.1
Computer	1.3	0.69
Collect	-0.97	-0.81
Read	1.37	1.45
Photography	1.08	0.32
Toilet	-2.49	-1.69
Hygiene	0.05	-1.35
Dress	-0.61	-1.62
Health	-0.14	-0.96
Meals	-2.25	-2.25
Prepare	-0.74	-0.66
Household	-0.16	-0.82
Communication	0.11	0.17
Mail	0.68	0.84
News	-0.51	-1.45
Schedule	-0.35	-0.97
Finances	-0.09	0.44
Shop	-0.33	0.7
Child	-0.74	-0.91
Drive	0.58	1.34
Homecare	-0.75	-0.5
Pet	-1.53	-2.4
Telephone	-1.17	-1.36

Appendix table 2. Unanchored and anchored item measures (in logits).

Appendix VII – Study data

Table 3 - Clinical and demographic data

Table 4 - Visual function data

Table 5 - Visual ability data

Table 6 - Low visual assessment record

Clinical and demographic data

ID	Recruitment date	Sex	Age	Ethnicity	DM Type	Dur DM	Dur DED
1	22/06/2009	M	57	B	2	10	5
2	29/06/2009	F	56	B	2	10	3
3	08/07/2009	M	52	B	2	12	1
4	10/07/2009	M	83	W	2	20	3
5	03/08/2009	F	69	B	2	19	9
6	11/08/2009	M	74	W	2	15	10
7	14/08/2009	F	62	W	1	53	20
8	18/08/2009	F	54	B	2	12	4
9	21/08/2009	M	53	W	2	20	4
10	21/09/2009	F	75	B	2	29	16
11	22/09/2009	F	49	W	1	41	18
12	13/10/2009	M	69	B	2	19	10
13	16/10/2009	F	54	B	2	12	4
14	19/10/2009	M	37	W	1	22	11
15	26/10/2009	M	66	B	2	6	5
16	27/10/2009	M	36	W	1	24	2
17	30/10/2009	M	60	W	2	21	2
18	23/11/2009	M	57	A	2	15	5
19	22/01/2010	M	56	W	1	49	26
20	25/01/2010	M	63	W	2	11	11
21	09/02/2010	M	39	W	1	31	6
22	10/02/2010	M	59	A	2	22	2
23	12/02/2010	M	77	B	2	34	2
24	12/02/2010	M	44	B	2	16	4
25	17/02/2010	M	38	W	1	31	15
26	02/03/2010	M	43	W	1	31	8
27	15/03/2010	M	83	W	1	67	40
28	16/03/2010	M	60	B	2	10	1
29	22/03/2010	M	69	W	1	42	30
30	23/03/2010	F	69	B	2	20	4
31	30/03/2010	F	70	B	2	20	9
32	12/04/2010	F	69	W	1	30	5
33	16/04/2010	F	54	A	2	33	5
34	26/04/2010	M	65	A	2	9	9
35	29/04/2010	M	48	W	2	15	4
36	14/05/2010	M	45	W	1	20	5
37	17/05/2010	M	77	W	2	30	10
38	18/05/2010	M	63	W	2	19	8
39	25/05/2010	F	41	W	1	29	14
40	25/05/2010	M	36	W	1	34	5
41	26/05/2010	F	58	B	2	30	10
42	11/06/2010	F	37	A	1	25	5
43	14/06/2010	M	48	W	1	27	10
44	18/06/2010	M	56	A	2	4	4
45	22/06/2010	M	46	C	2	10	10
46	25/06/2010	F	55	B	2	18	3
47	29/06/2010	M	56	W	2	6	6
48	29/06/2010	M	35	W	1	33	5

Appendix table 3. Full demographic and clinical data for all participants. M = male, F = female, B = Black, W = White, A = Asian, C = Chinese, DM = Diabetes mellitus, Dur DM = Duration of diabetes, Dur DED = duration of diabetic eye disease, NGP = National grading protocol, R = retinopathy, M = maculopathy, P = photocoagulation.

Clinical and demographic data

ID	Better eye	Severity Group	NGP grade
1	R	2	R2
2	L	1	R1
3	R	1	R1
4	R	2	R2
5	L	2	R2
6	R	1	R1
7	R	3	R2 + MP
8	L	1	R1
9	R	4	R3 + MP
10	R	1	R1
11	L	4	R3
12	L	3	R2 + M1
13	L	4	R3
14	R	4	R3
15	L	1	R1
16	R	1	R1
17	L	4	R3
18	R	3	R2 + MP
19	R	1	R1
20	R	2	R2
21	R	4	R3
22	L	1	R1
23	R	1	R1
24	R	2	R2
25	R	4	R3
26	R	4	R3
27	R	4	R3P + MP
28	R	1	R1
29	L	4	R3P
30	R	4	R3P + M1
31	L	2	R2
32	R	3	R2 + MP
33	R	4	R3P
34	R	4	R3P + MP
35	R	4	R3P
36	L	3	R2 + M1
37	R	2	R2
38	L	4	R3P + MP
39	R	4	R3P
40	R	4	R3P
41	L	1	R1
42	R	4	R3
43	R	4	R3P
44	L	4	R3P
45	R	4	R3P + MP
46	R	4	R3P + M1
47	L	3	R2 + MP
48	R	4	R3P

Appendix table 3 continued. Full demographic and clinical data for all participants. M = male, F = female, B = Black, W = White, A = Asian, C = Chinese, DM = Diabetes mellitus, Dur DM = Duration of diabetes, Dur DED = duration of diabetic eye disease, NGP = National grading protocol, R = retinopathy, M = maculopathy, P = photocoagulation.

Clinical and demographic data

ID	Recruitment date	Sex	Age	Ethnicity	DM Type	Dur DM	Dur DED
49	02/07/2010	M	82	B	2	33	7
50	06/07/2010	F	26	W	1	14	2
51	08/07/2010	F	66	W	2	14	2
52	20/07/2010	F	70	B	2	18	4
53	22/07/2010	M	55	W	2	22	8
54	23/07/2010	M	69	B	2	24	1
55	26/07/2010	M	63	W	2	17	1
56	29/07/2010	M	49	W	2	16	4
57	03/08/2010	F	69	W	2	27	9
58	05/08/2010	M	49	B	2	18	8
59	06/08/2010	F	54	W	2	28	2
60	13/08/2010	M	65	W	2	15	10
61	17/08/2010	F	50	W	1	26	5
62	20/08/2010	F	65	B	2	26	10
63	23/08/2010	M	60	B	2	6	3
64	24/08/2010	F	44	W	1	24	5
65	25/08/2010	M	55	W	2	5	5
66	07/09/2010	M	60	A	2	20	2
67	14/09/2010	F	60	B	2	20	3
68	16/09/2010	M	59	B	2	5	1
69	17/09/2010	M	60	W	2	8	6
70	20/09/2010	F	51	W	2	12	5
71	24/09/2010	F	64	W	2	21	4
72	11/10/2010	M	57	W	2	20	10
73	14/10/2010	F	59	B	2	30	10
74	18/10/2010	F	51	A	2	13	5
75	02/11/2010	M	63	W	2	10	10
76	09/11/2010	M	61	B	2	14	8
77	10/11/2010	F	51	W	2	9	1
78	11/11/2010	M	51	B	2	18	5
79	12/11/2010	F	47	W	1	16	7
80	15/11/2010	M	72	B	2	8	8
81	18/11/2010	M	66	B	2	10	10
82	23/11/2010	M	35	W	1	22	5
83	26/11/2010	M	57	W	2	23	10
84	30/11/2010	M	51	W	1	39	4
85	02/12/2010	F	37	W	1	33	18
86	02/12/2010	M	61	W	1	47	2
87	07/12/2010	F	81	W	2	30	14
88	06/01/2011	F	55	B	2	10	8
89	11/01/2010	F	59	B	2	19	7
90	14/01/2011	M	41	W	2	6	6
91	17/01/2011	M	63	W	2	42	20
92	18/01/2011	M	36	A	2	2	2
93	24/01/2011	M	35	W	1	34	2
94	27/01/2011	M	52	A	2	6	1
95	27/01/2011	M	67	B	2	18	5
96	03/02/2011	F	65	W	2	3	1

Appendix table 3 continued. Full demographic and clinical data for all participants. M = male, F = female, B = Black, W = White, A = Asian, C = Chinese, DM = Diabetes mellitus, Dur DM = Duration of diabetes, Dur DED = duration of diabetic eye disease, NGP = National grading protocol, R = retinopathy, M = maculopathy, P = photocoagulation.

Clinical and demographic data

ID	Better eye	Severity Group	NGP grade
49	L	4	R3P + MP
50	R	4	R3P
51	L	3	R2 + MP
52	L	3	R2 + MP
53	L	1	R1
54	R	2	R2
55	R	1	R1
56	R	3	R2 + MP
57	L	2	R2
58	L	2	R2
59	R	2	R2
60	L	2	R2
61	L	2	R2
62	R	1	R1
63	L	3	R2 + M1
64	L	3	R2 + M1
65	R	2	R2
66	L	3	R2 + MP
67	R	2	R2
68	L	1	R1
69	R	3	R2 + MP
70	L	2	R2
71	L	3	R2 + MP
72	L	1	R1
73	L	3	R2 + M1
74	L	1	R1
75	R	3	R2 + MP
76	L	2	R2
77	R	1	R1
78	R	2	R2
79	R	2	R2
80	R	2	R2
81	R	3	R2 + MP
82	L	1	R1
83	R	1	R1
84	L	4	R3P
85	L	4	R3P
86	L	1	R1
87	L	2	R2
88	R	4	R3P
89	L	4	R3P + MP
90	L	3	R2 + MP
91	R	4	R3 + MP
92	R	1	R1
93	R	4	R3P
94	L	4	R3P + MP
95	L	4	R3P + MP
96	R	1	R1

Appendix table 3 continued. Full demographic and clinical data for all participants. M = male, F = female, B = Black, W = White, A = Asian, C = Chinese, DM = Diabetes mellitus, Dur DM = Duration of diabetes, Dur DED = duration of diabetic eye disease, NGP = National grading protocol, R = retinopathy, M = maculopathy, P = photocoagulation.

Clinical and demographic data

ID	Recruitment date	Sex	Age	Ethnicity	DM Type	Dur DM	Dur DED
97	03/02/2011	F	56	W	1	30	12
98	07/02/2011	M	53	B	1	37	3
99	11/02/2011	F	52	A	2	5	4
100	15/02/2011	F	64	W	2	4	1

ID	Better eye	Severity Group	NGP grade
97	R	4	R3P + MP
98	L	4	R3P
99	L	1	R1
100	R	4	R3P + M1

Appendix table 3 continued. Full demographic and clinical data for all participants. M = male, F = female, B = Black, W = White, A = Asian, C = Chinese, DM = Diabetes mellitus, Dur DM = Duration of diabetes, Dur DED = duration of diabetic eye disease, NGP = National grading protocol, R = retinopathy, M = maculopathy, P = photocoagulation.

Visual function data

ID	HAD	CDA	CCS	HNA	HLS	HSS	CRA	CRS	CPS
1	0.02	-0.08	1.65	0.2	112	102	-0.04	161	0.3
2	0.04	-0.08	1.5	0.3	82	89	0.02	173	0.8
3	0.3	-0.08	1.55	0.4	137	104	0.15	200	0.4
4	0.2	0.02	1.55	0.3	222	153	0.03	257	0.6
5	0.12	0.02	1.35	0.4	75	56	0.13	113	0.5
6	0.02	0.02	1.55	0.3	187	155	0.04	244	0.6
7	0.36	0.3	1.2	0.2	172	170	0.31	229	0.6
8	0.2	0.02	1.45	0.3	207	199	0.04	312	0.5
9	0.2	-0.04	1.65	0.2	177	168	0	229	0.6
10	0.3	0.34	1.1	0.6	80	65	0.4	173	0.8
11	0.32	0.24	1.15	0.5	170	136	0.11	252	0.8
12	0.7	0.24	1.3	0.8	14	5	0.48	95	1.1
13	0.22	0.24	1.2	0.4	170	130	0.11	279	0.7
14	-0.1	-0.16	1.55	0	263	248	-0.45	433	0.2
15	0.04	-0.12	1.55	0.2	124	134	-0.13	200	0.7
16	-0.2	-0.26	1.4	0.1	225	249	-0.18	313	0.1
17	0.02	-0.02	1.55	0.3	140	129	-0.07	177	0.8
18	0.2	0.18	1.35	0.2	175	132	0.07	248	0.7
19	-0.08	-0.12	1.65	0.1	152	177	-0.11	229	0.2
20	0.16	0.1	1.3	0.4	78	77	0.12	134	0.7
21	0	-0.12	1.5	0	180	165	-0.06	218	0.6
22	0.06	-0.02	1.35	0.5	124	103	0.04	211	0.4
23	0.3	0.08	1.35	0.6	127	110	0.03	206	0.6
24	0.02	-0.02	1.45	0.3	138	122	-0.18	200	1.1
25	0.14	0.14	1.4	0.4	172	140	0.17	225	0.5
26	0.04	0	1.45	0.4	212	170	0.15	325	0.6
27	0.5	0.36	1.2	0.7	154	17	0.76	223	1.1
28	0.3	0.1	1.35	0.7	94	0	0.1	159	0.6
29	0	-0.08	1.5	0.3	172	162	0.12	269	0.4
30	0.4	0.26	1.1	0.6	138	76	0.52	134	0.8
31	0.12	-0.06	1.5	0.3	126	112	0.02	186	0.6
32	0.1	-0.02	1.6	0.4	190	172	0.01	223	0.6
33	0.72	0.64	0.95	0.7	63	0	0.72	113	1.4
34	0.48	0.44	1.15	0.3	211	168	0.5	289	1.1
35	0.24	0.2	1.1	0.5	105	19	0.3	217	0.7
36	0.04	-0.14	1.45	0.3	125	130	-0.04	232	0.3
37	0.34	0.18	1.15	0.5	170	203	0.08	269	0.4
38	1.2	0.82	0.8	1.1					
39	0.28	0.24	1.05	0.3	189	147	0.47	289	1.1
40	0	-0.08	1.45	0.2	168	168	-0.07	312	0.3
41	0.4	-0.1	1.45	0.3	147	130	-0.14	223	0.4
42	0.06	-0.08	1.55	0.1	194	187	-0.09	252	0.1
43	0.12	0.14	1.6	0.3	157	122	0.1	213	1
44	0.24	0.14	1.35	0.3	190	134	0.08	260	0.6
45	0.7	0.48	0.75	1	0	0	0.57	90	1.2
46	0.2	0.04	1.35	0.4	77	78	-0.05	147	0.6
47	0.2	0.04	1.55	0.3	153	142	0.14	180	0.7
48	0.12	0	1.4	0.3	213	210	0.02	278	0.6
49	0.3	0.32	1.2	0.6	84	118	0.23	173	1
50	0.22	0.22	1.25	0.4	137	138	0.13	279	0.9
51	0.22	0.16	1.3	0.6	169	144	0.49	205	1
52	0.7	0.36	1	0.6	62	39	0.59	150	1.1
53	0.02	-0.06	1.5	0.3	220	190	0.08	277	0.6

Appendix table 4. Full visual function data for all participants. Empty cells represent missing data. HAD = Habitual distance acuity, CDA = Corrected distance acuity, CCS = Corrected contrast sensitivity, HNA = Habitual near acuity, HLS = Habitual large reading speed, HSS = Habitual small reading speed, CRA = Corrected reading acuity, CRS = Corrected peak reading speed, CPS = Corrected critical print size, CI = Confusion Index, SI = Selectivity Index, EES = Esterman efficiency score, MS = Mean sensitivity, MD = Mean defect, CMS = Central mean sensitivity, PMS = Paracentral mean sensitivity, SS = Scotoma size, FIX = log BCEA.

Visual function data

ID	CI	SI	EES	MS	MD	CMS	PMS	SS	FIX
1	2.11	2.96	100	16.07	-3.4	15	16.4	16	3.07
2	1.7	1.2	100						
3	1.13	1.61	100	18.76	-0.7	19.13	18.65	5	2.92
4	1.09	1.55	99	15.78	-3.3	15.93	15.73	22	3.96
5	1.97	1.57	100	13.37	-5.7	13.44	13.35	40	2.81
6	1.71	2.5	100	17.28	-2	17.81	17.12	13	4.31
7	3.07	2.67	59	10.84	-7.7	8.88	11.44	47	3.24
8	1.26	1.8	100	16.76	-2.5	17.19	16.63	20	3.33
9	3.19	1.27	98	18.07	-1.4	18.94	17.81	12	2.93
10	1.62	2.18	88						
11	1.09	1.55	89	13.29	-5.6	14.81	12.83	46	3.52
12	3.24	3.23	94	10.53	-8.5	11.06	10.37	52	3.25
13	3.73	4.8	98	12.69	-6.8	11.13	13.17	56	2.95
14	1	1.42	100	18.73	-0.6	20	18.34	2	2.57
15	1.24	1.71	100	15.72	-3.5	16.63	15.44	25	2.26
16	1	1.42	100						2.68
17	1.64	1.71	99						2.61
18	1.52	2.16	99	14.4	-4.5	16.12	13.87	38	1.95
19	1.31	1.76	100	16.68	-2.7	18.13	16.23	17	2.81
20	3.32	2.01	94	7.38	-9.6	5.63	7.92	67	2.81
21	1.13	1.61	95	16.28	-3.3	16.31	16.27	34	2.85
22	3.41	1.19	100	16.06	-3.4	15.13	16.35	29	2.86
23	2.07	2.97	98	15.62	-3.7	15.25	15.73	29	2.92
24	1.46	2.02	99	16.15	-3.2	18.38	17	17	3.48
25	1.13	1.61	80	13.96	-4.2	15.94	13.35	39	2.64
26	2.89	2.33	82	16	-3.3	15.69	16.1	27	2.37
27	3.06	3.42	72	8.82	-9.5	9	8.77	52	3.67
28	1.72	2.43	98	15.43	-3.9	15.81	15.31	44	2.80
29	1.13	1.61	99	16.04	-3.1	17	15.75	25	2.71
30	2.37	1.98	90						
31	1	1.42	100	14.12	-4.6	15.56	13.67	32	3.28
32	1.79	2.61	96	12.5	-6.8	12.44	12.52	40	2.68
33	3.14	3.24	81						3.60
34	2.72	3.33	98	11.88	-7.2	10.25	12.38	55	2.73
35	1.68	2.04	79	8.29	-9.7	7.38	8.58	51	2.85
36	1	1.42	100	19.85	0.5	20	19.81	0	2.33
37	2.88	3.81	100						2.20
38	2.89	2.1	71	8.69	-10.2	6.19	9.46	64	2.84
39	1.49	2.12	92						2.75
40	1	1.42	96	15.49	-4.2	15.5	15.48	25	2.50
41	1.83	1.88	100	19.21	-0.2	19.88	19	1	3.19
42	1	1.42	99	17.97	-1.2	18	17.96	7	3.32
43	1	1.42	91	16.29	-2.4	16.94	16.1	18	2.76
44	3	3.14	61						3.02
45	3.45	3.52	90	4.44	-12.6	3.44	4.75	57	2.90
46	2.32	2.25	100	13.46	-5.8	10.63	14.33	53	2.86
47	1	1.42	87	12.21	-6.1	15.25	11.27	34	3.07
48	1	1.42	97	13.01	-5.7	13.75	12.81	40	2.41
49	2.49	3.28	85						
50	1.66	2.18	100	15.37	-4.4	14.56	15.62	45	3.40
51	3.04	2.53	100	13.84	-5.6	12.19	14.35	45	3.52
52	2.53	3.39	100						
53	2.01	2.61	100	18.88	-0.5	19.38	18.73	2	2.78

Appendix table 4 continued. Full visual function data for all participants. Empty cells represent missing data. HAD = Habitual distance acuity, CDA = Corrected distance acuity, CCS = Corrected contrast sensitivity, HNA = Habitual near acuity, HLS = Habitual large reading speed, HSS = Habitual small reading speed, CRA = Corrected reading acuity, CRS = Corrected peak reading speed, CPS = Corrected critical print size, CI = Confusion Index, SI = Selectivity Index, EES = Esterman efficiency score, MS = Mean sensitivity, MD = Mean defect, CMS = Central mean sensitivity, PMS = Paracentral mean sensitivity, SS = Scotoma size, FIX = log BCEA.

Visual function data

ID	HAD	CDA	CCS	HNA	HLS	HSS	CRA	CRS	CPS
54	0.28	0.26	1.35	0.7	114	32	0.45	164	0.8
55	0.2	-0.06	1.6	0.3	165	133	-0.1	206	0.4
56	0.1	0.08	1.4	0.4	187	140	-0.01	229	0.4
57	0.1	0.06	1.4	0.4	126	93	0.05	173	0.8
58	-0.1	-0.2	1.65	0.1	154	145	-0.18	260	0.5
59	0.1	0.1	1.45	0.4	68	48	0.06	137	0.4
60	0.3	0.2	1.2	0.3	82	99	0.11	173	0.9
61	0.06	-0.04	1.45	0.1	196	191	-0.17	223	0.7
62	0	-0.08	1.5	0.3	146	135	-0.18	181	0.1
63	0.12	-0.06	1.4	0.4	172	102	0.01	236	0.4
64	0.04	-0.02	1.45	0.2	159	179	0.08	248	0.6
65	0.16	-0.04	1.35	0.3	209	182	-0.04	339	0.6
66	0.5	0.32	1.2	0.5	110	77	0.31	157	0.8
67	0.18	0.12	1.6	0.2	160	143	0	228	1
68	0.4	0.04	1.55	0.4					
69	0.3	0.08	1.35	0.4	144	87	0.04	205	1.1
70	0.06	-0.06	1.55	0.3	128	122	-0.03	200	0.8
71	0.2	0.04	1.4	0.3	141	172	-0.02	252	0.6
72	0.1	0.04	1.4	0.4	173	138	0.01	232	0.4
73	0.4	0.3	1.2	0.7	92	66	0.3	177	0.9
74	0.06	0.04	1.35	0.4	100	91	0.1	190	0.8
75	0.24	0	1.55	0.4	111	105	-0.05	223	0.6
76	0.14	0.14	1.35	0.3	164	117	0.08	269	0.8
77	0.02	-0.1	1.6	0.2	204	207	-0.2	267	0.1
78	0.06	-0.1	1.6	0.3	145	144	0.04	248	0.4
79	0.1	-0.08	1.5	0.2	165	174	-0.08	200	0.2
80	0.08	-0.1	1.65	0.5	55	73	-0.09	128	0.4
81	0.2	-0.06	1.35	0.4	76	82	0.04	129	0.4
82	-0.2	-0.26	1.65	0	214	232	-0.3	260	0.4
83	-0.04	-0.08	1.6	0.1	203	215	-0.22	339	0.2
84	0.24	0.02	1.65	0.3	159	187	0.06	252	0.7
85	0.22	0.1	1.45	0.4	264	231	0.18	325	0.9
86	0.26	0.12	1.35	0	156	155	0.15	218	0.8
87	0.4	0.3	0.65	0.7	67	0	0.34	177	1.3
88	0.7	0.42	0.85	1.4	0	0	1.31	65	1.5
89	0.2	0.1	1.5	0.5	142	136	0.16	244	0.8
90	0.2	-0.04	1.45	0.1	238	230	-0.08	277	0.4
91	0.46	0.32	1.2	0.4	99	100	0.26	217	1
92	-0.04	-0.14	1.55	0.2	155	147	-0.14	180	0.3
93	0	-0.1	1.65	0.3	119	122	0.12	189	0.6
94	0.8	0.48	1	1.1	16	0	0.67	128	1.4
95	0.5	0.18	1.05	0.9	57	0	0.64	107	1.1
96	0.14	-0.06	1.45	0.3	130	99	0.06	166	0.6
97	-0.04	-0.04	1.55	0.3	190	193	-0.1	257	0.2
98	0.18	0.16	1.25	0.3	109	94	0.1	144	0.7
99	0.1	0.02	1.6	0.4					
100	0.3	0.24	1.3	0.4	155	117	0.11	211	0.7

Appendix table 4 continued. Full visual function data for all participants. Empty cells represent missing data. HAD = Habitual distance acuity, CDA = Corrected distance acuity, CCS = Corrected contrast sensitivity, HNA = Habitual near acuity, HLS = Habitual large reading speed, HSS = Habitual small reading speed, CRA = Corrected reading acuity, CRS = Corrected peak reading speed, CPS = Corrected critical print size, CI = Confusion Index, SI = Selectivity Index, EES = Esterman efficiency score, MS = Mean sensitivity, MD = Mean defect, CMS = Central mean sensitivity, PMS = Paracentral mean sensitivity, SS = Scotoma size, FIX = log BCEA.

Visual function data

ID	CI	SI	EES	MS	MD	CMS	PMS	SS	FIX
54	2.89	3.22	100	15.32	-4	13.56	15.87	30	2.72
55	1.13	1.61	100	17.24	-2.1	16.88	17.35	8	2.98
56	2.59	3.59	100	12.63	-6.8	11.13	13.1	49	2.89
57	1	1.42	100	15.15	-4.2	14.88	15.23	40	3.21
58	1.21	1.67	100	17.31	-1.6	17.63	17.21	16	2.48
59	1.57	1.7	98	6.82	-12.6	6.38	6.96	68	2.99
60	2.33	2.54	96						3.02
61	1.13	1.61	100	16.37	-3.1	15.81	16.54	20	2.96
62	1	1.42	100	16.27	-3.1	16.44	14.65	24	2.69
63	1.13	1.61	95	15.26	-4	17.06	14.71	31	3.23
64	1.13	1.61	100	18.21	-1	19.25	17.88	5	2.94
65	3.41	3.24		17.59	-1.8	17.5	17.62	13	2.70
66	2.96	2.56	98						
67	1	1.42	98	17.82	-1.6	18.75	17.54	12	2.81
68	1	1.42	100	17.43	-2.1	17.31	17.46	22	3.07
69	1.37	1.95	100	15.51	-4	15.25	15.6	30	3.34
70	2.12	2.26	97	17.1	-2	16.75	17.17	14	1.79
71	1.42	1.93	100	16.38	-2.4	17.34	16.08	24	2.01
72	3.23	2.66	97	18.06	-1.4	17.5	18.23	12	3.05
73	3.45	4.77	85	10.26	-8.9	10.06	10.33	57	3.23
74	1.18	1.67	95	16.59	-2.8	16.9	16.5	29	3.25
75	1.42	1.82	100	14.87	-4.5	14.56	14.96	34	2.42
76	1.33	1.83	100	15.51	-5.9	13.5	13.5	57	2.78
77	1	1.42	100	19.44	0.1	19.75	19.35	0	2.30
78	2.24	2.44	100	16.62	-2.7	18	16.19	20	3.75
79	1	1.42	99	17.69	-1.9	18.56	17.42	14	2.59
80	1.51	2.17	100	14.56	-4.9	16	14.12	47	2.37
81	3.09	3.46	90	8.11	-10.3	8	8.15	63	2.82
82	1	1.42	100	19.82	0.4	20	19.78	0	2.33
83	1.13	1.61	97	18.97	-0.2	19.31	18.87	2	2.64
84	1.38	1.87	87	17.64	-1.1	18.88	17.27	12	2.12
85	1.51	2.03	96	18.29	-1.3	19	18.08	11	2.89
86	1	1.42	100						
87	3.08	2.47	91						3.08
88	2.54	1.18	38						
89	3.39	4.03	96	17.91	-1.6	19.44	17.44	14	2.95
90	1.71	2.41	100	15.85	-3.1	17.44	15.37	24	2.81
91	2.52	2.1	91	11.14	-7.9	11.25	11.12	58	2.85
92	1.48	1.46	94	18.38	-0.8	19.63	18	5	2.95
93	1.71	2.5	100	19.18	-0.4	19.86	18.96	5	2.70
94	3	3.09	99	8.82	-10	8.94	8.79	65	4.12
95	3.68	3.68							3.63
96	1.48	1.81	95	19.26	-0.1	19.94	19.06	2	2.90
97	1.9	2.35	97	18.56	-0.4	19.75	18.19	6	2.51
98	2.11	1.69	91	16.9	-1.8	18.38	16.44	11	2.80
99	1.97	1.4	100	19.18	-0.4	19.81	18.98	2	3.33
100	1.79	2.61	100	12.03	-6.8	11	12.35	51	2.66

Appendix table 4 continued. Full visual function data for all participants. Empty cells represent missing data. HAD = Habitual distance acuity, CDA = Corrected distance acuity, CCS = Corrected contrast sensitivity, HNA = Habitual near acuity, HLS = Habitual large reading speed, HSS = Habitual small reading speed, CRA = Corrected reading acuity, CRS = Corrected peak reading speed, CPS = Corrected critical print size, CI = Confusion Index, SI = Selectivity Index, EES = Esterman efficiency score, MS = Mean sensitivity, MD = Mean defect, CMS = Central mean sensitivity, PMS = Paracentral mean sensitivity, SS = Scotoma size, FIX = log BCEA.

Visual ability data

ID	AI 0	AI 3	AI 6	Intervention
1	5.85	5.69	6.03	delayed
2	1.87	1.87	2.77	immediate
3	4.75	5.92	4.82	delayed
4	4.54	4.01	4.65	immediate
5	5.81	5.76	5.66	delayed
6	3.77	2.74	2.61	immediate
7	0.84	1.98	1.29	delayed
8	5.99	5.95	5.97	immediate
9	0.34	-0.19	-0.11	delayed
10	0.3	0.65	3.18	delayed
11	-0.59	-0.14	0.05	immediate
12	1.52			immediate
13	0.85	0.59	0.83	delayed
14	2.66	2.21	3.86	immediate
15	5.51	5.45	5.28	delayed
16	6.04	5.94	6.1	delayed
17	0.1	0.41	1.49	delayed
18	0.42	0.27	-0.47	immediate
19	5.77	3.31	5.73	delayed
20	0.99	1.3	0.83	immediate
21	1.22	1.66	1.88	delayed
22	-0.27	0.57	-0.32	delayed
23	0.88	1.35	1.56	immediate
24	2.55	2.8	3.28	immediate
25	1.26	1.64	2.23	immediate
26	3.13	2.68	4.15	immediate
27	1.84	2.79	1.88	delayed
28	5.7	5.54	5.66	immediate
29	3.7	2.56	2.9	delayed
30	2.6	0.75	0.22	immediate
31	5.68	3.79	4.6	delayed
32	0.45	3.65	1.33	immediate
33	-5.06	-2.49	-1.43	immediate
34	0.83	0.78	0.55	immediate
35	0.64	0.92	0.97	delayed
36	2.62	3.02	3.58	delayed
37	2.16	1.95	0.54	immediate
38	1.31	-0.1	0.48	delayed
39	0.38	0.65	0.55	delayed
40	5.87	5.8	5.92	immediate
41	5.62	3.16	4.07	immediate
42	5.62	5.83	5.62	delayed
43	5.89	4.57	4.61	immediate
44	0.56	0.62	1.99	delayed
45	-0.91	-0.54	-0.07	immediate
46	1.59	0.58	1.99	immediate
47	1.17	1	1.72	delayed
48	5.83	5.87	5.79	delayed
49	-0.54	0.33	0.61	immediate
50	1.67	2.56	3.82	delayed
51	1.24	0.96	0.5	immediate
52	0.36	-0.04	0.04	delayed
53	0.77	1.15	0.36	immediate

Appendix Table 5. Full visual ability score data at 0, 3 and 6 months for all participants. Intervention group is also given. AI = Activity Inventory.

Visual ability data

ID	AI 0	AI 3	AI 6	Intervention
54	2.51	1.41	5.75	delayed
55	1.68	2.2	3.9	delayed
56	0.16	0.25	5.54	delayed
57	1.36	2.14	1.3	delayed
58	3.79	5.74	5.74	immediate
59	2.44	1.75	3.1	immediate
60	2.07			delayed
61	2.74	4.79	6.02	immediate
62	3.68	4.59	5.63	immediate
63	2.58	6.15	5.95	immediate
64	2.22	5.52	4.4	immediate
65	5.45	5.45	5.48	delayed
66	-0.84			delayed
67	2.65	3.95	2.14	delayed
68	2.09	1.46	1.92	immediate
69	1.17	1.6	1.15	delayed
70	1.54	5.66	3.66	immediate
71	5.46	5.47	5.42	delayed
72	0.58			delayed
73	-0.55	-1	-0.99	immediate
74	0.05			immediate
75	0.44	1.63	1.25	immediate
76	2.4	2.15	3.52	delayed
77	1.42	4.34	5.66	delayed
78	5.72			immediate
79	1.33	1.83	1.92	delayed
80	3.57	2.5	2.39	immediate
81	5.39	5.2	5.43	immediate
82	6	6	5.96	delayed
83	5.88	6.01	5.88	delayed
84	1.26	1.31	2.12	immediate
85	1.8	1.12	3.13	delayed
86	0.53	1.8	3.15	immediate
87	0.42	0.16	-0.09	delayed
88	-1.64	-1.97	-1.3	delayed
89	0.51	1.39	0.46	immediate
90	4.31	5.26		delayed
91	0.97	0.28	0.2	immediate
92	1.61	1.3	1.51	immediate
93	1.38	0.29	0.62	delayed
94	-0.66			immediate
95	1.07	-0.92	-0.62	immediate
96	1.29	2.31	1.63	delayed
97	5.48	5.61	5.73	immediate
98	2.37	4.68	4.61	delayed
99	2.79	2.68	3.68	delayed
100	0.51	1.06	1.09	delayed

Appendix table 5 continued. Full visual ability score data at 0, 3 and 6 months for all participants. Intervention group is also given. AI = Activity Inventory.

Low vision assessment data

ID	Assessment date	NV gls needed	DV gls needed	NV LVA	DV LVA
1	11/09/2009	Y	N		
2	06/07/2009	N	N		
3	06/10/2009	N	Y		
4	17/07/2009	N	N		
5	28/10/2009	N	N		
6	25/08/2009	N	N		
7	13/11/2009	N	N	12D ill HM	
8	25/08/2009	N	N		
9	24/11/2009	N	N		
10	14/12/2009	N	N	Flatfield	
11	01/10/2009	N	N	12D ill HM	4x13 Microlux
12	19/10/2009	N	N	12D ill SM 16D ill HM	
13	22/01/2010	Y	N	50mm brightfield	
14	27/10/2009	N	N		
15	25/01/2010	N	N		
16	25/01/2010	N	N		
17	29/01/2009	N	N		
18	04/12/2009	N	N		
19	23/04/2010	N	N		
20	11/02/2010	N	N		
21	12/05/2010	N	N		
22	11/08/2010	N	N		
23	23/02/2010	Y	N		
24	01/03/2010	N	N		
25	03/03/2010	Y	N		
26	15/03/2010	Y	Y		
27	09/06/2010	N	N	12D ill HM	
28	24/03/2010	Y	N		
29	15/06/2010	N	N		
30	30/03/2010	Y	Y	Flatfield	
31	25/06/2010	N	N		
32	23/04/2010	N	N	HRA	
33	26/04/2010	N	N	12D ill HM 12D ill SM	
34	10/05/2010	N	N		
35	27/07/2010	Y	N		
36	09/08/2010	N	N		
37	24/05/2010	Y	N		
38	17/08/2010	N	N	12D ill HM HRA	6x17 Binocs
39	06/09/2010	N	N	16D ill HM	4x13 Microlux
40	10/06/2010	N	N		
41	08/06/2010	Y	N		
42	09/07/2010	N	N		
43	30/06/2010	N	Y		
44	15/09/2010	N	N		
45	06/07/2010	N	N	HRA	4x13 Microlux

Appendix table 6. Details of spectacles and low vision aids prescribed to all participants. NV = near vision, DV = distance vision, gls = glasses, LVA = low vision aid, D = dioptres, ill = illuminated, HM = hand magnifier, SM = stand magnifier, HRA = high reading add, Binoc = binoculars, Monoc = monocular.

Low vision assessment data

ID	Assessment date	NV gls needed	DV gls needed	NV LVA	DV LVA
46	09/07/2010	Y	Y		
47	22/09/2010	Y	N		
48	05/10/2010	N	N		
49	15/07/2010	Y	N		
50	12/10/2010	Y	N		4x13 Microlux
51	20/07/2010	Y	N	12D ill HM	
52	19/10/2010	N	N	HRA 20D ill HM	
53	11/08/2010	N	N	Flatfield	
54	20/10/2010	Y	Y		
55	20/10/2010	N	N		
56	02/11/2010	Y	Y		
57	02/11/2010	N	N		
58	14/10/2010	Y	N		
59	18/08/2010	N	N		
60					
61	01/09/2010	N	N		
62	06/09/2010	N	N		
63	06/09/2010	Y	N		
64	06/09/2010	N	N		
65	13/12/2010	N	N		
66					
67	09/12/2010	N	N		
68	30/09/2010	N	N		
69	17/12/2010	Y	N		4x10 Monoc
70	27/09/2010	N	N		
71	08/12/2010	N	Y		
72					
73	02/11/2010	Y	N	4x non ill folding HM 12D ill HM	
74	04/11/2010	Y	Y		
75	16/11/2010	Y	N		
76	11/02/2011	N	N	12D ill HM	
77	07/02/2011	N	N		
78					
79	08/02/2011	N	N		
80	25/11/2010	N	N		
81	01/12/2010	N	N		
82	03/03/2011	N	N		
83	28/02/2011	N	N		
84	07/12/2010	N	N		
85	01/03/2011	Y	Y	16D ill HM	
86	16/12/2010	Y	N		
87	02/03/2011	N	N	16D ill SM 20D ill HM	
88	01/04/2011	N	N	39D ill SM 39D ill HM	Max TV
89	25/01/2011	Y	N	12D ill HM	

Appendix table 6 continued. Details of spectacles and low vision aids prescribed to all participants. NV = near vision, DV = distance vision, gls = glasses, LVA = low vision aid, D = dioptres, ill = illuminated, HM = hand magnifier, SM = stand magnifier, HRA = high reading add, Binoc = binoculars, Monoc = monocular.

Low vision assessment data

ID	Assessment date	NV gls needed	DV gls needed	NV LVA	DV LVA
90					
91	02/02/2011	Y	Y	20D ill HM	
92	08/02/2011	N	N		
93	20/04/2011	N	N	3x non ill SM	
94	14/02/2011	N	N	16D ill HM 16D ill SM	8x21 Binocs
95	01/02/2011	Y	N		
96	10/05/2011	Y	N		
97	16/02/2011	N	N		
98	17/05/2010	N	N		
99	16/05/2010	N	N		
100	12/05/2011	Y	N	12D ill HM	

Appendix table 6 continued. Details of spectacles and low vision aids prescribed to all participants. NV = near vision, DV = distance vision, gls = glasses, LVA = low vision aid, D = dioptres, ill = illuminated, HM = hand magnifier, SM = stand magnifier, HRA = high reading add, Binoc = binoculars, Monoc = monocular.