Looking Ahead: Visual and Anatomical Endpoints in Future Trials of Diabetic Macular Ischemia

Chui Ming Gemmy Cheung^{a, b} Elizabeth Pearce^c Beau Fenner^a Piyali Sen^d
Victor Chong^c Sobha Sivaprasad^d

^aSingapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore; ^bOphthalmology and Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore, Singapore; ^cBoehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; ^dNIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London, UK

Keywords

Diabetic macular ischemia · Endpoints · Optical coherence tomography · Microperimetry

Abstract

Diabetic macular ischemia (DMI) is a common complication of diabetic retinopathy that can lead to progressive and irreversible visual loss. Despite substantial clinical burden, there are no treatments for DMI, no validated clinical trial endpoints, and few clinical trials focusing on DMI. Therefore, generating consensus on validated endpoints that can be used in DMI for the development of effective interventions is vital. In this review, we discuss potential endpoints appropriate for use in clinical trials of DMI, and consider the data required to establish acceptable and meaningful endpoints. A combination of anatomical, functional, and patient-reported outcome measures will provide the most complete picture of changes that occur during the progression of DMI. Potential endpoint measures include change in size of the foveal avascular zone measured by optical coherence tomography angiography and change over time in best-corrected visual acuity. However, these endpoints must be supported by further research. We also recom-

mend studies to investigate the natural history and progression of DMI. In addition to improving understanding of how patient demographics and comorbidities such as diabetic macular edema affect clinical trial endpoints, these studies would help to build the consensus definition of DMI that is currently missing from clinical practice and research.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

Diabetic macular ischemia (DMI) is a complication of diabetic retinopathy (DR) and is associated with a poor prognosis; in some patients, DMI results in severe loss of vision. DMI is a causative and potentially dominant factor for progressive visual impairment experienced by patients with DR, and greater DMI severity (graded by the Early Treatment Diabetic Retinopathy Study [ETDRS] protocol) is associated with a greater degree of visual loss [1, 2]. However, the ETDRS used fluorescein angiograms as the diagnostic methodology, which are unable to image the deeper capillary networks of the eye [3]. Recent advances in retinal imaging that improve visualization of the different retinal plexi (optical coherence tomography angiogra-

phy [OCTA]) have renewed interest in better understanding DMI. Nonetheless, at present there is no consensus regarding the definition, classification, diagnostic criteria, or even the optimal testing modalities for DMI.

Despite the limited literature available on DMI and a lack of consensus on its definition, several features are typically associated with its presence as part of DR. Changes occur in the retinal basement membrane, followed by pericyte loss, resulting in breakdown of the blood-retinal barrier. The loss of macular capillary vasculature may create larger intercapillary spaces, increasing oxygen diffusion time and eventually causing chronic hypoxia [2, 4, 5]. Leukostasis due to adhesion of leukocytes to abnormal endothelial cells may also contribute to capillary occlusion [6]. Fluid leakage from the diseased capillary bed may result in cystoid spaces in the retina, especially in the outer plexiform layer [7]. Ultimately, these events can lead to ischemia and edema in the retina [8, 9]. The degree of capillary bed ischemia required to cause loss of vision is unknown, but it may vary for different visual functions.

Although the precise relationship between retinal vasculature in different layers of the retina is unclear, DMI is associated with decreased retinal vessel density and/or non-perfusion of the macular superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris [10–14]. The capillary plexi form part of a dense vascular system that supply oxygen to the macula, with the SCP located in the retinal nerve fiber layer, and the DCP located at the outer border of the inner nuclear layer [15]. Damage to the retinal vasculature affects local oxygenation levels, which are vital for effective functioning of the macula; visual loss and macular photoreceptor disruption have been linked to non-perfusion of the DCP, as well as a decrease in SCP and DCP vessel density [15–17]. The degree of visual loss associated with DMI may depend on the relative level of ischemia between the SCP and DCP, with DCP ischemia causing more serious problems [15]. This is because the DCP plays a role in supplying blood to photoreceptors, which have a high oxygen demand [15, 18]. It may be surmised that there could be different phenotypes of DMI based on the relative abnormalities of the SCP and DCP. However, in our experience, identifying phenotypes of disease using images of the plexus is challenging due to the limited resolution of current imaging methods and/or imaging software.

DMI is also associated with enlargement and disruption of the foveal avascular zone (FAZ), the health of which is integral to maintaining normal visual acuity [19–21]. That said, there is some disconnect between an enlarged and dis-

rupted FAZ and neurosensory changes: not all enlarged or disrupted FAZ result in visual loss [22]. Loss of the retinal neurosensory layer is most likely a sequelae of hypoxia caused by ischemia [2]. Ischemia has a notable impact on the integrity and sensitivity of photoreceptors [13], and thinning of the retinal nerve fiber layer is also seen in patients with DMI [4]. Damage to the neurosensory retina and the retinal blood vessels from DMI forms a vicious circle: damage to the blood vessels of the retina leads to retinal neurosensory damage, and neurosensory damage promotes retinal capillary damage [2]. Furthermore, changes in neural activity within the retina induce changes in vascular blood flow and density, reinforcing the link between vasculature and neural tissue damage [23].

While there is limited research on the prevalence of DMI, it has been found in 46–77% of patients with DR, with higher prevalence in patients with more severe DR [1]. DMI is frequently associated with other complications of DR, most notably diabetic macular edema (DME). Retinal hypoxia caused by DMI results in upregulation of vascular endothelial growth factor, which can lead to edema [1, 4, 24]. Chronic edema tends to recur in the same locations [25], which may represent regions of focal capillary loss at the macula [25, 26]. However, the relationship between DMI and DME is unclear; some studies show that loss of visual acuity in DME may correlate with severity of macular ischemia in the eye, while other studies show no relationship [1, 27, 28].

As DMI is an important feature of DR progression and prognosis, establishing an accurate grading system is of great importance. Currently, there is no independent published system for grading DMI severity; however, DR is graded using the ETDRS grading system, and in some studies DMI has been graded as ETDRS-DMI using this system [1, 10, 29]. The ETDRS-DMI qualitatively grades DMI severity based on FAZ size using images acquired with fluorescein angiography (FA) [10]. However, some have questioned whether the ETDRS grading system remains relevant with the advent of higher-resolution imaging systems [30]. FA imaging is a 2D modality, and therefore cannot visualize the different retinal plexi, and leakage of fluorescein from the abnormal capillary bed can obscure the true FAZ boundary [31, 32].

Current Guidelines and Treatment

In addition to the lack of consensus on the definition of DMI, current guidelines for DR only recommend identification of DMI, rather than suggesting specific man-

agement options [33, 34]. Primarily, 2 imaging methods are used to detect DMI by assessing associated anatomical changes in the retina: optical coherence tomography (OCT) and FA [33, 34]. Historically, FA has been the primary diagnostic method for assessing macular disease [11]. Despite being the current gold standard, FA is invasive, costly, and time-consuming, taking roughly 10 min for framing acquisition; it also requires venipuncture [11, 35]. Furthermore, FA is associated with potentially severe medical complications for the patient [36]. OCT imaging only provides indirect evidence of DMI, but more recently, OCTA has been used to image the retinal microvasculature. Unlike FA, OCTA is a non-invasive method that can visualize blood vessels in 3D, thus showing retinal ischemia in greater detail [11, 34, 35]. OCTA devices use Fourier-domain and swept-source implementation to acquire high-resolution images in just 2–3 s [37, 38]. As an evolving technology, imaging artifacts remain a challenge when interpreting changes using OCTA [39–41]. However, software and hardware improvements are expected to resolve these challenges.

Despite its clinical burden, there are currently no approved therapies for the management of DMI [1, 2, 33, 34]. Furthermore, DMI may have a negative impact on the efficacy of treatment for other DR-associated complications, such as anti-vascular endothelial growth factor treatment for DME [42], highlighting the need for DMI-specific therapies.

Generating consensus on validated anatomical and/or visual endpoints that can be used in DMI is vital for the development of effective interventions [43].

Appropriate Endpoints for Use in Clinical Trials of DMI

Given the lack of literature available on DMI, identifying appropriate endpoints is challenging: very few, if any, clinical trials focus explicitly on DMI treatment. However, endpoints used in trials for other ocular diseases that seek to assess similar symptoms may be appropriate for use in DMI. Geographic atrophy (GA), an advanced form of age-related macular degeneration (AMD), may be a relevant comparator. Although DMI and GA are very different (affecting the retinal plexi and choriocapillaris, respectively), it can be argued that the signs of DMI follow a similar “patchy” visual loss pattern as observed in GA [44–46]. Therefore, endpoints that have been used in clinical trials of GA may be of interest, including those previously explored in the observational MACUSTAR

study, including microperimetry, low luminance acuity, and contrast sensitivity [47]. Similarly, endpoints discussed in the National Eye Institute (NEI)/US Food and Drug Administration (FDA) workshops for DR and AMD, such as the ETDRS letter chart and visual field modelling and analysis (VFMA) with microperimetry, might be of interest [43, 48].

Visual Function Endpoints

Best-Corrected Visual Acuity

Change in best-corrected visual acuity (BCVA) is the most commonly used endpoint to assess visual function in eye disease [13]. Some patients with DMI are reported to have BCVA as low as Snellen 20/400 [5]. BCVA is determined by the patient reading a letter chart at a distance; the letters decrease in size line by line [49]. The Snellen letter chart is a widely used method in clinical practice for the assessment of visual acuity [49]. However, due to a number of shortcomings, including poor reliability and repeatability, other measures of acuity such as the log-MAR-based ETDRS letter chart are preferable for clinical research [49, 50]; for US FDA registration trials, the ETDRS chart is required to assess visual outcomes [49]. The proportion of patients with a change of at least 15 letters in ETDRS BCVA relative to baseline is generally an accepted endpoint in clinical trials of retinal disease [48, 51].

Assessment of BCVA has been used as the primary endpoint in a number of clinical trials, including those assessing aflibercept, bevacizumab, and ranibizumab in DR [52–54] (Table 1). However, European regulators have noted the shortfalls of BCVA as a functional endpoint, highlighting the need for novel functional endpoints [48]. Measurement of BCVA with a letter chart often provides insufficient information on the actual function of the retina due to foveal sparing and parafoveal scotoma in GA [55, 56]. Despite its prevalence as an endpoint in retinal diseases, BCVA may not accurately capture the problems faced by those with DMI [1]. The mean change in number of letters from baseline at a particular time point, such as 12 months, is another possible endpoint; a change of 4–6 letters at 12 months may be clinically meaningful. However, this has not yet been used as an endpoint.

Low Luminance Vision Testing

Low luminance vision testing is designed to replicate the real-world problem of reduced vision in low illumina-

Table 1. Visual function endpoints

Endpoint	Test	Indication	Clinical trials	Current data on DMI	Suitable for DMI?
BCVA	Mean change in BCVA	DR, DME, AMD, IRD	NCT03904056 (DR) NCT03246152 (DME) NCT02432547 (DR) NCT03349801 (AMD) NCT00999609 (IRD) NCT03714308* (AMD) NCT00327470 (AMD)	Patients with moderate-to-severe DMI may have vision ranging from 20/63 to 20/80 [1], but some patients have been reported to reach 20/400 [5]	Yes
Low luminance visual acuity	Mean change from baseline	AMD	NCT03349801		Yes
Contrast sensitivity	Change in visual performance	RA, AMD	NCT02147171 (RA) NCT00327470 (AMD)		No
Microperimetry	Scotopic/mesopic sensitivity	AMD	NCT03349801	A value of 18 dB is considered to be typical retinal sensitivity [13]; one clinical study reported that retinal sensitivity ranges from 10.7 to 12.8 dB in patients with DMI [5]	Yes
mfERG	Change from baseline	GA	NCT03919019 NCT01258335		No
Dark adaptometry	Change in visual performance	RA	NCT02147171		No
Reading speed	Vision impairment in low luminance, mean change in reading speed	AMD	NCT03349801 NCT00327470		Yes

* Trial ongoing. AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; DME, diabetic macular edema; DMI, diabetic macular ischemia; DR, diabetic retinopathy; IRD, inherited retinal dystrophy; mfERG, multifocal electroretinography; RA, retinal aging.

tion. If DMI predominantly affects the DCP, it could reduce blood supply to the photoreceptors with resultant decrease in low luminance acuity. Many patients with early-stage DR have impaired rod photoreceptor function and impaired dark-adapted visual sensitivity [57]. As such, low-luminance vision testing may provide a more DMI-relevant measure of visual function than BCVA. Low luminance vision can be measured by placing a neutral density filter in front of the study eye and asking the participant to read an illuminated letter chart, or by inserting a mesopic filter in front of the letter chart [58, 59]. Low luminance deficit (the difference between normal and low luminance measures) is predictive of future visual acuity loss in GA [60]. However, it is important to note that low luminance visual acuity primarily tests foveal function and therefore may not detect changes as a result of DMI.

Contrast Sensitivity

Measures of contrast sensitivity are often used to assess visual function and may be better than measures of visual acuity at tracking the progressive loss of vision associated with eye diseases [61, 62]. Contrast sensitivity testing evolved because it was shown that those with AMD had poor contrast discrimination. Similarly, DR is associated with a loss of contrast sensitivity [63].

The Pelli-Robson test for contrast sensitivity comprises letters arranged into triplets, with 2 triplets per line; the intensity of the letter contrast decreases from one triplet to the next [64]. The Pelli-Robson chart is considered the gold-standard contrast sensitivity measurement but can be difficult to set up accurately and illuminate evenly, as well as to replicate at each visit [64]. Additionally, the range of measurements is small, making it difficult to assess subtle differences between patients.

Later, the Mars Letter Contrast Sensitivity Test was developed to address the shortcomings of the Pelli-Robson chart, such as the viewing distance and large, impractical chart size [65]. Unlike the Pelli-Robson chart, the intensity of the letter contrast decreases gradually over the course of the Mars chart, with the first letter displaying the highest contrast and the last letter displaying the lowest [64, 66]. Notably, patients with low vision tend to have better repeatability when tested with the Mars chart versus the Pelli-Robson chart [64].

More recently, the Ora variable contrast flicker test (Ora-VCF™) has been developed [67]. A diffuse light source is used to bleach most of the patient's cone photopigment, after which macular recovery is tracked using a variable contrast flickering stimulus [67]. The Ora-VCF has previously identified significant differences in visual performance between patients with and without GA, which were not picked up by the Pelli-Robson chart [68].

However, contrast sensitivity may be a less clinically meaningful measure of vision for patients and may not have sufficient sensitivity to detect changes in DMI. Furthermore, in our experience, it can be challenging to replicate the lighting conditions during each session, rendering accurate tracking of improvements difficult.

Microperimetry

Another possible endpoint for measuring visual function in DMI is microperimetry. Microperimetry combines fundus imaging with functional measures to detect retinal sensitivity by measuring the minimum light intensity that patients can perceive when spots of light stimulate specific areas of the retina and has the potential to map structure to function in the retina [2, 5, 13, 69, 70]. High-resolution maps of retinal sensitivity can be created with the use of VFMA, which allow for topographic correlation with other imaging modalities [71].

Microperimetry devices, such as Macular Integrity Assessment (MAIA), are US FDA approved [72], and microperimetry using the MAIA and Nidek systems can be adjusted for patients with poor vision by using an enhanced fixation light. Microperimetry can track the fundus even in patients who have unsteady or non-foveal fixation, which is vital for accurate measurements in patients with visual loss [69]. Although scotopic microperimetry can be quite time-consuming [73], mesopic microperimetry may be a reliable and quicker alternative that requires minimal dark adaptation [74, 75].

However, the availability of multiple microperimetry devices may make standardizing measurements between clinical centers a challenge. In addition, microperimetry

uses complex machinery and requires a trained specialist, which may not be practical in all clinical situations. Despite this, microperimetry remains an attractive endpoint for metrics of retinal sensitivity in DMI, especially if short, custom-made programs can be developed [76].

Multifocal Electroretinography

Multifocal electroretinography (mfERG) is one method of recording retinal responses to stimuli and may be appropriate as a measure of retinal function in DMI [2, 77]. During mfERG testing, patients view a fast sequence of images on a monitor while retinal response is recorded [77]. However, one previous study has indicated that mfERG amplitudes may not correlate with ischemic areas of the retina [78]. Furthermore, mfERG is time-consuming and requires a skilled technician. As such, mfERG is unlikely to be an ideal endpoint in clinical trials of DMI.

Dark Adaptometry

Similar to the Ora-VCF, dark adaptometry measures the length of time it takes for the retina to regain maximal sensitivity to low amounts of light after it has been exposed to bright light then returned to darkness [79–81]. Dark adaptometry has been used in patients with diabetic retinopathy, showing that rod recovery function degrades earlier than cone function [81]. Time to recovery of baseline visual sensitivity after a period of photostress has also been used as a measure of macular function in elderly subjects (mean age 75 years) [67].

Although dark adaptometry is a quantitative and reproducible measure of photoreceptor function, it is time-consuming (~30 min per eye) and is unlikely to isolate the impact of DMI on visual function; this means that it is not a particularly promising endpoint for clinical trials of DMI.

Reading Speed

Reading speed is a functionally important measure of visual ability from the patient's perspective. Tests of reading speed, such as MNREAD and International Reading Speed Texts (IReST), may provide practical visual function endpoints that measure the impact of DMI on daily tasks [82–84].

In MNREAD and IReST, patients read through text aloud while being timed by an investigator [82, 83]. MNREAD is a continuous text reading acuity chart; every 3 lines, the size of the text decreases by a certain font point number [83]. Reading acuity, maximum reading speed, and critical print size (smallest print that supports the maximum reading speed) can be determined via MN-

READ [83]. MNREAD is now available as an iPad application, making it accessible to a wider patient population [85]. IReST comprises 10 paragraphs of simple text (~132 words per paragraph) that are available in multiple languages. The simplicity of the words and equivalent availability in multiple languages makes IReST resilient against the confounding effects of education and nationality [82].

Tests of reading speed provide a functionally relevant endpoint that may be sensitive to local disturbances in vision, such as those caused by DMI. Although there are some shortcomings for use in certain patient populations (e.g., those who are illiterate or for whom an equivalent translation has not been developed) and in the test duration, they are a meaningful measure of improvement from a patient perspective. IReST may represent a more realistic daily reading situation than MNREAD and has the advantage of not being limited to English-speaking participants.

Visual Function Endpoints for DMI

Currently, BCVA is an established and regulator-approved endpoint; however, it may not have adequate sensitivity to detect change in patients with DMI. As such, including other measures of visual function is important in trials of DMI. Microperimetry measures of retinal sensitivity may be promising as a functional endpoint in DMI and may detect changes that are too subtle to detect using BCVA. Developing a suitable, short, and validated microperimetry protocol for use in patients with DMI will be a vital first step prior to the conduct of any clinical trial. Tests of reading speed and low luminance BCVA may provide insight into how improvements in visual function result in better functional vision for patients with DMI. Furthermore, reading tests may be more sensitive to local visual disturbance resulting from scotoma/FAZ disruption than BCVA. However, DMI is unlikely to cause deep scotomas, and thus reading speed may not reveal any significant changes as a result of treatment over the course of a typical 12-month clinical trial. Crucially, measures of visual function must be correlated with appropriate anatomical measures to provide a complete picture of retinal changes over time.

Anatomical Endpoints

DMI is primarily identified by anatomical hallmarks [34]; it follows that endpoints focusing on changes in retinal anatomy may be useful in clinical trials. FA and OCTA are US FDA-approved methods for acquiring anatomical measurements of the retina. At present, 4 OCTA

devices have been approved by the US FDA [38]. Image processing software (e.g., ImageJ [Fiji] and MATLAB) can be used to quantify features seen with OCTA, such as the level of macular non-perfusion [18].

Optical Coherence Tomography Angiography

OCTA is a relatively novel method for assessing visual disease; little is known about which OCTA metric is most likely to be associated with visual or functional loss. Commercial devices that can use wide-field OCTA patterns are now available [86] and may be critical in characterizing the full extent of DMI pathology. As a relatively new technology, it is worth noting that there is no consensus on terminology for OCTA metrics across different retinal diseases; however, there is growing interest in establishing such a consensus nomenclature [87].

A number of issues with OCTA and OCT need to be resolved before their metrics can be incorporated as endpoints in clinical trials. These include the variability of measurements from the multiple instruments available (each with their own segmentation software and associated errors), problematic image artifacts typically caused by patient eye movements, and failure of the operator to focus and center the scan [39–41]. At present, OCTA is more prone to artifacts than OCT [88]: for example, segmentation failure may occur during image analysis, particularly when retinal pathology is present [40]. Furthermore, as OCTA image reconstruction methods are designed to enhance retinal vasculature, they may also enhance background elements that by chance share image features with genuine blood vessels [89], confounding DMI-relevant measures of perfusion. The formation of cataracts and edema in particular can have a substantial effect on OCTA measurements of retinal blood flow [90]. As the technology develops, it will be critical to develop algorithms that can account for the specific pathology of DMI during image segmentation and analysis.

Several OCTA metrics may be appropriate anatomical endpoints for DMI. Change in FAZ size is one potential endpoint because increased FAZ size is associated with DMI [1, 21, 91]. One recent publication has indicated that larger FAZ area as measured by OCTA predicts worse visual outcomes in patients with DR [92]. Change in the FAZ has been used as an endpoint in clinical trials of bevacizumab and pegaptanib in ischemic DME and ischemic maculopathy (Table 2) [53, 93]. Notably, measures of FAZ by OCTA are robust even in the presence of cataracts [90], which is important given that the risk of cataracts and DR increase with age [94, 95]. Measurements of vessel density and/or capillary perfusion may also be insight-

Table 2. Anatomical endpoints

Endpoint	Test	Indication	Clinical trials	Current data on DMI	Suitable for DMI?
FAZ size	Change in FAZ area and/or perimeter by OCTA	iDME, IM	NCT01175070 (iDME) NCT03246152 (IM)	The size of the FAZ can increase by up to 0.94 mm in DMI [2] or by 5–10% of the baseline FAZ area per year [21]	Yes
Vessel density/perfusion	Capillary perfusion/density by OCTA	RI, DME, DR, IM	NCT04038125 (DME, RI) NCT03246152 (DME, IM)		Yes
Conversion to DME/PDR	OCTA metrics of decreased vessel density in the SCP		None as of yet		Yes
Retinal thinning	Mean change from baseline by OCT	AMD, DME	NCT03349801 (AMD) NCT04116398* (DME) NCT03714308* (AMD)		Maybe
Area of ellipsoid zone defects	Rate of change in ellipsoid area defect measured by OCT	MT	NCT03316300		Yes (in phase 3)
DRIL	Presence	DME	NCT04116398*		Yes
Adaptive optics	High-resolution imaging	AMD, GA	NCT01866371*		No (yes for exploratory PoCP)

* Trial ongoing. AMD, age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy; DRIL, disorganization of retinal inner layers; EMA, European Medicines Agency; FAZ, foveal avascular zone; iDME, ischemic DME; IM, ischemic maculopathy; GA, geographic atrophy; mfERG, multifocal electroretinography; MT, macular telangiectasia; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PDR, proliferative diabetic retinopathy; PoCP, proof of clinical concept; RI, retinal ischemia; SCP, superficial capillary plexus.

ful endpoints in DMI trials. Although such measures are often collected in current trials, they are not typically assessed as main outcomes, and it remains unclear whether these metrics are predictive of functional loss. Decreased capillary perfusion and vessel density in the SCP, DCP, and choriocapillaris are linked to DMI [10–14]. Capillary perfusion has been used as an endpoint in clinical trials of bevacizumab and the dexamethasone intravitreal implant in DR and ischemic maculopathy (Table 2) [53, 96]. Retinal capillary closure quantified by OCTA has recently been shown to identify and predict the severity progression of DR and may be considered as a proxy measurement of DMI extent [97, 98]. Finally, some evidence suggests that DMI may be a precursor of DME/proliferative diabetic retinopathy (PDR); OCTA metrics of decreased vessel density in the SCP can predict conversion to DME [35], while reduced measures of vessel density in the DCP can predict conversion to PDR [35]. Quantifying treatment-related delay in these conversions using OCTA may be a meaningful endpoint in clinical trials of DMI.

Optical Coherence Tomography

In addition to OCTA, OCT metrics could serve as useful endpoints. Retinal thickness has been used to assess disease in patients with DR [52, 93]. A reduction in inner

retinal thickness, as measured by OCT, may be an indicator of DMI in early-stage DR [99]. However, evaluating retinal thickness in the context of DMI is challenging because anatomical changes progress slowly [4, 20, 100]. In addition, it should be noted that common DR comorbidities, such as DME, can cause misidentification, segmentation errors, and artifacts in OCT imaging [101], which could interfere with imaging of DMI. This, alongside the slow progression of neurodegeneration, indicates that retinal thickness may not be a reliable anatomical endpoint for patients with DMI. Another possible OCT metric is the detection of change in the ellipsoid zone (EZ). EZ defects or “breaks” are believed to be the product of photoreceptor loss [102], and OCT measurements of EZ defects correlate with changes in retinal sensitivity measured by microperimetry [103, 104]. Rate of change in the EZ area has been used as a primary endpoint in phase 3 clinical trials of macular telangiectasia [105], an ocular disease that can involve ischemia [106]; thus, it may be appropriate as an endpoint in advanced clinical trials of DMI.

Disorganization of the Retinal Inner Layers

Disorganization of the retinal inner layers (DRIL) is defined as the inability to identify boundaries between the ganglion cell-inner plexiform layer complex, inner nucle-

ar layer, and outer plexiform layer [107]. The presence of DRIL may be a proxy for the severity of DMI in the retina and thus could be a useful endpoint. DRIL measurements using spectral-domain OCT have been suggested as potential biomarkers of visual recovery in eyes with center-involved DME [42]. Although DRIL is associated with retinal capillary non-perfusion (i.e., DMI), the absence of DRIL does not rule out the presence of DMI [17, 107]. However, the grading of DRIL may be subjective, limiting its use as a clinical trial endpoint.

Adaptive Optics

Adaptive optics (AO) laser scanning ophthalmology is a non-invasive imaging technique that has been used to measure retinal blood flow and velocity in patients with DR [108, 109]. AO can visualize individual rods and cones, enabling detailed assessment of retinal structure [110]. The Imagine Eyes rtx1TM AO retinal camera has been able to identify microscopic hemorrhages, edematous cyst walls, modified arteriolar structure, and microaneurysms in patients with DR [111–113] and those with pre-diabetic conditions [114]. However, at present, there are only 2 commercially available AO machines (Imagine Eyes rtx1 and Boston Micromachines ApaerosTM Retinal Imaging System [115, 116]), which may limit its widespread use in clinical trials. In addition, AO is extremely time-consuming (~1 h), and the currently available software for quantification is only used in research. Although AO may be a promising future endpoint, it is not appropriate in its current form. However, the prevention or reduction of further photoreceptor loss measured by AO could be used as an endpoint to establish efficacy in a proof-of-clinical principle study.

Anatomical Endpoints for DMI

At present, OCTA appears to be the most precise, quantifiable, and objective method for detecting anatomical features linked with visual loss and DMI. The image quality and reliable range of metrics OCTA provides will be invaluable in the assessment of outcomes for clinical trials of DMI. Although the most appropriate metric is unknown, potential OCTA endpoints include the size of the FAZ within the SCP or DCP, and measures of vessel density and perfusion. Future hardware and software improvements are expected, as there are several companies developing OCTA devices. In addition, the presence of DRIL and conversion to PDR or DME are worth exploring further as endpoints. Furthermore, short-term anatomical endpoints that predict long-term irreversible visual function loss, but can be measured over the time

course of a typical clinical trial (analogous to changes in GA lesion size that are a marker of future visual loss [117]), should be considered. Such predictive endpoints could be used to establish a 1- or 2-step progression/regression model of DR/DMI grading; similar systems have been shown to strongly predict PDR progression within DR ($p < 0.0001$) [118].

Patient-Reported Outcome Endpoints

Patient-reported outcomes (PROs) that assess patients' vision-related quality of life are increasingly used in clinical trials (Table 3). PROs are supported by patient advocacy groups and focus on different aspects of visual loss, from functional effects to emotional impact of visual loss.

EuroQoL 5 Dimensions

A range of surveys are available, but the most general and widely used health-related option is the EuroQoL 5 dimensions (EQ-5D). The EQ-5D is a standardized outcome measure across 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), designed for self-completion [119]. Although the EQ-5D captures a wide range of health-related endpoints, it may not be specific enough for patients with DMI.

25-Item National Eye Institute Visual Function Questionnaire

A more specific and commonly used survey is the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which assesses the influence of visual impairment on health-related quality of life [120]. Scores are assessed using 25 questions across 3 areas (general health and vision, difficulty with activities, and responses to vision problems). Higher scores in the NEI-VFQ-25 equate to better function and quality of life [121]; an increase in score relative to baseline indicates improvement in the relevant area.

Impact of Vision Impairment Questionnaire

The Impact of Vision Impairment Questionnaire (IVI) is a 28-item questionnaire (now available digitally) that measures the impact of vision impairment on vision-related quality of life [122]. It comprises 3 subscales: "reading and accessing information," "mobility and independence," and "emotional wellbeing." A decrease in score relative to baseline indicates improvement in the relevant subscale.

Table 3. PRO endpoints

Endpoint	Test	Indication	Clinical trials	Current data on DMI	Suitable for DMI?
EQ-5D	Change from baseline	AMD	NCT03714308* NCT00327470		No
NEI-VFQ-25	Change from baseline	AMD (GA), AMD	NCT01229215 (GA) NCT03714308* (AMD) NCT00327470 (AMD)		Yes
IVI	Change from baseline at 1 year	AMD	NCT03046485†		Yes
FRI index	Not an endpoint but recorded	AMD (GA)	NCT01229215		Maybe

* Trial ongoing, † Trial withdrawn due to meeting primary endpoint early. AMD, age-related macular degeneration; DMI, diabetic macular ischemia; EQ-5D, EuroQoL 5 dimensions; FRI, Functional Reading Independence; GA, geographic atrophy; IVI, intravitreal injection; NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; PRO, patient-reported outcome.

Functional Reading Independence

Finally, the Functional Reading Independence (FRI) Index provides insight into a very common visual task (reading) that may also link with more specific measures of visual function, such as MNREAD. The FRI is a 7-item interview-based questionnaire, focusing on daily reading activities under different circumstances (e.g., books, cheque-writing, food labels, television). A higher score indicates a greater level of independence [123]. The FRI has been used as an outcome measure in a clinical trial of GA [124], which may position it as a useful endpoint in DMI.

PRO Endpoints for DMI

PROs may help to highlight statistically significant results that are also clinically meaningful and to demonstrate non-inferiority for interventions that differ in cost [51, 125]. Generally speaking, PRO questionnaires are easy to administer, providing a low-cost measure of changes in patient quality of life. The use of several DMI-relevant PRO endpoints, such as the FRI and NEI-VFQ-25, may give a broader view of trial outcomes.

Conclusions

DMI is a key risk factor for profound visual loss in patients with DR. Despite its substantial impact on patient quality of life and independence, there are currently no approved treatments for DMI. The paucity of literature and lack of consensus on DMI outline how crucial it is to develop a robust and generally agreed definition and severity grading system that can be used consistently in

clinical trials. Future studies on the natural history and progression of DMI will help to delineate its relationship with other DR complications, such as DME, DRIL, and PDR. A thorough understanding of DMI will build understanding of how patient demographics and comorbidities (such as hypertension, age, and cardiovascular problems) can affect clinical trial endpoints. In addition, such research would contribute towards the consensus definition of DMI that is currently lacking in clinical practice and research. Establishing a new classification system for DMI based on functional correlations (e.g., retinal threshold sensitivity using microperimetry), with structural features detected by OCT and OCTA, will be central to moving forward.

Table 4 summarizes the advantages and disadvantages of the endpoints discussed in this review. At present, OCTA is the most precise and quantifiable method for detecting anatomical features linked with visual loss and DMI. Using OCTA to examine longitudinal changes in anatomical features of DMI, such as the FAZ size, will provide greater insight into the general progression and prognosis of the disease. Although there are several technical aspects that must be resolved to yield the most reliable data for clinical trials, including comparability between instruments and studies, and the impact of image artifacts, OCTA is a promising imaging method with a variety of potentially DMI-relevant endpoints. Promising endpoints to predict functional visual outcomes in trials could include the stabilization of FAZ size and SCP/DCP vessel density.

OCTA does not provide any functional information, which limits the conclusions that can be drawn from metrics. Therefore, it makes sense to include several func-

Table 4. Advantages and disadvantages of discussed endpoints

Endpoint	Test	Advantages	Disadvantages
<i>Visual function endpoints</i>			
BCVA	Mean change in BCVA	Commonly used, regulator-approved, validated in other visual diseases	May not be sensitivity to changes in DMI, may not detect change over short (e.g., 12-month) trial periods
Low luminance visual acuity	Mean change from baseline and difference between normal and low luminance (low luminance deficit)	Low luminance vision may be impaired in patients with early DR	Primarily tests foveal function
Contrast sensitivity	Change in visual performance	May be suitable for tracking progressive loss of vision	Measurement range is small, some tests may be difficult to set up, may be a less clinically meaningful measure of vision, may not be sensitive enough to detect changes from DMI
Microperimetry	Scotopic/mesopic sensitivity	High resolution and sensitivity, can be mapped to other imaging modalities, can be adjusted for use with patients who have poor vision or fixation	Scotopic microperimetry is time-consuming, requires expertise to administer, and can be tiring for the patient
mERG	Change from baseline	Provides a measure of retinal function	mERG may not correlate with ischemic areas of the retina, is time-consuming, and requires a skilled technician
Dark adaptometry	Change in visual performance	Has been used in DR populations previously	Time-consuming and unlikely to isolate the impact of DMI on vision
Reading speed	Mean change in reading speed	Functionally important measure from a patient's perspective, sensitive to local disturbances in vision	Cannot be used in illiterate populations, unlikely to detect change over the course of a 12-month trial
<i>Anatomical endpoints</i>			
FAZ size	Change in FAZ area and/or perimeter by OCTA	Increased FAZ is associated with DMI, has been used in clinical trials, robust even in the presence of cataracts, perimeter irregularities can be seen as DR progresses	FAZ area is very variable even in unaffected populations
Vessel density/perfusion	Capillary perfusion/density by OCTA	Reduced vessel density and perfusion are associated with DMI, has been used in clinical trials	Unclear which metrics are predictive of visual loss
Conversion to DME/PDR	OCTA metrics of decreased vessel density in the SCP	Some evidence suggests DMI may be a precursor to DME/PDR	Limited information available at present, not used in any clinical trials
Retinal thinning	Mean change from baseline by OCT	May be an indicator of DMI in early-stage DR	Unlikely to detect change over short time frame (e.g., 12 months)
Area of ellipsoid zone defects	Rate of change in ellipsoid area defect measured by OCT	Has been used as an endpoint in previous trials of ocular disease, is associated with photoreceptor loss, correlates with microperimetry measures	Has not been studied in DMI
DRIL	Presence	DRIL may be a proxy for DMI severity	Grading may be subjective, limited information on the relationship between DRIL and DMI
Adaptive optics	High-resolution imaging	Very high-resolution imaging of retinal structure	Few commercially available machines, very time-consuming, current software only used in research
<i>PRO endpoints</i>			
EQ-5D	Change from baseline	Widely used measure of health-related outcomes	Not specific to visual diseases, relies on patient report
NEI-VFQ-25	Change from baseline	Commonly used, vision specific	Relies on patient report
IVI	Change IVI from baseline at 1 year	Vision specific	Relies on patient report
FRI index	Not an endpoint, but recorded	Functionally relevant, vision specific, used in clinical trials of GA	Relies on patient report

BCVA, best-corrected visual acuity; DME, diabetic macular edema; DMI, diabetic macular ischaemia; DR, diabetic retinopathy; EQ-5D, EuroQoL-5 dimensions; FAZ, foveal avascular zone; FRI, functional reading independence; GA, geographic atrophy; IVI, intravitreal injection; mERG, multifocal electroretinogram; NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PDR, proliferative diabetic retinopathy; PRO, patient-reported outcome; SCP, superficial capillary plexus.

tional measurements as a complement, with a view to correlating functional and anatomical changes. Microperimetry is an attractive functional endpoint for DMI; measurement of change in retinal sensitivity could be a DMI-appropriate endpoint that is sensitive to subtle treatment-related changes, while also having adequate resolution to correlate with high-resolution anatomical imaging methods such as OCTA. In addition, BCVA remains a gold standard, regulator-approved measure of visual function and should be considered as an endpoint in DMI. Tests of reading speed and low-luminance visual acuity could also be considered to provide a greater breadth of information. In addition to anatomical and functional endpoints, PROs such as the NEI-VFQ-25 and IVI may provide useful context for clinical outcomes.

In summary, research confirming suitable endpoints for DMI is needed; identifying a short-term anatomical endpoint that can predict future irreversible visual loss should be a focus of future work. Furthermore, establishing how measures of visual function and PROs map onto the anatomical changes that occur in DMI, and as a result of its treatment, are vital to better understand the disease. The personal views and collated data in this paper are intended as a starting point to guide discussion in the retinal disease community. We recommend that formal study groups comprising clinicians, basic scientists, imaging experts, pharmaceutical and regulatory body representatives be convened to improve understanding of DMI.

References

- 1 Sim DA, Keane PA, Zarranz-Ventura J, Fung S, Powner MB, Platteau E, et al. The effects of macular ischemia on visual acuity in diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2013 Mar;54(3):2353–60.
- 2 Usman M. An overview of our current understanding of diabetic macular ischemia (DMI). *Cureus*. 2018 Jul;10(7):e3064.
- 3 Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015 Jan;133(1):45–50.
- 4 Sim DA, Keane PA, Fung S, Karampelas M, Sadda SR, Fruttiger M, et al. Quantitative analysis of diabetic macular ischemia using optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2014 Jan;55(1):417–23.
- 5 Pereira F, Godoy BR, Maia M, Regatieri CV. Microperimetry and OCT angiography evaluation of patients with ischemic diabetic macular edema treated with monthly intravitreal bevacizumab: a pilot study. *Int J Retina Vitreous*. 2019 Sep;5(1):24.
- 6 Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. *ISRN Ophthalmol*. 2013 Jan;2013:343560.
- 7 Yanoff M, Fine BS, Brucker AJ, Eagle RC Jr. Pathology of human cystoid macular edema. *Surv Ophthalmol*. 1984 May;28 Suppl:505–11.
- 8 Ljubimov AV, Burgeson RE, Butkowski RJ, Couchman JR, Zardi L, Ninomiya Y, et al. Basement membrane abnormalities in human eyes with diabetic retinopathy. *J Histochem Cytochem*. 1996 Dec;44(12):1469–79.
- 9 Kusahara S, Fukushima Y, Ogura S, Inoue N, Uemura A. Pathophysiology of diabetic retinopathy: the old and the new. *Diabetes Metab J*. 2018 Oct;42(5):364–76.
- 10 Bradley PD, Sim DA, Keane PA, Cardoso J, Agrawal R, Tufail A, et al. The evaluation of diabetic macular ischemia using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016 Feb;57(2):626–31.
- 11 de Barros Garcia JM, Isaac DL, Avila M. Diabetic retinopathy and OCT angiography: clinical findings and future perspectives. *Int J Retina Vitreous*. 2017 Mar;3(1):14.
- 12 Gildea D. The diagnostic value of optical coherence tomography angiography in diabetic retinopathy: a systematic review. *Int Ophthalmol*. 2019 Oct;39(10):2413–33.
- 13 Scarinci F, Varano M, Parravano M. Retinal sensitivity loss correlates with deep capillary plexus impairment in diabetic macular ischemia. *J Ophthalmol*. 2019 Oct;2019:7589841.
- 14 Abdelshafy M, Abdelshafy A. Functional and structural changes of the retinal nerve fiber layer and ganglion cell complex in heavy smokers. *Clin Ophthalmol*. 2020 Feb;14:397–404.
- 15 Scarinci F, Nesper PL, Fawzi AA. Deep retinal capillary nonperfusion is associated with photoreceptor disruption in diabetic macular ischemia. *Am J Ophthalmol*. 2016 Aug;168:129–38.
- 16 Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JL, et al. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. *Ophthalmology*. 2017 Feb;124(2):235–44.

Acknowledgment

Medical writing support was provided by Imogen Allred, DPhil, and Tom Priddle, DPhil, of OPEN Health Communications (London, UK), funded by Boehringer Ingelheim.

Conflict of Interest Statement

C.M.G.C. declares funding from a Biomedical Research Council Singapore grant: SPF2014/002, and National Medical Research Council Open Fund Large Collaborative Grant: NMRC/LCG/004/2018. B.F. and P.S. have no conflicts of interest to declare. V.C. is an employee of Boehringer Ingelheim. E.P. is an employee of Boehringer Ingelheim. S.S. has received research grants from Boehringer Ingelheim, Novartis, Bayer, Allergan, Roche, Opthea, and Optos, and has attended advisory board meetings of Boehringer Ingelheim, Novartis, Bayer, Allergan, Roche, Opthea, Optos, Oculus, Oxurion, and Apellis.

Funding Sources

Funding was provided by Boehringer Ingelheim.

Author Contributions

All authors were involved in the conceptual design of the manuscript, drafting, and development, and agreement to publish.

- 17 Moussa M, Leila M, Bessa AS, Lolah M, Abou Shousha M, El Hennawi HM, et al. Grading of macular perfusion in retinal vein occlusion using en-face swept-source optical coherence tomography angiography: a retrospective observational case series. *BMC Ophthalmol*. 2019 Jun;19(1):127.
- 18 Garcia JM, Lima TT, Louzada RN, Rassi AT, Isaac DL, Avila M. Diabetic macular ischemia diagnosis: comparison between optical coherence tomography angiography and fluorescein angiography. *J Ophthalmol*. 2016;2016:3989310.
- 19 Provis JM, Dubis AM, Maddess T, Carroll J. Adaptation of the central retina for high acuity vision: cones, the fovea and the avascular zone. *Prog Retin Eye Res*. 2013 Jul;35:63–81.
- 20 Sim DA, Keane PA, Zarranz-Ventura J, Bunce CV, Fruttiger M, Patel PJ, et al. Predictive factors for the progression of diabetic macular ischemia. *Am J Ophthalmol*. 2013 Oct;156(4):684–92.
- 21 Balaratnasingam C, Inoue M, Ahn S, McCann J, Dhrami-Gavazi E, Yannuzzi LA, et al. Visual acuity is correlated with the area of the foveal avascular zone in diabetic retinopathy and retinal vein occlusion. *Ophthalmology*. 2016 Nov;123(11):2352–67.
- 22 Hsieh YT, Alam MN, Le D, Hsiao CC, Yang CH, Chao DL, et al. OCT angiography biomarkers for predicting visual outcomes after ranibizumab treatment for diabetic macular edema. *Ophthalmol Retina*. 2019 Oct;3(10):826–34.
- 23 Kern TS. Interrelationships between the retinal neuroglia and vasculature in diabetes. *Diabetes Metab J*. 2014 Jun;38(3):163–70.
- 24 Stone J, Itin A, Alon T, Pe'er J, Gnessin H, Chan-Ling T, et al. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. *J Neurosci*. 1995 Jul;15(7 Pt 1):4738–47.
- 25 Spaide RF. Retinal vascular cystoid macular edema: review and new theory. *Retina*. 2016 Oct;36(10):1823–42.
- 26 Jang JH, Kim YC, Shin JP. Correlation between macular edema recurrence and macular capillary network destruction in branch retinal vein occlusion. *BMC Ophthalmol*. 2020 Aug;20(1):341.
- 27 Fan W, Uji A, Wang K, Falavarjani KG, Wykoff CC, Brown DM, et al. Severity of diabetic macular edema correlates with retinal vascular bed area on ultra-wide field fluorescein angiography: DAVE study. *Retina*. 2020 Jun;40(6):1029–37.
- 28 Hsiao CC, Yang CM, Yang CH, Ho TC, Lai TT, Hsieh YT. Correlations between visual acuity and macular microvasculature quantified with optical coherence tomography angiography in diabetic macular oedema. *Eye (Lond)*. 2020 Mar;34(3):544–52.
- 29 Group E; Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airle House classification. ETDRS report number 10. *Ophthalmology*. 1991 May;98(5 Suppl):786–806.
- 30 Solomon SD, Goldberg MF. ETDRS grading of diabetic retinopathy: still the gold standard? *Ophthalmic Res*. 2019;62(4):190–5.
- 31 Hwang TS, Jia Y, Gao SS, Bailey ST, Lauer AK, Flaxel CJ, et al. Optical coherence tomography angiography features of diabetic retinopathy. *Retina*. 2015 Nov;35(11):2371–6.
- 32 Jia Y, Bailey ST, Hwang TS, McClintic SM, Gao SS, Pennesi ME, et al. Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. *Proc Natl Acad Sci USA*. 2015 May;112(18):E2395–402.
- 33 Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on diabetic eye care: the International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology*. 2018 Oct;125(10):1608–22.
- 34 Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, et al. Diabetic retinopathy preferred practice pattern(R). *Ophthalmology*. 2020 Jan;127(1):66–P145.
- 35 Sun Z, Tang F, Wong R, Lok J, Szeto SK, Chan JC, et al. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: a prospective study. *Ophthalmology*. 2019 Dec;126(12):1675–84.
- 36 Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W, et al. Fluorescein angiography complication survey. *Ophthalmology*. 1986 May;93(5):611–7.
- 37 Potsaid B, Baumann B, Huang D, Barry S, Cable AE, Schuman JS, et al. Ultrahigh speed 1050nm swept source/Fourier domain OCT retinal and anterior segment imaging at 100,000 to 400,000 axial scans per second. *Opt Express*. 2010 Sep;18(19):20029–48.
- 38 Ong SS, Patel TP, Singh MS. Optical coherence tomography angiography imaging in inherited retinal diseases. *J Clin Med*. 2019 Nov;8(12):E2078.
- 39 Gao SS, Jia Y, Zhang M, Su JP, Liu G, Hwang TS, et al. Optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016 Jul;57(9):OCT27–36.
- 40 Bhende M, Shetty S, Parthasarathy MK, Ramya S. Optical coherence tomography: a guide to interpretation of common macular diseases. *Indian J Ophthalmol*. 2018 Jan;66(1):20–35.
- 41 Onishi AC, Fawzi AA. An overview of optical coherence tomography angiography and the posterior pole. *Ther Adv Ophthalmol*. 2019 Apr;11:2515841419840249.
- 42 Babiuch AS, Han M, Conti FF, Wai K, Silva FQ, Singh RP. Association of disorganization of retinal inner layers with visual acuity response to anti-vascular endothelial growth factor therapy for macular edema secondary to retinal vein occlusion. *JAMA Ophthalmol*. 2019 Jan;137(1):38–46.
- 43 Nair P, Aiello LP, Gardner TW, Jampol LM, Ferris FL 3rd. Report from the NEI/FDA diabetic retinopathy clinical trial design and endpoints workshop. *Invest Ophthalmol Vis Sci*. 2016 Oct;57(13):5127–42.
- 44 Holz FG, Bellman C, Staudt S, Schütt F, Völcker HE. Fundus autofluorescence and development of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2001 Apr;42(5):1051–6.
- 45 Lindblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris FL 3rd, Klein ML, et al. Age-Related Eye Disease Study Research Group. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009 Sep;127(9):1168–74.
- 46 Prasad S, Galetta SL. Approach to the patient with acute monocular visual loss. *Neurol Clin Pract*. 2012 Mar;2(1):14–23.
- 47 Finger RP, Schmitz-Valckenberg S, Schmid M, Rubin GS, Dunbar H, Tufail A, et al. on behalf of the MACUSTAR consortium. MACUSTAR: development and clinical validation of functional, structural, and patient-reported endpoints in intermediate age-related macular degeneration. *Ophthalmologica*. 2019;241(2):61–72.
- 48 Csaky K, Ferris F 3rd, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA Endpoints workshop on age-related macular degeneration and inherited retinal diseases. *Invest Ophthalmol Vis Sci*. 2017 Jul;58(9):3456–63.
- 49 Kaiser PK. Prospective evaluation of visual acuity assessment: a comparison of Snellen versus ETDRS charts in clinical practice (An AOS Thesis). *Trans Am Ophthalmol Soc*. 2009 Dec;107:311–24.
- 50 Elliott DB. The good (logMAR), the bad (Snellen) and the ugly (BCVA, number of letters read) of visual acuity measurement. *Ophthalmic Physiol Opt*. 2016 Jul;36(4):355–8.
- 51 Varner P. Ophthalmic pharmaceutical clinical trials: design considerations. *Clin Invest*. 2015;5(5):457–75.
- 52 NCT03904056. ETDRS panretinal photocoagulation (PRP) combined with intravitreal ranibizumab (IVR) versus retinal photocoagulation targeted to ischemic retina combined with IVR for the treatment of proliferative diabetic retinopathy. Available at <https://clinicaltrials.gov/ct2/show/NCT03904056>. Accessed 5th May 2020.
- 53 NCT03246152. Evaluation of the effect of repeated intravitreal injections of anti-VEGF on macular perfusion in diabetic patients using optical coherence tomography angiography. Available at <https://clinicaltrials.gov/ct2/show/NCT03246152>. Accessed 5th May 2020.
- 54 NCT02432547. A phase IV randomised clinical trial of laser therapy for peripheral retinal ischaemia combined with intravitreal aflibercept (eylea®) versus intravitreal aflibercept monotherapy for diabetic macular oedema. Available at <https://clinicaltrials.gov/ct2/show/NCT02432547>. Accessed 5th May 2020.

- 55 Sadda SR, Chakravarthy U, Birch DG, Staurenghi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016 Oct;36(10):1806–22.
- 56 Csaky KG, Patel PJ, Sepah YJ, Birch DG, Do DV, Ip MS, et al. Microperimetry for geographic atrophy secondary to age-related macular degeneration. *Surv Ophthalmol*. 2019 May - Jun;64(3):353–64.
- 57 Jackson GR, Scott IU, Quillen DA, Walter LE, Gardner TW. Inner retinal visual dysfunction is a sensitive marker of non-proliferative diabetic retinopathy. *Br J Ophthalmol*. 2012 May;96(5):699–703.
- 58 Do DV, Nguyen QD, Mostafa SH, Bressler SB. Evaluation of visual acuity measurements with standard luminance compared with low luminance in eyes with geographic atrophy from age-related macular degeneration. *Invest Ophthalmol Visual Sci*. 2015;56:2821.
- 59 Brodnar Z, Shields AR, Dobrota S, Do DV. Low luminance deficits in retinal disease. *Invest Ophthalmol Vis Sci*. 2018;59:3424.
- 60 Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008 Sep;115(9):1480–8, 1488.e1–2.
- 61 Della Sala S, Bertoni G, Somazzi L, Stubbe F, Wilkins AJ. Impaired contrast sensitivity in diabetic patients with and without retinopathy: a new technique for rapid assessment. *Br J Ophthalmol*. 1985 Feb;69(2):136–42.
- 62 Dorr M, Lesmes LA, Lu ZL, Bex PJ. Rapid and reliable assessment of the contrast sensitivity function on an iPad. *Invest Ophthalmol Vis Sci*. 2013 Nov;54(12):7266–73.
- 63 Stavrou EP, Wood JM. Letter contrast sensitivity changes in early diabetic retinopathy. *Clin Exp Optom*. 2003 May;86(3):152–6.
- 64 Thayaparan K, Crossland MD, Rubin GS. Clinical assessment of two new contrast sensitivity charts. *Br J Ophthalmol*. 2007 Jun;91(6):749–52.
- 65 Arditi A. Improving the design of the letter contrast sensitivity test. *Invest Ophthalmol Vis Sci*. 2005 Jun;46(6):2225–9.
- 66 Latham K. The Mars contrast sensitivity chart. Available at: <http://assets.markallengroup.com/article-images/image-library/147/uploads/importedimages/mars.pdf>. Accessed July 13 2020. The Optician. 2007.
- 67 Rodriguez JD, Wallstrom G, Narayanan D, Welch D, Abelson MB. An alternative psychophysical diagnostic indicator of the aging eye. *J Ophthalmol*. 2019 Nov;2019:2036192.
- 68 Ora-VCF Contrast test: Dry AMD Model. Available at: <https://www.oraclinical.com/our-services/therapeutic-areas/posterior-segment/ora-vcf-contrast-test/>. Accessed 13th July 2020.
- 69 Acton JH, Greenstein VC. Fundus-driven perimetry (micropertimetry) compared to conventional static automated perimetry: similarities, differences, and clinical applications. *Can J Ophthalmol*. 2013 Oct;48(5):358–63.
- 70 Tsai ASH, Gan ATL, Ting DSW, Wong CW, Teo KYC, Tan ACS, et al. Diabetic macular ischemia: correlation of retinal vasculature changes by optical coherence tomography angiography and functional deficit. *Retina*. 2020 Nov;40(11):2184–90.
- 71 Della Volpe-Waizel M, Traber GL, Maloca P, Zinkernagel M, Schmidt-Erfurth U, Rubin G, et al. New technologies for outcome measures in retinal disease: review from the European Vision Institute special interest focus group. *Ophthalmic Res*. 2020;63(2):77–87.
- 72 Businesswire. <https://www.businesswire.com/news/home/20140604005144/en/CenterVue-Announces-FDA-Clearance-Generation-Macular-Integrity>. Accessed September 2020.
- 73 Welker SG, Pfau M, Heinemann M, Schmitz-Valckenberg S, Holz FG, Finger RP. Retest reliability of mesopic and dark-adapted microperimetry in patients with intermediate age-related macular degeneration and age-matched controls. *Invest Ophthalmol Vis Sci*. 2018 Mar;59(4):AMD152–9.
- 74 Corvi F, Pellegrini M, Belotti M, Bianchi C, Staurenghi G. Scotopic and fast mesopic microperimetry in eyes with drusen and reticular pseudodrusen. *Retina*. 2019 Dec;39(12):2378–83.
- 75 Han RC, Gray JM, Han J, Maclaren RE, Jolly JK. Optimisation of dark adaptation time required for mesopic microperimetry. *Br J Ophthalmol*. 2019 Aug;103(8):1092–8.
- 76 Edington M, Sachdev A, Morjaria R, Chong V. Structural-functional correlation in patients with diabetic macular edema. *Retina*. 2017 May;37(5):881–5.
- 77 Hood DC, Odel JG, Chen CS, Winn BJ. The multifocal electroretinogram. *J Neuroophthalmol*. 2003 Sep;23(3):225–35.
- 78 Tyrberg M, Ponjavic V, Lövestam-Adrian M. Multifocal electroretinogram (mfERG) in patients with diabetes mellitus and an enlarged foveal avascular zone (FAZ). *Doc Ophthalmol*. 2008 Nov;117(3):185–9.
- 79 Kiser AK, Mladenovich D, Eshraghi F, Bourdeau D, Dagnelie G. Reliability and consistency of dark-adapted psychophysical measures in advanced eye disease. *Invest Ophthalmol Vis Sci*. 2006 Jan;47(1):444–52.
- 80 Jackson GR, Scott IU, Kim IK, Quillen DA, Iannaccone A, Edwards JG. Diagnostic sensitivity and specificity of dark adaptometry for detection of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2014 Mar;55(3):1427–31.
- 81 Bavinger JC, Dunbar GE, Stem MS, Blachley TS, Kwark L, Farsi S, et al. The effects of diabetic retinopathy and pan-retinal photocoagulation on photoreceptor cell function as assessed by dark adaptometry. *Invest Ophthalmol Vis Sci*. 2016 Jan;57(1):208–17.
- 82 Trauzettel-Klosinski S, Dietz K; IREST Study Group. Standardized assessment of reading performance: the New International Reading Speed Texts IREST. *Invest Ophthalmol Vis Sci*. 2012 Aug;53(9):5452–61.
- 83 Calabrèse A, Cheong AM, Cheung SH, He Y, Kwon M, Mansfield JS, et al. Baseline MN-READ measures for normally sighted subjects from childhood to old Age. *Invest Ophthalmol Vis Sci*. 2016 Jul;57(8):3836–43.
- 84 Calabrèse A, Owsley C, McGwin G, Legge GE. Development of a reading accessibility index using the MNREAD acuity chart. *JAMA Ophthalmol*. 2016 Apr;134(4):398–405.
- 85 Calabrèse A, To L, He Y, Berkholtz E, Rafian P, Legge GE. Comparing performance on the MNREAD iPad application with the MN-READ acuity chart. *J Vis*. 2018 Jan;18(1):8.
- 86 Li XX, Wu W, Zhou H, Deng JJ, Zhao MY, Qian TW, et al. A quantitative comparison of five optical coherence tomography angiography systems in clinical performance. *Int J Ophthalmol*. 2018 Nov;11(11):1784–95.
- 87 Munk MR, Kashani AH, Tadayoni R, Korobelnik JF, Wolf S, Pichi F, et al. Standardization of optical coherence tomography angiography nomenclature in retinal vascular diseases: first survey results. *Ophthalmol Retina*. 2021. <https://doi.org/10.1016/j.oret.2020.12.022>.
- 88 Vangipuram G, Rezaei KA. Optical coherence tomography angiography as an imaging modality for evaluation of diabetic macular edema. *J Ophthalmic Vis Res*. 2017 Oct-Dec;12(4):359–60.
- 89 Arya M, Rashad R, Sorour O, Moulton EM, Fujimoto JG, Waheed NK. Optical coherence tomography angiography (OCTA) flow speed mapping technology for retinal diseases. *Expert Rev Med Devices*. 2018 Dec;15(12):875–82.
- 90 Yu S, Frueh BE, Steinmair D, Ebner A, Wolf S, Zinkernagel MS, et al. Cataract significantly influences quantitative measurements on swept-source optical coherence tomography angiography imaging. *PLoS One*. 2018 Oct;13(10):e0204501.
- 91 Safi H, Anvari P, Naseri D, Shenazandi H, Kazemi P, Farsi P, et al. Quantitative analysis of optical coherence tomography angiography metrics in diabetic retinopathy. *Ther Adv Ophthalmol*. 2020 Jan;12:2515841419897459.
- 92 Tsai AS, Jordan-Yu JM, Gan AT, Teo KY, Tan GS, Lee SY, et al. Diabetic macular ischemia: influence of optical coherence tomography angiography parameters on changes in functional outcomes over one year. *Invest Ophthalmol Vis Sci*. 2021 Jan;62(1):9.
- 93 NCT01175070. A phase IV open-labelled prospective pilot study of intravitreal macugen (pegaptanib) for ischaemic diabetic macular oedema (MIDME study). Available at <https://clinicaltrials.gov/ct2/show/NCT01175070>. Accessed 5th May 2020.
- 94 Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH; FinnDiane Study Group. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. *Diabetes Care*. 2010 Jun;33(6):1315–9.

- 95 Chang JR, Koo E, Agrón E, Hallak J, Clemmons T, Azar D, et al.; Age-Related Eye Disease Study Group. Risk factors associated with incident cataracts and cataract surgery in the Age-related Eye Disease Study (AREDS): AREDS report number 32. *Ophthalmology*. 2011 Nov;118(11):2113–9.
- 96 NCT04038125. Increase in capillary plexus density level following the use of ozurdex for the treatment of DME (RMSM ICOD STUDY). Available at <https://clinicaltrials.gov/ct2/show/NCT04038125>. Accessed 5th May 2020.
- 97 Marques IP, Madeira MH, Messias AL, Martinho AC, Santos T, Sousa DC, et al. Different retinopathy phenotypes in type 2 diabetes predict retinopathy progression. *Acta Diabetol*. 2021 Feb;58(2):197–205.
- 98 Santos T, Warren LH, Santos AR, Marques IP, Kubach S, Mendes LG, et al. Swept-source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR. *Br J Ophthalmol*. 2020 Dec;bjophthalmol-2020-317890.
- 99 van Dijk HW, Kok PH, Garvin M, Sonka M, Devries JH, Michels RP, et al. Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2009 Jul;50(7):3404–9.
- 100 van de Kreeke JA, Darma S, Chan Pin Yin JM, Tan HS, Abramoff MD, Twisk JW, et al. The spatial relation of diabetic retinal neurodegeneration with diabetic retinopathy. *PLoS One*. 2020 Apr;15(4):e0231552.
- 101 Bazvand F, Ghassemi F. Artifacts in macular optical coherence tomography. *J Curr Ophthalmol*. 2020 Apr;32(2):123–31.
- 102 Pauleikhoff D, Bonelli R, Dubis AM, Gunnemann F, Rothaus K, Charbel Issa P, et al.; MacTel Study Group. Progression characteristics of ellipsoid zone loss in macular telangiectasia type 2. *Acta Ophthalmol*. 2019 Nov;97(7):e998–1005.
- 103 Mukherjee D, Lad EM, Vann RR, Jaffe SJ, Clemmons TE, Friedlander M, et al.; MacTel Study Group. Correlation between macular integrity assessment and optical coherence tomography imaging of ellipsoid zone in macular telangiectasia type 2. *Invest Ophthalmol Vis Sci*. 2017 May;58(6):BIO291–9.
- 104 Sallo FB, Leung I, Clemmons TE, Peto T, Chew EY, Pauleikhoff D, et al. Correlation of structural and functional outcome measures in a phase one trial of CNTF in type 2 idiopathic macular telangiectasia. *Retina*. 2018 Jan; 38(Suppl 1):S27–32.
- 105 NCT03316300. A phase III multicenter randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia Type 2. Available at: <https://clinicaltrials.gov/ct2/show/NCT03316300>. Accessed 22nd September 2020.
- 106 Lorusso M, Zito R, Nikolopoulou E, Ferrari L, Cicinelli MV, Querques G, et al. Progression of retinal ischemia in a case of macular telangiectasia type 1 after ranibizumab injection: optical coherence tomography angiography findings. *Retin Cases Brief Rep*. 2020;14(4):372–76.
- 107 Nicholson L, Ramu J, Triantafylloulou I, Patrao NV, Comyn O, Hykin P, et al. Diagnostic accuracy of disorganization of the retinal inner layers in detecting macular capillary non-perfusion in diabetic retinopathy. *Clin Exp Ophthalmol*. 2015 Nov;43(8):735–41.
- 108 Karst SG, Lammer J, Radwan SH, Kwak H, Silva PS, Burns SA, et al. Characterization of in vivo retinal lesions of diabetic retinopathy using adaptive optics scanning laser ophthalmoscopy. *Int J Endocrinol*. 2018 May;2018:7492946–46.
- 109 Palochak CM, Lee HE, Song J, Geng A, Linsenmeier RA, Burns SA, et al. Retinal blood velocity and flow in early diabetes and diabetic retinopathy using adaptive optics scanning laser ophthalmoscopy. *J Clin Med*. 2019 Aug;8(8):1165.
- 110 Godara P, Dubis AM, Roorda A, Duncan JL, Carroll J. Adaptive optics retinal imaging: emerging clinical applications. *Optom Vis Sci*. 2010 Dec;87(12):930–41.
- 111 Bek T. Fine structure in diabetic retinopathy lesions as observed by adaptive optics imaging. A qualitative study. *Acta Ophthalmol*. 2014 Dec;92(8):753–8.
- 112 Lombardo M, Parravano M, Serrao S, Ziccardi L, Giannini D, Lombardo G. Investigation of adaptive optics imaging biomarkers for detecting pathological changes of the cone mosaic in patients with type 1 diabetes mellitus. *PLoS One*. 2016 Mar;11(3):e0151380.
- 113 Paques M, Meimon S, Rossant F, Rosenbaum D, Mrejen S, Sennlaub F, et al. Adaptive optics ophthalmoscopy: application to age-related macular degeneration and vascular diseases. *Prog Retin Eye Res*. 2018 Sep;66:1–16.
- 114 Zaleska-Żmijewska A, Piątkiewicz P, Śmigielka B, Sokołowska-Oracz A, Wawrzyniak ZM, Romaniuk D, et al. Retinal photoreceptors and microvascular changes in prediabetes measured with adaptive optics (rtx1™): a case-control study. *J Diabetes Res*. 2017;2017:4174292.
- 115 Boston Micromachines Corporation. <http://www.bostonmicromachines.com/aparos-retinal-imaging-system-aoslo.html>. Accessed August 2020.
- 116 Imagine Eyes. <https://www.imagine-eyes.com/products/rtx1/>. Accessed August 2020.
- 117 Fleckenstein M, Charbel Issa P, Helb HM, Schmitz-Valckenberg S, Finger RP, Scholl HP, et al. High-resolution spectral domain-OCT imaging in geographic atrophy associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2008 Sep;49(9):4137–44.
- 118 Klein R, Klein BE, Moss SE. How many steps of progression of diabetic retinopathy are meaningful? The Wisconsin epidemiologic study of diabetic retinopathy. *Arch Ophthalmol*. 2001 Apr;119(4):547–53.
- 119 Whynes DK; TOMBOLA Group. Correspondence between EQ-5D health state classifications and EQ VAS scores. *Health Qual Life Outcomes*. 2008 Nov;6(1):94.
- 120 Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD; National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001 Jul;119(7):1050–8.
- 121 The National Eye Institute 25 item Visual Function Questionnaire (VFQ-25). Manual, Version 2000. Available at https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/vfq/vfq25_manual.pdf. Accessed 6th May 2020.
- 122 Goldstein JE, Fenwick E, Finger RP, Gothwal V, Jackson ML, Lamoureux E, et al. Calibrating the Impact of Vision Impairment (IVI): creation of a sample-independent visual function measure for patient-centered outcomes research. *Transl Vis Sci Technol*. 2018 Dec;7(6):38.
- 123 Kimel M, Leidy NK, Tschosik E, Dolan C, Souied EH, Varma R, et al. Functional Reading Independence (FRI) index: a new patient-reported outcome measure for patients with geographic atrophy. *Invest Ophthalmol Vis Sci*. 2016 Nov;57(14):6298–304.
- 124 A phase III, multicenter, randomized, double-masked, sham-controlled study to assess the efficacy and safety of lampalizumab administered intravitreally to patients with geographic atrophy secondary to age-related macular degeneration. NCT02247479. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT02247479>. Accessed 26 May 2020.
- 125 Braithwaite T, Calvert M, Gray A, Pesudovs K, Denniston AK. The use of patient-reported outcome research in modern ophthalmology: impact on clinical trials and routine clinical practice. *Patient Relat Outcome Meas*. 2019 Jan;10:9–24.