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Leveraging Visual Outcome Measures to Advance Therapy Development in Neuroimmunologic Disorders

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Abstract

The visual system offers unparalleled precision in the assessment of neuroaxonal damage. With the majority of patients with multiple sclerosis (MS) experiencing afferent and efferent visual dysfunction, outcome measures capturing these deficits provide insight into neuroaxonal injury, even in those with minimal disability. Ideal for use in clinical trials, visual measures are generally inexpensive, accessible, and reproducible. Quantification of visual acuity, visual fields, visual quality of life, and electrophysiologic parameters allows assessment of function, whereas optical coherence tomography (OCT) provides reliable measures of the structural integrity of the anterior afferent visual pathway. The technology of oculomotor biometrics continues to advance, and discrete measures of fixation, smooth pursuit, and saccadic eye movement abnormalities are ready for inclusion in future trials of MS progression. Visual outcomes allow tracking of neuroaxonal injury and aid in distinguishing MS from diseases such as neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody–associated diseases (MOGAD). OCT has also provided unique insights into pathophysiology, including the identification of foveal pitting in NMOSD, possibly from damage to Müller cells, which carry an abundance of aquaporin-4 channels. For some study designs, the cost-benefit ratio favors visual outcomes over more expensive MRI outcomes. With the next frontier of therapeutics focused on remyelination and neuroprotection, visual outcomes are likely to take center stage. As an international community of collaborative, committed, vision scientists, this review by the International MS Visual System Consortium (IMSVISUAL) outlines the quality standards, informatics, and framework needed to routinely incorporate vision outcomes into MS and NMOSD trials.

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IMSVISUAL coinvestigators are listed in the appendix at the end of the article.

Glossary

AQP4 = aquaporin-4; **CS** = contrast sensitivity; **EDSS** = Expanded Disability Status Scale; **EDTRS** = Early Treatment Diabetic Retinopathy Study; **ERGs** = Electroretinograms; **GCIPL** = ganglion cell + inner plexiform layer; **GCL** = ganglion cell layer; **HCVA** = High-contrast visual acuity; **IMSVISUAL** = International MS Visual System Consortium; **INL** = inner nuclear layer; **ISCEV** = International Society for Clinical Electrophysiology of Vision; **LCLA** = low-contrast letter acuity; **LGN** = lateral geniculate nucleus; **MD** = mean deviation; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **MSFC** = MS Functional Composite; **NEI-VFQ** = National Eye Institute Visual Function Questionnaire; **NMOSDs** = neuromyelitis optica spectrum disorders; **OCT** = optical coherence tomography; **ON** = optic neuritis; **ONH** = optic nerve head; **ONL** = outer nuclear layer; **OPL** = outer plexiform layer; **ONTT** = optic neuritis treatment trial; **OR** = optic radiation; **OT** = optic tract; **QoL** = quality of life; **RGC** = Retinal ganglion cells; **RNFL** = retinal nerve fiber layer; **VEPs** = Visual Evoked Potentials.

The first revolution in ophthalmology occurred in 1845 with the invention of the ophthalmoscope. Before this time, there was no clear way to differentiate visual disorders; diseases were categorized only as either ophthalmia or blindness.[1] Progress was made into the early 20th century when optic neuritis (ON) was distinguished from other forms of optic disc swelling and linked to MS.[1] A century later, we now have tools that visualize retinal damage to 5–6 μm resolution and hold strong promise as outcome measures for clinical trials.

At least 50% of patients with MS experience ON during the course of their disease, with many more experiencing subclinical damage to retinal ganglion cells.[2] Up to 70% will also experience efferent dysfunction from oscillopsia to subtle smooth pursuit dysfunction and impaired gaze stabilization.[2] In neuromyelitis optica spectrum disorders (NMOSDs), nearly half of patients may have a risk of developing clinical blindness in the first 5 years of disease.[3] Recently, myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) has emerged as pathophysiologically distinct from classic NMOSD with an even stronger preponderance for optic nerve involvement.

The visual system is highly amenable to quantification, with well-understood structure-function relationships, and yet it has been underutilized in clinical trials. Rigorous methods have recently emerged to quantify visual injury in neuroinflammatory diseases. Herein, the International MS Visual System Consortium (IMSVISUAL) (imsvisual.org) reviews structure-function relationship and utility in clinical trials of both afferent and efferent visual system outcome measures that have—in light of relatively low costs, high reliability, and exquisite sensitivity for pathology—the potential to transform the next generation of MS, NMOSD, and MOGAD clinical trials.

Afferent Visual System Anatomy

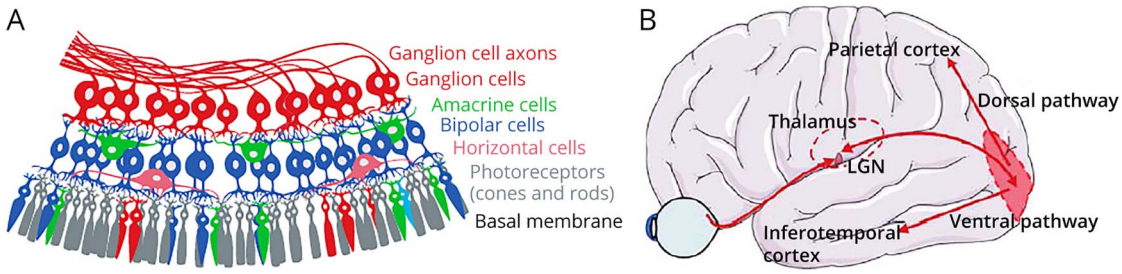
Retinal ganglion cells (RGCs) represent the anterior visual pathway and are affected by inflammation, demyelination, and neuroaxonal degeneration during ON or subclinical optic neuropathy (Figure 1A). RGC axons track along the inner retinal nerve fiber layer (RNFL) and converge at the optic nerve head (ONH) to form the optic nerve. RGC cell bodies are in the retinal ganglion cell layer (GCL). Subjacent to the GCL, the inner nuclear layer (INL) may also be affected by neuroimmunologic diseases.[4,e1-e5] Minimal changes in outer retinal layers have been reported after ON but may be transient[5] or specific to progressive forms of MS.[6] Nonneuronal retinal cells have not been as well studied, but astrocyte reactivity plays a crucial role in neuroimmunologic disease, especially in NMOSD, and advancing metrics targeting these cell types are of interest.[7]

Beyond the cribriform plate, the optic nerve is myelinated and travels approximately 4 cm to the optic chiasm, where the axons from the contralateral nasal and ipsilateral temporal hemiretinas join to form the optic tract (OT). Lesions that involve the chiasm or OT[8] are more common in aquaporin-4 (AQP4)-IgG+ NMOSD than in MS, and longitudinally extensive intraorbital optic nerve involvement is more frequent in MOGAD than in AQP4-IgG+ NMOSD.[e6] The OT carries visual signals through the dorsal thalamic lateral geniculate nucleus (LGN) and secondary LGN neurons within the optic radiation (OR) to the primary visual cortex (Figure 1B). Anterograde and retrograde transsynaptic degeneration can occur across the synapse in the dorsal LGN9[e7] and is of interest in the context of visual outcome measures in trials. The primary visual (calcarine/striate) cortex is organized into columns in which neurons are grouped according to their function. The occipital cortical thickness reflects this complex cytoarchitecture, and this thickness can be captured with MRI surface-based cortical reconstruction.[e8] From the primary visual cortex, there are projections to the parietal (dorsal pathway for visually guided movements) and temporal lobes (ventral pathway for object recognition) (Figure 1B). The extrastriate occipital cortex also has areas with functional specificity that may be involved in neuroplasticity recovery processes after ON.[e9]

Afferent Visual Function Measures

An array of tools captures complementary measures of afferent visual function. These include assessments of visual acuity,

Figure 1 Afferent Visual System Anatomy



(A) Phototransduction occurs in photoreceptor cells in the outer retina. These visual signals are processed and transmitted by horizontal and bipolar cells residing in the inner nuclear layer (INL). Bipolar cell axons form synapses with the dendrites of retinal ganglion cells (RGCs) in the inner plexiform retinal layer. The optic nerve is formed by the unmyelinated axons of RGCs, tracking along the inner retinal surface in the nerve fiber layer (RNFL) and converging at the optic nerve head. Subjacent to the ganglion cell layer (GCL), the INL consists of the bipolar, horizontal, and amacrine cells as well the cell bodies of astrocytic Müller cells. (B) Beyond the cribiform plate, the RGC axons of the optic nerve are myelinated and travel approximately 4 cm to the optic chiasm. The optic nerve partially decussates at the chiasm: The axons from the contralateral nasal and ipsilateral temporal hemiretinas join to form the optic tract (OT). The OT carries visual signals to the thalamic lateral geniculate nucleus (LGN). The secondary LGN neurons project to the primary visual cortex through the optic radiations (OR). From the primary visual cortex, projections go through the extrastriate cortex of the occipital lobe to the parietal lobe (the dorsal pathway for visually guided movements) and the temporal lobe (the ventral pathway for object recognition). Parts of the figure are provided by courtesy of neurodial.de (neurodial.de/2017/08/25/schematic-figure-retina-creative-commons-license/).

formal perimetry, electrophysiology, and self-reported visual quality of life (QoL). Key to applying these measures is recognizing that the magnitudes of deficits are expected to be different in eyes with prior ON vs subclinical injury. Consistent across most clinical trials has been the application of the ON diagnostic criteria used in the optic neuritis treatment trial (ONTT).[e10]

High- and Low-Contrast Visual Acuity in ON and MS

High-contrast visual acuity (HCVA), black letters on a white background, is part of the visual functional system score in the Expanded Disability Status Scale (EDSS). Standardized HCVA tools include the 100% Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Precision Vision, La Salle, USA) and Snellen Charts. Methods that generate continuous variables amenable to statistical models (letters correct, logMAR, and decimal vision scores) are preferable for clinical trials. A clinically meaningful change in HCVA is generally accepted as a minimum 5-letter difference.[e11]

A normal HCVA result, however, does not exclude MS-related optic nerve injury.[10] Low-contrast vision assessments are more sensitive and include measures of contrast sensitivity (CS) and low-contrast letter acuity (LCLA). In the former, the patient is asked to read letters of constant size but decreasing contrast to determine the CS threshold. In the ONTT, CS determined by the Pelli-Robson Chart[11] demonstrated greater sensitivity to detect visual injury than HCVA.[12] For LCLA, the level of contrast is held constant and the letters decrease in size, similar to how HCVA is measured, but instead of 100% black on white contrast, light gray colors are used (e.g., 2.5% or 1.25% contrast). The Sloan low-contrast charts[e12] have been frequently used to provide LCLA measurements, but other tools are also available. As an example, the standardized low-contrast Landolt C Broken Rings Chart (at 3 M) with direct data entry into an electronic data capture system was used for visual outcomes in the N-Momentum trial of inebilizumab (NCT02200770) in NMOSD. As the level of contrast required for letter perception is affected by letter size,[e13-e14] the Sloan LCLA may be more sensitive than CS in detecting subtle losses.[13] Furthermore, Sloan LCLA correlates strongly with optical coherence tomography (OCT), electrophysiologic, brain imaging, and self-reported QoL outcomes.[13] Consequently, Sloan LCVA has been proposed as a primary outcome measure for visual function in ON, MS, and NMOSD and recommended as a potential (4th) component of the MS Functional Composite (MSFC) scale of MS disability.[13] A seven-letter loss in LCVA has been validated as clinically meaningful.[e13] LCVA is the primary outcome for an ongoing trial of nanocrystalline gold as a remyelinating agent (NCT03536559).

For assessment of neurologic acuity deficits, it is critical to address confounding refractive error. Ideally, a formal refraction and lens correction is performed; however, correction with pinhole devices has also been accepted. Assessments should be performed under standard lighting conditions throughout a trial.

Digital tools created to capture both HCVA and LCLA[e15-e16] may have challenges with backlighting on devices, but these tools can provide standardization across trial sites (less issue with ambient lighting in traditional testing), allow home use, and ease data collection processes.

Visual Fields

Substantial visual deficits may be missed if outcomes focus on central acuity measures alone. In MS, NMOSD, and MOGAD, VF defects may vary, but a diffuse central scotoma is most commonly observed in acute ON.[14] After recovery, patients may

show an arcuate scotoma due to the predominant temporal loss of retinal nerve fibers and ganglion cells.[14] VF defects are not limited to optic nerve patterns and may include those consistent with injury to the optic chiasm, optic tract, optic radiations, or occipital lobe.

VF can be assessed with different techniques. Standard static automated perimetry evaluates the central 10–30 degrees of vision and provides a qualitative depiction of field loss pattern and 2 quantitative indices: the mean deviation (MD), which measures the sensitivity deviation at each test location from the age-adjusted healthy population, and the pattern SD (PSD), which is the average sensitivity deviation from the normal slope after correction for global sensitivity differences. Kinetic perimetry can be used in patients with difficulty focusing or those with expected peripheral field loss, but quantification of results can be challenging for clinical trials.

VF interpretation can be limited because of defect variability, severely impaired VA, or impaired cognition. Standardization can be reached in trials by defining light conditions and predefining cutoffs for loss of fixation frequency, false negatives, and false positives.[15] In acute ON, automated perimetry has been successfully used as a primary outcome as in the ONTT[12,15] and in a recent NMO trial (Table 1).[16] For trials using acute ON as a model for remyelination and neuroprotection, perimetry has been used as a secondary outcome.[e16-e18]

Electrophysiology

Across electrophysiology methods, recordings are dependent on stimulus parameters, the patient's anatomy, and the testing environment. To differentiate true signal from electrical background potentials, signal amplification and averaging techniques are used. When using electrophysiologic outcomes for clinical trials, clear and standardized protocols are essential.[e19]

Visual Evoked Potentials

Visual Evoked Potentials (VEPs) have been successfully used as outcomes in trials for acute ON or MS-related chronic optic neuropathy (Table 2, eTable 1, links.lww.com/NXI/A675). They are electrical potentials generated in the occipital cortex (captured with occipital electrodes) in response to visual stimuli.[e19] As VEPs are hidden in EEG signals, they are evaluated with averaged waveform signals from repetitive stimulation. For quality control, the International Society for Clinical Electrophysiology of Vision (ISCEV) standards should be applied. A variety of stimulation paradigms may be used. Flash VEPs (using bright-light stimuli) have been shown to be inferior to pattern-reversal VEPs (using mostly checkerboard stimuli) and are reserved for patients unable to fixate or with severe central vision loss (e.g., NMOSD-ON).[e19] Pattern-reversal (or full-field) VEP analysis is based on the first major positive deflection of the signal waveform, which occurs approximately 100 ms after the stimulus (P100 latency).[e19] This latency reflects conduction speed and myelin integrity. The upper P100 latency limit of normal differs according to the reference population and VEP method, and values should always be interpreted within the context of the individual, taking previous and contralateral eye measurements into account. The P100 amplitude peak is more variable than latency and should be used with caution in clinical trials, but it may help differentiate demyelinating ON from noninflammatory/ischemic optic neuropathies.[e19]

During acute demyelinating ON, the P100 latency is typically delayed (>125 ms) and the peak amplitude reduced. In cases of severe vision loss (central acuity <20/100–20/200), the patient may be unable to fixate to complete a pattern-reversal VEP, or the response may be absent.[e20] For this reason, it is challenging to measure correlation between VEP and visual acuity during an acute episode of ON. With remittance of the ON, the amplitude recovers, and the latency may slowly shorten over weeks to 2 years.[16] Latency improvement is most pronounced in the first 3–6 months with decreasing inflammation and presumed early remyelination. Lack of latency recovery or insidious worsening of latency delay is associated with overall disability.[e21-e23] Latency insidious worsening in ON or non-ON eyes may indicate chronic global demyelination without sufficient remyelination.[17,18] In recovered ON or non-ON MS eyes, correlations between LCLA and VEP latency are observable in cross-sectional analyses.[e24]

Given the changes of VEP latencies over time following ON, the timing of when to measure VEPs in a clinical trial requires consideration of the intervention and desired effect/outcome. For remyelinating therapies, given the lack of a widely accepted gold standard for MRI-based myelin measurements, P100 latency has been prominent as a primary or secondary outcome measure.[19] Two recent trials using VEP as the primary outcome for remyelination interventions demonstrated greater P100 latency reduction by clemastine in chronic MS optic nerve injury[19] and by liothyronine sodium in an acute ON model.[20] Other potential remyelinating or neuroprotective agents showed negative VEP results for treatment effects, including the phase 2 trials of anti–LINGO-1 antibodies[21] and phenytoin.[22] Advancement in the basic science of evoked potentials and several ongoing trials with remyelinating therapies (NCT03586557, NCT03605238, NCT03062579, NCT01883661, NCT01364246, NCT02671682, NCT01337986, NCT04042363, NCT04002934, NCT03774407, and NCT04121468) will enlighten and continue to improve the application of VEP for clinical trials.

Electroretinograms

Electroretinograms (ERGs) recorded from the cornea or periorbital skin capture electrical potentials generated in the retina.[e19] For flash ERGs, the first negative (consisting of rod and cone photoreceptor cell signals; ca. 14 msec) and positive (b-wave consisting of the slower bipolar cell signals; ca. 30–35 msec) waveform deflections are evaluated.[e19] In contrast, a pattern ERG records the response to a pattern-reversal stimulus (e.g., alternating checkerboard); the resulting b-wave (N95; ca. 95 msec) is suggested to reflect the activation of RGCs.[e19] In MS and NMOSD—especially but not exclusively

Table 1 Clinical Trials and Interventional Studies Using Visual Fields as an Outcome Measure

Trial (Number/name; publication)	Patients	Drug	VF outcome	Effect on VF
Visual recovery in the acute phase optic neuritis				
NCT00000146 (ONTT; Beck et al. Arch Ophthal 1993; 111: 773–775)	457	Methylprednisolone + oral prednisone vs oral prednisone vs placebo	Primary	Accelerated visual recovery at 6 mo in the methylprednisolone group. No intergroup difference in visual recovery at 12 mo.
Not registered (Merle H et al., Arch Ophthalmol 2012; 130: 858–862)	36 (NMO)	Plasma exchange + methylprednisolone vs methylprednisolone	Primary	Significant effect (p = 0.02)
NCT04155424	15 (pediatric NMOSD)	Eculizumab (open label)	Secondary	Ongoing
Visual recovery in the chronic phase of optic neuritis				
NCT01337986	53	Dalfampridine vs placebo	Secondary	Significant effect (p = 0.04)
NCT02220244 (Tourbah A et al., CNS Drugs 2018; 32: 661–672)	93	MD1003 vs placebo	Secondary	No significant effect
NCT01274702 (VISION; Schinzel J et al., Trials 2012; 13)	80	Vision restoration therapy vs saccadic Training (control intervention)	Primary	Ongoing
NCT04148781 (FAMP-ON)	20	Fampridine (open label)	Primary	Ongoing
Neuroprotection in acute ON				
NCT00355095 (Sühs KW et al., Ann Neurol 2012; 72: 199–210)	40	Erythropoietin vs placebo	Secondary	No significant effect
Not registered (2012 Esfahani MR et al., Graefes Arch Clin Exp Ophthalmol. 2012 Jun; 250(6):863–9)	50	Memantine vs placebo	Secondary	No significant effect
NCT01294176 (Falardeau J et al., Mult Scler J - Exp Transl Clin 2019; 5: 205521731985019)	31	Lipoic Acid vs placebo	Secondary	No significant effect (incomplete recruitment)
NCT01802489				
(ACTION; McKee JB et al., BMJ Open 2015; 53)	46	Amiloride vs placebo	Secondary	Ongoing
NCT01962571 (TONE; Diem R et al., BMJ Open 2016; 6)	100	Erythropoietin vs placebo	Secondary	Ongoing
NCT04042363 (ONSTIM)	45	Active transorbital electrical stimulation vs sham transorbital electrical stimulation (control intervention)	Secondary	Ongoing
NCT03862313 (ACSON)	30	Repetitive transorbital alternating current stimulation vs sham stimulation (control intervention)	Secondary	Ongoing
EudraCT: 2020-003147-29 (NCT # pending)	36	ACT-01 vs placebo	Primary	Ongoing
Neuroprotection in multiple sclerosis				
NCT00395200 (Connick P et al., Lancet Neurol 2012; 11: 150–156)	10 (SPMS)	Autologous mesenchymal stem cells (open label)	Secondary	No significant effect

Abbreviations: ONTT = optic neuritis treatment trial; NMOSD = neuromyelitis optica defined in the study by the presence of anti–aquaporin-4 antibodies; NMOSD = neuromyelitis optica spectrum disorder defined in the study by the 2015 Criteria; SPMS = secondary progressive MS.

after ON—N95 is prolonged, and the amplitude is diminished, indicative of retinal damage.[23,e25-26] A novel ERG protocol recently identified b-wave changes in AQP4-IgG–seropositive NMOSD in line with Müller glial dysfunction, suggesting a potential relevance of ERG for differential diagnosis and trial outcome parameters in NMOSD.[7]

Multifocal VEP and ERG

Multifocal VEP and ERG approaches divide the visual field into sectors, which are stimulated and assessed separately.[e27-28] The waveforms are comparable to those of full-field approaches, and multifocal methods are objective alternatives to VF measurements.[e29] However, a high demand for patient

Table 2 Electrophysiologic and MRI Outcomes in Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Clinical Trials

Trial (Trial name, patients)	Drug/treatment	VEP measures	Imaging measure
NCT00355095 40 (acute ON)	Erythropoietin (33000IU IV for 3 days) vs placebo	Secondary (change in ffVEP latency and amplitude) Improved latency in intereye analysis ($p < 0.001$), no effect on amplitude	Optic nerve volume: no change over 16 wks
NCT00261326 (10) 64 (acute ON)	Simvastatin (80 mg) vs placebo	Secondary (change in ffVEP P100 latency and amplitude) Effect on VEP latency ($p = 0.0132$) and VEP amplitude ($p = 0.0103$)	T2 lesion activity: no change
NCT02220244 (11) 93 (MS, chronic optic neuropathy)	MD1003 (100 mg) vs placebo	Secondary (presence of clear wave, change in ffVEP P100 latency) No significant differences	—
NCT00772525 (12) 31 (MS)	Nerispirdine (50 mg or 400 mg) vs placebo	Primary (ffVEP P100 latency)—ongoing	—
NCT03350633[144] 118 (NMOSD)	Tocilizumab vs azathioprine	Exploratory (change in P100 latency and amplitude change over 60 wks) P100 latency increased compared with those in the tocilizumab group ($p = 0.009$)	T2 lesion activity: used to confirm relapses
NCT03586557 (2) 142 (acute ON, AQP4-IgG–positive NMOSD)	Corticosteroid and plasma exchange vs corticosteroids alone	Secondary (changes in flash VEP latency)—ongoing	—
NCT02671682 (17) 60 (MS or CIS)	Immunoabsorption vs plasmapheresis	Secondary (change in ffVEP latency)—unknown	—
NCT02040298 (19) (ReBUILD) 50 (early MS)	Cross-over trial for clemastine fumarate (4 mg) vs placebo	Primary (change in ffVEP P100 latency) Reduced P100 latency delay by 1.7 ms/eye ($p = 0.0048$)	DTI: secondary–white matter FA—no effect found; MTR: secondary—white matter—no effect
NCT02521311[145] 90, acute ON	RCT clemastine 12 mg and 8 mg vs placebo	Primary (change in ffVEP P100 latency)—ongoing	MTR: secondary—whole brain MTR
NCT01721161 (RENEW)[146] 82 (acute ON)	Anti–LINGO-1 mAb (BIIB033, 100 mg/kg IV) vs placebo	Primary (change in ffVEP P100 latency)—no significant differences	T2 lesion activity: T2 and enhancing lesions recorded—no difference between groups
NCT01864148 (SYNERGY)[100]	Anti–LINGO-1 vs placebo in RRMS		T2 lesion activity: exploratory—new or enhancing T2 lesions DTI: subgroup—improved disability outcomes in 10 mg/kg group if lower baseline DTI-RD MTR : exploratory. In post hoc analysis of 10 mg/kg dose: lower baseline lesion MTR improved outcomes
NCT01451593[148] 86 (acute ON)	Phenytoin (4 mg/kg) vs placebo	Primary (change in ffVEP P100 latency and amplitude)—no significant differences	T2 lesion activity: Secondary—optic nerve lesion length—no difference Optic nerve volume: Secondary—no difference
NCT01337986 (23) 53 (MS, chronic optic neuropathy)	Cross-over trial for dalfampridine (10 mg) vs placebo	Secondary (change in ffVEP latency)—no significant differences	—
NCT04042363 (ONSTIM) (24) 45 (acute ON in early RRMS)	Active transorbital electrical stimulation vs sham	Primary (change in ffVEP P100 latency)—ongoing	—
NCT04002934 (ReWRAP) (25) 50 (female, RRMS)	Delayed start trial bazedoxifene acetate (40 mg) vs placebo + late bazedoxifene acetate	Primary (change in ffVEP P100 latency)—ongoing	—
NCT03536559 (VISIONARY-MS) (26) 150 (early RRMS)	CNM-Au8 (15 mg or 30 mg) vs placebo	Secondary (ffVEP and mfVEP latency)—ongoing	T2 lesion activity: secondary—new or enhancing T2 lesions

Continued

Table 2 Electrophysiologic and MRI Outcomes in Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Clinical Trials *(continued)*

Trial (Trial name, patients)	Drug/treatment	VEP measures	Imaging measure
NCT04121468 (33) 30 (children, MS, recent ON event)	Delayed start trial for metformin (500 mg/m^2/day) vs placebo	Secondary (ffVEP latency) —ongoing	—
NCT01802489 (ACTION)[149] 46 (acute ON, RRMS)	Amiloride (10 mg) vs placebo	Secondary (differences in ffVEP and pattern ERG) VEP latency prolonged in the amiloride group compared with placebo (p = 0.004), no significant differences for ERG	—
NCT00355095 40 (acute ON)	Erythropoietin (33000IU IV for 3 days) vs placebo	Secondary (change in ffVEP latency and amplitude) Improved latency in intereye analysis (p < 0.001), no effect on amplitude	Optic nerve volume: no change over 16 wks
NCT00261326 (10) 64 (acute ON)	Simvastatin (80 mg) vs placebo	Secondary (change in ffVEP P100 latency and amplitude) Effect on VEP latency (p = 0.0132) and VEP amplitude (p = 0.0103)	T2 lesion activity: no change
NCT02220244 (11) 93 (MS, chronic optic neuropathy)	MD1003 (100 mg) vs placebo	Secondary (presence of clear wave, change in ffVEP P100 latency) No significant differences	—
NCT00772525 (12) 31 (MS)	Nerispirdine (50 mg or 400 mg) vs placebo	Primary (ffVEP P100 latency)—ongoing	—
NCT03350633[144] 118 (NMOSD)	Tocilizumab vs azathioprine	Exploratory (change in P100 latency and amplitude change over 60 wks) P100 latency increased compared with those in the tocilizumab group (p = 0.009).	T2 lesion activity: used to confirm relapses
NCT03586557 (2) 142 (acute ON, AQP4-IgG–positive NMOSD)	Corticosteroid and plasma exchange vs corticosteroids alone	Secondary (changes in flash VEP latency)—ongoing	—
NCT02671682 (17) 60 (MS or CIS)	Immunoabsorption vs plasmapheresis	Secondary (change in ffVEP latency)—unknown	—
NCT02040298 (19) (ReBUILD) 50 (early MS)	Cross-over trial for clemastine fumarate (4mg) vs placebo	Primary (change in ffVEP P100 latency) Reduced P100 latency delay by 1.7 ms/eye (p = 0.0048)	DTI: secondary—white matter FA—no effect found; MTR: secondary—white matter—no effect
NCT02521311[145] 90, acute ON	RCT clemastine 12 mg and 8 mg vs placebo	Primary (change in ffVEP P100 latency)—ongoing	MTR: secondary-whole brain MTR
NCT01721161 (RENEW)[146] 82 (acute ON)	Anti–LINGO-1 mAb (BIIB033, 100 mg/kg IV) vs placebo	Primary (change in ffVEP P100 latency)—no significant differences	T2 lesion activity: T2 and enhancing lesions recorded—no difference between groups
NCT01864148 (SYNERGY)[100]	Anti–LINGO-1 vs placebo in RRMS		T2 lesion activity: exploratory—new or enhancing T2 lesions DTI: subgroup—improved disability outcomes in 10 mg/kg group if lower baseline DTI-RD MTR: exploratory. In post hoc analysis of 10 mg/kg dose: lower baseline lesion MTR improved outcomes
NCT01451593[148] 86 (acute ON)	Phenytoin (4 mg/kg) vs placebo	Primary (change in ffVEP P100 latency and amplitude)—no significant differences	T2 lesion activity: secondary—optic nerve lesion length—no difference Optic nerve volume: secondary—no difference
NCT01337986 (23) 53 (MS, chronic optic neuropathy)	Cross-over trial for dalfampridine (10 mg) vs placebo	Secondary (change in ffVEP latency)—no significant differences	—
NCT04042363 (ONSTIM) (24) 45 (acute ON in early RRMS)	Active transorbital electrical stimulation vs sham	Primary (change in ffVEP P100 latency)—ongoing	—

Continued

Table 2 Electrophysiologic and MRI Outcomes in Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Clinical Trials *(continued)*

Trial (Trial name, patients)	Drug/treatment	VEP measures	Imaging measure
NCT04002934 (ReWRAP) (25) 50 (female, RRMS)	Delayed start trial bazedoxifene acetate (40 mg) vs placebo + late bazedoxifene acetate	Primary (change in ffVEP P100 latency)—ongoing	—
NCT03536559 (VISIONARY-MS) (26) 150 (early RRMS)	CNM-Au8 (15 mg or 30 mg) vs placebo	Secondary (ffVEP and mfVEP latency)—ongoing	T2 lesion activity: secondary—new or enhancing T2 lesions
NCT04121468 (33) 30 (children, MS, recent ON event)	Delayed start trial for metformin (500 mg/m^2/day) vs placebo	Secondary (ffVEP latency) —ongoing	—
NCT01802489 (ACTION)[149] 46 (acute ON, RRMS)	Amiloride (10 mg) vs placebo	Secondary (differences in ffVEP and pattern ERG) VEP latency prolonged in the amiloride group compared with placebo (p = 0.004), no significant differences for ERG	—
NCT00355095 40 (acute ON)	Erythropoietin (33000IU IV for 3 days) vs placebo	Secondary (change in ffVEP latency and amplitude) Improved latency in intereye analysis (p < 0.001), no effect on amplitude	Optic nerve volume: no change over 16 wks
NCT00261326 (10) 64 (acute ON)	Simvastatin (80 mg) vs placebo	Secondary (change in ffVEP P100 latency and amplitude) Effect on VEP latency (p = 0.0132) and VEP amplitude (p = 0.0103)	T2 lesion activity: no change
NCT02220244 (11) 93 (MS, chronic optic neuropathy)	MD1003 (100 mg) vs placebo	Secondary (presence of clear wave, change in ffVEP P100 latency) No significant differences	—
NCT00772525 (12) 31 (MS)	Nerispirdine (50 mg or 400 mg) vs placebo	Primary (ffVEP P100 latency)—ongoing	—
NCT03350633 [144] 118 (NMOSD)	Tocilizumab vs azathioprine	Exploratory (change in P100 latency and amplitude change over 60 wks) P100 latency increased compared with those in the tocilizumab group (p = 0.009).	T2 lesion activity: used to confirm relapses
NCT03586557 (2) 142 (acute ON, AQP4-IgG–positive NMOSD)	Corticosteroid and plasma exchange vs corticosteroids alone	Secondary (changes in flash VEP latency)—ongoing	—
NCT02671682 (17) 60 (MS or CIS)	Immunoabsorption vs plasmapheresis	Secondary (change in ffVEP latency)—unknown	—
NCT02040298 (19) (ReBUILD) 50 (early MS)	Cross-over trial for clemastine fumarate (4 mg) vs placebo	Primary (change in ffVEP P100 latency) Reduced P100 latency delay by 1.7 ms/eye (p = 0.0048)	DTI: secondary—white matter FA—no effect found; MTR: secondary—white matter—no effect
NCT02521311[145] 90, acute ON	RCT clemastine 12 mg and 8 mg vs placebo	Primary (change in ffVEP P100 latency)—ongoing	MTR: secondary—whole brain MTR
NCT01721161 (RENEW)[146] 82 (acute ON)	Anti–LINGO-1 mAb (BIIB033, 100 mg/kg IV) vs placebo	Primary (change in ffVEP P100 latency)—no significant differences	T2 lesion activity: T2 and enhancing lesions recorded—no difference between groups

alertness and fixation as well as issues of intersubject variability, especially for multifocal VEP (mfVEP), has been limiting. Newer stimulation and analysis algorithms may provide a better standardization and user friendliness. These mfVEP devices have been used in a subanalysis of the anti–LINGO-1 remyelination clinical trial[24] and are currently used as in an ongoing study investigating the effects of nanocrystalline gold to treat remyelinating failure (NCT03536559). Multifocal ERG responses have been studied in MS and NMOSD,[31] albeit without application in neuroimmunology clinical trials.

Additional Measures

Other afferent measures include the analog and digital flicker tests, object from motion (OFM), and critical flicker frequency (CFF). Digital administration may expand the accessibility of new visual outcomes for trials. As an example, the digital Aulhorn flicker test showed superior diagnostic sensitivity (sensitivity 93% and specificity 96%) compared with the Aulhorn analog flicker test (sensitivity 76% and specificity 100%).[e32] The digital CFF test associates with disability in patients with MS.[e33] OFM generates a hidden object that is

perceived through motion detection and can be used to assess de/remyelination.[e34] These tests, while not yet in trials, may hold promise for use in future designs.

Vision QOL

Although patients with MS rate visual function as a top concern,[25] vision-related patient-reported outcomes have been widely neglected in pivotal trials of MS immunotherapy.[e35] Visual QoL in both MS and NMOSD correlates with LCLA and structural measures of retinal damage.[26-28] The commonly used 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ) comprises 12 individual subscales for general health, general vision, ocular pain, near activities, distance activities, driving, color vision, peripheral vision and vision-specific social functioning, mental health, role difficulties, and dependencies. A final composite score is generated by averaging all subscale scores except the general health item. An additional version with 39 and 25 items and a neuro-ophthalmic supplement have since been established and have been applied to measure vision-related QoL in MS.[29,30] Use of the NEI-VFQ with the neuro-ophthalmic supplement would be recommended for neuroimmunology trials.

Afferent Visual System Structural Measures

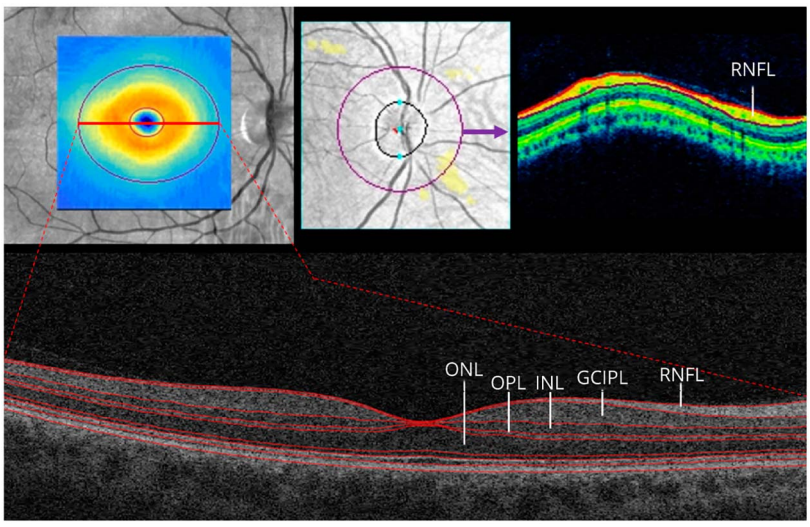
Optical Coherence Tomography (OCT) Peripapillary and Macular Measurements

OCT uses light waves passing through the pupil, vitreous, and retinal layers and then reflecting off the pigmented retinal epithelium to reconstruct images of the retina and assess tissue integrity. Over the past 20 years, studies describing OCT outcomes in MS, NMOSD, and MOGAD have exponentially increased.[31] Initial work used time-domain OCT, whereas recent studies have leveraged the faster acquisition speeds, higher-resolution images (axial resolution 4–6 μm), and improved reproducibility of spectral domain OCT.[e36-e37] Segmentation of the images, typically performed using automated algorithms, allows the quantitative assessment of discrete retinal neuronal and axonal layers (Figure 2). With appropriate quality control in acquisition,[32] these quantitative measures demonstrate excellent test-retest reliability, a critical feature for clinical trial outcomes.[33]

MS, NMOSD, and MOGAD observational OCT studies have largely focused on the macular ganglion cell + inner plexiform layer (GCIPL) and peripapillary RNFL (pRNFL) thickness, representing the integrity of RGC cell bodies and axons, respectively. Following acute ON, there is rapid thinning of the GCIPL, often within the first month of onset, and this process is largely completed by 3 months.[34,35] The pRNFL frequently exhibits increased thickness during acute ON due to swelling, which confounds the baseline measurement and leads to a delayed time course of detecting atrophy of the pRNFL compared with the GCIPL.[34,35] It is best to measure pRNFL 6 months after onset for assessment of axonal loss from an acute ON event.[34,35]

Selecting the specific OCT outcome for a trial depends on the disease state and time course of interest (Table 3). Important considerations for incorporating OCT measures in trials of putative neuroprotective agents in acute ON include the following: 1) GCIPL thickness is superior to pRNFL thickness at early time points, given the lack of swelling at baseline, 2) GCIPL thinning occurs rapidly during the first month after ON, and participants should be enrolled shortly after symptom onset; very early intervention (within 2–4 weeks) with therapeutics may be required to change the outcome,[36] 3) a 6-month trial duration could be sufficient to detect a difference in GCIPL or pRNFL thinning between treatment groups (though

Figure 2 Optical Coherence Tomography Peripapillary and Macular Measurements



Upper left: Fundus image with superimposed macular GCIPL thickness map. Bottom: Horizontal macular OCT B-scan traversing the fovea, corresponding to the red horizontal line shown in the fundus photograph (upper left). The scan has been automatically segmented (boundaries between retinal layers are outlined in red). Upper right: Peripapillary RNFL ring scan; the shown OCT B-scan shown corresponds to the purple peripapillary ring shown superimposed on the fundus image. RNFL = retinal nerve fiber layer; GCIPL = ganglion cell + inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer.

Table 3 Summary Recommendations for Application of Visual Outcome Measures for Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Trials Based on the Study Design

Visual outcome measure	Traditional DMT trials	Acute ON neuroprotection or remyelination trials	Chronic injury neuroprotection or remyelination trials
HCVA	Best-corrected monocular HCVA should be collected at baseline and follow-up visits	Capture HCVA at visual nadir and recovery values at 3, 6, and/or 12 mo.	Best-corrected monocular HCVA should be collected at baseline and follow-up visits.
Low-contrast vision (LCLA and contrast sensitivity)	Best-corrected monocular LCLA should be collected at baseline and follow-up visits. CS also appropriate, but LCLA may be more sensitive to change over time.	Capture LCLA or CS at visual nadir and recovery values at 3, 6, and/or 12 mo.	Best-corrected monocular LCLA should be collected at baseline and follow-up visits. CS is also appropriate, but LCLA may be more sensitive to change over time.
VF perimetry	May not have as high utility in this design.	Capture perimetry at visual nadir and recovery values at 3, 6, and/or 12 mo. Assess data quality and ability to fixate (may be impaired in severe ON).	May not have as high utility in this design.
VEP, mfVEP	May not have as high utility in this design.	Capture VEP or mfVEP at visual nadir and recovery values at 3, 6, and/or 12 mo. Assess data quality and ability to fixate (may be impaired in severe ON).	Capture VEP or mfVEP at baseline and all follow-up visits. Assess data quality and ability to fixate (may be impaired in eyes with a history of severe ON).
OCT	Obtain spectral domain imaging at baseline and semiannual or annual follow-up visits, capturing pRNFL, total macular volume, and automated retinal layer segmentation outcomes. Account for history of and new events of ON during study, as well as baseline OCT values. Adhere to OSCAR-IB criteria[68] and APOSTEL recommendations[127]	Obtain spectral domain imaging at 1, 6, and 12 mo of follow-up. At 1 mo may capture early GCIPL thinning; early pRNFL measures will reflect edema more than atrophy. Also, capture total macular volume, and automated retinal layer segmentation outcomes. Adhere to OSCAR-IB criteria[68] and APOSTEL recommendations[127]	Obtain spectral domain imaging at baseline and semiannual or annual follow-up visits, capturing pRNFL, total macular volume, and automated retinal layer segmentation outcomes. Account for history of and new events of ON during study, as well as baseline OCT values. Adhere to OSCAR-IB criteria[68] and APOSTEL recommendations.[127]
Advanced MRI measures (DTI and MTR) of visual pathway structures	May provide baseline and follow-up information about acute inflammatory activity, but more broad use of measures across brain structures may be more appropriate.	Obtain at visual nadir and final follow-up visit. Recommend to consider using these as predictors to response to therapy and final functional visual outcome measures.	Obtain at baseline and final follow-up visit. Recommend to consider using these as predictors to response to therapy and final functional and structural visual outcome measures.
Visual QOL	Should be included with other PROs in secondary analyses.	Obtain at visual nadir and final study visit. Recommend to include in all of these studies as secondary outcome.	Obtain at baseline and final study visit. Recommend to include in all of these studies as secondary outcome.

should consider if investigative medication could alter typical time course of retinal layer thinning).

Consistent with postmortem findings,[e2] pRNFL and GCIPL thicknesses are lower than in the healthy population even in those without a history of clinical ON, but thinning is more severe in ON eyes.[37] The etiology of insidious optic nerve injury in MS is not fully understood but may have contributions from subclinical optic nerve inflammation or transsynaptic retrograde degeneration from posterior visual pathway injury. Compared with MS ON eyes, eyes with AQP4-IgG and MOGAD-associated ON have greater pRNFL and GCIPL thinning, which appears to be commensurate with greater losses in HCVA and LCLA in AQP4-IgG, but not MOG-IgG, associated ON.[38] While not as prominent as in MS, there is some evidence to suggest that subclinical retinal neuroaxonal loss may occur in NMOSD, possibly caused by an attack-independent astrocytopathy.[e4, e38-e41] Consistent with this, attack-independent tissue loss and associated functional changes were found in the parafoveal region, which is rich in astrocytes and AQP4-expressing Müller cells.[7,e40-e42]

Accelerated rates of inner retinal atrophy in MS eyes are associated with inflammatory disease activity, global disability progression, and increased brain atrophy.[6,39,e43-e44] Disease-modifying therapies (DMTs) may differentially affect pRNFL and GCIPL thinning in MS, mainly in the relapsing-remitting stage.[40] Important to trial design, there are floor effects in eyes that have already had significant retinal injury. This is in part why one might consider adjusting for baseline OCT values, even in randomized trials. Also relevant for study design and inclusion criteria, the proportion of pRNFL and GCIPL thinning attributable to MS decreases with older age. After age 65 years, >80% of the rate of thinning in these layers is attributable to normal aging.[6] pRNFL and GCIPL thinning is faster earlier in the RRMS disease course (when there is more tissue to lose), whereas progressive disease subtype (which is associated with older age) is independently associated with faster inner retinal layer thinning.[6] Normative values of retinal layer thicknesses differ by race, with African American patients with MS exhibiting faster rates of retinal atrophy.[41,e45] Differential effects of sex on levels of retinal injury exist, with men and boys demonstrating worse atrophy after ON.[42,43] These data highlight the importance of accounting for patient demographics on rates of pRNFL/GCIPL thinning when designing trials.

In addition to pRNFL and GCIPL, deeper retinal neuronal layers have been proposed as biomarkers of chronic neurodegeneration, with accelerated INL and ONL atrophy

reported in progressive MS compared with both relapsing-remitting MS and healthy controls.[6] Notably, the INL exhibits a complex spectrum of abnormalities in MS including microcystoid macular pathology, increased thickness in association with inflammatory disease activity, reduction in thickness following DMT initiation, and atrophy in late, progressive disease.[e2-e4]

OCT has also been used to support the identification of clinical and subclinical ON by identifying intereye differences in the pRNFL and GCIPL layers.[44,e46-e47] OCT has also been used for participant selection criteria to identify those who may be more likely to benefit from remyelination therapies.[19]

A special consideration for MOGAD trials is the relative preserved central acuity despite moderate to severe retinal injury. Compared with NMOSD, for a given level of pRNFL thinning, there are better HCVA outcomes in MOGAD.[38] This may be due to less involvement of the papillomacular bundle in MOGAD, but definitive studies are needed.

OCT outcomes have been studied in the pediatric population. As in the adult MS population, decreased RNFL and GCIPL are noted early in the disease course[43,45] with evidence for progressive RNFL and GCIPL loss through time. Thus, despite having better visual function recovery, children have similar burden of retinal thinning.[43,45] As in adult patients, distinct OCT patterns can distinguish pediatric neuroinflammatory disorders such as MOG-IgG– and AQP4-IgG–related neuroinflammation from MS.[e48]

MRI Visual System Structural Measures

Complementary to OCT, MRI outcomes evaluate anterior and posterior afferent visual pathway injury. Methodological advances have overcome the challenges of optic nerve imaging posed by its small size, mobility, and location adjacent to nasal cavities, orbital fat, and CSF.[e49] Particularly in MOGAD, optic nerve MRI can speed diagnosis—showing characteristic features including anterior longitudinal extensive optic nerve lesions and perineural or periorbital gadolinium enhancement.[e50-e52]

Optic nerve cross-sectional area can be reliably assessed using a short-echo fast fluid-attenuated inversion recovery sequence with fat and CSF suppression.[e53] In a 12-month acute ON longitudinal study of this method, there was an 11.7% greater decline in affected vs unaffected optic nerve volumes.[46] Optic nerve atrophy correlated with RNFL thinning[47] after ON, and with both HCVA and P100 latency in chronic optic neuropathy[e49], supporting potential use of this approach in trials (Table 1).

Diffusion tensor imaging (DTI) captures three-dimensional magnitude and direction of water diffusion. After acute ON, diffusion parallel to axons (axial diffusivity, AD) is low, whereas diffusion perpendicular to the axon, or radial diffusivity (RD), remains in a normal range.[48] In a 12-month longitudinal study of 37 patients with acute ON,[49] reduced AD at baseline correlated with pRNFL thinning and mfVEP amplitude loss at 6 and 12 months. Importantly, early reductions in AD also predict VA recovery at 6 months,[49,e54] suggesting that acute ON therapies that normalize optic nerve AD could also promote axon survival and improve visual outcomes. Baseline measurements of optic nerve DTI (Table 2) may also help select patients who are most likely to benefit from intervention.[50] DTI can be obtained on most commercial scanners but, unfortunately, adds significant acquisition time and cost. Advanced image processing and analytical requirements are additional barriers to widespread implementation, but we anticipate reduction of these barriers with improved, standardized software.

Application of optic nerve DTI in acute NMOSD-ON has not been as well studied. In 1 retrospective study of 57 patients with NMOSD-ON,[e55] a radiomics model using whole-brain DTI measures correlated strongly with visual outcomes after IV methylprednisolone, suggesting its potential as a predictor of response to acute therapy.

The magnetization transfer ratio (MTR) indicates the balance between protons bound to molecules (protein and lipids) vs free protons. Postmortem studies have confirmed a strong association between a reduced MTR and demyelination,[e56] whereas others have shown a similar correlation between MTR and axonal density or both.[e57] It is accepted that a higher MTR indicates more bound protons, as seen in normal, myelinated tissue. MTR decreases in acute ON[e58] with an approximate 8-month nadir[46] and correlates with P100 latency, HCVA,[46] mfVEP amplitude, and RNFL thinning.[e59,e60] MTR in the optic nerve, whole brain, or T2 lesions have been used in clinical trials (Table 2, Table e1, links.lww.com/NXI/A675). Timing and location of MTR measurement in relation to the acute injury is critical for interpretation of results. In the anti–LINGO-1 RRMS trial, baseline lesional MTR was associated with disability outcomes in the 10 mg/kg group.[50]

New Structural Biomarkers

OCT advances may offer novel biomarkers for future trials.[e61-e62] New machine learning retinal segmentation algorithms decrease rater dependence, improve reliability, and allow automatic quantification of disease-specific changes such as microcystic macular edema.[e63] Novel 3D methods resample standard OCT images to depict retinal shape changes,[e40,e64-e65] which may be especially useful to standardize assessment of NMOSD foveal morphology changes.[e40,e42,e66]

Another new addition, OCT angiography (OCTA), uses the movement of erythrocytes to create maps of the superficial and deep retinal vascular plexuses and to calculate retinal vascular flow rates. In MS and NMOSD, vessel reduction in OCTA images is correlated with neuroaxonal damage, and in MS, also with general disability (EDSS).[51,e67-e68] Relative blood flow velocity is decreased around the optic nerve head

and fovea in patients with MS and AQP4-IgG–seropositive ON.[52,53]

Finally, new MRI sequences such as double-inversion recovery sequences can help detect early optic nerve injury and improve timely trial inclusion.[e69] Atlas-based automated segmentation and volumetry of the LGN may facilitate understanding of anterograde and retrograde neurodegeneration and visual function.

Recommendations for Implementation of Afferent Assessments in Clinical Trials

With the increasing use of afferent visual assessments, it is important to understand the best methods in a specific study design and the main challenges and pitfalls in applying them (Tables 3 and 4).

Study Design

Balancing the needs of generalizability vs risks of heterogeneity impairing detection of treatment effects, clinical trials should clearly define the disease state measured (e.g., acute optic neuritis and chronic optic neuropathy), inclusion and exclusion criteria, and measurement protocols. Depending on the intervention's mechanism of action, different time points or assessments should be considered; these decisions can be critical to the success of the trial.

It is important to take into account differential pathophysiologic features of MS, NMOSD, and MOGAD as well as to consider aging effects and potential basement effects (e.g., testing putative neuroprotective therapies in eyes with severe optic neuropathy), and disease- or treatment-related retinal changes such as microcystoid and/or fingolimod-associated macular edema.[e5,e70]

Other important considerations are excluding patients with confounding primary ophthalmologic pathologies (e.g., severe myopia, glaucoma, central serous retinopathy, or diabetic retinopathy) and identifying the up to 16% of patients with MS who may have unrelated morphologic macular abnormalities such as drusen or epiretinal membranes, which can induce OCT segmentation errors or be associated with nonneurologic causes of visual dysfunction.[e71]

In ON, conduction block and inflammatory edema may limit the use of standard VEP and pRNFL OCT measurements at early time points. For chronic optic neuropathy, pathologic sensitivity of some measures may change in the setting of gliosis[e72] or visual repair (e.g., functional neuroplasticity).[e9] Importantly, regulatory authorities are likely to always prefer a clinical outcome for phase III RCTs, and trial duration of up to 12 months may be needed to fully capture the effects of an intervention on visual recovery.[12]

Advanced imaging techniques may provide the means to better stratify and select trial participants most likely to benefit from early intervention with a potential neuroprotective therapy. Optic nerve DTI measurements such as AD, especially if assessed outside the anatomical segment with acute inflammatory change, could more directly assess the degree of axonal involvement. Similarly, MTR could also potentially be used as an early stratification tool when allocating patients to different treatment groups.[e73]

Data Acquisition

A strong study protocol defines the specific device(s), measurement parameters, required environment (e.g., illumination and noise level), and patient needs (e.g., refractive correction). Frequency of assessments needs to be tailored to the clinical model (acute or chronic ON), temporal flux in visual and paraclinical measures, and safety requirements. For assessments requiring focus and alertness such as electrophysiologic or VF perimetry, patients with fatigue or cognitive dysfunction may require accommodations.[54,e74] Efferent dysfunction can negatively affect fixation and acquisition of afferent measures. Severe acute ON can impair ability to fixate, resulting in poor-quality electrophysiology and OCT studies. Awareness of these pitfalls can help troubleshoot ways to acquire the best data (e.g., fixate with the unaffected or less affected eye during OCT acquisition).

Data Analysis

Ideally, multicenter trials should use identical devices and protocols for data acquisition. When this is not feasible, the statistical analysis plan should account for device and protocol effects. Efforts to harmonize data from different OCT devices are under way, and initial results are promising. Multisite success has been demonstrated for automated retinal segmentation software.[55] In nonrandomized studies, multivariable modeling to account for confounding variables (sex, age, ethnicity, history of ON, and baseline disability measures) is important. Even in randomized studies, tracking the ON status of each eye and considering adjustments for baseline values of measurements are important as the meaning and magnitude of change in measures may notably differ based on these variables, particularly for OCT studies. In analyses for which each participant contributes data from both eyes, intereye correlations must be adjusted for using mixed-effects models or generalized estimating equations. When possible, both eyes of a patient should be included, but for correlations with MRI outcomes, either the best or worst eye in terms of the outcome measure could be used. Averaging values between eyes may result in losing information about injury as the worse eye may be more informative about disease injury than an averaged value. Eyes should be tested individually for HCVA and LCLA. If binocular measures are included, the impact of the neuroimmunologic disease on binocular summation/inhibition should be considered. In adult MS, binocular summation may be impaired[e75] and could be an outcome measure to consider if appropriate for the research question.

Table 4 Systematic Approach to Common Pitfalls in Visual System Assessments for Clinical Trials and Observational Studies

Pitfall	Systematic approach
Study design	
Study criteria too liberal with participant heterogeneity and confounding of comorbid ophthalmologic disease	Design the cohort as homogenously as possible and appropriate for the research question Clearly specify the study population (RMS vs PMS, AQP4-IgG– vs MOG-IgG–positive disorders). Exclude patients with certain systemic comorbidities and diagnoses that could influence outcome measures such as severe myopia, CSR, glaucoma, or diabetic retinopathy. Depending on your research question, consider excluding patients with disease- or treatment-related retinal pathologies that could bias/influence your results such as microcystic macular edema, fingolimod-associated macular edema, prior ON, or optic radiation lesions.
Simplified protocols for multicenter studies	Be as specific as possible about device(s) needed, measurement parameters, and environment (e.g., illumination, dilatation, distance required, and type of visual acuity correction).
Data acquisition	
Interference of non–vision-related symptoms	Consider the impact of other disease-related symptoms such as cognitive changes and fatigue on obtaining data, and if this affects the quality of the study, consider excluding patients with specific symptoms.
Interference of vision-related symptoms	If possible, use newest generation devices that may help mitigate other vision- and disease-related symptoms interfering with the patient's fixation abilities or functional measurements such as Pulfrich and Uhthoff phenomenon, binocular summation, or sex-specific disease characteristics.
Interference of data quality	OCT results are biased by low signal strength or cyclotorsion and other measurement artifacts (e.g., nystagmus-induced motion artifact), and a premature classification of VEP latencies as absent can significantly decrease the usability of the data.
pRNFL edema confounding atrophy measurements	The pRNFL thickness in OCT can be dramatically affected by edema (thickened) during the acute stage of ON and cannot be used as a marker of retinal neurodegeneration until >3–6 mo post-AON. The combined GCIPL layer is less likely to be confounded by edema in early measurements.
Confounding of longitudinal measurements by aging or development of ocular diseases	To ensure correct longitudinal assessments, many devices allow to measure in a follow-up mode. However, multiple influencing factors such as age and myopia and learning effects have to be considered when comparing longitudinal data to a normative cohort.
Data analysis	
Increased error of point estimates from combining data from multicenter and multidevice studies	For most OCT and electrophysiologic assessments, the data from different devices and/or protocols are not yet comparable. Advanced analysis approaches have to be applied to allow a merged data analysis.
Reliability and reproducibility across centers	The intertest and intratest variability vary dramatically between centers and device operators. Ideally, the range of variability should be established for each center, and (significant) results that are within the range of retest variability should be interpreted with caution.

Abbreviations: RMS = relapsing MS; PPMS = primary progressive MS; MOG = myelin oligodendrocyte protein; AQP4 = aquaporin-4 channel; ON = optic neuritis; OCT = optical coherence tomography; VEP = visual evoked potential; CSR = central serous retinopathy; pRNFL = peripapillary retinal nerve fiber layer.

Quality Control and Reporting of OCT Results

Given the complexity of OCT technology, as well as its susceptibility to artifacts or confounding pathologies, complete reporting of methodology and quality control are of paramount importance. Investigators are recommended to adhere to the OSCAR-IB criteria[32] and APOSTEL recommendations[56] for quality control and reporting of OCT studies, respectively.

Efferent Visual System and Oculometrics

Most people with MS experience efferent visual dysfunction from disorders of fixation to intereye misalignment. Efferent oculometric assessments may reveal deficits not readily appreciated at bedside and associate with overall disability in MS.[57] An eye-tracking paradigm was able to detect subtle cerebellar dysfunction in participants without ataxia.[58] Even in the very young, with pediatric onset MS and no discernible disability on examination, saccadic latencies can distinguish eyes of patients with MS from those of healthy controls.[59] For rapidly quantifying disease burden largely driven by the brainstem and cerebellum (key contributors to overall disability scores), eye-tracking approaches offer objective, reliable means to collect these data.

Despite the great promise of efferent oculometric techniques in quantifying neuroimmunologic disease burden, these approaches have not percolated significantly into clinical trials. One interventional neuromodulation study lists video nystagmography as an exploratory outcome of treatment efficacy (NCT02252666). A primary reason may be the variety of eye-tracking devices and software and a lack of widely accepted protocol parameters for data quality. However, these are surmountable obstacles, and similar consensus and quality approaches could be applied as has been done for the afferent measurements highlighted here.

Advantages of Assessments in the Visual System

Low Cost and Correlations With Other Outcome Measures—Atrophy, Cognition, and Employment Status

RNFL and GCIPL thinning on OCT are low-cost measures that have shown considerable cross-sectional and longitudinal associations with other outcome measures of tissue damage in MS, including brain volume loss,[39,e76-e77] in particular when ON eyes are removed from analyses.[e78-e79] These associations likely emerge from a common pathophysiologic denominator and suggest that in some settings, retinal measures may be used as surrogates of MRI measures. Anterograde or retrograde transsynaptic degeneration involving retrogeniculate parts of the visual pathway may influence these associations.[e80-e81] Retinal damage may also relate to functional connectivity changes in the visual system and other networks in ON, MS, and NMOSD.[e82-e84]

RNFL and GCIPL thinning have been associated with worse cognitive performance,[e85-e86] suggesting a shared underlying pathobiology of diffuse CNS tissue destruction. However, reduced visual function might affect cognitive test performance, and cognitive dysfunction may alter the capability to execute more demanding visual tests such as LCLA testing.[e74] Finally, higher serum neurofilament light chain (NfL) has been associated with lower RNFL and GCIPL thickness values in the non-ON eyes of participants with MS.[e87]

Precision and in Vivo Human Microstructural/Sensitive Functional Assessments Unparalleled in the Other Systems Affected by MS

The availability of sensitive measures has enabled rigorous measurement of structural and functional changes in the injured visual system to a greater degree than is possible in other regions of the CNS.[e88] Structural changes on OCT are strongly correlated with changes in LCLA and visual QOL. One can estimate the functional consequence of a 5–10-μm change in RNFL thickness. Such precision has not been clearly recorded for the corticospinal tracts, for example.

IMSVISUAL View of the Landscape and Proposed Role of Visual System for Trials of Agents in the Pipeline

IMSVISUAL aims to improve care, research, and education in MS and other neuroinflammatory disorders by advancing our understanding of the visual system and by providing a framework and international standards for applying vision tools in clinical trials. These methods are sensitive, reliable, and cost-effective with strong structure-function correlations. Different tools provide complementary information and have ideal time points for use along the temporal course of visual injury (Table 4). Best practices and even published standard criteria exist to guide rigorous study design in visual outcome applications. For all paradigms of trials in MS and NMOSD (and future trials in MOGAD), from standard DMT trials or those of neuroprotection and remyelination, and even trials of comparative efficacy, applications[e90-e94] of visual outcome tools offer cost-effective mechanisms to capture widespread and focal injury across disease subtypes and may lead to more rapid development of new therapeutics for these disabling diseases.

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E. Ann Yeh, MD	Division of Neurology, Department of Pediatrics, Division of Neuroscience and Mental Health, Hospital for Sick Children, Hospital for Sick Children Research Institute, and University of Toronto, Toronto, Canada	Drafting/revision of the manuscript for content, including medical writing for content
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/NXI/A677.

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