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SCORE2 Report 5: Vision-Related Function in Patients with Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion

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INTRODUCTION

Retinal vein occlusion is the most common retinal vascular disorder after diabetic retinopathy, affecting an estimated 1–2% of the population older than 40 years,^{1,2} and 16 million persons worldwide.³ Macular edema (ME) is the leading cause of vision loss in patients with retinal vein occlusion.^{4–6} The *Study of COmparative Treatments for REtinal Vein Occlusion 2* (SCORE2) is a phase 3 randomized controlled clinical trial conducted to investigate whether bevacizumab is non-inferior to aflibercept with respect to visual acuity (VA) in eyes with ME associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).^{7,8} Between September 2014 and November 2015, 305 patients with CRVO and 57 patients with HRVO were enrolled at 66 private practice or academic centers in the United States and randomly assigned to receive intravitreal injection of bevacizumab (1.25 mg) or aflibercept (2.0 mg) at randomization and every 4 weeks through Month 5. The primary outcome is change from baseline in best-corrected electronic Early Treatment Diabetic Retinopathy Study (e-ETDRS) VA letter score (VALS) at Month 6, with a non-inferiority margin of 5.^{7,8} The purpose of the current report is to describe the baseline patient-reported vision-related function, measured with the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25),^{9–11} in patients with ME secondary to CRVO or HRVO in SCORE2; to evaluate the relationship between NEI-VFQ-25 scores and 1) visual acuity and 2) central retinal thickness (assessed by central subfield thickness [CST] on

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spectral domain optical coherence tomography [SD-OCT]) at baseline; and to compare the baseline NEI-VFQ-25 scores of SCORE2 participants with those of normal vision reference populations and patients in other retinal vein occlusion clinical trials.

METHODS

SCORE2 is a multicenter, non-inferiority randomized controlled trial. The SCORE2 design and methods have been described in detail⁷ and are summarized here. The study adhered to the tenets of the Declaration of Helsinki¹² and is registered on <http://www.clinicaltrials.gov> (identifier: NCT01969708). Institutional review board (IRB) approval of the protocol was obtained from either a site-specific or centralized IRB (Chesapeake IRB, Columbia, Maryland), and written informed consent was obtained from all participants before eligibility screening and again before randomization into the study.

At the baseline visit, each participant was interviewed to obtain demographic information and medical history, including ocular history and current medications; received blood pressure, height and weight measurements; and received comprehensive ophthalmologic evaluation of each eye, including E-ETDRS visual acuity measurement at 3 meters by a SCORE2 certified technician, intraocular pressure measurement by Goldmann applanation tonometry or tonopen, slit-lamp and dilated funduscopy examinations, modified 3-field stereoscopic color fundus photography, SD-OCT assessment including CST measurement and, at sites with an Optos ultra-widefield model 200Tx camera, ultra-widefield fluorescein angiography (FA). All imaging tests (color fundus photographs, FA and SD-OCT) were sent to the Fundus Photograph Reading Center at the University of Wisconsin-Madison for grading. The 25-item NEI-VFQ-25 (http://www.rand.org/health/surveys_tools/vfq/) was administered to participants by clinical center coordinators who were certified in NEI-VFQ-25 administration by The Emmes Corporation.

The NEI-VFQ-25 is the short form of the NEI-VFQ Field Test Version that was developed to include general health, general vision, ocular pain, near vision activities, distance vision activities, social functioning, vision-specific role difficulties, vision-specific mental health, dependency because of vision, driving, peripheral vision, and color vision.¹¹ Item responses were transformed to a scale of 0 to 100, with higher scores indicating better patient-reported vision-related function. The NEI-VFQ-25 composite score was calculated as the average of the 25 items, and the subscale scores are the averages of the responses to items within each subscale.

The composite and each subscale score for the NEI-VFQ-25 were calculated according to published algorithms.¹⁰ Basic summary statistics, including mean, standard deviation, median, and number and percent of SCORE2 participants' responses at the maximum (i.e., ceiling) and minimum (i.e., floor) for the NEI-VFQ-25 composite and for each subscale were computed. Cronbach's standardized α was calculated to assess the internal consistency and reliability of the multi-item subscales. Generally, Cronbach's α values of 0.7 or greater are considered acceptable.¹³ The relationship between NEI-VFQ-25 scores and baseline factors of VALS (better eye and worse eye) and CST was assessed using Pearson correlation coefficients. The relationship between NEI-VFQ-25 scores and binary baseline factors

(medical conditions, HRVO or CRVO disease type, months from diagnosis, prior anti-vascular endothelial growth factor [anti-VEGF] treatment) was assessed using t-tests. P-values from statistical tests examining these relationships were adjusted for multiple testing to ensure family-wide error of 0.05 within each table according to a method in which the p-values of an ensemble of t-tests or correlations are adjusted based on the simulated distribution of the minimum p-value in the ensemble under a permutational hypothesis.¹⁴ NEI-VFQ-25 scores from SCORE2 participants were also compared to normal vision populations from three different studies^{10,15,16} and to baseline NEI-VFQ-25 scores observed in four retinal vein occlusion clinical trial populations; two in CRVO, the CRUISE^{17,18} (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; ClinicalTrials.gov identifier NCT00485836) and COPERNICUS¹⁹ (Vascular Endothelial Growth Factor Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion; ClinicalTrials.gov identifier NCT00943072) trials; and two in branch retinal vein occlusion (BRVO), the BRAVO^{17,20} (Ranibizumab for the Treatment of Macular Edema after Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; ClinicalTrials.gov identifier NCT00486018), and VIBRANT²¹ (Study to Assess the Clinical Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Branch Retinal Vein Occlusion; ClinicalTrials.gov identifier NCT01521559) trials, based on Bonferroni-corrected t-tests and confidence intervals to ensure family-wide error of 0.05 within each table or figure. SAS versions 9.3 and 9.4 (SAS Inc, Cary, North Carolina) were used to conduct statistical analyses.

RESULTS

Study Population

Baseline characteristics of the SCORE2 study population have been described in detail,⁷ and selected characteristics are presented in Table 1. The mean age of SCORE2 participants was 69 years, with 43% women, and 76% white. Participants had ME for an average of 7 months (range: 0 to 104 months) before randomization. Mean CST was 666 μ m (range: 219 μ m to 1420 μ m), 33% had received anti-VEGF treatment prior to study participation, and 16% were diagnosed with HRVO.¹ Mean VALS in the study eye was 50 (approximate Snellen 20/100), lower than the mean VALS of 81 (approximate Snellen 20/25) in the non-study eye. The study eye had the worse VALS in 94% of the SCORE2 participants, with the mean VALS of the better eye at baseline of 83 (approximate Snellen 20/25) compared to the mean VALS in the worse eye of 48 (approximate Snellen 20/125). The VALS of the better eye was 79 or better (approximate Snellen 20/25 or better) in 74.3% of patients and was 69 or better (approximate 20/40 or better) in 90.2% of patients.

Table 2 presents summary statistics for the NEI-VFQ-25 scores for the SCORE2 participants. The mean NEI VFQ-25 composite score was 77, with lower subscale scores observed for general health (mean=58), general vision (mean=64), near activities (mean=68), and mental health (mean=65). A number of the scales showed high scores, with large ceiling effects where more than 25% of the SCORE2 population had the highest possible score, which included ocular pain, social functioning, role difficulties, dependency, color vision, and peripheral vision. The internal consistency estimates of the NEI-VFQ-25

scores in SCORE2 participants as measured by Cronbach's α ranged from 0.66 to 0.91, with 8 of the 9 categories with multi-item subscales having a Cronbach's α greater than 0.7, which is considered an acceptable level for internal consistency.¹³

Pearson correlation coefficients between the NEI-VFQ-25 scores and baseline VALS and CST in the study eye are presented in Table 3. Only VALS in the better eye at baseline showed a statistically significant correlation with NEI-VFQ-25 subscale scores after multiple testing adjustments, as noted for the following 6 subscales: general vision, near activities, role difficulties, dependency, color vision, and the NEI VFQ-25 composite score. The statistically significant correlations in these 6 areas were positive, and ranged from 0.19 (role difficulties) to 0.26 (general vision and near activities). The association between NEI-VFQ-25 subscales and baseline co-morbidities (coronary heart disease, diabetes, and hypertension) and other participant (prior anti-VEGF treatment) and ocular characteristics (disease type and months from diagnosis of macular edema) are presented in Table 4. After adjustment for multiple testing, only presence of hypertension and presence of diabetes showed significantly worse general health subscale scores on the NEI-VFQ-25. The mean general health subscale scores for SCORE2 participants without diabetes or hypertension was 69. The scores were lower in those participants with hypertension only (mean score=60) or those with diabetes only (mean score=52). Participants having both conditions had the lowest mean general health score of 47 (data not shown in tables).

SCORE2 NEI-VFQ-25 scores were compared to those of three populations with normal vision.^{10,15,16} Each of the 3 normal vision reference populations was an elderly population, similar to SCORE2, and all had approximately 20/20 vision (Table 1). The NEI-VFQ-25 scores of the 3 normal vision reference populations were similar to each other, and all mean NEI-VFQ-25 subscale scores in these populations were higher than those observed in SCORE2 participants (Table 5A). In addition, except for ocular pain, all mean NEI-VFQ-25 subscale scores in the SCORE2 population are statistically significantly lower than the corresponding subscale scores in the normal vision populations, as demonstrated by non-overlapping Bonferroni-corrected confidence intervals (Figure 2).

Table 5B and Figure 3 show the mean NEI-VFQ-25 scores for the SCORE2 population compared with NEI-VFQ-25 scores measured at baseline in two CRVO trials, CRUISE¹⁷ and COPENICUS¹⁹, and in two BRVO trials, BRAVO,¹⁷ and VIBRANT²¹ (note that only a subset of NEI-VFQ-25 scores were reported in COPENICUS and VIBRANT). The NEI-VFQ-25 scores observed in these four retinal vein occlusion trials show non-significant differences to SCORE2 based on pairwise testing (Table 5B) and on overlapping Bonferroni-corrected confidence intervals (Figure 3), suggesting that participants in each of five retinal vein occlusion trials exhibit similar patient-reported vision-related function. Further, when analysis is limited to the three studies with the full set of NEI-VFQ-25 subscale scores (i.e., SCORE2, CRUISE and BRAVO), the mean subscale scores are highly correlated with each other, with rank correlation coefficients ranging from 0.97 to 0.99. Similarly, the mean subscale scores of the normal vision populations studied by Mangione,¹⁰ Owsley,¹⁵ and Chia¹⁶ are highly correlated, with coefficients ranging from 0.86 to 0.97. In contrast, correlations between the three retinal vein occlusion and three normal vision reference groups are weaker, ranging from 0.67 to 0.80.

DISCUSSION

Results of the current study demonstrate that CRVO and HRVO have a major impact on patient-reported vision-related function, despite the fact that retinal vein occlusion is typically a unilateral condition. In the population-based Blue Mountains Eye Study, 94.9% of retinal vein occlusions were unilateral,¹ and in SCORE2 93% (338 out of 362 SCORE2 participants) of participants had unilateral retinal vein occlusion (defined as no history of retinal vein occlusion in the fellow eye). Although the affected eye was the worse-seeing eye in 94% of SCORE2 participants, and the mean VALS in the unaffected eye was 81 (approximate Snellen 20/25), NEI-VFQ-25 scores were significantly lower in SCORE2 participants compared to three normal vision reference populations of similar or older age. Thus, in SCORE2, even if fellow eye vision is excellent, the presence of CRVO or HRVO in one eye impacts patient-reported vision-related function significantly. This may be because when the visual acuity in the two eyes is substantially disparate, binocular inhibition reduces the effective binocular visual acuity, thus leading to a reduced ability to function.^{17,22}

Prior studies in patients with age-related macular degeneration (AMD)^{23,24} and a variety of retinal diseases (including such diseases as AMD and diabetic retinopathy)²⁵ reported significant correlations between self-reported vision-related function and visual acuity not only in the better-seeing eye, but also in the worse-seeing eye. In contrast, NEI-VFQ-25 scores in the SCORE2 population were significantly correlated with better eye, but not worse eye, visual acuity. This difference may be because conditions such as AMD and diabetic retinopathy are typically bilateral diseases, so that better-eye and worse-eye visual acuities are more similar in patients with these conditions than in patients with retinal vein occlusion, which is typically unilateral. For example, in the Age-Related Eye Disease Study (AREDS), the mean VALS was 81.5 in the better eye and 69 in the worse eye (a difference of 12.5 letters)²³ while in SCORE2, the mean VALS was 83 in the better eye and 48 in the worse eye (a difference of 35 letters). Another potential explanation for this difference is that the SCORE2 analyses were adjusted for multiple comparisons, while the analyses in the afore-mentioned studies^{23–25} were not; in support of this hypothesis, the reported correlation coefficients in SCORE2 between self-reported vision-related function and visual acuity in the worse-seeing eye were generally smaller than the corresponding correlation coefficients for the better-seeing eye.

In the SCORE2 population, the scores of all NEI-VFQ-25 subscales except ocular pain are significantly lower than the corresponding subscale scores in three normal vision reference populations. Similarly, in a study of 51 patients with CRVO at a single academic medical center, scores for all NEI-VFQ-25 subscales except ocular pain were significantly lower than in a reference group without ocular disease (one of the reference populations used in the current study¹¹).²⁶ This finding is not surprising since retinal vein occlusions are typically associated with a painless loss of vision.

There is remarkable consistency of NEI-VFQ-25 scores of the SCORE2, CRUISE, COPERNICUS, BRAVO and VIBRANT populations. Not only are the differences (with a Bonferroni correction) among the scores of all five trials non-significant for each of the NEI-VFQ-25 subscales for which published data for such comparisons are available, but the rank

correlation of the subscales from lowest to highest score is highly consistent among the three trial populations (SCORE2, CRUISE, and BRAVO) with published NEI-VFQ-25 scores for all of the NEI-VFQ-25 subscales. This consistency supports the validity of the NEI-VFQ-25 in retinal vein occlusion patients and provides strong evidence of the relative impact of retinal vein occlusion on the various domains of vision-related functioning assessed by the NEI-VFQ-25. Given the systemic associations of such conditions as hypertension with retinal vein occlusion, and the known decrease in visual acuity associated with macular edema due to retinal vein occlusion, it is not surprising that general health and general vision are the two subscales with the lowest NEI-VFQ-25 scores in the SCORE2, CRUISE and BRAVO populations. It may be somewhat surprising, however, that the next lowest NEI-VFQ-25 subscale score in all three retinal vein occlusion trial populations is mental health. This may be due, at least in part, to associated anxiety and challenges of coping with the generally unexpected and sudden onset of a retinal vein occlusion, the relatively burdensome treatment regimen of monthly intravitreal injections, and the uncertain and guarded prognosis associated with retinal vein occlusion. In the SCORE2, CRUISE, COPENICUS, BRAVO and VIBRANT populations, the near activities subscale score is 6 or 7 points lower than the distance activities subscale score. As noted above, the visual acuity in the two eyes of retinal vein occlusion patients is typically substantially disparate, with the contralateral eye being the better-seeing eye in more than 90% of patients in SCORE2, CRUISE and BRAVO (the proportion of patients with the contralateral eye being the better-seeing eye is not reported in COPENICUS¹⁹ or VIBRANT²¹); perhaps the contralateral eye compensates better for distance activities than for the fine detail vision required for many near activities. Similarly, perhaps the contralateral eye also compensates better for color vision, social functioning, and dependency, all of which were scored relatively higher on the NEI-VFQ-25 by the SCORE2, CRUISE and BRAVO populations.

In sum, although typically unilateral, CRVO and HRVO have a major impact on patient-reported vision-related function even in patients with excellent fellow eye visual acuity. In the SCORE2 population, the scores of all NEI-VFQ-25 subscales except ocular pain are significantly lower than the corresponding subscale scores in three normal vision reference populations. There is also remarkable consistency of NEI-VFQ-25 scores of the SCORE2, CRUISE, COPENICUS, BRAVO and VIBRANT populations.

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Figure 1.

NEI-VFQ-25 Results in SCORE2 Participants. The box in the box and whisker plot is the 25th to 75th percentile (the inner quartile range), with the median shown as a line within the box and the mean shown as a diamond. The whiskers extend to the minimum observation above the lower fence and maximum observation below the upper fence, which are defined as 1.5 times the inner quartile range below the 25th percentile and above the 75th percentile. The outliers, shown as circles, mark any observation below the lower fence or above the upper fence.

Figure 2.
Comparisons of Mean NEI-VFQ-25 Subscale Scores with 95% Bonferroni-corrected Confidence Intervals of SCORE2 Participants with Three Normal Vision Populations.^{10,15,16}
Note that Mangione¹⁰ composite score confidence intervals are not available.

Figure 3.
Comparisons of Mean NEI-VFQ-25 Subscale Scores with 95% Bonferroni-corrected Confidence Intervals of SCORE2 Participants with Four Retinal Vein Occlusion Clinical Trial Populations, CRUISE¹⁷, COPENICUS¹⁹, BRAVO¹⁷, and VIBRANT.²¹

Table 1
Baseline Characteristics of SCORE2 Population and Normal Vision Reference Populations

	SCORE2 Population		Normal Vision Reference Populations		
	N	%	Mangione ¹⁰	Owsley ¹⁵	Chia ¹⁶
Total	362	100.0	N=122	N=365	N=736
Female	157	43.4	62%	66%	56.1% *
Age, years (mean, SD)	69 (12)		59 (14)	33% 70 years or older	60.8 *
White	276	76.2	NR	95%	NR
Diabetic	114	31.5	NR	NR	NR
Coronary artery disease	56	15.5	NR	NR	NR
Hypertensive	278	76.8	NR	NR	NR
Months between diagnosis of macular edema and randomization (mean, SD)	7 (14)				
< 2 months	235	64.9	NA	NA	NA
2 months	127	35.1	NA	NA	NA
Disease type					
CRVO	305	84.3	NA	NA	NA
HRVO	57	15.7	NA	NA	NA
Prior anti-VEGF treatment	121	33.4	NA	NA	NA
Visual acuity letter score (mean; SD)					
Study eye	50.3 (15.2) [approximate Snellen 20/100]		NA	NA	NA
Non-study eye	81.1 (17.0) [approximate Snellen 20/25]		NA	NA	NA
Better eye	83.1 (10.3) [approximate Snellen 20/25]		20/20	20/20 (logMAR=0.02)	Better than 20/40 **
Worse eye	48.4 (16.9) [approximate Snellen 20/125]		20/20	NR	Better than 20/40 **
Worse eye treated	341	94.2	NA	NA	NA
Central subfield thickness in treated eye (microns); mean (SD)	665.8 (224.3)		NA	NA	NA

SD=standard deviation; VEGF=vascular endothelial growth factor; CRVO=central retinal vein occlusion; HRVO=hemiretinal vein occlusion; NR=Not Reported; NA=Not applicable; logMAR=logarithm of the minimum angle of resolution.

* Reported in full population of 892 participants.

Reported as 6/12.
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Table 2

NEI-VFQ-25 Subscale and Composite Scores in SCORE2 Participants

NEI-VFQ-25 Subscale	N	Mean	SD	Median	Cronbach's α	Ceiling		Floor	
						N	%	N	%
General health	362	58	22	50	NA	29	8.0	5	1.4
General vision	362	64	17	60	NA	4	1.1	0	0.0
Ocular pain	362	86	18	88	0.66	180	49.7	0	0.0
Near activities	362	68	22	75	0.79	30	8.3	1	0.3
Distance activities	361	75	21	75	0.72	73	20.2	1	0.3
Social functioning	362	89	17	100	0.78	221	61.0	0	0.0
Mental health	362	65	27	69	0.81	23	6.4	5	1.4
Role difficulties	362	72	27	75	0.78	120	33.1	8	2.2
Dependency	362	83	24	92	0.85	176	48.6	2	0.6
Driving	295	74	22	83	0.78	51	17.3	0	0.0
Color vision	359	92	17	100	NA	280	78.0	0	0.0
Peripheral vision	362	79	23	75	NA	169	46.7	1	0.3
NEI VFQ-25 composite score	362	77	16	80	0.91	0	0.0	0	0.0

Correlations of NEI-VFQ-25 Subscale and Composite Scores with Better and Worse Eye Baseline Visual Acuity and Baseline Central Subfield Thickness in Treated Eye

Table 3

	Visual Acuity Letter Score in Better Eye			Visual Acuity Letter Score in Worse Eye			Central Subfield Thickness in Treated Eye (microns)		
	Corr	Raw	Adj*	Corr	Raw	Adj*	Corr	Raw	Adj*
General health	0.11	0.0686	0.7920	0.07	0.2415	0.9981	-0.08	0.1879	0.9922
General vision	0.26	0.0000	0.0006	0.18	0.0029	0.0792	-0.11	0.0706	0.8058
Ocular pain	0.06	0.3257	1.0000	-0.02	0.6907	1.0000	0.02	0.7355	1.0000
Near activities	0.26	0.0000	0.0006	0.12	0.0395	0.6017	-0.07	0.2483	0.9991
Distance activities	0.17	0.0034	0.0894	0.09	0.1384	0.9616	-0.02	0.7570	1.0000
Social functioning	0.16	0.0077	0.1820	0.04	0.5484	1.0000	-0.01	0.9181	1.0000
Mental health	0.14	0.0195	0.3741	0.18	0.0025	0.0690	-0.18	0.0028	0.0783
Role difficulties	0.19	0.0017	0.0480	0.13	0.0261	0.4611	-0.12	0.0499	0.6870
Dependency	0.20	0.0006	0.0191	0.18	0.0029	0.0791	-0.07	0.2373	0.9989
Driving	0.18	0.0018	0.0524	0.12	0.0428	0.6303	-0.05	0.3794	1.0000
Color vision	0.20	0.0009	0.0278	-0.04	0.5117	1.0000	0.02	0.7000	1.0000
Peripheral vision	-0.01	0.8338	1.0000	0.09	0.1267	0.9475	-0.06	0.3415	1.0000
NEI VFQ-25 composite score	0.22	0.0002	0.0074	0.14	0.0185	0.3619	-0.09	0.1404	0.9655

* Highlighted p-values represent those statistically significant at $p < 0.05$ after adjustment for multiple testing.

Table 4

T-test P-values* for Association between Health Issue Presence/Absence and NEI-VFQ-25 Subscale and Composite Scores

	Coronary artery disease		Diabetes		Hypertension		Disease type (HRVO)		Prior anti-VEGF treatment		< 2 months from diagnosis	
	raw	adj	raw	adj	raw	adj	raw	adj	raw	adj	raw	adj
General health	0.2600	1.0000	<0.0001	<0.0001	0.0002	0.0115	0.2417	1.0000	0.4043	1.0000	0.8354	1.0000
General vision	0.8470	1.0000	0.0717	0.9617	0.2201	0.9999	0.4943	1.0000	0.0352	0.8088	0.0040	0.1920
Ocular pain	0.8566	1.0000	0.5405	1.0000	0.8781	1.0000	0.1375	0.9988	0.1190	0.9964	0.1825	0.9999
Near activities	0.8146	1.0000	0.1366	0.9987	0.5610	1.0000	0.7656	1.0000	0.5235	1.0000	0.2751	1.0000
Distance activities	0.6970	1.0000	0.1200	0.9969	0.4972	1.0000	0.6050	1.0000	0.9548	1.0000	0.7477	1.0000
Social functioning	0.6099	1.0000	0.3096	1.0000	0.4038	1.0000	0.9799	1.0000	0.5415	1.0000	0.3084	1.0000
Mental health	0.9077	1.0000	0.5515	1.0000	0.4953	1.0000	0.5372	1.0000	0.0407	0.8525	0.0257	0.7061
Role difficulties	0.5836	1.0000	0.1635	0.9997	0.3074	1.0000	0.5140	1.0000	0.8892	1.0000	0.8153	1.0000
Dependency	0.9446	1.0000	0.7168	1.0000	0.5773	1.0000	0.9058	1.0000	0.1191	0.9965	0.0643	0.9462
Driving	0.9155	1.0000	0.8965	1.0000	0.8586	1.0000	0.1923	0.9999	0.7994	1.0000	0.8867	1.0000
Color vision	0.9009	1.0000	0.0825	0.9765	0.3398	1.0000	0.9560	1.0000	0.6797	1.0000	0.9472	1.0000
Peripheral vision	0.6379	1.0000	0.7529	1.0000	0.2681	1.0000	0.5015	1.0000	0.7383	1.0000	0.7342	1.0000
NEI VFQ-25 composite score	0.9140	1.0000	0.2877	1.0000	0.5099	1.0000	0.6303	1.0000	0.4887	1.0000	0.3207	1.0000

* Highlighted p-values represent those statistically significant at p<0.05 after adjustment for multiple testing.

Table 5A

Comparisons of Mean NEI-VFQ-25 Subscale Scores of SCORE2 Participants to Normal Vision Reference Populations

	Normal Vision Reference Populations: Mean (Standard Deviation)				CRVO - SCORE2** Mean (SD)
	Mangione ¹¹	P-value*	Owsley ¹⁵	Chia ¹⁶	
Sample size	N=122		N=365	N=736	N=362
General health	69 (24)	<0.01	74 (22)	64 (24)	58 (22)
General vision	83 (15)	<0.01	84 (11)	78 (14)	64 (17)
Ocular pain	90 (15)	1.00	90 (12)	89 (16)	86 (18)
Near activities	92 (13)	<0.01	92 (11)	89 (14)	68 (22)
Distance activities	93 (11)	<0.01	93 (9)	92 (11)	75 (21)
Social functioning	99 (3)	<0.01	98 (5)	99 (8)	89 (17)
Mental health	92 (12)	<0.01	95 (8)	90 (14)	65 (27)
Role difficulties	93 (13)	<0.01	96 (10)	90 (16)	72 (27)
Dependency	99 (6)	<0.01	99 (4)	99 (8)	83 (24)
Driving	87 (18)	<0.01	89 (11)	92 (14)	74 (22)
Color vision	98 (8)	<0.01	98 (9)	98 (8)	92 (17)
Peripheral vision	97 (10)	<0.01	95 (12)	95 (14)	79 (23)
Composite	93 (NR)		94 (6)	89 (8)	77 (16)

* P-values comparing to the SCORE2 population based on t-tests, corrected for multiple comparisons based on Bonferroni method

** For SCORE2, sample size for subscales that were less than the full sample size of 362 include: distance activities (n=361), driving (n=295), and color vision (n=359).

Table 5B
Comparisons of Mean NEI-VFQ-25 Subscale Scores of SCORE2 Participants to Other Retinal Vein Occlusion Populations

	Retinal Vein Occlusion Populations: Mean (Standard Deviation)								CRVO - SCORE2 Mean (SD)
	BRVO				CRVO				
	BRAVO ^{17**}	P-value [*]	VIBRANT ²¹	P-value [*]	CRUISE ^{17***}	P-value [*]	COPERNICUS ¹⁹	P-value [*]	
Sample size	N=392		N=181		N=385		N=187		N=362
General health	61 (23)	0.99	NR	NA	61 (22)	1.00	NR	NA	58 (22)
General vision	61 (17)	1.00	NR	NA	63 (16)	1.00	NR	NA	64 (17)
Ocular pain	85 (19)	1.00	NR	NA	86 (18)	1.00	NR	NA	86 (18)
Near activities	69 (21)	1.00	70 (20)	1.00	71 (22)	1.00	70 (21)	1.00	68 (22)
Distance activities	76 (20)	1.00	77 (20)	1.00	77 (21)	1.00	77 (21)	1.00	75 (21)
Social functioning	89 (17)	1.00	NR	NA	89 (18)	1.00	NR	NA	89 (17)
Mental health	63 (26)	1.00	NR	NA	65 (25)	1.00	NR	NA	65 (27)
Role difficulties	70 (27)	1.00	NR	NA	73 (28)	1.00	NR	NA	72 (27)
Dependency	83 (24)	1.00	84 (23)	1.00	82 (26)	1.00	83 (26)	1.00	83 (24)
Driving	72 (26)	1.00	NR	NA	69 (30)	0.51	NR	NA	74 (22)
Color vision	93 (17)	1.00	NR	NA	92 (17)	1.00	NR	NA	92 (17)
Peripheral vision	78 (24)	1.00	NR	NA	78 (24)	1.00	NR	NA	79 (23)
Composite	76 (16)	1.00	77 (16)	1.00	77 (17)	1.00	78 (16)	1.00	77 (16)

NR=Not reported. NA=Not applicable.

* P-values comparing to the SCORE2 population based on t-tests, corrected for multiple comparisons based on Bonferroni method

** For BRAVO, sample size for subscales that were less than the full sample size of 392 include: social functioning (n=391), driving (n=355), color vision (n=387), and peripheral vision (n=388).

*** For CRUISE, sample size for subscales that were less than the full sample size of 385 include: general vision (n=384), driving (n=347), color vision (n=383), and peripheral vision (n=383).

**** For SCORE2, sample size for subscales that were less than the full sample size of 362 include: distance activities (n=361), driving (n=295), and color vision (n=359).