Online Appendix

The development of the ETDRS DME severity scale is summarized in Appendix Tables 1A and 1B, from Gangnon, R, et al. IOVS 2005;46:ARVO E-Abstract 3269 (Table 1A is from the final poster and differs slightly from the table in the E-Abstract, principally because the scale steps were renumbered). Table 1A presents mean baseline visual acuity score (VA) for both eyes of 3711 ETDRS participants cross-classified by location of retinal thickening and its extent within one disc diameter of the center of the macula and by degree of retinal thickness at the center. Cells with similar VA were combined as shown using cluster analysis and clinical judgment. The diagonal pairing of many of the cells in levels 2 through 5B is as might be expected when two additive risk factors are cross-classified. The advantage of subdividing the large number of eyes (1363) with center thickness ≥1X, <2X reference thickness by area of thickening within 1 DD of center (the "inner zone") is apparent, as mean VA in the subdivisions falls from 81.8 to 64.3 letters as the area of involvement increases. Table 1B shows the cells of Table 1A pooled to produce the scale.

Appendix Table 2A presents median (quartiles) OCT-measured retinal thickness in the central subfield for the 435 eyes analyzed in this report in each cell of a table cross-classifying the same photographic variables as those in Table 1A. For the analyses in this report, the ETDRS DME severity scale was modified in three ways. First, the three lowest levels (1A, 1B, and 1C), which contain eyes with no retinal thickening at the center of the macula and little (<1 DA) or no retinal thickening within 1 DD of center, were combined because the OCT measures to be analyzed in this report would be expected to differ little between them. Second, levels 3A and 3B, which were similar in the original scale and had small numbers in our data set, were combined. Finally, the largest category for inner zone thickening provided by the original scale (>=2 DA) was divided into two parts: >=2 DA but <3 DA and >=3 DA. As a result of this modification, separation of the 61 eyes in row 6, column 4, from the 47 eyes in row 5, column 4, made the scale more suitable for the large proportion of eyes with very severe DME in this data set. Appendix Table 2B shows the cells of Table 2A pooled to produce the modified scale.

Reproducibility of the photograph gradings underlying the modified ETDRS DME severity scale was assessed by regrading baseline and 12-month visits of 60 eyes selected to represent all steps in the scale at baseline but without regard to photo quality. The regradings were carried out without knowledge of the original gradings but graders were aware that this was a quality control exercise. Baseline and month 12 gradings were carried out independently of each other. For 2 of the 120 original gradings, the regrading was cannot grade for one or both of the abnormalities required for calculation of the scale and these gradings were excluded, leaving 118 replicate gradings. There was exact agreement in 42%, agreement within one step in 83%, and agreement within two steps in 93%. The weighted Kappa statistic (1-step disagreements weighed 0.75 and all other disagreements zero) was 0.58 (SE 0.05). Weighted Kappa statistics for the components of the scale were similar (0.58 for degree of thickening at the center of the macula and 0.67 for area of thickening in the inner zone categorized as it was in the ETDRS.

Appendix Table 1A. Mean (standard deviation) baseline visual acuity score* in ETDRS eyes cross-classified by location and extent of retinal thickening and by thickness of the retina at the center of the macula assessed in stereoscopic color fundus photographs.

	Retinal Thickness at Center of the Macula															Total			
	None			Questionable			<1X Reference †			>=1X, <2X Ref †			>=2X Ref †						
Extent of Retinal Thickening	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	
None in Field 2	86.8	5.8	2463													86.8	5.8	2463	Level 1A
None within 1 DD of center	86.2	6.2	761													86.2	6.2	761	Level 1B
Questionable within 1 DD of center	85.0	7.1	401	82.2	8.5	216										84.0	7.7	617	Level 1C
Definite, <1/2 DA within 1 DD of center	85.2	6.7	522	82.5	8.9	315	81.2	8.5	175	81.8	8.2	102	75.0	NA	1	83.5	8.0	1115	Level 2
>=1/2 DA, <1 DA within 1 DD of center	83.2	8.2	145	81.1	10.2	216	78.9	9.6	235	77.2	10.9	223	72.5	14.1	6	79.8	10.1	825	Level 3A
>=1 DA, < 2 DA within 1 DD of center	82.2	9.0	30	79.6	11.9	90	75.1	12.3	282	72.8	12.4	571	66.7	15.0	34	74.1	12.7	1007	Level 3B
>=2 DA within 1 DD of center	60.7	13.9	3	87.0	8.5	7	72.1	13.3	58	64.3	14.6	467	59.8	13.6	99	64.5	14.7	634	Level 4
Total	86.2	6.3	4325	81.8	9.5	844	77.5	11.1	750	71.3	13.9	1363	62.2	14.4	140	81.6	11.2	7422	Level 5 A
																			Level 5 B

DD, disc diameter; DA, disc area

*Sneller equivalents: 100 = 20/10, 85 = 20/20, 70 = 20/40, 65 = 20/50, 60 = 20/63

†Reference thickness is the maximum thickness of normal retina 0.5 to 1.0 disc diameter from the center of the macula.

Appendix Table 1B. Mean (standard deviation) baseline VA score by level on ETDRS DME severity scale

	Mean	SD	N
Level 1A	**86.8**	5.8	2463
Level 1B	**86.2**	6.2	761
Level 1C	**84.8**	7.1	1068
Level 2	**81.9**	9.0	1055
Level 3A	**79.1**	10.4	335
Level 3B	**76.1**	11.8	505
Level 4	**72.7**	12.5	635
Level 5A	**64.5**	14.6	501
Level 5B	**59.8**	13.6	99

Appendix Table 2A. Median (quartiles) OCT-measured retinal thickness at baseline in the central subfield of 435 DRCR network eyes cross-classified by area of retinal thickening and thickness of the retina at the center of the macula assessed in stereoscopic color fundus photographs, within each of the cells that are combined to produce in the modified ETDRS DME severity scale.

	Retinal Thickness at the Center of the Macula																
RT area inner zone disc areas	None			Questionable			<1X Reference*			>=1X, <2X Ref*			>=2X Ref*			Total	
	Level	Median (Quartiles)	N	Level	Median (Quartiles)	N	Level	Median (Quartiles)	N	Level	Median (Quartiles)	N	Level	Median (Quartiles)	N	Median (Quartiles)	N
0	1A & 1B‡	235 (210, 269)	74													235 (210, 269)	74
<0.5	1C	237 (214, 262)	63	2	250 (202, 268)	11	2	239 (210, 267)	3	2	289 (277, 300)	2	2		0	239 (214, 267)	79
0.5 - <1.0	1C	244 (217, 263)	23	2	237 (217, 261)	15	3A	296 (258, 363)	8	3B	306 (298, 355)	8	4		0	252 (225, 293)	54
1.0 - <2.0	2	214 (204, 258)	7	3A	268 (238, 341)	14	3B	265 (244, 304)	25	4	334 (287, 401)	46	5A		0	290 (253, 359)	92
2.0 - <3.0	3A	281	1	3A	191	1	4	290 (263, 324)	10	5A	363 (282, 424)	47	5B	430 (373,486)	2	343 (278, 419)	61
>= 3.0	3A		0	4	259	1	5A	323 (187, 404)	3	5B	436 (298, 545)	61	5C	517 (455, 598)	10	445 (318, 545)	75
Total		236 (214, 264)	168		244 (225, 271)	42		272 (244, 315)	49		365 (290, 451)	164		503 (451, 570)	12	273 (233, 364)	435

RT, retinal thickening; inner zone, area within 1 disc diameter of the center of the macula (total = 4 disc areas).

*Reference thickness is the maximum thickness of normal retina 0.5 to 1.0 disc diameter from the center of the macula.

‡Level 1A=no RT in photographic field 2; 1B=RT in field 2, but none in the inner zone.

42
43

Appendix Table 2B. Median (quartiles) OCT-measured retinal thickness in the central subfield in each level of the modified ETDRS DME severity scale.		
	Median (Quartiles)	**N**
Level 1	**236** (214, 264)	**160**
Level 2	**238** (214, 267)	**38**
Level 3	**274** (244, 315)	**57**
Level 4	**327** (283, 394)	**57**
Level 5A	**355** (282, 420)	**50**
Level 5B	**436** (298, 545)	**63**
Level 5C	**517** (455, 598)	**10**

44