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Short-term Assessment of Glaucoma Progression in Clinical Trials Using Trend-based Visual Field Progression Analysis

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Objective: To evaluate the effect of disease stage, frequency and clustering of visual field (VF) tests, inclusion of 1 or both eyes, and 1 (1 arm; before and after a treatment) or 2 groups (2 arms; treatment and control arm) on sample size calculation in clinical trials.

Design: Clinical cohort study.

Participants: A series of VFs were simulated based on test-retest VF data in the early, moderate, and advanced stages of glaucoma with 231, 204, and 226 eyes, respectively.

Methods: The mean of mean deviation (MD) slope was −0.75 decibels (dB)/year before treatment initiation in the 1-arm trial, and in the control group in the 2-arm trial. Visual field measurements were scheduled as 8 times in 2 years.

Main Outcome Measures: Sample size calculation in clinical trials.

Results: In the 1-arm trial, when only 1 eye was used in each patient, the 80% probability of significance in the moderate stage was observed with sample size = 70 eyes. Disease in the early stage and inclusion of both eyes decreased this number to 30 eyes; these decreasing effects were significantly larger than performing 1 or 2 additional VFs at the beginning and end of the observation. Conversely, a greater number of eyes was necessary in advanced stage than in moderate stage. In the 2-arm trial (80% probability of significance, and 1 eye per patient), the 80% probability of significance was observed with sample size = 80 eyes in each arm, a tendency that was similar to what observed for the 1-arm trial. Similar tendency was observed in the simulations with much slower VF progression (mean MD slope = −0.25 dB/year).

Conclusions: The present study highlights the importance of considering disease stage when planning a clinical trial.

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Glaucoma is a progressive and irreversible optic neuropathy that can result in irrevocable visual field (VF) damage. This disease is one of the leading causes of blindness worldwide and hence, various clinical trials have been conducted to evaluate the efficacy of new treatments for either decelerating or even preventing vision loss, using VF as the primary progression outcome. However, the progression rate of glaucoma is generally slow, thereby indicating that clinical trials require significantly large sample sizes or very long follow-up times. For instance, a recent clinical trial investigating the efficiency of a neuroprotective treatment (oral memantine) was conducted with ≥2000 participants during a ≥4-year period; however, it failed to show the usefulness of the treatment.[1] The investigators discussed that different results may be observed when those in earlier disease stage were recruited. Consequently, to ensure significant clinical outcomes, these studies need to be lengthy, and are therefore expensive, which is a critical issue when testing new glaucoma therapies in clinical trials.

Historically, progression of glaucoma in clinical trials has been detected by making use of the even-based analysis.[1–8] In contrast, various alternatives to reduce both the sample size and length of such trials have been proposed during recent years. For instance, short-term trials may be feasible by using trend-based analysis to evaluate the progression rate of VF mean deviation (MD).[8–10] In addition, a similar result can be expected by increasing the frequency of VF tests[11] or clustering VF tests at the beginning and end of

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the observation period,[12] as well as by adopting more sensitive analytical approaches.[13–18]

Besides, VF is always affected by measurement variability, and the power to detect progression is therefore largely influenced by variability in measurements.[19,20] In glaucoma, test-retest reproducibility has been reported to decrease with disease progression,[21] implying that disease stage would have a nonnegligible effect on sample power calculation; however, such investigation has not been conducted in detail. Therefore, the purpose of the present study was to evaluate the effect of disease stage on sample size calculation and subsequently compare this effect to that of frequency and clustering of VF tests.

In addition, the required sample sizes would differ depending on the specific case examined, such as when both eyes are used and when only 1 eye is used, and when comparison is made between 2 groups (2 arms; treatment and control arm) and within 1 group (1 arm; before and after a treatment). The effect of such conditions was also investigated in detail in the current study.

Methods

This study was approved by the institutional review board of Seirei Hamamatsu General Hospital and Seirei Center for Health Promotion and Preventive Medicine (institutional review board No. 3306) and conducted according to the tenets of the Declaration of Helsinki. Patients provided written consent for their information to be stored in the hospital database and used for research.

Participants

Patients with primary open-angle glaucoma were recruited from the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG) dataset[22] or from their medical records at the Department of Ophthalmology, Seirei Hamamatsu General Hospital and Department of Ophthalmology, Shimane University Hospital.

Test-Retest Dataset

First, all reliable VFs measured within a 3-month period were collected. Reliable VF was defined as fixation loss rate <33%, false positive rate <33%, and false negative rate <33%. All VFs were measured using the Humphrey Field Analyzer (24-2 Swedish Interactive Threshold Algorithm, SITA, standard program). Only 1 eye was selected from each single patient, and 1 eye was chosen randomly when both eyes were eligible.

All patients enrolled in the study fulfilled the following criteria: (1) glaucoma was the only disease causing VF damage; (2) the presence of typical glaucomatous changes in the optic nerve head, such as a rim notch with a rim width 0.1 disc diameters or a vertical cup-to disc ratio of 0.7 or a retinal nerve fiber layer defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape; and (3) gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification, regardless of the presence of glaucomatous VF change.

Simulation of VFs

All the simulations described below were conducted in the early, moderate, and advanced stages. These disease stages were defined as MD >−6 decibels (dB), between −6 and −12 dB, and <−12 dB, respectively.[23]

One-Arm Trial. Simulated VFs were generated using the method presented by Mayama et al.[24] First, a covariance matrix was created based on the early stage test-retest dataset. Consequently, based on the covariance matrix, VF variability was generated using a variability generator according to a 68-dimensional normal distribution. Then, to create simulated baseline VFs, the variability was added to total deviation at each test point of a randomly chosen initial single VF in the early stage test-retest dataset. This task was repeated 1000 times to create 1000 simulated baseline VFs, where new variability was created and added each time.

In the present study, we assumed that 95% of MD progression rates were between −0.5 and −1.0 dB/year before treatment initiation. Assuming a normal distribution, the mean value and standard deviation (SD) of MD slopes were −0.75 dB/year and 0.179 dB/year, respectively, calculated by the ordinary least squares regression of MD against time.[25,26] The variation of MD slope was generated based on the SD value of 0.179 dB/year, i.e., MD slope = −0.75 dB/year + variation. This calculation was performed to each of the 1000 created baseline VFs. Thus, all subsequent VFs were created by adding the generated MD progression rate (−0.75 + variation dB/year) x (duration from baseline, year) and VF variability (created according to a 68-dimensional normal distribution for each VF series) to each of the simulated baseline VFs. This process was iterated to generate 6 VFs in 3 years for 1000 eyes, resulting in a total of 18 000 simulated VFs for 1000 eyes.

Assuming that the effect of treatment was 30%, 40%, and 50% reduction of MD progression rate, simulated VFs after treatment initiation were generated by the addition of VF variability (created according to a 68-dimensional normal distribution for each VF series) to 0.70/0.60/0.50 x simulated MD progression rates before treatment initiation x (duration from treatment initiation, year) in each of the 1000 simulated VFs. The schedule of measurement sessions for VF was assumed to be 8 times within a period of approximately 2 years (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 years). In addition, other schedules were also simulated, i.e., 10 times (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 years) and 12 times (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 years) in approximately 2 years.

Subsequently, a second normal distribution with an SD value of 0.179 dB/year and a correlation coefficient of 0.319 was generated to calculate the variation of MD slope in the fellow eye. The correlation coefficient of 0.319 was derived from the correlation of MD progression rates between right and left eyes.[22] Then, MD progression rate before treatment initiation was calculated as −0.75 dB/year + second variation. Other processes were the same as in the case of 1 eye per patient described above.

The same simulations were also performed for moderate and advanced stages of glaucoma using the test-retest dataset in moderate and advanced stages, respectively.

In addition, subsequently, another series of simulation was performed assuming 95% of MD progression rates were between −0.5 and 0 dB/year.

Two-Arm Trial. Similar to the 1-arm trial, a total of 8000 simulated VFs for 1000 eyes in the control arm were created assuming that 95% of MD progression rates were between −0.5 and −1.0 dB/year in approximately 2 years (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 years).

Then, assuming the effect of treatment as 30%, 40%, and 50% reduction of MD progression rate, simulated VFs in the treatment arm were generated by adding VF variability (created according to a 68-dimensional normal distribution for each VF series) to 0.70/0.60/0.50 x simulated MD progression rate (−0.75 ± 0.319 dB/

year) before the initiation of treatment x (duration from the initiation of treatment, year) in each of the 1000 simulated VFs. The schedule of VF measurement was designed as either of (1) 8 times in approximately 2 years (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 years), (2) 10 times in approximately 2 years (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 years), and (3) 12 times in approximately 2 years (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 years). These schedules are "VF schedule pattern 1," "VF schedule pattern 2," and "VF schedule pattern 3," respectively. The simulation of the fellow eye was performed following the method for the 1-arm trial.

All these simulations were performed in other stages of moderate and advanced stages, where the test-retest dataset in moderate and advanced stages were used respectively. In addition, subsequently, another series of simulation was performed assuming 95% of MD progression rates were between −0.5 and 0 dB/year.

Statistical Analysis

When simulating the 1-arm trial, 10 patients were randomly selected from the 1000 simulated VF sequences. Then the MD progression rate was compared between before and after treatment initiation, using the paired Wilcoxon test (1 eye per patient) or the linear mixed model, with patients being the random effect (both eyes per patient). This process was iterated for 1000 times, and we calculated the probability that the MD progression rate after treatment initiation was significantly slower than that before treatment initiation. Similar investigations were also conducted for 20, 30, 40, 50, 60, 70, 80, 90, and 100 eyes. In the 2-arm trial, investigations involved 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 eyes for each of the control and treatment groups. Comparisons were made between the 2 groups, following the method for the 1-arm trial.

All analyses were performed using the statistical programming language R (R version 4.1.3; The Foundation for Statistical Computing).

Results

The characteristics of the test-retest dataset for each stage of the disease are summarized in Table 1. More specifically, there were 231, 204, and 226 eyes in the early, moderate, and advanced stage groups, respectively. In the early stage group, the mean (± SD) MD in the initial and second VFs was −1.6 ± 2.0 and −1.8 ± 2.2 dB, respectively, while in the moderate and advanced stage groups, these values were −8.5 ± 1.9 dB and −8.5 ± 3.0 dB, and −18.0 ± 4.2 and −17.3 ± 4.9 dB, respectively. There was no significant difference in the age of patients among the 3 groups ($P > 0.05$, Wilcoxon test). The root mean squared error between the first and second VFs were 7.6 ± 6.4, 12.5 ± 10.9, and 13.1 ± 15.2 dB in the early, moderate, and advanced stage, respectively.

One-Arm Trial

The probabilities of a significant difference in the MD progression rate before and after treatment initiation in various scenarios are shown in Table 2. For example, the required number of eyes to observe 80% probability of significance assuming a 50% treatment effect with mean MD slope = −0.75 dB/year in the moderate stage were as follows:

- Disease stage: When only 1 eye was used, the required sample size was 70 eyes with VF schedule pattern 1. On the other hand, the required sample size decreased to 30 eyes in the early stage, whereas it increased to 100 eyes in the advanced stage with VF schedule pattern 1.
- Inclusion of 1 eye or 2 eyes in each patient: When 2 eyes were used, the required sample size was 30 eyes with VF schedule pattern 1.
- Visual field schedule pattern: When only 1 eye was used, the required sample sizes were 50 and 40 eyes with VF schedule pattern 2 and 3, respectively.

Compared with the 50% treatment effect, a larger number of eyes was required for 40% and 30% treatment effects; however, the influence of disease stage, use of 1 or 2 eyes, and VF schedule pattern all exhibited very similar tendencies regarding the number of eyes required (Tables 3 and 4). Similar tendency was also observed in the simulations with much slower VF progression (mean MD slope = −0.25 dB/year).

Two-Arm Trial

The probabilities of a significant difference in the MD progression rate between control and treatment arms in various scenarios are shown in Tables 5−7. For example, the required number of eyes to observe 80% probability of significance assuming a 50% treatment effect in the moderate stage were as follows:

- Disease stage: When only 1 eye was used, the required sample size was 80 eyes in each arm with VF schedule pattern 1. On the other hand, the required sample size decreased to 40 eyes in each arm in the early stage, whereas it increased to >100 eyes in each arm in the advanced stage with VF schedule pattern 1.
- Inclusion of 1 eye or 2 eyes in each patient: When 2 eyes were used, the required sample size was 40 eyes in each arm with VF schedule pattern 1.
- Visual field schedule pattern: When only 1 eye was used, the required sample sizes were 60 and 40 eyes in each arm with VF schedule patterns 2 and 3, respectively.

Compared with the 50% treatment effect, a greater number of eyes was required in the 40% and 30% treatment effects; however, the influence of disease stage, VF schedule pattern, and use of 1 or 2 eyes all exhibited very similar tendencies regarding the number of eyes required. Similar tendency was also observed in the simulations with much slower VF progression (mean MD slope = −0.25 dB/year).

Discussion

The present study investigated the effects of various parameters, including disease stage, VF schedule, and inclusion of 1 or both eyes, on sample size calculation, and our findings suggested that all factors were nonnegligible. More specifically, our results showed that an approximate number of 60 eyes in each arm was a prerequisite to obtain 90%

Table 1. General Characteristics of the Study Participants

Stage	VF	Eyes	MD (dB, Mean [SD])	Age (Yrs, Mean [SD])	RMSE (Yrs, Mean [SD])
Early	1st	231	−1.6 [2.0]	61.7 [13.2]	7.6 [6.4]
	2nd	231	−1.8 [2.2]		
Moderate	1st	204	−8.5 [1.9]	60.7 [12.6]	12.5 [10.9]
	2nd	204	−8.5 [3.0]		
Advanced	1st	226	−18 4.2]	63.2 [11.9]	13.1 [15.2]
	2nd	226	−17.3 [4.9]		

dB = decibels; MD = mean deviation; RMSE = root mean squared error; SD = standard deviation; VF = visual field.

power and thus detect differences between control and treatment groups when a 50% treatment effect and mean MD slope = −0.75 dB/year was assumed in the early stage group (Table 5). In addition, power was 89% with 100 eyes (in each arm) in the moderate stage group, which is approximately in line with the findings presented in Crabb et al,[12] suggesting that 99 eyes (in each arm) were needed to obtain 90% power with 50% treatment effect. However, it would be unwise to make a direct comparison because sample size requirements were largely influenced by various conditions, such as VF measurement frequency and progression rate in the cohort. Indeed, the VF schedule in the current study was 8 VFs in 2 years compared with 10 VFs in 2 years in Crabb et al.[12] Furthermore, we assumed that the MD progression rate without treatment was −0.75 dB/year as opposed to −0.57 dB/year in Crabb et al.[12] Moreover, we used an ordinal MD linear trend analysis, whereas Crabb et al used a linear mixed model,[12] despite the similarity in the disease stage: early and moderate stages (mean MD = −7.79 dB) in Crabb et al.[12] Our simulation with much slower mean MD progression rate of −0.5 dB/year resulted in much lower probability of significance; however, similar results were obtained regarding the effect of the diseases stage on sample size calculation.

Various attempts have been made to reduce the required sample size or follow-up duration when conducting clinical trials using trend analysis. For instance, more frequently performing VF measurements renders the estimation of VF progression more accurate, thereby enabling a higher

Table 2. The Probabilities of a Significant Difference in the MD Progression Rate Before and After Treatment Initiation in 1000 Times Simulation (One Arm, Treatment Effect = 50%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	163	225	254	399	540	374	511	608	742	**873**	120	175	191	276	389
	N = 20	323	441	532	691	**833**	670	**849**	**915**	**969**	**997**	207	311	354	449	617
	N = 30	486	664	717	**861**	**954**	**872**	**970**	**993**	**997**	1000	307	454	537	615	792
	N = 40	615	781	**843**	**929**	**987**	**954**	**996**	**999**	**999**	1000	384	584	669	755	**915**
	N = 50	707	**863**	**911**	**972**	**999**	**984**	**999**	1000	1000	1000	476	699	767	**853**	**959**
	N = 60	792	**925**	**958**	**992**	1000	**996**	1000	1000	1000	1000	544	789	**841**	**907**	**978**
	N = 70	**870**	**970**	**983**	**996**	1000	1000	1000	1000	1000	1000	628	**850**	**916**	**949**	**990**
	N = 80	**912**	**990**	**994**	1000	1000	1000	1000	1000	1000	1000	717	**909**	**945**	**966**	**995**
	N = 90	**933**	**994**	**999**	1000	1000	1000	1000	1000	1000	1000	764	**948**	**971**	**987**	**998**
	N = 100	**969**	**997**	1000	1000	1000	1000	1000	1000	1000	1000	**832**	**966**	**982**	**996**	1000
Mean MD slope = −0.25 dB/yr	N = 50	146	193	211	333	436	262	382	434	601	746	114	140	154	239	311
	N = 60	183	238	238	373	482	310	419	489	654	**810**	141	168	173	288	366
	N = 70	191	268	283	399	556	371	484	561	719	**853**	155	186	204	313	404
	N = 80	225	313	336	444	607	407	529	604	777	**903**	159	224	233	345	475
	N = 90	246	323	361	493	649	436	589	654	**820**	**933**	190	239	267	378	499
	N = 100	268	377	396	533	700	474	617	694	**852**	**955**	213	276	294	415	544
	N = 200	429	580	606	796	**923**	722	**867**	**902**	**985**	**998**	325	414	452	638	**819**
	N = 300	527	700	751	**898**	**984**	**840**	**944**	**950**	**999**	1000	429	542	582	779	**925**
	N = 400	619	779	**820**	**944**	**997**	**913**	**969**	**969**	**999**	1000	494	633	670	**852**	**968**
	N = 500	689	**842**	**858**	**974**	1000	**949**	**987**	**989**	1000	1000	575	702	750	**901**	**988**

dB = decibels; MD = mean deviation; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

Table 3. The Probabilities of a Significant Difference in the MD Progression Rate before and after Treatment Initiation in 1000 Times Simulation (One Arm, Treatment Effect = 40%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	124	165	190	306	407	247	367	420	537	717	91	120	127	200	281
	N = 20	226	316	364	515	668	450	662	751	**843**	**953**	136	203	227	316	436
	N = 30	332	461	551	671	**831**	669	**860**	**917**	**955**	**988**	195	307	342	414	599
	N = 40	431	594	673	**803**	**930**	**810**	**941**	**981**	**992**	**999**	246	397	466	518	734
	N = 50	511	673	752	**877**	**970**	**886**	**978**	**989**	**999**	**1000**	288	480	551	637	**831**
	N = 60	598	770	**836**	**921**	**986**	**936**	**987**	**998**	**1000**	**1000**	360	576	651	722	**897**
	N = 70	669	**843**	**901**	**960**	**998**	**975**	**998**	**1000**	**1000**	**1000**	390	638	702	782	**938**
	N = 80	749	**897**	**938**	**981**	**1000**	**986**	**1000**	**1000**	**1000**	**1000**	439	708	790	**846**	**955**
	N = 90	**808**	**936**	**956**	**991**	**1000**	**995**	**1000**	**1000**	**1000**	**1000**	503	771	**835**	**881**	**975**
	N = 100	**849**	**965**	**977**	**996**	**1000**	**997**	**999**	**1000**	**1000**	**1000**	556	**835**	**885**	**920**	**984**
Mean MD slope = −0.25 dB/yr	N = 50	114	151	161	257	325	190	261	306	442	581	90	108	108	181	234
	N = 60	146	182	193	293	377	218	311	354	508	643	118	129	136	215	278
	N = 70	148	203	222	319	419	249	367	417	563	714	124	143	156	248	323
	N = 80	169	237	249	353	481	288	402	467	609	753	139	175	174	270	348
	N = 90	193	252	276	389	508	315	434	504	662	822	152	182	195	290	388
	N = 100	217	286	293	424	557	349	472	547	704	851	175	201	217	328	422
	N = 200	333	443	471	656	**817**	544	702	772	**919**	**982**	256	325	338	509	682
	N = 300	427	555	606	784	**934**	687	**824**	**863**	**973**	**998**	359	423	450	667	**840**
	N = 400	501	649	691	**860**	**971**	772	**880**	**907**	**997**	**1000**	416	500	525	724	**887**
	N = 500	561	721	763	**901**	**993**	**835**	**916**	**925**	**998**	**1000**	459	574	598	793	**943**

dB = decibels; MD = mean deviation; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

Table 4. The Probabilities of a Significant Difference in the MD Progression Rate before and after Treatment Initiation in 1000 Times Simulation (One Arm, Treatment Effect = 30%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	80	106	124	200	266	151	208	237	336	459	64	86	95	127	190
	N = 20	157	211	225	327	464	270	413	491	559	747	89	120	133	207	284
	N = 30	218	301	344	457	607	384	595	694	750	**906**	108	172	201	252	377
	N = 40	264	365	413	561	736	516	745	**820**	**889**	**968**	137	242	264	297	474
	N = 50	305	432	496	655	**815**	589	**823**	**896**	**934**	**989**	149	269	310	366	578
	N = 60	372	499	594	722	**887**	697	**897**	**952**	**971**	**999**	173	317	379	432	646
	N = 70	423	584	665	**810**	**941**	754	**945**	**980**	**983**	NA	204	354	430	479	715
	N = 80	495	671	744	**857**	**962**	798	**975**	**992**	**995**	NA	207	414	490	549	773
	N = 90	534	723	793	**904**	**981**	**861**	**987**	**997**	**999**	NA	234	459	537	598	**828**
	N = 100	601	780	**840**	**923**	**991**	**915**	**993**	**996**	NA	NA	254	500	590	657	**864**
Mean MD slope = −0.25 dB/yr	N = 50	92	111	112	176	231	137	176	200	309	405	75	81	72	141	174
	N = 60	113	132	137	221	287	167	210	235	354	460	94	102	102	154	207
	N = 70	117	144	159	244	316	180	243	281	402	527	96	106	117	179	230
	N = 80	138	171	173	269	347	205	288	322	448	580	115	122	126	198	260
	N = 90	151	186	189	290	379	233	307	346	479	630	117	134	133	231	282
	N = 100	179	200	211	329	405	254	347	382	523	671	134	151	155	245	320
	N = 200	258	321	320	504	660	396	517	586	792	**920**	186	232	236	376	507
	N = 300	347	435	422	641	**822**	523	660	719	**904**	**970**	265	300	314	516	665
	N = 400	399	507	509	717	**879**	616	732	798	**945**	**992**	315	375	387	587	741
	N = 500	442	566	579	780	**935**	682	798	**838**	**977**	**996**	336	407	443	653	**814**

dB = decibels; MD = mean deviation; NA = not applicable; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

Table 5. The Probabilities of a Significant Difference in the MD Progression Rate before and after Treatment Initiation in 1000 Times Simulation (2 Arms, Treatment Effect = 50%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	126	192	259	244	463	259	393	492	327	**854**	112	148	190	171	327
	N = 20	247	351	460	474	798	460	721	**837**	670	**991**	185	263	347	385	670
	N = 30	363	524	657	691	**944**	657	**917**	**968**	**830**	**1000**	253	388	499	510	**830**
	N = 40	504	668	**806**	**827**	**985**	**806**	**974**	**995**	**923**	**1000**	354	503	650	642	**923**
	N = 50	602	749	**892**	**878**	**995**	**892**	**991**	**999**	**957**	**1000**	427	615	743	762	**957**
	N = 60	680	**836**	**937**	**951**	**999**	**937**	**999**	**999**	**990**	**1000**	517	689	**825**	**840**	**990**
	N = 70	759	**897**	**964**	**978**	**1000**	**964**	**999**	**1000**	**997**	**1000**	600	765	**897**	**892**	**997**
	N = 80	**816**	**929**	**977**	**984**	**1000**	**977**	**1000**	**1000**	**996**	**1000**	654	**818**	**933**	**920**	**996**
	N = 90	**864**	**951**	**991**	**993**	**1000**	**991**	**1000**	**1000**	**1000**	**1000**	722	**858**	**945**	**957**	**1000**
	N = 100	**886**	**967**	**993**	**998**	**1000**	**993**	**1000**	**1000**	**1000**	**1000**	749	**891**	**960**	**973**	**1000**
Mean MD slope = −0.25 dB/yr	N = 50	107	141	180	197	343	180	299	378	471	672	82	109	135	155	280
	N = 60	124	171	224	246	395	224	369	464	559	768	101	125	169	188	313
	N = 70	138	192	243	269	442	243	421	537	586	**815**	107	147	184	197	360
	N = 80	162	208	265	304	491	265	470	587	647	**849**	126	163	200	222	400
	N = 90	164	225	300	332	534	300	507	650	696	**892**	132	157	211	259	426
	N = 100	174	232	312	371	585	312	547	704	729	**913**	130	168	226	271	493
	N = 200	284	433	566	628	**833**	566	**858**	**936**	**921**	**988**	189	292	398	447	693
	N = 300	424	615	762	738	**900**	762	**975**	**996**	**967**	**995**	296	445	595	593	799
	N = 400	561	771	**900**	**811**	**951**	**900**	**996**	**1000**	**988**	**999**	399	577	750	683	**842**
	N = 500	697	**903**	**969**	**868**	**971**	**969**	**1000**	**1000**	**995**	**1000**	505	729	**876**	725	**890**

dB = decibels; MD = mean deviation; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

Table 6. The Probabilities of a Significant Difference in the MD Progression Rate before and after Treatment Initiation in 1000 Times Simulation (2 Arms, Treatment Effect = 40%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	96	143	175	163	356	175	284	363	387	730	80	120	142	123	254
	N = 20	168	251	329	333	650	329	530	655	715	**966**	124	191	256	265	541
	N = 30	236	369	465	514	**855**	465	753	**854**	**917**	**995**	171	259	354	344	717
	N = 40	330	474	611	627	**945**	611	**861**	**951**	**972**	**1000**	238	345	454	450	**830**
	N = 50	399	564	703	735	**970**	703	**932**	**978**	**983**	**1000**	287	425	541	578	**904**
	N = 60	493	654	792	**833**	**991**	792	**964**	**992**	**1000**	**1000**	358	503	642	660	**957**
	N = 70	560	739	**854**	**876**	**998**	**854**	**985**	**996**	**999**	**1000**	414	565	709	708	**961**
	N = 80	623	794	**913**	**915**	**1000**	**913**	**995**	**1000**	**1000**	**1000**	456	631	776	764	**983**
	N = 90	686	**828**	**932**	**948**	**1000**	**932**	**997**	**1000**	**1000**	**1000**	506	686	**833**	**835**	**997**
	N = 100	713	**865**	**948**	**978**	**1000**	**948**	**998**	**1000**	**1000**	**1000**	559	728	**854**	**864**	**996**
Mean MD slope = −0.25 dB/yr	N = 50	81	112	132	148	268	132	197	257	344	557	67	80	108	118	222
	N = 60	91	122	159	181	323	159	266	324	409	648	75	100	124	141	265
	N = 70	108	130	167	204	363	167	272	365	443	700	87	112	134	159	292
	N = 80	116	146	178	221	408	178	310	410	496	756	97	113	144	162	325
	N = 90	129	154	198	246	426	198	352	450	514	784	100	114	148	198	336
	N = 100	123	156	215	273	488	215	372	472	580	**823**	92	113	164	201	402
	N = 200	189	281	367	480	723	367	664	**806**	**823**	**957**	135	197	264	350	577
	N = 300	271	409	545	611	**825**	545	**864**	**946**	**906**	**983**	195	295	403	467	714
	N = 400	349	531	694	696	**900**	694	**958**	**992**	**924**	**995**	244	378	512	556	765
	N = 500	447	672	**832**	739	**917**	**832**	**993**	**1000**	**957**	**996**	301	484	661	603	**811**

dB = decibels; MD = mean deviation; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

Table 7. The Probabilities of a Significant Difference in the MD Progression Rate before and after Treatment Initiation in 1000 Times Simulation (2 Arms, Treatment Effect = 30%)

	Stage	Moderate					Early					Advanced				
	One or both eyes	*One eye*			*Both eyes*		*One eye*			*Both eyes*		*One eye*			*Both eyes*	
	VF schedule pattern	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*	*1*	*2*	*3*	*1*	*2*
Mean MD slope = −0.75 dB/yr	N = 10	79	101	123	108	269	123	183	226	262	544	62	93	96	75	204
	N = 20	121	165	210	210	504	210	332	418	502	**898**	98	126	158	163	418
	N = 30	144	206	293	308	714	293	496	593	690	980	112	159	225	209	560
	N = 40	197	279	373	395	**841**	373	620	733	776	1000	133	209	290	274	672
	N = 50	241	360	448	495	911	448	712	**836**	903	1000	182	262	328	342	779
	N = 60	304	434	536	546	957	536	793	**898**	931	1000	218	323	411	420	**855**
	N = 70	341	492	604	640	978	604	**863**	943	960	1000	248	349	465	478	**896**
	N = 80	381	531	658	681	983	658	901	969	980	1000	271	386	519	505	936
	N = 90	430	586	718	759	996	718	935	978	995	1000	305	438	572	595	964
	N = 100	464	615	772	**826**	999	772	948	982	996	1000	321	458	603	618	972
Mean MD slope = −0.25 dB/yr	N = 50	52	68	93	105	206	93	130	158	232	446	49	56	75	92	173
	N = 60	70	82	103	119	251	103	158	198	269	512	56	77	81	109	220
	N = 70	82	91	114	148	287	114	169	226	290	561	68	81	95	120	240
	N = 80	84	101	121	164	318	121	189	247	337	601	72	83	101	114	250
	N = 90	97	102	128	173	330	128	201	274	333	651	75	81	105	142	276
	N = 100	87	95	137	195	395	137	216	289	377	697	76	78	99	151	310
	N = 200	113	161	213	340	619	213	408	524	622	**888**	81	121	162	263	473
	N = 300	163	238	324	463	728	324	590	730	765	940	110	161	206	338	599
	N = 400	192	305	414	568	**817**	414	750	**869**	788	962	132	218	285	411	657
	N = 500	223	397	547	597	**861**	547	**888**	963	**853**	977	136	240	376	448	718

dB = decibels; MD = mean deviation; VF = visual field.
VF schedule pattern 1: 8 VFs in approximately 8 yrs (0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, and 2.1 yrs); VF schedule pattern 2: 10 VFs in approximately 8 yrs (0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.1 yrs); and VF schedule pattern 3: 12 VFs in approximately 8 yrs (0, 0, 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.1, and 2.1 yrs). Letters in bold suggest ≧80%. Underlined values suggest ≧90%.

detection rate of progression in a fixed period.[11,12] Moreover, Crabb et al suggested that clustering VF measurements at the beginning and end of the follow-up period resulted in 4% and 13% increase of power to detect progression, respectively, compared with when these measurements were evenly spaced after VFs.[12] The results of the present study are in line with the findings of previous studies in that the consideration of 1 or 2 additional VFs at the beginning and end of the follow-up period resulted in approximately 10% to 20% improvement of detecting progression. This tendency was consistent across all sample sizes, disease stages, assumed treatment effects, inclusion of 1 or both eyes, and 1- or 2-arm trials.

Our findings indicate that the effect of including both eyes on the required sample size is generally not lower than that of the VF schedule patterns. For instance, considering the 2-arm trial simulation, the number of eyes required to obtain 80% power was 80 (in each arm) when VFs were measured 8 times in approximately 2 years (i.e., every 0.3 years), whereas this value decreased to 60 and 40 eyes by performing 1 or 2 additional VFs, respectively, at the baseline and end point (Table 5). The same 80% power was obtained even when performing only 1 VF measurement at each visit (VF schedule pattern 1), when both eyes of 40 patients (80 eyes in each arm) were included. Of note, the same 80% power was also obtained by performing only 1 VF measurement at each visit (VF schedule pattern 1) in 40 eyes (in each arm) in the early stage. Moreover, only 30 eyes (in each arm) were required when including both eyes in the early stage. These differences according to the disease stage can be attributed to the difference in VF variability, because the accuracy of MD progression rate is largely affected by VF variability.[20] Indeed, Montesano et al have suggested that eyes with low intertest variability can significantly improve the power and reduce the sample size needed in a trial.[27] For instance, Chauhan et al reported that VF progression of −1.0 dB/year can be detected at 2 years with low variability when performing 3 VF measurements per year; however, high variability would result in an increase to 4.3 years.[19] Nonetheless, the test-retest reproducibility becomes poor,[21] and the measured sensitivity itself loses the accuracy according to disease progression.[28] Consequently, the present study underlines the merit of including eyes in the early stage to reduce the number of eyes required in clinical trials. However, a careful consideration is still necessary when applying our results to clinical trials, due to the difference in the treatment effect across different stages of the disease. For example, psychophysical tests for early detection of functional losses in glaucoma, such as VF, do not consider the relative amounts of loss for various subpopulations of optic nerve fibers and their inherent redundancy.[29] Moreover, early glaucomatous VF damage tends to be focal which is not sensitively reflected in the change of MD.

Although the present study employed the ordinal MD trend analysis, other more advanced statistical analysis methods have been proposed to enable early detection of progression. For instance, Proudfoot et al and Wu et al have reported the usefulness of applying the linear mixed model with follow-up

time as a fixed effect.[10,13] In Wu et al, this method reduced the sample size from 603 to 90 eyes when obtaining 90% power with 50% treatment effect.[13] Despite the fact that this was beyond the scope of the current study, a further investigation pertaining to the merits provided by this approach should be conducted in the future. In addition, other statistical methods have been proposed for the early detection of VF progression, such as permutation analyses of pointwise linear regression,[30] nonstationary Weibull error regression and spatial enhancement,[16] binomial pointwise linear regression,[31,32] and variational Bayes linear regression,[18,33] Although these methods were developed to enable early detection of progression, not reducing the sample size/duration required to observe progression between 2 arms, it may be possible to divert these models to that purpose.

This study has some limitations. First, we assumed specific conditions, such as MD progression rate of -0.75 ± 0.319 dB/year without treatment; however, the estimated sample size would be different when using a different progression rate. Similarly, sample sizes would also differ with different VF schedule patterns. In contrast, the effect of variables, such as disease stage, VF schedule pattern, and inclusion of 1 or both eyes, would not be significant. Third, a further validation is necessary when using the Humphrey Field Analyzer 10-2 test, because the test-retest reproducibility is not identical. In addition, a future study needs to investigate whether similar findings are observed in other ocular diseases such as retinitis pigmentosa.

In conclusion, the present study highlights the importance of not only considering VF schedule or inclusion of 1 or both eyes, but also disease stage when planning a clinical trial. Our findings can act as a guide to design clinical trials with significantly reduced sample size or length of the follow-up period.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This study was approved by the institutional review board of Seirei Hamamatsu General Hospital and Seirei Center for Health Promotion and Preventive Medicine (institutional review board No. 3306) and conducted according to the tenets of the Declaration of Helsinki. Patients provided written consent for their information to be stored in the hospital database and used for research.

No animal subjects were used in this study.

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Analysis and interpretation: Asaoka, Murata

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Abbreviations and Acronyms:
dB = decibels; **MD** = mean deviation; **SD** = standard deviation; **VF** = visual field.

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