Dropout Rates for Intent-to-Treat and Per Protocol Analyses

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• PURPOSE: To describe dropout rates for the intent-to-treat and per protocol analyses from prospective clinical trials.

• METHODS: Review of prospective multi-center parallel studies of 100 patients or more from 1996 onwards.

• RESULTS: We identified 33 articles (70 treatment arms) that fit the criteria for this study. No statistical differences in dropout rates were observed among drug classes for either the intent-to-treat ($P = .075$) or per protocol analyses ($P = .40$). A difference was observed in the percent dropout rate for the intent-to-treat analyses decreasing with the length of the study ($P < .0001$). This finding was not observed by the number of study visits ($P = .44$). However, a statistically greater percent dropout rate was observed for the per protocol analyses increasing with the length of the study ($P = .034$) and number of study visits ($P = .01$). No statistical differences were observed or with increasing sample size of the study for either the intent-to-treat or per protocol analyses ($P > .05$).

• CONCLUSIONS: Known discontinuation rates for per protocol and intent-to-treat analyses may help in planning sample sizes for future clinical trials. (Am J Ophthalmol 2004;137:639–645. © 2004 by Elsevier Inc. All rights reserved.)

SAMPLE SIZE CALCULATION IS CRITICAL FOR CLINICAL trial design when evaluating a glaucoma agent. Enough patients must be included to provide sufficient power to exclude a significant difference between treatment groups. Typically a parallel, two-armed clinical trial includes approximately 160 patients to provide an 80% power to exclude a 1.5 mm Hg difference in intraocular pressure, assuming a standard deviation of 3.5 mm Hg (typical for clinical trials).[1,2] However, when designing a clinical trial, additional patients must be included because some patients may discontinue during the study. In contrast, enrolling too many patients may increase costs and recruiting time, whereas too many completed patients may overpower the study resulting in a significant statistical difference that is not clinically important. Unfortunately, little information is available currently that provides the discontinuation rate in glaucoma trials.

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METHODS

IN THE CURRENT ANALYSIS WE REVIEWED PROSPECTIVE, randomized, parallel trials with results published between January 1996 to June 2003 that evaluated common topical glaucoma monotherapy and fixed combination agents and included more than 100 patients with glaucoma or ocular hypertension. Predominant journals reviewed were: *American Journal of Ophthalmology*, *Archives of Ophthalmology*, *Investigative Ophthalmology and Visual Science*, *Journal of Glaucoma*, *Ophthalmology*, and *Survey of Ophthalmology*. Each article included was prospective and parallel in design, consisting of two or more treatment groups. Placebo groups were not analyzed. The drug classes reviewed were carbonic anhydrase inhibitors, α-adrenergic agonists, β-adrenergic blockers, and $F_2\alpha$ prostaglandin analogs. Fixed combination products of these drug classes also were included.

In each article the following information was collected (Table 1): the comparator medications, the number of patients randomized to each medication, the number of patients who were not available for the intent-to-treat (patients that were discontinued from the study for any reason, including protocol violations, before an efficacy measurement [Goldmann applanation tonometry]) and additional patients who were not available for per protocol analyses (patients who did not complete the entire protocol and all efficacy evaluations as planned).[3–35] Journal articles that did not provide this information or provided unclear information, and studies that had a crossover design, or design changes after randomization, were excluded from this analysis. The data were collected by one author (A.L.J.) and verified by another author (J.N.J.).

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TABLE 1. Clinical Studies Included in This Analysis

Reference	Medication	Sample Size	Patients Not Available for Intent-to-Treat Analysis*		Patients Not Available for Per Protocol Analysis†	
			n	%	n	%
3	Brimonidine	383	8	2.1	103	26.9
	Brimonidine-purite	381	9	2.4	81	21.3
4	Timolol	413	42	10.2	3	0.7
	Brimonidine	513	47	9.2	5	1.0
5	Betaxolol	101	5	5.0	2	2.0
	Brimonidine	105	3	2.9	4	3.8
6	Timolol	191	8	4.2	40	20.9
	Brimonidine	292	12	4.1	137	46.9
7	Timolol	108	3	2.8	3	2.8
	Brimonidine	111	5	4.5	6	5.4
8	Timolol	95	0	0.0	5	5.3
	Timolol GS	191	0	0.0	16	8.4
9	Carteolol HCL	87	0	0.0	7	8.0
	Timolol	89	0	0.0	6	6.7
10	Carteolol HCL	57	4	7.0	0	0.0
	Timolol	55	0	0.0	1	1.8
11	Timolol	65	9	13.8	4	6.2
	Brinzolamide bid	150	15	10.0	10	6.7
	Brinzolamide tid	148	21	14.2	16	10.8
	Dorzolamide	149	17	11.4	10	6.7
12	Timolol	112	1	0.9	1	0.9
	Dorzolamide	109	0	0.0	4	3.7
	DTFC	114	0	0.0	8	7.0
13	Timolol	98	0	0.0	9	9.2
	Dorzolamide	51	0	0.0	2	3.9
	DTFC	104	0	0.0	10	9.6
14	Timolol	75	0	0.0	27	36.0
	Brinzolamide bid	150	0	0.0	54	36.0
	Brinzolamide tid	153	0	0.0	63	41.2
15	DTFC	123	14	11.4	4	3.3
16	Latanoprost	223	0	0.0	12	5.4
17	Latanoprost	50	0	0.0	4	8.0
	LTFC	49	0	0.0	4	8.2
18	DTFC	93	3	3.2	0	0.0
	Latanoprost	90	5	5.6	0	0.0
19	Latanoprost	54	2	3.7	8	14.8
20	Timolol	126	10	7.9	5	4.0
	Latanoprost	127	9	7.1	5	3.9
	LTFC	116	4	3.4	7	6.0
21	Dorzolamide	112	8	7.1	0	0.0
	Latanoprost	112	0	0.0	3	2.7
22	Timolol	20	0	0.0	0	0.0
23	DTFC	75	0	0.0	0	0.0
	LTFC	73	0	0.0	1	1.4
24	Timolol	200	5	2.5	13	6.5
	Latanoprost	196	3	1.5	8	4.1
	Travoprost	200	3	1.5	13	6.5
25	Timolol	185	1	0.5	22	11.9
	Travoprost	197	0	0.0	21	10.7
26	Betaxolol	140	0	0.0	14	10.0
	Timolol	138	3	2.2	9	6.5
	Unoprostone	278	0	0.0	40	14.4
27	Brimonidine	192	4	2.1	43	22.4
	Latanoprost	187	0	0.0	5	2.7

TABLE 1. Clinical Studies Included in This Analysis (*Continued*)

Reference	Medication	Sample Size	Patients Not Available for Intent-to-Treat Analysis*		Patients Not Available for Per Protocol Analysis†	
			n	%	n	%
28	Timolol	202	3	1.5	14	6.9
	Travoprost	201	22	10.9	17	8.5
29	Timolol	140	0	0.0	36	25.7
	Latanoprost	140	0	0.0	24	17.1
	LTFC	138	0	0.0	13	9.4
30	Timolol	241	0	0.0	27	11.2
	Bimatoprost qd	483	0	0.0	103	21.3
	Bimatoprost bid	474	0	0.0	59	12.4
31	Latanoprost	84	0	0.0	1	1.2
32	Latanoprost	136	0	0.0	11	8.1
33	Timolol	145	0	0.0	14	9.7
	Latanoprost	149	0	0.0	12	8.1
34	Timolol	140	0	0.0	10	7.1
	Latanoprost	128	0	0.0	10	7.8
35	Timolol	95	12	12.6	5	5.3
	Latanoprost	89	9	10.1	4	4.5

DTFC = dorzolamide/timolol fixed combination; GS = gel-forming solution; HCL = hydrochloride; LTFC = latanoprost/timolol fixed combination; n = number of patients.

*Discontinued before efficacy data were measured.

†Discontinued before completion of protocol as designed.

Any differences found between the reviewers (n = 2) were resolved among the authors. Some articles required calculations from data provided within the article to ascertain the dropout rates reported in this study.

After collection of the above data the articles were summarized by length of study and drug class (Tables 2 and 3). The individual studies were separated according to treatment arms. The description of the results was placed into tables. An analysis of variance (ANOVA) test was performed on the mean discontinuation rate for all drug classes together to test for the difference over time separately for the intent-to-treat and per protocol analyses. Also, for all study time periods together an ANOVA test was used to evaluate differences among drug classes for dropout rates for both the intent-to-treat and per protocol analyses. A correlation coefficient was used to analyze differences in the dropout rates across the different number of visits.

RESULTS

THIS STUDY INCLUDED 33 ARTICLES WITH 70 TREATMENT arms. Five additional articles were excluded from analyses. Included articles are shown in Table 1. The results for the intent-to-treat and per protocol analyses are shown in Tables 2 and 3, respectively.

Table 2 demonstrates the mean percent for patients who discontinued the study before any efficacy data were collected including protocol violations. These patients were not available for an intent-to-treat analysis. Table 3 shows the additional mean percent for patients who discontinued the study before the final efficacy visit. These patients were not available for the per protocol analysis.

A difference was observed in the percent dropout rate for the intent-to-treat analyses decreasing with the length of the study ($P < .0001$; Table 2). This finding was not observed with the number of study visits ($P = .44$). However, a statistically greater percent dropout rate was observed for the per protocol analyses increasing with the length of the study ($P = .034$) and number of study visits ($P = .01$; Table 3). No statistical differences were observed among drug classes (intent-to-treat $P = .075$, per protocol $P = .40$) or with increasing sample size of the study (intent-to-treat $P = .11$, per protocol $P = .18$).

Data from Tables 2 and 3 can be used to approximate those patients who may not be available for the intent-to-treat or per protocol analyses in a prospective, randomized glaucoma trial. The use of the Tables is performed by the following procedures.

- **INTENT-TO-TREAT ANALYSES:** Find drug class and length of study on Table 2. The corresponding number provides the mean discontinuation rate. This number would represent the average percent of patients not available for the intent-to-treat analyses for the length of the study and drug class treatment arm.

TABLE 2. Percent of Subjects Unavailable for Intent-to-Treat Analysis*

Months Duration	2–3		4–6		7–12		>12	
	n		n		n		n	
Beta-blocker	12	4.3 ± 5.7	11	0.6 ± 1.0	6	4.2 ± 4.1	1	0 ± 0
Alpha-agonist	1	1.9 ± 0	2	3.3 ± 1.7	4	4.4 ± 3.3		
CAI	9	8.7 ± 5.4					2	0 ± 0
Prostaglandin	5	4.4 ± 3.8	9	0.3 ± 0.7	6	1.7 ± 2.7		
DTFC	5	3.3 ± 4.7						
LTFC	1	0 ± 0	2	0 ± 0	1	3.4 ± 0		

CAI = carbonic anhydrase inhibitor; DTFC = dorzolamide/timolol fixed combination; LTFC = latanoprost/timolol fixed combination.
*Mean percent ± SD; n = number of studies.

To determine the number of patients to be added to the required number of patients to complete a study, perform the following:

$$\frac{\#\text{ of patients required to complete ITT}}{(100 - \%\text{ dropout}) \div 100} = \#\text{ of patient to enroll}$$

For a more conservative estimate, adding one standard deviation to the mean average provides approximately an 83% chance that the number of enrolled patients is adequate. Adding two standard deviations to the mean average would provide a 97.5% chance that the number of enrolled patients is adequate.

For example, a 3-month β-blocker study has a mean dropout rate for the intent-to-treat analysis of 4.3 ± 5.7. Consequently, to find the number of patients required for randomization to have a 50% chance of having an adequate number of patients to be available for the intent-to-treat, the formula for a typical parallel comparison study (usually 80 patients per arm) would be:

$$\frac{80\text{ patients}}{(100 - 4.3\%) \div 100} = 83.6\text{ patients to enroll}$$

To have an 83% chance of having sufficient patients the 5.7 standard deviation should be added to the 4.3 to equal 10.0%:

$$\frac{80\text{ patients}}{(100 - 10.0\%) \div 100} = 88.9\text{ patients to enroll}$$

For two standard deviations from the mean the total expected percent dropout would be 15.7% requiring 94.9 patients to be enrolled to have 80 patients available for the intent-to-treat analysis.

• **PER PROTOCOL ANALYSES:** For the per protocol analysis the dropout rate in Table 3 needs to be added to the dropout rate in Table 2 to get a complete potential dropout rate from randomization.

TABLE 3. Percent of Subjects Unavailable for Per Protocol Analysis*

Months Duration	2–3		4–6		7–12		>12	
	n		n		n		n	
Beta-blocker	12	5.1 ± 3.1	11	8.7 ± 6.0	6	9.2 ± 7.1	1	36.0 ± 0
Alpha-agonist	1	3.8 ± 0	2	13.9 ± 12.0	4	12.0 ± 23.3		
CAI	9	6.2 ± 3.4					2	38.6 ± 3.7
Prostaglandin	5	1.5 ± 1.8	9	9.2 ± 4.4	6	9.8 ± 6.6		
DTFC	5	3.2 ± 3.7						
LTFC	1	1.4 ± 0	2	8.8 ± 0.9	1	2.6 ± 0		

CAI = carbonic anhydrase inhibitor; DTFC = dorzolamide/timolol fixed combination; LTFC = latanoprost/timolol fixed combination.
*Mean percent ± SD; n = number of studies.

For example with a 3-month β-blocker study, the 4.3% from Table 2 needs to be added to the additional patients (5.1%) that would be unavailable to get a cumulative dropout rate of 9.4%.

DISCUSSION

THE INTENT-TO-TREAT ANALYSIS, ON THE "FULL ANALYSIS set," is variably defined but often refers to a set of all randomized patients with a valid baseline measurement and at least one efficacy evaluation.[36] This analysis has the advantage of: first, to preserve the initial randomization; second, to prevent bias that would influence the results (that is, patients discontinuing early); and lastly, to provide estimates of treatment effects that are more likely to mirror those is subsequent practice.[37] The intent-to-treat analysis is often considered a conservative strategy. Randomized patients not included in the intent-to-treat analysis typically are those with protocol violations or who did not take a dose of the trial medication.[37]

The per protocol analysis is typically defined as a set of all patients who reasonably followed the protocol procedures and completed the minimum prespecified amount of time for participation.[36,37] In addition, the primary efficacy variable measurement should be available. The advantage that a per protocol analysis provides for a new treatment to show additional efficacy and it most closely reflects the scientific model underlined in the protocol.[37] However, the disadvantage is from bias by eliminating patients who may have had adverse events, or in which the study medicine had no effect, therefore influencing the results.[37]

In the current review the dropout rates were evaluated for intent-to-treat and per protocol analyses from prospective, multi-centered, parallel comparative pharmaceutical glaucoma trials. The results were intended to be useful in planning patient sample sizes for future glaucoma studies.

This study found that the percent of discontinued patients generally increased with the length of the study for the per protocol analyses. This finding is logical because to be allowed in the per protocol analyses patients must have had all primary efficacy measures completed. Consequently, the longer the study the greater the chance of a medical or life complication that would prevent inclusion into the per protocol data set.

In contrast, the percent of patients excluded from the intent-to-treat analyses decreased with the length of the study. This finding was a surprise to the authors and may not be completely explainable by our results. This reduction over time may not be factual because of a trend of higher dropout rates for carbonic anhydrase inhibitors, which were almost all 3-month studies. However, fewer dropouts for the intent-to-treat were observed over time for the prostaglandins generally and β-blockers at 4 to 6 months. Possibly for longer studies more patients were entered due to a greater anticipated discontinuation rate. Because intent-to-treat dropouts typically occur at the beginning of a study (that is, adverse events before any efficacy measurement, protocol violations), this may have allowed a lower percent intent-to-treat dropout rate for longer studies. However, this decreased dropout rate with the intent-to-treat analyses was not observed with an increasing number of visits.

Regarding the individual drug classes, for 3-month studies, more discontinued patients were observed with the topical carbonic anhydrase inhibitors, whereas for 12-month studies α-agonists tended to show the greatest incidence of discontinued patients. However, for all time periods combined, no statistical differences were observed between drug classes for either the intent-to-treat or per protocol analyses.

Surprisingly, both fixed combination products reviewed, despite containing timolol maleate, generally had a lower discontinuation rate than the β-blocker group alone. The reason for this is not exactly known, but potentially the fixed combination treated patients were prescribed timolol maleate before beginning an adjunctive trial, and may have previously demonstrated clinical acceptance of the medicine. Fewer studies were available, however, to evaluate the fixed combination products.

The data collected in this analysis potentially could be used to help plan the sample size of prospective, parallel trials. However, the number of studies available for this analysis is limited and provides only approximate sample size estimations. Further research is needed to more fully understand the exact discontinuation rates for the intent-to-treat and per protocol analyses. Further, future investigations may also provide techniques to help minimize dropout rates in glaucoma clinical trials.

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