Serious Adverse Event Reporting

Dear Editor:

Well-controlled clinical trials are the backbone of determining the efficacy and safety for medicines used in clinical practice.[1] However, such trials necessitate a large cost in human and financial resources. Consequently, careful pre-study planning may allow more efficient use of resources by the sponsor. One parameter that must be captured in well-controlled clinical trials is the serious adverse event (SAE), which is defined generally as any experience which causes: death, a life-threatening condition, disability, hospitalization, or congenital anomaly (February 23, 2009, Good Clinical Practice Guidelines, http://www.ich.org/LOB/media/MEDIA436.pdf).

The cost and time burden of SAEs has not been assessed in ophthalmology to our knowledge. We created an internal assessment of time commitment based on our 17 years of trial management experience. We estimated that one SAE, considered by the investigator unrelated to the study medicine, requires approximately 10 hours from pharmaceutical personnel for regulatory reporting. Cost for outsourced project manager and clinical research associate time, which would handle the SAE administratively varies, but a reasonable estimate for their combined cost would be $100/hour. This would provide approximate cost of $1000 per SAE. At the clinical site an unrelated SAE requires approximately 4 hours of effort. In contrast, an SAE considered related to the medicine could require approximately 24 hours of effort at an estimated cost of $2400 and 8 hours at the clinical site.

We reviewed all prospective, randomized, multicenter, parallel, active-controlled, comparative clinical trials of glaucoma studies with at least 70 patients per treatment arm performed from January 1996 to September 2008. We derived these studies from PubMed (MEDLINE [Internet]. Bethesda (MD): National Library of Medicine (US). [1960] - [cited 2008 Sep 9]. Available from: http://pubmed.gov/) and from the literature file of one of the authors (WCS). We compiled data on all articles that noted SAE results to determine factors associated with this type of adverse event using the intent to treat analyses.

This analysis included 43 studies and 20,094 patients (Table 1, available at http://aaojournal.org). These studies included on average: 502±311 patients, 30±1.5 clinical sites per study as well as 2.2±0.6 treatment arms lasting 7.7±9.6 months. There were 8616 (42.9%) males and 9298 (46.3%) females; 2017 (10.0%) African Americans, 15,248 (75.9%) Caucasians, and 1436 (7.1%) other races,[1] as well as 18,724 monotherapy (93.2%) and 1379 (6.8%) adjunctive therapy patients. The average age was 63.4±1.8 years. There were 7 studies missing at least some demographic data. Of the included studies, 35 evaluated prostaglandins, 34 beta-blockers, 14 carbonic anhydrase inhibitors (CAI), and 7 alpha-agonists as well as studies evaluating prostaglandin (n = 1), alpha-agonist (n = 2), and CAI (n = 2) based fixed combinations.

We found 449 (2.3%) total SAEs in the reviewed articles. Of these, 20 (4.5%) were deaths, 41 (9.1%) hospitalizations/surgeries, and 377 (84.0%) with type not reported. Also, 11 (2.5%) SAEs were related to the study medicine by the investigator.

The average number of SAEs per study was 11.2±3.1. In addition, there were 1.5±1.0 SAEs per month per study. The mean number of SAEs per patient was 0.02±1.0, SAEs per patient per month was 0.003±1.0, SAEs per site was 0.3±0.7, and SAEs per site per month was 0.04±0.07.

Separate multilinear regression analyses for patient and study characteristics associated with SAEs demonstrated that risk factors for these events were advanced age ($P<0.0001$) and increased study length ($P<0.0001$).

Our data indicate that many common study design and logistical characteristics used in glaucoma trials generally do not place the patient at greater risk for SAEs including class of medicine (currently available), adjunctive therapy, or the number of sites, treatment arms, or patients per site.

In contrast, the risk for higher SAE incidence potentially may be related to larger sample size, longer study length, and older age. However, any favorable effect of altering study design to potentially reduce SAE incidence should be carefully assessed by the impact on the study conclusions, especially patient safety, and the regulatory labeling.

These data may be used roughly to assess SAE costs in a future trial for budgetary purposes. For example, based on the above clinical data and cost assumptions for a 12-month study consisting of 400 patients, 14 total SAEs with 1 related to the medicine might be anticipated. The corresponding cost in time for pharmaceutical personnel would be 128 hours (approximately $12,800) and 60 hours total at clinical sites. Financial compensation for SAE costs at the site may be indirectly paid in budgetary overhead or is separately negotiated. This review suggests that in glaucoma trials evaluating the most current classes of available medicines SAEs are unusual and rarely considered related to the medicine. Potential factors associated with greater risk of SAEs appear to be greater study length and size, as well as patient age.

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Reference

1. Silverman SL. From randomized controlled trials to observational studies. Am J Med 2009;122:114–20.

Table 1. Analysis of 43 Studies and 20,094 Patients

First Author	Journal Citation	Name of Medicine(s)	ITT Patients
Lass JH	Arch Ophthalmol 1998;116:1003–10	Betaxolol, dorzolamide, timolol	298
Hedman K	Surv Ophthalmol 2002;47:65–76	Latanoprost, timolol	829
Fellman RL	Ophthalmology 2002;109:998–1008	Travoprost, timolol	605
Aung T	Ophthalmology 2005;112:267–71	Latanoprost, timolol, dorzolamide	275
Camras CB	J Glaucoma 2005;14:161–7	Latanoprost, brimonidine	303
Przydryga JT	Eur J Ophthalmol 2004;14:416–22	Travoprost	1590
Higginbotham EJ	Arch Ophthalmol 2002;120:915–22	Latanoprost, timolol	418
Patelska B	Am J Ophthalmol 1997;124:279-86	Latanoprost	160
Kampik A	J Glaucoma 2002;11:90–6	Latanoprost	379
Goldberg I	J Glaucoma 2001;10:414–22	Travoprost, timolol	572
Watson PG	Ophthalmology 1998;105:82–7	Latanoprost, timolol	249
Jampel HD	Am J Ophthalmol 2002;134:863–72	Latanoprost, unoprostone	164
Nordmann J-P	Am J Ophthalmol 2002;133:1–10	Unoprostone, betaxolol, timolol	556
Noecker RS	Am J Ophthalmol 2003;135:55–63	Bimatoprost, latanoprost	269
Haverkamp F	Eur J Ophthalmol 2004;14:407–15	Latanoprost	1068
Alm A	Arch Ophthalmol 2004;122:957–66	Latanoprost	519
Hedman K	J Glaucoma 2003;12:463–5	Latanoprost, timolol	441
Hughes BA	J Glaucoma 2005;14:392–9	Travoprost, timolol	305
Sherwood M	Surv Ophthalmol 2001;45:S361–8	Bimatoprost, timolol	1198
Camras CB	Am J Ophthalmol 1998;126:390–9	Latanoprost, timolol	268
Parrish RK	Am J Ophthalmol 2003;135:688–703	Latanoprost, bimatoprost, travoprost	410
Emmerich KH	Graefes Arch Clin Exp Ophthalmol 2000;238:19–23	Latanoprost, timolol, dorzolamide	183
O'Donoghue EP	Br J Ophthalmol 2000;84:579–82	Latanoprost, dorzolamide	224
Mundorf TK	Clin Ther 2004;26:541–51	Timolol-LA, timolol	332
Sall KN	Ophthalmology 2003;110:615–24	Dorzolamide, timolol	295
Rouland JF	Ophthalmologica 2002;216:449–54	Timolol-LA, timolol	210
Schuman JS	Ophthalmology 2000;107:1171–7	Brimonidine, timolol	926
Sall KN	Surv Ophthalmol 2000;44:S155–62	Brinzolamide, dorzolamide	463
Silver LH	Surv Ophthalmol 2000;44:2:S141–5	Brinzolamide, dorzolamide	213
LeBlanc RP	Ophthalmology 1998;105:1960–7	Brimonidine, timolol	463
Silver LH	Am J Ophthalmol 1998;126:400–8	Brinzolamide, dorzolamide, timolol	572
Kaback M	Ophthalmology 2008;115:1728–34	Brinzolamide, timolol	517
Cantor LB	Br J Ophthalmol 2006;90:1370–3	Bimatoprost, travoprost	157
Serle JB	Surv Ophthalmol 1996;41:S39–47	Brimonidine, betaxolol	199
Mundorf TK	Clin Ther 2004;26:541–51	Timolol-LA, timolol	332
Holló G	Eur J Ophthalmol 2006;16:816–23	Timolol, brinzolamide, travoprost	201
Craven ER	J Ocul Pharmacol Ther 2005;21:337–48	Brimonidine, timolol	1159
Netland PA	Adv Ther 2003;20:149–63	Travoprost, latanoprost, timolol	787
Camras CB	Ophthalmology 1996;103:138–47	Latanoprost, timolol	268
Watson P	Ophthalmology 1996;103:126–37	Latanoprost, timolol	294
Boyle JE	Ophthalmology 1998;105:1945–51	Dorzolamide, timolol	256
Clineschmidt CM	Ophthalmology 1999;106:17–24	DTFC, timolol, dorzolamide	335
Barnebey HS	Am J Ophthalmol 2005;140:1–7	Travoprost, timolol	263

DTFC = Dorzolamide/timolol fixed combination; ITT = intention to treat; Timolol-LA = Timolol with potassium sorbate (Istalol).