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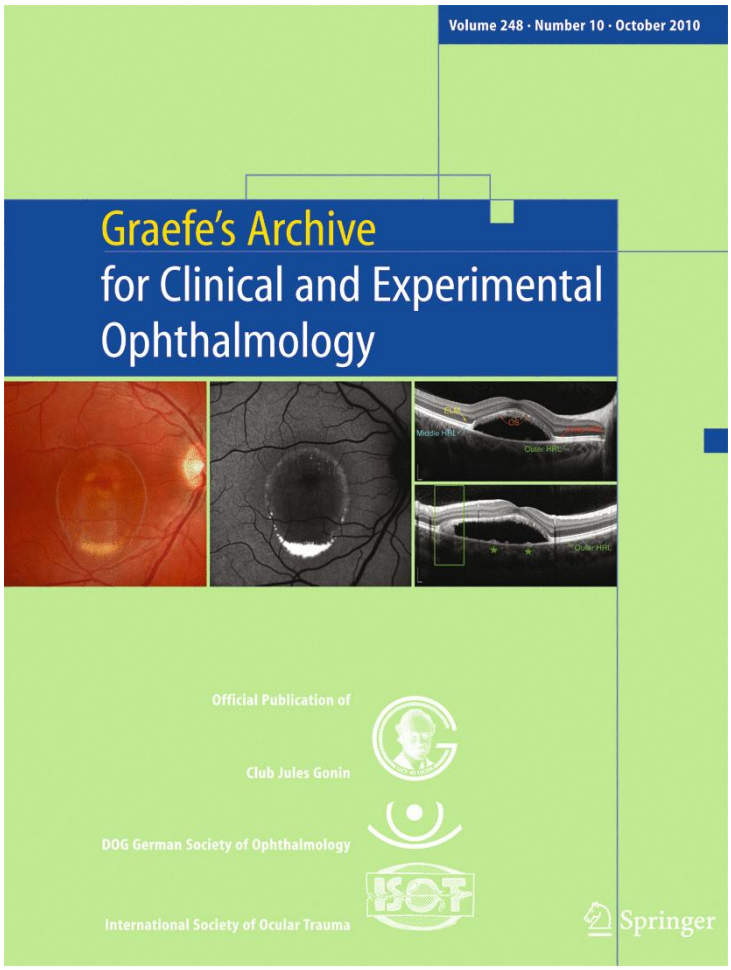

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LETTER TO THE EDITOR

Factors associated with site requirement for glaucoma clinical trials

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Dear Editor:

Prospective well-controlled clinical trials are the backbone of determining the efficacy and safety for ophthalmic medicines [1]. Although expensive, careful pre-study planning may maximize the use of financial resources.

One logistical requirement in planning trials is estimating the number of clinical sites required to complete enrollment in a timely fashion. However, the financial burden of opening a clinical site has not been previously assessed in ophthalmology to our knowledge.

We estimated that to open one clinical site requires about 40 hours of pharmaceutical personnel time, which, when added to travel and Ethics Committee costs, provides an approximate overall cost of $11,100 per site. To maintain a site throughout the study requires about 10 hours per month, plus travel time, for an approximate cost of $2,280 (internal data, PRN). The purpose of this study was to determine factors associated with increased number of sites and reduced number of patients per site in clinical trials.

We reviewed prospective, randomized, parallel, active-controlled, clinical glaucoma trials with ≥70 patients per treatment arm performed between 1996 and 2008. We included studies found on Pubmed (www.ncbi.nlm.nih.gov/pubmed/) and from the literature files of one of the authors (WCS).

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This analysis included 39 studies and 18,437 patients at 1,350 clinical sites. These trials included on average 449.7± 319.8 patients and 2.3±0.7 treatment arms over 8.1 ± 9.8 months duration. There were 17,484 monotherapy and 953 adjunctive therapy patients; 10,661 patients in the United States, 5,639 in Europe, 607 in Asia and 1,530 at unreported locations. Of the included studies, 36 evaluated prostaglandins, 29 beta-blockers, 11 carbonic anhydrase inhibitors, five alpha-agonists and seven fixed combinations (prostaglandin [n=2], alpha-agonist [n=2], and carbonic anhydrase inhibitors [n=3]).

Our analysis found, using a matrix correlation coefficient, that the number of patients per site was reduced with increasing study length (P=0.322, P=0.044). Further, separate multi-linear regression analyses for risk of reduced patients per site and more sites per study were significant for a greater number of: treatment arms (P=0.01), patients (P<0.0001), and study length (higher number of sites only, P=0.0008). These results are shown in Table 1.

Our data indicate that several important features of clinical study design and logistics do not influence the number of sites or the number of patients per site, including: class of glaucoma medicine (currently available), monotherapy versus adjunctive therapy, or United States or European location.

In contrast, when desired, limiting the number of sites or increasing the number of patients per site might be accomplished by assuring proper statistical sizing of the study, using fewer treatment arms, and reducing study length. However, any favorable effect of such design modifications discussed in this review should be assessed by the impact on the study conclusions or the potential product labeling.

The rationale behind limiting the number of patients and treatment arms to decrease the number of clinical sites

Table 1 Multi-linear regression analyses

Factor	Lower number of patients per site	Higher number of sites per study
Greater number of treatment arms	0.01	<0.0001
Increased study length	0.06	0.0008
Class of medications	0.6	1.0
Mono-versus adjunctive therapy	0.9	0.9
Location (United States, Europe, Asia)	0.9	0.8
Number of patients	<0.0001	<0.0001

appears self-apparent. However, the reason a longer study would increase the number of sites while potentially reducing the number of patients per site is less clear. Possibly, patients and/or physicians may have less desire to participate in longer-term studies. In contrast, a higher study sample size might reduce the number of patients per site, because the need for more investigators could force the selection of less qualified sites, which might recruit poorly.

Limiting the number of clinical sites and maximizing the number of patients per site may be important to reduce study expense. For example, based on the above cost estimates, if five new sites were opened to enhance recruitment in a year-long study, the costs to initiate and keep the sites open (including 3 months recruiting time) would be approximately $226,500.

This study suggests glaucoma clinical trial costs potentially may be reduced if scientifically appropriate by limiting the number of clinical sites, which might be accomplished by proper sample size power calculations as well as limiting the number of treatment arms and study length.

Reference

1. Silverman SL (2009) From randomized controlled trials to observational studies. Am J Med 122:114–120