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Glaucoma clinical trial design: A review of the literature

Abstract

The purpose of this article is to review the prior research evaluating design techniques for glaucoma clinical trials to help ophthalmologists and pharmaceutical sponsors better develop literature-based studies that are cost- and time-efficient. We performed this study using known published articles by the authors and literature found on Pub Med. We included 24 articles that analyzed specifically the results of clinical trial methods and/or interpretation. This review found that studies have evaluated glaucoma specific aspects of glaucoma clinical trials including: Predicting the results of later phase clinical trials based on early phase clinical trials and animal studies; protocol design parameters such as intraocular pressure, inclusion criteria, method of pressure measurement, study population, and side effect evaluation; and study planning issues such as number of clinical sites as well as subjects, dropout rates, estimated serious adverse events, and protocol violations. This review suggests that the medical literature supports some aspects of glaucoma clinical trial study design. Additional design features might be derived from government regulations, guidance, as well as agency contacts, consultants, and clinical community standards. Study design decisions that must be made beyond the aforementioned resources should be made carefully, with appropriate consultation as needed, considering the risk/benefit ratio to the study. However, more research is needed to better evaluate the design procedures and methods involved in glaucoma clinical trials to best provide a cost- and time-efficient study while achieving quality efficacy and safety results.

Key words: Clinical trial, glaucoma, trial design, trial methods

INTRODUCTION

The well-controlled, randomized, masked, clinical trial is the bedrock for evaluating new medications for approval from the regulatory bodies as well as acceptance by the academic and medical communities.^[1] Unfortunately, such a study can be expensive with an estimated total pharmaceutical sponsor cost of \$20-25,000 per subject and lasting up to a year.^[2-4] Consequently, the clinical trial design becomes important not only for gaining approval

from the regulatory bodies and medical community but also to limit costs in time and money.

The purpose of this article is to review the prior research evaluating design techniques for glaucoma clinical trials to help ophthalmologists and pharmaceutical sponsors better develop literature-based clinical protocols that are cost- and time-efficient. We have not intended to review studies that evaluated procedures and diagnostic techniques apart from clinical trials. Moreover, we assume, for this review, the appropriateness of procedures and diagnostic tests for glaucoma studies that are accepted by the ophthalmic community.

MATERIALS AND METHODS

We performed this study using known published articles by the authors and literature found on PubMed

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	DOI: 10.4103/2229-3485.134306

(<http://www.ncbi.nlm.nih.gov/pubmed>) published between 1990 and 2012. In the advanced search option on Pub Med, we limited the search to: Clinical trial, meta-analysis, practice guideline, randomized controlled trial, and review. Glaucoma method trials were reviewed by searching the following specific terms, “glaucoma” and: Inclusion/exclusion criteria, pigment dispersion (PD), exclusion period, laser-assisted *in situ* keratomileusis, pachymetry, intraocular pressure (IOP), diagnosis, patient age, ocular surgery, laser trabeculectomy, injury, patient history, ocular inflammation, visual acuity, hypersensitivity, animal model, phase, commercialization, higher limit, IOP measurement technique, masking, withdrawals, serious adverse event (SAE), protocol deviations, and symptom query. “Glaucoma” as well as “design” and “protocol” were searched in combination with: Optic disc examination, automated perimetry, interpretation,

number of patients, clinical sites, and washout. The searches were performed independently by two of the authors (WCS, LAN). We included articles that analyzed specifically the results of clinical trial methods and/or interpretation.

RESULTS

Predicting glaucoma clinical trial results

Table 1 summarizes the 24 articles discussed in this review. Key to the development of a new glaucoma medicine is the assessment of whether it will reach successful commercialization based upon its ocular hypotensive efficacy. IOP is used typically as a short-term measure for long-term efficacy in reducing the incidence of progression.^[5-8] Several time points in pharmaceutical

Table 1: Summarized articles included in review

Abbreviated citation	Main measure	Conclusion
Stewart WC, <i>et al.</i> 2011 ^[9]	Animal model studies and parameters associated with commercial availability	Animal models provide some success in predicting commercialization of glaucoma medicine. Caution must be used in interpreting individual models or studies
Stewart WC, <i>et al.</i> 2008 ^[10] Gehr BT, <i>et al.</i> 2006 ^[11]	The predictive value of early phase trials (I-II) to Phase III and IV Effect size decreases over time	Early phase trials usually approximate the results of later regulatory and marketing studies The effectiveness of medical therapies reported in randomized, controlled trials decreases over time
Stewart WC, <i>et al.</i> 2013 ^[12]	Influence of pigment dispersion or exfoliation glaucoma patients on clinical trial results	Clinical studies can include pigment dispersion or exfoliation glaucoma patients with only a small impact on IOP and a low number of such subjects enrolled
DeMill DL, <i>et al.</i> 2013 ^[13]	Average eye versus highest intraocular pressure analyses in glaucoma clinical trials	The highest IOP analysis method generally provides slightly higher IOPs at baseline than the average IOP analysis method
Heijl A, <i>et al.</i> 2011 ^[14]	Relationship between IOP reduction with a fixed treatment protocol and untreated IOP level; consistency of IOP reduction over time; and if there is a threshold pretreatment IOP level below which IOP reduction might be less effective	When effects of IOP-lowering treatment are reported, the baseline IOP levels should be specified as well
Stewart WC, <i>et al.</i> 2001 ^[15]	IOP washout time after discontinuing brimonidine twice daily and latanoprost once in the evening	Following discontinuing latanoprost or brimonidine, latanoprost demonstrates a trend to a longer washout period although a wide variation exists among individuals
Dubiner HB, <i>et al.</i> 2004 ^[16] Sit AJ, <i>et al.</i> 2006 ^[17]	The duration of travoprost’s IOP-lowering efficacy up to 84 hours after the final dose Diurnal and nocturnal persistency of IOP reduction after omission of up to 2 doses of once-daily topical travoprost	Travoprost produces reductions in IOP that may be sustained for up to 84 hours after dosing IOP lowering after omission of 1-2 travoprost doses is attenuated in the diurnal period but sustained in the nocturnal period, the time corresponding to the highest baseline habitual IOP
Hong YJ, <i>et al.</i> 1995 ^[18]	Effect on IOP of a 2-week washout following long-term topical levobunolol or timolol	2-week washout after long-term topical beta-blockers appears insufficient to restore IOP to pretreatment baseline in blacks and whites with brown irides
Stewart WC, <i>et al.</i> 2004 ^[19]	If repeated measures influence the IOP reading beyond the first measurement	Extra measurements, on average, may not alter the IOP from the initial reading
Stewart WC, <i>et al.</i> 2009 ^[20]	Standard deviation for treatment groups, generally, and among individual classes of medicines	Standard deviation of 3.5 mm Hg generally reflects accurately the distribution of the IOP in clinical trials.
Stewart WC, <i>et al.</i> 2004 ^[21]	Dropout rates for the intent-to-treat and per-protocol analyses from clinical trials.	Discontinuation rates for intent-to-treat and per-protocol analyses may help in planning sample sizes for clinical trials
Stewart WC, <i>et al.</i> 2010 ^[22]	Risk factors for subject withdrawals from glaucoma clinical trials	Subject withdrawals for administrative errors or adverse events might be reduced by choosing sites with lower protocol violations rates or medication dispensing errors

Contd...

Table 1: Contined

Abbreviated citation	Main measure	Conclusion
Stewart WC, <i>et al.</i> 2010 ^[23]	Factors associated with number of sites and patients/site in clinical trials	Clinical trial costs may be reduced by limiting clinical site numbers, by proper sample size power calculations and limiting the number of treatment arms and study length
Stewart WC, <i>et al.</i> 2009 ^[24]	Cost and time burden of serious adverse event reporting	Serious adverse events are unusual and rarely considered related to the medicine. Factors associated with greater risk of serious adverse events are greater study length, study size and patient age
Stewart WC, <i>et al.</i> 2010 ^[25]	Motivation of glaucoma study subjects for performing clinical trials	Clinical study subjects, while generally wishing to be helped by the study medicine, usually indicate altruistic motives in performing research studies
Bent S, <i>et al.</i> 2006 ^[26]	Effect of methods of questioning patients about adverse events in a clinical trial and frequency of reported events	Different methods of collecting patient data regarding adverse events lead to differences in rates of adverse events in clinical trials
Krufft B, <i>et al.</i> 2007 ^[27]	Influence of collection method on side effects adverse event incidence of reported	A specific ophthalmic symptom query more often elicits a positive response than a general query

IOP=Intraocular pressure, Graefes=Graefes arch clin exp ophthalmol

development are important in assessing the medicine's commercial viability: In the preclinical phase based on animal efficacy data, and in the early clinical phases (I and II) before reaching the larger and more expensive Phase III studies. Please see Table 2 for an explanation of trial phases.

Stewart *et al.*,^[9] recently reviewed the literature on the capacity of preclinical animal studies to predict later commercialization of a new glaucoma medication. The best performing model for both the peak and diurnal curve IOPs was the hypertensive monkey model. However, among publically evaluated normotensive and hypotensive animal models, none consistently predicted the commercial viability of a new glaucoma product, showing a weak association to ultimate commercialization with just an approximately 55% and 65% sensitivity and specificity, respectively.

In addition, Stewart *et al.*,^[10] have evaluated the ability of Phase I and II clinical trials to predict Phase III and IV results. This study found that for currently available medication classes early phase clinical trials generally approximated Phase III and IV results based on the reduction from untreated IOP baseline. These studies indicate that predicting future commercialization based on preclinical animal data is difficult, whereas Phases I and II more accurately predict IOP results later in the product's life.

Interestingly, Gehr *et al.*,^[11] reviewed commercialized glaucoma medications (timolol and latanoprost) and found the results of earlier studies were better than those from later studies following commercialization, caused mainly by baseline differences. The reason for this finding is not clear. DeMill *et al.*, have found higher baseline IOPs in double-masked trials of the type that are performed earlier in development (internal data). These higher baseline IOPs might allow for a larger absolute drop in IOP and may be

Table 2: Definitions of pharmaceutical phases of development

Trial	Definition
Preclinical	<i>In vitro</i> or <i>in vivo</i> pharmacology and toxicology testing of experimental drugs - that occurs before trials in humans may be conducted
Phase I	Initial human study to determine the metabolism and pharmacologic, safety, dosing, and initial efficacy; may include healthy participants and/or patients
Phase II	Short-term clinical studies to evaluate the effectiveness, safety, and dosing of the drug in patients with the target disease
Phase III	Expanded trials intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for regulatory approval
Phase IV	Postmarketing studies to delineate additional information including the drug's risks, benefits, and optimal use

Definitions amended from ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/info/glossary>)

a partial explanation of Gehr's finding. More research is needed to evaluate these results.

Inclusion criteria IOP

The baseline untreated inclusion IOP level is important to identify a group of patients with the disease the new medicine is intended to treat. Generally, the minimum untreated inclusion IOP is 22 mm Hg, which is associated with the definition of ocular hypertension and primary open-angle glaucoma, the typical diagnoses included in well-controlled clinical trials.^[28] However, questions exist if modifying this basic inclusion criterion would potentially ease recruiting or allow for better differentiation between glaucoma medications.

Type of glaucoma

Several common secondary types of open-angle glaucoma exist, PD, and exfoliation glaucoma (EXG)

that are often included in clinical trials usually to assist recruiting. Stewart *et al.*,^[12] recently found in US-based clinical trials in which these diagnoses are allowed approximately 4% of patients have PD or EXG. The baseline IOPs were higher for the morning and diurnal curve but not for the active treatment IOPs. These results indicated that US-based glaucoma clinical studies generally can include PD and EXG patients with only a small impact on IOP and a low number of such subjects typically are enrolled.^[12]

Average versus highest IOP analysis

Since the IOPs are not independent between eyes only one measure per subject can be included in study analyses. DeMill *et al.*,^[13] recently evaluated the two most common methods to account for the lack of independence between eyes, the average (average of both eyes together) and the highest (highest of the two eyes) IOP methods. For both prostaglandin (PTG) and beta-blocker (BB) studies they found the highest IOP method demonstrated about 1 mm Hg higher baseline IOPs in the morning, and for the diurnal curve, than the average eye method. These differences generally were not found on the last active treatment visit for either class of medicine.

Limits of IOP inclusion criteria

Another common issue is specifying an upper limit for IOP inclusion criteria. Such a limit provides a safety margin that a subject with an IOP so high that it would not be controlled safely by the study medicine would not be enrolled into the study.

DeMill *et al.*,^[13] recently found that a higher (34–36 mmHg) or no upper limit of IOP, compared with 30 mm Hg, is associated with a higher baseline IOP for both the morning and diurnal curve IOPs (internal data). Further, the IOPs at the active treatment visit remained elevated for PTGs for the morning and diurnal IOPs, but not for BBs. However, the IOP reduction from untreated baseline for the morning and diurnal IOPs for both PTG and BB groups were not different between inclusion criteria. This study suggests that differences in the upper limit inclusion IOP in well-controlled clinical trials may influence the baseline and active treatment IOPs in some cases.

Alternative inclusion criteria may be important because higher rather than lower entry IOPs may allow for a greater reduction in IOPs with treatment.^[14] Further, there is some belief that this greater drop in IOP might better differentiate the ocular hypotensive efficacy between two products. However, currently there is no evidence this is the case and it remains a controversial topic.

Washout times

To ensure an accurate baseline IOP, the prior medication must be discontinued and “washed out” for an appropriate period of time. A correct baseline is important so that the active treatment medication evaluated in the study may have the best opportunity to demonstrate a decrease from baseline. Too short a washout time might make it appear that the active treatment medicine is weaker than its actual efficacy, while too long unnecessarily lengthens the study and the time the subject is exposed to an elevated IOP.

Standard washout times are used by the industry depending on the class of medicine. However, very little published evidence supports these times. Stewart *et al.*,^[15] evaluated the washout times of brimonidine and latanoprost and found brimonidine was washed out in 15 patients in 5 weeks, whereas with latanoprost the washout time was up to 8 weeks in 17 patients, with one patient still slightly below baseline. Dubiner *et al.*, and Sit *et al.*,^[16,17] have shown separately that travoprost remains unwashed out after 2 weeks. Hong *et al.*,^[18] demonstrated that a 2 week washout for timolol was not adequate.

Study design

Several prior studies have specifically evaluated pertinent issues over the design of clinical trials.

IOP measurement

Key to the success of a glaucoma clinical trial is not only the IOP inclusion criteria, as mentioned previously, but also the method of IOP measurement. Although not proven specifically Goldmann applanation tonometry is the assumed standard measure of IOP by the ophthalmic community and thus is used in clinical pharmaceutical trials. However, several modifications to the techniques of acquiring these measurements may be utilized to attempt to decrease recruitment errors by limiting subjects with falsely high IOPs from entering the trial, thus limiting a placebo effect. The extent of the placebo effect in Phase II trials has been evaluated by Stewart *et al.*, and found to be 2.3 mm Hg for the 8 am IOP and 1.5 mm Hg for the diurnal curve (internal data).

Stewart *et al.*,^[19] assessed past clinical trials that had measured the IOP more than once. They found that repeated IOP measurements, up to three times, at the same time-point by the same person were essentially the same in almost all cases and were not effective in identifying poorly performed IOPs.

Stewart *et al.*, also evaluated techniques from past reported trials to limit the placebo effect by using: Two individuals to measure the IOP, an afternoon IOP entry measurement requirement, and a second qualification day. They found

that the placebo effect was not reduced in trials which utilized these techniques (internal data).

Masking

Also important to the planning of a study is masking the medication. This is typically done in a Phase III trial by using sterile techniques to transfer the reference medication into bottles that are alike in appearance and labeling to those containing the medication under investigation so all parties are masked to the study medicine (double-masked). In Phase IV and early regulatory trials a single-masked method sometimes is implemented which uses commercially available bottles of the reference medication over-labeled with a study-specific label. Both the reference and test medication bottles are stored in an opaque container and study subjects are instructed not to reveal the contents to the investigator or study staff.

Stewart *et al.*, recently investigated the impact of masking techniques on the IOP (internal data). They found, to their surprise, that the baseline IOP was higher in double- compared with single-masked studies. The reason for this is not known. They speculated that investigators recruited subjects more likely to present with a qualifying, and thus higher, IOP for Phase III trials (using double-masking) which are generally perceived as more important and subject to higher scrutiny than later trial phases.

Study planning

Several previous studies have evaluated germane issues over the planning of clinical trials.

Number of subjects and clinical sites

Critical to the planning and success of a clinical study is the number of subjects required and the number of sites needed to recruit these subjects. Generally, the regulatory agencies require a 1.5 mm Hg difference in IOP between two medications to declare a clinically significant difference. The standard deviation (SD) often used for prestudy unpaired sample size calculations is 3.5 mm Hg. Stewart *et al.*,^[20] analyzed prior well-controlled clinical glaucoma studies and their SD for monotherapy trials and found a mean SD, near the commonly assumed prestudy value, of 3.7 mmHg (range 2.7-5.4 mm Hg).

Once the number of subjects required to demonstrate a statistical difference has been determined several other factors may influence the number of subjects required. Stewart *et al.*,^[21] have found from prior clinical trials that the percent dropout rate in glaucoma clinical studies for the intent-to-treat analyses was proportional with the length of the study. Further, a proportional increase in the dropout rate was observed for the per-protocol analyses with the length of study and number of study visits. However, no

differences in dropout rate were observed by increasing the sample size of the study for either the intent-to-treat or per-protocol analyses.

The number of disqualified subjects from a trial also may influence the number needed to enroll. Stewart *et al.*, evaluated prior glaucoma trials and found a positive association for medication errors and protocol violations to subject withdrawals due to ocular adverse events (AEs) and total administration errors.

Further, protocol violations were associated to subject withdrawals for any adverse event or systemic AEs. Alpha-agonists were associated to withdrawals for poor IOP control, while alpha-agonists, BB, and carbonic anhydrase inhibitor/BB fixed combinations were associated with systemic AEs.^[22]

The authors concluded that subject withdrawals from clinical trials for administrative errors or AEs potentially might be reduced by choosing sites with lower historical rates of protocol violation or medication dispensing errors. Drug class may also influence subject withdrawals for AE and IOP control.^[22]

Stewart *et al.*,^[23] assessed factors influencing the number of subjects per clinical site. They found that an average number of subjects per site in a glaucoma trial was 13.6. However, the authors also noted that the number of subjects per site might be reduced by several factors including: Increasing study length, a higher number of treatment arms, and a greater number of required subjects.

The number of clinical sites is important also for costing the study. In the above study, the authors estimated to open one clinical site requires about 40 h of pharmaceutical personnel time, which, when added to travel and ethics committee costs, provides an approximate cost of 11,100 USD per site. To maintain a site throughout the study necessitates about 10 h per month, plus travel time, for an approximate cost of 2,280 USD.^[23]

Stewart *et al.*,^[24] also have evaluated the costs of SAE reporting. They estimated one SAE, considered unrelated to the study medicine, requires approximately 10 h from pharmaceutical personnel for regulatory reporting at an approximate cost of 1000 USD. At the clinical site, an unrelated SAE requires approximately 4 h of effort. In contrast, an SAE considered related to the medicine requires approximately 24 h of effort at an estimated cost of 2400 USD and 8 h at the clinical site.

The authors found that the average number of SAEs per study was 11.2 ± 3.1 . SAEs per subject per month were

0.003 ± 1.0 and SAEs per site per month was 0.04 ± 0.07. Risk factors for SAEs were advanced age and increased study length.^[24]

Their data also indicated that many common study design and logistical characteristics employed in glaucoma trials generally do not place the subject at greater risk for SAEs including the class of medicine (currently available), adjunctive therapy, or the number of sites, treatment arms or subjects per site.^[24]

Recruiting

Patient recruitment is necessary obviously for success of a clinical trial. Patients who perform clinical trials must meet certain criteria but also must be motivated to perform the trial because of the extra visits, procedures and risks.

Stewart *et al.*,^[25] recently investigated the motivational aspect of patients who participate in clinical trials and found that their primary medical reason for enrolling was to be helped by the study medicine ($n = 121$, 61%), while their primary nonmedical reason was to assist humankind ($n = 145$, 73%). The most positive aspect of participating was their interaction with the clinic staff ($n = 141$, 71%). In contrast, 139 (70%) listed no negatives about performing the clinical trial, while 27 (14%) complained of stress of induced by examinations and visits. Greater than 60% believed their participation provided a greater understanding of the medication's clinical use, efficacy, and safety while benefiting the care of other patients. The paper suggested that a caring, service-oriented relationship of the investigator to their patients might further help study subject recruiting.

Safety

Bent *et al.*,^[26] have shown in systemic studies that if a specific symptom query is used more side effects are captured than with a general query such as "How are you doing?" Kruff *et al.*,^[27] evaluated this issue in a meta-analysis of four glaucoma clinical trials and also found that using a specific symptom query elicited more side effects than the general non-specific query. They noted that 13/14 survey questions provided a greater adverse event rate compared with a general query with the only exception being for photophobia. In total, 77% of patients gave at least one positive response to a specific symptom survey, while a general query generated an 11% response rate.

DISCUSSION

Generally, glaucoma clinical trial design generally reflects the procedures and methods used for glaucoma evaluation and diagnosis in clinical practice. However, special techniques are

employed in clinical protocols to help assure quality control within the study. Most of these techniques are related to the inclusion and exclusion criteria, IOP measurement technique, good clinical practices as indicated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-ICH (e.g. the qualifications of the investigator, ethics committee approval, protection of patients)^[29] masking of the medication, randomization, the careful management of the study itself, especially non-serious as well as SAEs, and informed consent.

Study design and management choices may make important differences in the cost in time as well as money and the approval of the drug by the regulatory authorities. Therefore, trial protocols should be developed, as much as possible, according to the available literature, assumed accepted medical community practice standards, regulatory authority guidance and good clinical practice regulations.^[29]

Requiring supplemental procedures or inclusion/exclusion criteria not supported by the regulatory authorities, usual clinical practice or by the medical literature, solely because they were utilized in a prior protocol should be considered carefully within an analysis by the sponsor of their needs, the risk/benefit ratio to the development, patient safety and the recruiting process.

How can this review be used clinically? Sponsors designing clinical protocols for glaucoma should realize their design principles will be derived from several important sources. This review has dealt with one source, the design features based in the medical literature. Unfortunately, these data support or exclude only a minority of clinical features in a protocol.

Consequently, sponsors must derive other aspects of the protocol design from several different areas including: Medical community standards for glaucoma diagnosis and follow-up (e.g. common measures for glaucoma such as IOP, VF, and fundus), regulatory agencies for specific regulations and guidances; and consulting advice from a development or clinical glaucoma subspecialist. In some cases, questions may arise where there is still uncertainty regarding the design approach based on the insufficient discussion in the literature, regulations and medical community standards. In such a case, approaching the appropriate regulatory or clinical consultant or regulatory agency for pharmaceutical development may provide further guidance.

This review suggests that the medical literature supports some aspects of glaucoma clinical trial study design. Additional design features might be derived from

government regulations, guidance, as well as agency contacts, consultants, and clinical community standards. Study design decisions that must be made beyond the aforementioned resources should be made carefully, with appropriate consultation as needed, considering the risk/benefit ratio to the study. This review was limited to the exploration of the medical literature and its assistance to glaucoma clinical trial design. The influence upon trial design of other trial procedures commonly accepted or proposed by regulatory groups or community-accepted practices was not explored. More study is needed to fully evaluate the techniques of glaucoma clinical trials in order to increase efficiency, reduce costs while maintaining subject safety.

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How to cite this article: Stewart WC, Stewart JA, Nelson LA. Glaucoma clinical trial design: A review of the literature. *Perspect Clin Res* 2014;5:108-14.

Source of Support: Nil. **Conflict of Interest:** None declared.