

## Ophthalmic pharmaceutical clinical trials: design considerations

Evidence-based medicine requires diligent literature review in order to assess the findings of published clinical reports. Sound experimental procedures, based on the Scientific Method are conducted with a consideration of several background factors underlying clinical trial research. A discussion of these underpinnings and other factors influencing clinical trial design as they apply to ophthalmic pharmaceutical trials is provided, with the intent of providing a means of applying these considerations to literature review.

**Keywords:** clinical trial • ophthalmic • trial assumptions • trial design

*"I had never heard then of 'randomized controlled trials,' but I knew there was no real evidence that anything we had to offer had any effect on tuberculosis, and I was afraid that I shortened the lives of some of my friends by unnecessary intervention."* - AL Cochrane, a reflection as a POW medical officer [1].

More than 40 years after Dr Cochrane committed these words to print, it may still be said that the proof for the ideal treatment of many medical conditions remains forthcoming. In the absence of definitive evidence regarding a therapeutic treatment, competing strategies naturally emerge as providers seek to 'provide regimens for the good of patients' as admonished by the Hippocratic Oath. Naturally, curious providers question interventions and wish to know the 'best' treatment for a given condition, and they seek information to help them weigh treatment options. Clinical trials are medicine's quest to provide scientific evidence and identify optimal strategies for the healing arts. Evidence-based medicine demands this process, and increasing health care costs provide an additional financial impetus to make these distinctions.

In the most basic sense, clinical trials are biological experiments designed to investi-

gate specific hypotheses related to human health. Volunteers are studied under controlled conditions in order to determine if a particular entity (medication, surgery, or other intervention) is effective. The ultimate goal of clinical trials is to improve patient care. Without the medical evidence afforded by clinical trials, providers, patients and funders of healthcare cannot know if a given intercession is effective, safe, or even better than doing nothing at all.

Well-defined protocols delineate study parameters and provide the framework for clinical trials. These rules are intended to provide safety to study participants, to guarantee that measurements are obtained accurately and consistently, and to ensure that the obtained results reflect the original intent of the study hypothesis. Protocols are established prior to patient recruitment in order to standardize the experimental process, to address specified outcomes, and to provide reassurance to study participants [2,3].

Pharmaceutical clinical trials specifically address medical effectiveness of therapeutic agents and are mandated prior to market entry. Due to the ethical nature of experimental chemical substance testing in humans, these clinical trials are strictly governed by regulatory agencies, such as the Medicines

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and Healthcare Products Regulatory Agency in the United Kingdom, European Medicines Agency in the European Union, Pharmaceutical and Medical Devices Agency in Japan, The National Agency for Sanitary Vigilance in Brazil, and the US FDA.

Ophthalmic pharmaceutical clinical trials are those research studies designed to investigate the effectiveness of medications in reducing ocular morbidity, and they follow the same guidelines as other trials involving pharmaceuticals. Considering that approximately 60% of all medical research funding is supplied by industry [4,5], a majority of ophthalmic pharmaceutical clinical trials falls under the aegis of Pharma. Thus an understanding of these trial designs is imperative for clinicians to interpret publications in the ophthalmic literature.

### Trial underpinnings

#### What constitutes an ideal clinical trial?

Consideration of any clinical trial design must begin with an important caveat: no clinical trial design, observation method or data set is perfect [6]. Following the Scientific Method, clinical trials seek to answer biological questions by regimented, experimental means; however, it is the design of those experiments that determine scientific success or failure [7]. Understanding the different facets of clinical trial design helps readers of medical literature better interpret study findings.

In general, the goal of clinical research study design is to reduce bias, defined as any tendency that prevents unprejudiced consideration of a question [8]. In medical research, bias can result in distortion of a statistical finding away from the true value and can be the result of the data sampling process [9]. The introduction of bias can occur at any stage of the research process (planning, implementation or analysis), and is nearly always present to some degree in published studies [10].

The expectations for a clinical trial are exceedingly demanding. The design of any research trial should reduce bias, allow for the collection of precise data, prevent statistical over-analysis, be highly reproducible and yield results that are clinically significant. In addition to controlling for potential bias, clinical trials that meet these basic requirements also satisfy the ethical considerations for human trials, allow for efficient use of trial resources, reduce the possibility of confounding, control for precise measurements, reduce random effects, simplify data analysis and increase the external validity of the trial [11]. It is also important to emphasize that skilful statistical calculations cannot overcome the shortcomings of poor trial design. These observations hold true for all clinical trials – including those

involving ophthalmic pharmaceuticals – and are the culmination of Dr Cochrane's challenge to medicine those decades ago.

#### Expectations of researchers

Do investigator expectations determine outcomes? Expectancy Theories of behavior indicates that humans make decisions based on desired outcomes [12]. This phenomenon has not yet been directly studied with respect to trial design in medical research, but sophisticated clinical trial designs seek to mitigate these effects.

It may be surmised that medical researchers are swayed by questions of funding, complex trial regulations, excessive monitoring, issues of patient privacy and misunderstandings regarding methodology [13] – interesting considerations beyond the scope of this paper. The effect of corporate sponsorship on research is well-known, but parallel consequences for independent or government-sponsored research remain indeterminate.

Investigator behavior can affect many factors in clinical research: selection of sample sizes, masking, choice of study vehicles, etc. Readers should be aware of the possibility that options of study design parameters can be made without conscious realization that such decisions may inadvertently influence the entire study, and, therefore, the reported outcomes. In the present research environment involving multiple investigators and sites, it is hoped that these considerations are minimized or at least counter-balanced in the planning stages of clinical research.

#### Underlying trial assumptions

Although not explicitly stated, all clinical pharmaceutical trials are predicated on two underlying assumptions. First, the natural history of the disease must be understood well enough to believe that an intervention will reduce morbidity or – rarer for ophthalmic cases – mortality. Second, preliminary studies conducted using animal models (or more infrequently, human donor tissue for selected surgical interventions) must have suggested a benefit for human testing. In practice, animal models are necessary to gain understanding of human disease mechanisms and to investigate new treatments [14]. The challenge for researchers continues to be locating appropriate animal models and extrapolating harvested data to humans [15]. Because not all data derived from animal studies may be applied to human physiology, subsequent testing on humans is still required. This is specifically true for human studies of eyes, which are highly specialized neurological tissues in primates.

Discerning the natural history of some diseases remains a challenge, as most providers can cite mul-

multiple examples of ‘exceptions to the rule’ of clinical courses. It may be surmised that these exceptions are disease variants – or perhaps unrecognized subtypes – that may not follow the same course as ‘typical’ cases. Great care must be exercised during the patient selection process in an attempt to identify variant presentations in order that clinical research trials target only a single disease entity.

Ophthalmic examples to demonstrate this concept abound. The natural history of cataract can still be seen everywhere in the world due to various challenges of access to healthcare that serve as barriers to the amelioration of this common eye disease. Although there is currently no treatment for cataract (i.e., reducing lenticular opacification – cataract surgery is prosthetic rehabilitation), the natural history is still seen frequently enough for all clinicians to agree generally upon a similar pattern of development. For this medical condition, there has been no formal research trial to ‘prove’ efficacy of modern cataract surgery. Indeed, most clinicians would consider such to be superfluous and probably unethical. Cataract extraction and secondary prosthetic lens implantation is accepted as a viable, very successful, low-risk alternative to the natural history of the disease.

Treatment for the natural course of other ophthalmic diseases may not be so clear cut. As an alternative example to cataract and its highly successful remediation, consider proliferative diabetic retinopathy (PDR). Due to the lack of standardized treatment available for PDR prior to the Diabetic Retinopathy Study (DRS), the natural history of the neovascular phase of the disease and its profound complications were – unfortunately – well-known to clinicians. This wide-spread recognition provided the impetus for study of alternatives to the untreated natural course of this disease.

Beginning with Meyer-Schwickerath’s pioneering work with ophthalmic xenon photocoagulators in the 1950s, researchers quickly realized that retinal photocoagulation could alter the course of PDR [16]. But which wavelength photocoagulator, what criteria should be treated, and how much retinal tissue should be treated to provide the most effective treatment for PDR? Rigorous clinical trials answered these important clinical questions. The DRS demonstrated the superiority of argon scatter panretinal laser photocoagulation in altering the natural course of this disease [17] and offered specific treatment guidelines for clinicians to follow. In fact, laser photocoagulation based on the results of the DRS remains the primary treatment for PDR more than 30 years after publication of these findings.

Interestingly enough, the mechanism for the effectiveness of laser photocoagulation remains unknown

and clinical trials have yet to demonstrate effectiveness of therapeutic agents for ophthalmic complications of diabetes [18]. However, perhaps this should come as no surprise as an exact animal model for PDR remains elusive [19]. Indeed, future ophthalmic pharmaceutical clinical trials must demonstrate their effectiveness against laser photocoagulation – the gold standard for treatment of PDR.

Contrary to cataract and PDR, the natural histories of other common, chronic ophthalmic diseases are less clear. A limited amount of clinical data is available for the natural histories of open-angle glaucoma [20] and some forms of age-related macular degeneration [21,22]; regrettably, there are currently no treatments available to greatly alter the natural progression of these highly prevalent ophthalmic conditions across a broad spectrum of affected patients. It must be reiterated, though, at present there are no animal models available to facilitate this ophthalmic research – somehow a connection to humans based on tissue-ablative animal models is lacking.

### Ethical considerations

Medical research trials are conducted under a combination of concepts: equipoise and the uncertainty principle. Equipoise implies that there must be a *genuine* doubt in the mind of an *individual* investigator regarding which intervention in a trial is better [23]. The uncertainty principle (alternatively, and confusingly termed ‘clinical equipoise’) embodies the broader idea that there is *general* doubt within the medical *community* regarding two treatment options [24]. While both notions have been questioned [25–27], the general ideas are important bases for clinical trials in medicine – especially pharmaceutical research.

Consider treatment options for ocular melanoma, an eye disorder with life-threatening implications: debate regarding the importance of/need for the Collaborative Ocular Melanoma Study (COMS) occurred prior to its initiation [28–30]. In the absence of definitive data regarding enucleation – the most profound ophthalmic intervention possible – a significant number of investigators at multiple sites were directly confronted with these important ethical concepts. Ultimately, enough uncertainty among ocular oncologists existed in order to facilitate completion of the COMS and the important results of its three branches [31].

Although not explored for ophthalmic pharmaceutical clinical trials, oncology and rheumatology research indicate that industry-funded trials violate these ethical principles [32,33], and this seems applicable to other medical specialties. Equipoise and clinical uncertainty underlie the ‘Principle of Clinical Discovery,’ under which veritable scientific study via randomized

controlled (or clinical) trials (RCTs) predicts no more than a 50% success rate (i.e., 50/50 outcomes) for discovering new treatments [34].

Ultimately then, equipoise and the uncertainty principle are the unstated, yet underlying principle in the determination of a clinical gold standard, so necessary to evidence-based medicine.

### Gold standard

This term – borrowed from economists who referenced the precious metal – has been co-opted by medicine to indicate the current standard for a diagnostic test, medical procedure, or clinical method [35]. Whether a true gold standard for healthcare is ever attained is a matter of debate [36,37]; however, the use of this term is so widespread in the medical community that the phrase does provide a standard of reference for discussion of clinical research.

There are many claims of a gold standard, but it must be remembered that this can only truly be determined by scientific study. Expert opinion notwithstanding, until proved otherwise, the default gold standard for any disease is nil. Medical intervention – hopefully based on sound understanding of the natural course of the disease, and with appropriate animal models demonstrating preliminary effectiveness for a treatment – is pursued with the intent of reducing morbidity. For ophthalmic research this most often translates to restoring – or at least maintaining – visual function. Only once an intervention improves upon the natural course of the disease can it be said to become the new gold standard.

In order to satisfy the ethics of equipoise and the uncertainty principle, and in order to reduce investigator bias, the best RCT designs to determine gold standards include placebo or sham control (discussed below) whenever possible. Surgery and instances of overwhelming evidence of obvious treatment effect are notable exceptions. Once a therapeutic standard of care is established over the natural course of the disease (or the placebo for masked RCTs), further studies should provide head-to-head comparisons of new interventions against the current clinical standard. A placebo should not, in good conscience, be used in the presence of a well-established standard of care. Failure to follow this ethical practice should alert all clinicians to the possibility of a marketing study versus a scientific one.

Following the Principle of Clinical Discovery, gold standards change with time. Intracapsular cataract extraction with aphakic spectacle correction was an improvement over the natural history of cataract formation, but was replaced with a new gold standard in extracapsular cataract extraction. Phacoemulsification further advanced the technique of cataract surgery, and

represents the current gold standard for surgical lenticular pathology. As future interventions are developed and tested, those procedures must be compared with phacoemulsification in order to determine a possible, new optimal treatment for this condition.

A few important changes in ophthalmic retinal gold standards over the past decade include: intravitreal anti-VEGF injections for: neovascular age-related macular degeneration (AMD) over sham treatment (*de facto* observation) [38]; persistent clinically-significant macular edema versus focal coagulation [39]; and retinal venous occlusion over sham treatment (also *de facto* observation) [40].

During the same time frame, gold standard equivalent results have been reported for digital imaging versus clinical examination for diabetic retinopathy [41], bevacizumab and ranibizumab for neovascular AMD [42,43], tube shunt surgery and trabeculectomy for poorly controlled glaucoma [44], and Descemet's stripping automated endothelial keratoplasty versus penetrating keratoplasty for chronic corneal edema [45].

Note: In some cases, RCTs are not performed against the gold standard. The treatment of effect of penicillin against bacterial infection was so great that placebo-controlled comparison was unnecessary [24]. Similarly for ophthalmic trials, photodynamic therapy for neovascular AMD [46] was not compared with macular photocoagulation (the first gold standard for subfoveal choroidal neovascularization) due to the limitations of the latter mode of therapy to improve functional visual outcomes. Similarly, use of neodymium-YAG laser was not directly compared with surgical dissection for posterior capsular opacification due to the immediate recognition of the superiority of the noninvasive alternative [47].

In addition to the treatments, changes in the clinical trial designs themselves undergo permutations to discover best practices. The Principle of Clinical Discovery also applies here, and the RCT has become the current gold standard in clinical research and ophthalmic studies [48,49]. Thus, results of nonrandomized or uncontrolled clinical research are not received with the same credence as data derived from RCTs.

### Study sponsorship

Funding for clinical trials is generally provided by government, commercial (biotechnology, medical device, pharmaceutical) or nonprofit entities. To date the direct effect of the sponsor on the reporting of ophthalmic clinical trial information has not been reported; however, concern has been expressed regarding maintenance of scientific integrity under the sponsorship of Pharma in general [50].

As a measure of transparency for medical reporting, authors are asked to disclose potential conflicts of interest with their scientific publications, and clinical trial registry [51] is required prior to publication in most medical journals [52]. Readers are provided these extra measures of credibility for clinical research papers. Unfortunately, even after the courageous move by medical journal editors to mandate clinical trial registration prior to publication, underreporting continues. Results from less than half of all registered trials remain unavailable for critical assessment [53,54], with a trend that industry-sponsored trial results are less likely to be published [54]. Diligent reviewers of medical literature are left to marvel at this finding. Does this mean that a majority of clinical research reflects negative findings, and therefore are undisclosed? This gap in reporting is both intriguing and troubling.

The direct effects of sponsorship on the specifics of study design have not been described, but in light of this nonreporting – and because negative reports tend to be underreported [55] – the results of proprietary studies that *do* appear in journals should be interpreted with the understanding that the results of many studies remain hidden from the public domain.

Finally, industry is not the only source of conflict of interest in ophthalmic research. Pressures within academia [56] and political factors surely both influence priorities of ophthalmic research, but have not been systematically studied.

### Quality of clinical reporting

The purpose of medical reporting is to create a public and professional forum for human health research, and has generally become more sophisticated over time. More than 20 years ago, the CONSolidated Standards Of Reporting Trials (CONSORT) group of experts realized the poor quality of reported RCTs and sought to rectify this deficit. The CONSORT group has produced an evolving checklist to assist researchers in the standardized publication of RCTs [57], and this represents a minimum standard of reporting for clinical research [58].

The top four ranking journals in general clinical ophthalmology either require [59–61] or encourage [62] adherence to the CONSORT statement for manuscript submission in order to provide more meaningful publications of results to benefit readers. Despite such ambitious recommendations, these same four journals show ‘substantial heterogeneity’ in quality of reporting [63]. Although informal review of several National Eye Institute-sponsored studies in the US showed general compliance to initial CONSORT guidelines [64], regrettably there is little evidence to show overall improved adherence of ophthalmic reports to the CONSORT guidelines between 2001 [65] and 2011 [66].

A reminder of these important underpinnings of clinical research now allows for careful consideration of the specifics of the structure of clinical trials.

### Trial structure

Research trials vary by the type of study and design used to relay the discovered information. Terminology varies, but **Figure 1** broadly classifies the two main kinds of research studies – observational and experimental – and also summarizes the most important study design considerations.

### Type of study

Although no ideal clinical trial structure has yet been discovered, some trial designs lend themselves better to certain findings than others. There is a natural progression of clinical trial design that is corollary to clinical discovery and reporting. All medical literature is replete with case reports of novel or variant clinical conditions. Single reports form the basis of preliminary clinical understanding, and the ophthalmic literature is no exception. Publication of modern case reports is largely contingent upon novel contribution to medical knowledge or to update changes in diagnostic or clinical practice [67].

Claims of therapeutic or preventive interventions generally require stronger evidence than can be obtained from a single case, so are typically conveyed as a case series (usually three or more cases). Both case reports and case series can be observational or experimental, depending on the intent of the author(s).

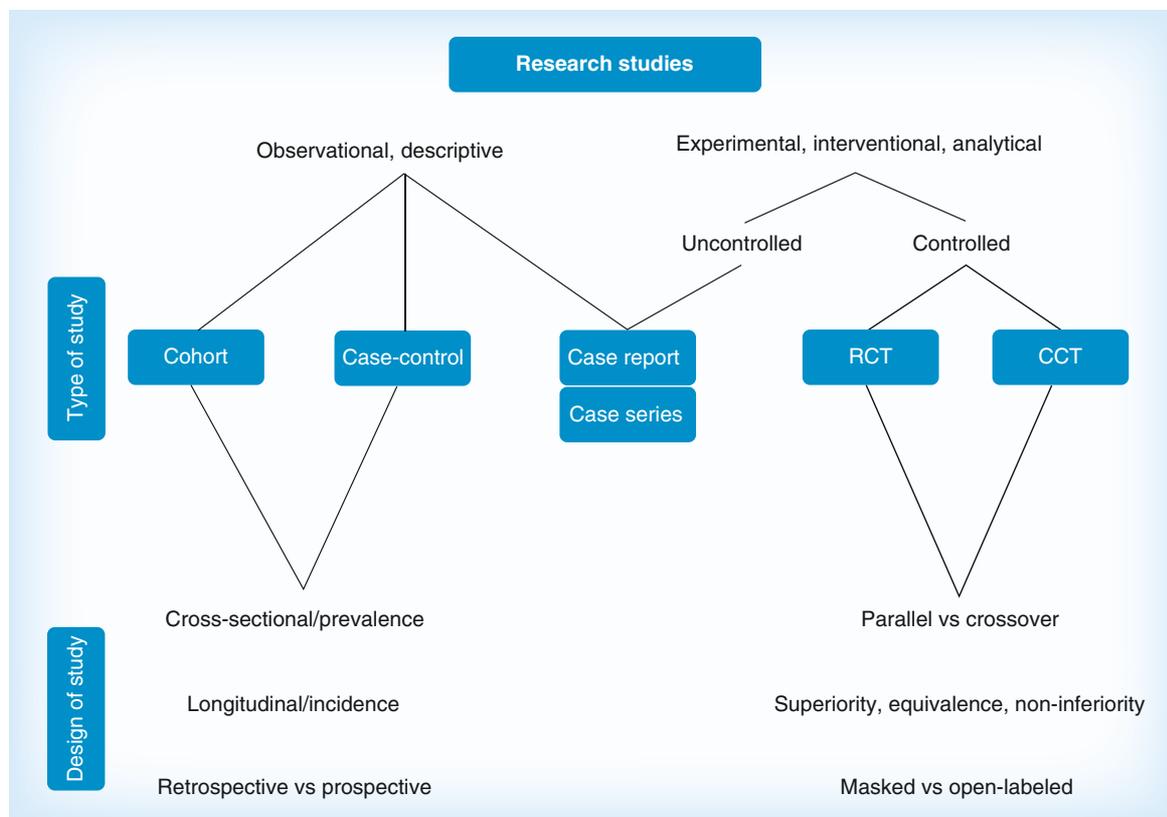
Case-control and Cohort forms of observational studies give much information regarding clinical features of diseases as well as prevalence and incidence data. Frequently-occurring conditions are most often reported with a cohort (a group sharing a particular characteristic [68]), though these reports seldom call it such. For conditions that are rare, case-control studies are used to compare an individual with the representative condition (the ‘case’) to a similar, normal patient (i.e., the ‘control’) for the purposes of extracting clinically useful information.

Experimental clinical trials test hypotheses related to human disease, are more structured, and are most often controlled and randomized (i.e., RCT). A majority of clinical research and Phase III pharmaceutical trials fall into this category, although in certain cases a Controlled Clinical Trial may be performed before a formal RCT (e.g., Phase I/II pharmaceutical trials).

### Design of study

Study designs vary by the type of information that researchers hope to discover.

Cross-sectional observational studies provide a snapshot of disease prevalence at one point in time, whereas



**Figure 1. Summary of clinical research types and designs.**  
 CCT: Controlled clinical trial; RCT: Randomized controlled trial.

longitudinal research gives information about incident cases over time. These are mutually exclusive study designs. Population-based studies are specific longitudinal studies that yield long-term data regarding disease incidences within a specific geographic area.

Observational data can be obtained in retrospective or prospective fashion, depending on the intent of the researchers. Retrospective studies examine clinical data *ex post facto*, but seek to delineate information regarding potential treatment options, which can only be confirmed via prospective clinical research.

Controlled trials provide the best scientific method for biological experimentation and are all prospective in nature. In these studies, there are well-defined protocols and mechanisms in place to prevent bias and to offer clinical treatment based on rigorous medical study. Controlled studies seek to eliminate multiple variables and confounders that can confuse data interpretation. Randomization (to be discussed) helps further decrease bias and is typically employed in clinical pharmaceutical trials. These considerations help form the basis of a RCT and are crucial in pharmaceutical studies where researchers seek to determine clinical superiority without bias.

Parallel RCTs compare treatments (A vs B). This is the most common of experimental studies, but is

not often explicitly stated as being such. Crossover studies compare all treatments in all groups (A vs B; then B vs A). Crossover trials have the advantage of an additional means of control in comparing one treatment against another in the same subject, but with the disadvantages of additional study time and expense.

Superiority trials seek to demonstrate that one treatment is more advantageous than another (A is better than B), and these designs are commonly used. Equivalence trials only strive to demonstrate equality of interventions (A = B); whereas noninferiority trials intend to show that one treatment is no worse than a second (B is no worse than A). Noninferiority design is most appropriately used when the gold standard is nil – the most robust application of the uncertainty principle. This choice in study design may be related projected treatment effect, which in turn affects sample size determination (see below).

Masked trials obscure treatment options from participants; open-labeled trials remove masking. In general double masking of participant and investigator is preferable in order to reduce biased study results (more below).

A well-written RCT report clearly distinguishes these various trial characteristics.

### Trial design considerations

During the 20th Century, medicine underwent a paradigm shift from the treatment of acute, infectious conditions with obvious signs and symptoms over short durations to management of chronic, multifactorial diseases with more subtle, life-long courses. The astounding successes of the Penicillin Revolution are long gone and the focus of medicine has now shifted to chronic diseases [69]. Like other medical specialties, a review of any current ophthalmology journal reveals the overabundance of articles dealing with chronic conditions versus those of an acute nature.

The consequence of this shift from acute to chronic diseases is that cure rates are rarely mentioned. Rather, more modest treatment effects of medical interventions are considered. In fact, the realization of ‘large’ treatment effects for chronic diseases may be unrealistic [24], and this certainly seems to be the case in current ophthalmic research.

An examination of the components of clinical trial design reveals how intricate modern medical research has become. An understanding of these features helps readers interpret findings in terms of narrow treatment effects.

### Trial length

The ideal length for an ophthalmic pharmaceutical clinical trial has not been determined. However, a nonsystematic review of some ophthalmic pharmaceutical trials is instructive (Table 1, Phase III trials reported when possible). This informal review suggests a dichotomy between topical treatments and other ophthalmic interventions.

Appropriate length for topical ophthalmic pharmaceutical clinical trials in acute settings (infectious or allergic) appears to be in the 2–4 week range, whereas for chronic ophthalmic conditions, trial length efficacy tends to be reported for 3–6-month periods.

Non-topical ophthalmic treatment trials tend to be longer in duration, perhaps reflecting the time course to achieve stability of findings: often 1 year for more acute findings, and typically 5 years for more chronic conditions. The latter finding has a well-known medical corollary: 5-year mortality rates are standard time-frames for reports of cancer survival.

It is hoped that these observations might stimulate further thought and give reviewers of ophthalmic literature a general guideline for what constitutes an ophthalmic pharmaceutical clinical trial of ‘acceptable’ duration.

### Sample size

There is also currently no research standard regarding sample sizes ( $n$  values) for medical research, and this

determination is the result of mathematical decision-making for the trial [102]. In general, larger  $n$  values would be expected to offer better reliability than smaller ones, so as to provide greater generalization of sample findings to the larger population; although, this consideration must be carefully balanced against the resources available for the trial.

The determination of the sample size for clinical trial is dependent on several mathematical factors: desired significance level (typically  $p < 0.05$ ), statistical power required to reject the null hypothesis (often 0.80), precision of findings (ability to detect the minimally detectable clinical difference between groups; smaller difference requires larger sample size to detect), participant attrition rate, whether results may better *or* worse than a standard (i.e., fall mathematically in multiple directions, necessitating two-sided tests), data collection (single vs paired data), study of continuous (wide spectrum of possible findings, fewer participants required) versus categorical (few possibilities, more participants needed) variables, and whether data from one eye or two per patient are used [102–105]. Estimation of these parameters ultimately makes sample size determination ‘speculative at best’ [49].

Sample sizes for Phase III pharmaceutical studies are not mandated, but typically fall in the 100–1000 range [102]. Table 2 provides  $n$  values for the same studies summarized in Table 1, and seems to provide support for this recommendation – but with great variability. Prior to widespread usage (and marketing) of a new pharmacological agent, reviewers of literature would hope for data based on experimentation in several hundred patients with the disease in question.

### One eye or two?

There is a consideration nearly unique to ophthalmic research, where two end organs for study may be readily observed without invasive means: should clinical trial data be reported per eye or per patient (i.e., include both eyes)? Table 2 also suggests that results are more often reported per patient than per eye.

The advantages of using both eyes are having more data available for review, better precision (in the mathematical sense: smaller standard deviation, narrower confidence intervals, and smaller  $p$  values), increased statistical power of the study, and better use of trial resources [106].

While inter-eye data are highly correlated, their use may not be to the benefit of the general population. Inclusion of data from both eyes may result in higher precision of statistical calculation, but with the effect that the sample measurement may not accurately reflect the overall population data [107]. More vari-

ability (i.e., using only one eye) is better to generalize sample size data to the population.

'Between eye correlation' can be assessed with kappa ( $\kappa$ ) statistics or use of an average measure of the two eyes, but this seems uncommon. The degree to which ophthalmic researchers report single-eye versus patient data remains quite variable [63,108].

It may be that trials for conditions with asymmetric ocular presentations can probably use 'per eye' randomization; whereas results for highly symmetric eyes may be most valid with 'per patient' randomization with only a single eye of study. The validity of this generalization remains unseen.

**Masking**

Masking (or 'blinding' in everything but research involving the eyes) is the process under which the subject, the investigator, or both are prevented from knowing whether they are receiving/using the intervention in question or its alternative [109]. Masking provides an extra guard against experimental bias and is required to achieve equipoise. Unmasked, open-label pharmaceutical trials are still used in certain cases – especially extension trials, which are *de facto* open-label, case series studies of survivors of original trials who elect to continue taking the study medication [110].

In ophthalmic research, subjective results (visual acuities, reporting of symptoms, etc.) are believed to require masking in order to avoid bias. The role of masking has been called into question when visual acuity is the primary outcome [111,112], but further study is unavailable at this time. For some ophthalmic interventions (injections, laser procedures, surgery) it may be impossible or unethical to provide entirely masked, sham-controlled or placebo-controlled trials [113]. However, for ophthalmic pharmaceutical clinical trials that require the highest level of evidence, use of masking may help ensure the greatest validity of results.

**Placebo/sham control**

In order to complete perfect masking, neither participant nor investigator should know which treatment is being administered. This can generally be achieved in pharmaceutical trials by administering a placebo ('a substance having no pharmacological effect' [114]), as the placebo medication can be produced to appear identical in appearance to the active substance. Since 1962, when the US FDA mandated proof of effectiveness of medications prior to market entry [115], placebo-controlled trials have gained widespread acceptance; although, more recently, 'placebo effects' in medical research have been questioned [116]. Use of

Table 1. Examples of ophthalmic pharmaceutical clinical trial length in humans.

Conditions			Duration of trial	Ref.	
<b>Eye drops</b>					
<b>Acute conditions</b>	Infectious	Trifluridine	14 days	[70]	
		Tobramycin	11 days	[71]	
		Povidone Iodine	3-4 days	[72]	
		Ofloxacin	11 days	[73]	
		Azithromycin	5 days	[74]	
		Natamycin	21 days	[75]	
	Acute allergic	Loteprednol	4 weeks	[76]	
		Olopatadine	3-4 weeks	[77]	
	<b>Chronic conditions</b>	Dry eyes	Cyclosporine	6 months	[78]
			Autologous serum	3 months	[79]
IOP-lowering		Timolol	2.5 months	[80]	
		Latanoprost	6 months	[81]	
		Timolol/Dorzolamide	3 months	[82]	
Inflammation/chronic allergic		Fluorometholone	2–2.5 months	[83]	
		Tacrolimus	6 months	[84]	
Corneal neovascularization		Aganirsen	6 months	[85]	

**Table 1. Examples of ophthalmic pharmaceutical clinical trial length in humans (cont.).**

Conditions				Duration of trial	Ref.
<b>Other ophthalmic Treatments</b>					
<b>Conditions of immediate stability</b>	CNVM	Verteporfin	TAP	1 year	[45]
			VIP	1 year	[86]
		Pegaptanib	1 year	[87]	
		Ranibizumab vs Bevacizumab	MARINA	2 years	[38]
		CATT	1 year	[42]	
	IOP-lowering	Argon Laser	IVAN	1 year	[43]
			GLT	2 years	[88]
		Aqueous Shunt	ABC	1 year	[89]
	Refractive surgery	LASIK	AVB	1 year	[90]
			Myopia	6 months	[91]
LASIK		Hyperopia	1 year	[92]	
<b>Conditions of indeterminate stability</b>	Non-exudative AMD	Vitamins/antioxidants	AREDS1	5 years	[93]
			AREDS2	5 years	[94]
	Ocular hypertension		OHTS	5 years	[95]
			EGPS	5 years	[96]
	Glaucoma		GLT Follow-up Trial	7 years	[97]
			AGIS (surg sequences)	7 years	[98]
			CNTGS	5+ years	[99]
			CIGTS (meds vs surg)	5 years	[100]
			EMGT (immed vs delayed tx)	6 years	[101]
	Ocular melanoma		TVT (tube vs shunt)	3 years	[44]
COMS			5 years	[31]	

a cross-over trial design is used to help control for this effect in pharmaceutical clinical trials, but with the disadvantages previously mentioned.

In medical research, sham refers to an alternative control for an experimental treatment or procedure. A sham is similar to the intervention under study, yet omits a key therapeutic element [117]. Subthreshold laser photocoagulation in retinal research is an example. Masking of intravitreal injections can be achieved with sham procedures [118], but success has not been studied for sham retinal photocoagulation or other ophthalmic interventions to date.

Regardless, it is important to consider that sham procedures may provide masking for study participants, but not for investigators. Until definitive evidence precludes placebo control of pharmaceutical trials, or even sham procedures in general, their inclusion would seem to add credibility to ophthalmic research.

**Single versus multiple site involvement**

Due to clinical reputation that develops over many years, single research sites or organizations are sometimes recognized for specific expertise in ophthalmic disease: for example, Moorfields Hospital in London for scleritis, or the Aravind Eye Care System in India for mycotic corneal ulcers. Nevertheless, for the purposes of clinical research, multicentered clinical trials using standardized protocols have the advantages of statistical power of pooled data and increased generalizability of findings. Geographic variations that could potentially result in skewed findings can be identified and studied systematically. Although not expected for chronic ophthalmic disease, this might be important for acute ocular morbidities where allergens or infectious agents could vary between locations.

It is also not unusual for multicentered clinical research to be carried out in tertiary care facilities, as these settings provide the greatest opportunity of clini-

Table 2. Eyes versus patients AND *n* values of the ophthalmic pharmaceutical clinical trials from Table 1.

Conditions				Eyes	Patients	
<b>Eye drops</b>						
<b>Acute</b>	Infectious	Trifluridine		102		
		Tobramycin		511		
		Povidone iodine		40		
		Ofloxacin		194		
		Moxifloxacin (two trials)		30/30		
		Natamycin		323		
	Acute allergic	Loteprednol		113		
		Olopatadine		169		
<b>Chronic</b>	Dry eyes	Cyclosporine		877		
		Autologous serum		31	16	
	IOP-lowering	Timolol		28		
		Latanoprost		829		
		Timolol/dorzolamide		335		
	Inflammation/chronic allergic	Fluorometholone		60	50	
Tacrolimus			1436			
Corneal neovascularization	Aganirsen		69			
<b>Other ophthalmic treatments</b>						
<b>Acute</b>	CNVM	Verteporfin	TAP	609		
			VIP	120		
		Pegaptanib		1186		
		Ranibizumab vs bevacizumab	MARINA	716		
			CATT	1208		
			IVAN	610		
		IOP-lowering	Argon laser	GLT	271	
			Aqueous shunt	ABC	276	
				AVB	238	
Refractive surgery	LASIK	Myopia	57	57		
	LASIK	Hyperopia	326	178		
<b>Chronic</b>	Non-exudative AMD	Vitamins/antioxidants	AREDS1	3640		
			AREDS2	1940	1608	
Ocular hypertension			OHTS	1636		
			EGPS	1081		
Glaucoma			GLT Follow-up trial	203		
			AGIS (surg sequences)	789	591	
			CNTGS	230		
			CIGTS (meds vs surg)	207		
			EMGT (immed vs delayed tx)	255		
			TVT (tube vs shunt)	212	212	
Ocular melanoma			COMS (small tumor trial)	220		
			COMS (medium tumor trial)	1317		
			COMS (large tumor trial)	1003		

cal and support staff necessary to participate in large clinical studies. It is worth mentioning that those patient populations may differ markedly from 'typical' clinical populations in that 'worst-case scenario' cases tend to be referred to the tertiary sites, and these patient populations form the pool of possible trial participants. As a result, findings from tertiary care sites in multiple locations may not generalize to local, nontertiary care populations.

It is interesting to note that neither of these factors (single vs multiple and tertiary vs primary care sites) has been systematically studied in the general or ophthalmic medical literature. It may be surmised that data from multiple sites carries more credence than that from a single site. Yet due to the advanced nature of the cases to be found in tertiary care settings, entirely valid results reported from clinical trial in these sites results may differ from observations in local clinics.

### Study endpoints

All clinical research must have an end point, at which time success, failure or equivalence of an intervention can be gauged. Outcomes of medical research are reported in terms of the stated endpoints. An endpoint is 'an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial' [119]. Study endpoints must be succinctly defined in the study objectives, well-known to all participants and investigators prior to the start of the trial, and be easily recognized by reviewers of reported findings in order to be meaningful.

Clinical end points could include presence/absence of a disease, a specific sign or laboratory result, a symptom or quality of life. The importance of the primary outcome of a study is paramount as it is this marker that is used to determine the overall result of a study. As such, there can be only one primary outcome [102], including for RCTs [120]. Secondary outcomes are used to assess other trends or effects of the intervention [121]. Clinical end points for pharmaceutical studies are easier to discern for acute conditions, but more challenging for chronic conditions.

Not all disease end points are directly assessable with current technology, so other markers must be used in order to evaluate study outcomes. Surrogate endpoints serve as substitutes for morbidity endpoints [122]. While the validity of surrogate measures has been questioned for other specialties [123–125] and could lead to interpretation bias, ophthalmic research relies heavily upon these measures. Visual acuity is the most common measure of visual function [126], although this does not directly or objectively assess retinal function at the fovea, and its usefulness in masking has been questioned as mentioned above [111,112].

There does appear to be some emerging consensus regarding surrogate measures in ophthalmic research, and these markers may take on gold standard status of their own. Regarding visual acuity, 'significant' change appears to be when a doubling (or conversely, halving) of the visual angle as defined by a gain (or loss) of 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart can be demonstrated. The ETDRS visual acuity chart is generally considered to be the optimal method for assessment for visual acuity, with conversion to logMAR (logarithm of the minimal angle of resolution) values for statistical analysis [126]. MARINA, FOCUS, ANCHOR studies of ranibizumab for neovascular AMD helped reinvalidate the use of this end point in determining outcomes in retinal studies [38,127–128], even though shortcomings of this criterion have been discussed [129].

Progression of optic nerve disease is difficult to assess via direct clinical observation; therefore, ophthalmic researchers rely upon results of peripheral visual field testing as a surrogate end point of optic nerve function. Unfortunately, there is currently no consensus concerning visual field progression for glaucomatous optic neuropathy [130–135]. Thus, researchers and reviewers of the ophthalmic literature on glaucoma do not yet have a reliable measure for assessing visual field progression based on this proxy measure. The need for different outcome measures and consensus end points in glaucoma research has been identified [136,137].

The use of ocular coherence tomography (OCT) as a surrogate measure of retinal function has been explored [138], and has the potential to serve as a clinical trial end point [139], although it should be pointed out that correlation between OCT findings (objective) and visual acuities (subjective) is variable [140].

The old adage, 'the operation was a success, but the patient died' is really a comment on the difference between objective and subjective medical outcomes. Due to heightened fears by patients regarding vision loss (as opposed to other sensorineural losses), in addition to objective, or structural endpoints, ophthalmic researchers must also consider subjective, or functional, endpoints from the point of view of study participants [141]. Patient-Reported Outcomes (PROs) address quality of life issues germane to patient experiences. These findings are important, especially in the differentiation of statistically-significant from clinically-significant results obtained in clinical trials.

In general, subjective patient perceptions of successful objective outcomes tend to be positively correlated across a wide spectrum of ophthalmic procedures [142–146]. Formal assessment of Quality of Life issues in ophthalmic research has been studied and validated in American populations via the National Eye Institute Visual Func-

tioning Questionnaire (VFQ-25) [147]. There appears to be growing interest to use this or similar surveys in ophthalmic research in order to query patient feelings regarding the success of their interventions.

It may become important for most future clinical research, then, to consider perceived outcomes from participants. If a clinical report includes subjective data in its reports, then readers are also given an extra measure of credibility for the data. Perhaps then – rather than insisting on a single primary outcome for a study – researchers may need to specify a primary *objective* outcome and a primary *subjective* outcome for interventions; however, this concept remains to be evaluated.

### Recruitment of participants

Accrual of study participants typically occurs from cases identified within clinics of participating research sites. Due to the widely-accepted tenets of the important Declaration of Helsinki [148], researchers must provide full disclosure of experiment to participants, and subjects must consent to be studied. Under these conditions, by default, a study sample may *only* consist of subjects who are voluntarily willing to participate in the experiment. For various reasons, some potential participants are more likely to participate than others – sometimes creating a phenomenon known as volunteer bias [149].

Paying individuals for research study sometimes occurs for Phase I pharmaceutical testing (normal subjects without disease), although payment is rarely (perhaps never) mentioned in clinical reports. Remuneration has been shown to affect participation [150]; these effects have not been systematically studied. Volunteer bias has been recognized within ophthalmic research [151], but the potential effects on study participants and outcomes remain unknown.

Statements regarding adherence to Declaration of Helsinki principles should be present for all clinical trials, and the effects of volunteer bias might be considered for some – especially pharmaceutical trials.

### Inclusion/exclusion criteria

Not all potential volunteers may participate in a study. Selection of research participants requires determinations of who can join (is willing, has the disease in question, and can be ‘included’) and who cannot (is unwilling, does not have the condition under study, and must be ‘excluded’). These factors are described as inclusion and exclusion criteria [152].

Inclusion/exclusion criteria are important means of establishing validity of data collection, or – in scientific parlance – better ‘control’ of the experimental process. There are fine lines that can be crossed in the selection of study subjects: too many inclusion/too few exclusion

criteria, or too few inclusion/too many exclusion criteria make results nongeneralizable from the study sample to the overall population. Inclusion/exclusion criteria are also used to reduce other forms of volunteer bias (volunteers tend to be healthier than nonvolunteers) and participant exuberance (tendency to inflate self-reported outcomes).

In general, inclusion/exclusion criteria should be clearly described, and in detail [153]. Readers should be able to easily determine how research subjects were included for study and how many exclusions there were and why.

### Consecutive patient enrollment

Ideally, consecutive patients with a given condition and meeting inclusion criteria are recruited for medical research in order to prevent selection bias (errors that stem from inappropriate choice of subjects). Consecutive enrollment ensures accurate representation of the disease under study, and prevents indiscriminate inclusion of patients who might have the best results from an intervention or exclusion of patients whom researchers feel might be poor responders to a treatment. In sum, consecutive patient enrollment guards against Gaussian outliers.

Nonconsecutive enrollment of patients in clinical trials has been problematic in cardiology [154–156], but has yet to be studied systematically for ophthalmic trials. Thus consecutive enrollment has more credence than haphazard methods of participant accrual and is specified as such in the best clinical reports.

### Time for accrual

For common clinical conditions, the accrual period for participants should be relatively quick or investigators run the risk that findings for an alternate treatment may render the results obsolete. When multiple sites are involved, this can usually take place over about a year, as seen in retina trials for neovascular AMD [38,127–128].

Rare conditions may recruit participants for many years, as evidenced by the Collaborative Ocular Melanoma Study, which required more than 11 years to accumulate the target enrollment figures [157]. Conversely, one arm of the Herpetic Eye Disease Study I (Herpes Simplex Virus Iridocyclitis, Receiving Topical Steroids [HEDS-IRT]) discontinued enrollment after failing to reach 50% recruitment within 4 years [158].

Whether reporting conditions associated with immediate stability or chronic diseases, study accrual times should be explicitly provided for review. It might be expected to be 1 year or less for ophthalmic pharmaceutical trials.

**Randomization**

The importance of randomization in clinical trials is quickly recognized – hence the name *randomized* controlled trials. Randomization is essentially mandatory for experimental research and – as such, forms an important part of the CONSolidated Standards of Reporting Trials (CONSORT) Statement [159]. In brief, randomization protects against selection bias, provides identical treatment groups for study, and allows for the use of probability theory to calculate outcomes [160].

It should be emphasized that random does not mean ‘haphazard,’ but also carries a specific, technical meaning [161]. It is the allocation to treatment groups by chance. For large studies – including pharmaceutical trials – randomization schedules are generated by various computerized algorithms, pairing subjects with experiment identification numbers known only by study coordinators (when possible) in order to ensure masking of the study. Subjects are then sequentially assigned to treatment groups in strict order, proceeding down the list of random assignments, in order to maintain the validity of the randomization.

The results of the randomization scheme should be specified, and CONSORT diagrams help reviewers of clinical research easily follow patient numbers through their treatment groups throughout the course of the study. In the best clinical studies and reports, all subjects are completely accounted for – including those lost to follow-up – and the total numbers of subjects in all treatment groups who finish the trial are readily apparent.

**Patient safety**

Prior to human research, approval of medical study protocols is required at site-level through local Research Ethics Committees (REC) or Institutional Review Boards (IRB). These bodies ensure that clinical research is conducted strictly under the aegis of international, federal and ethical principles—foremost among these is the Declaration of Helsinki [121]. Voluntary, uncoerced participation in medical trials is requisite to ethical research and is critical in groundbreaking areas, such as gene therapy and stem cell research.

Once compliance with the ethical considerations delineated by the Declaration of Helsinki – including informed consent – has been established for entry into a clinical trial, ongoing monitoring for participant safety *during* the trial is an ethical mandate. The CONSORT statement advocates improved reporting of harms during medical research [57]. To achieve this end, active monitoring of adverse events by a Data Monitoring Committee independent of study

investigators is commonly employed [49]. The recommendations of this committee can halt a study if preliminary findings indicate untoward outcomes – as was the case in the Ischemic Optic Nerve Decompression Trial (IONDT) [162].

Although standardization of reporting these events in ophthalmic clinical trials remains challenging [163], concurrent use of a patient questionnaire may help improve event reporting [164]. In the review of a clinical report, some mention regarding care for patient safety is expected.

**Measures of patient compliance**

It is hoped that volunteers who expend the time and energy to enroll in a trial will comply with the protocol to which they are assigned. The length of the trial and the complexity of the intervention can both influence participant adherence to the experimental process. A run-in period can be used to assess compliance prior to formal trial initiation [49]. Albeit uncommon in ophthalmic trials, report of a run-in period should be interpreted as a measure to control selection bias.

**Conclusion**

Review of ophthalmic clinical pharmaceutical trial methodology must be concluded prior to evaluation of results. These concepts are based on the underpinnings of all human medical research. Readers should be mindful of the fact that all of the factors discussed in this paper are *a priori* considerations – all of them should be determined before enrollment of the first trial participant. An accompanying paper will discuss interpretation of findings after conclusion of the clinical trial.

**Future perspective**

In the years to come, RCT design is expected to continue developing in order to resolve many of the unanswered questions raised in this report. It is also anticipated that the reporting of clinical trial research will become more standardized – along the CONSORT statement guidelines – providing readers with a consistent framework within which trial results can be critically reviewed and their results judged.

**Disclaimer**

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### Executive summary

#### Summary of trial underpinnings

- No clinical trial design is perfect.
- Researchers involved in those trials can be influenced internally by their own expectations regarding the trial and its expected outcomes, or externally by pressures from sponsors, academia or government. These considerations are mitigated by multiple investigators at multiple sites.
- An understanding of the natural course of the disease in humans is required to recognize when that course can be effectively altered.
- Study in appropriate animal models provides the best evidence that an intervention has potential clinical effect in humans.
- Ethical considerations of equipoise and the uncertainty principle underlie medical research on humans.
- The best RCTs face the scrutiny of comparison to the gold standard.
- Pharma negatively affects the scientific integrity of medical research.
- Disclosures of potential conflicts of interest for all researchers are expected.
- Adherence to CONSORT guidelines ensures standardized and complete reporting of RCT results.

#### Summary of factors affecting trial structure

- Different types of studies provide different clinical information.
- The highest level of clinical information comes from RCTs.
- Expected trial length for:
  - Topical treatment of acute ophthalmic conditions: 2–4 weeks.
  - Topical treatment of chronic ophthalmic conditions: 3–6 months.
  - Non-topical treatment of conditions of immediate stability: 1 year.
  - Non-topical treatment of conditions of indeterminate stability: 5 years.
- Expected sample size for a pharmaceutical clinical trial: several hundred patients.
- Studies with single-eye data are more generalizable.
- Double-masking prevents experimental bias and achieves equipoise.
- Placebo control of pharmaceutical trials remains the best way to retain masking.
- Data from multicentered studies are more generalizable, although results from these tertiary care sites may vary from local clinics.
- Study endpoints must be clearly outlined and data reported according to original endpoints.
- Use of surrogate measures to gauge study endpoints is common in ophthalmic research.
- Use of subjective *and* objective endpoints may give results more credence.
- Adherence to Declaration of Helsinki tenets is expected for patient recruitment.
- The effect of payment to study subjects for participation is poorly studied and may represent volunteer bias.
- Strict inclusion and exclusion criteria provide greater control of the experimental process.
- Consecutive patient enrollment guards against selection bias.
- Accrual time is related to chronicity of disease and the number of sites involved in the study. For multicentered research, target subject accrual may be one year; rare or chronic conditions may require many years to obtain projected sample sizes.
- Whenever possible, randomization for clinical research is expected.
- Research Ethics Committee or Institutional Review Board approval and compliance with the Declaration of Helsinki to ensure patient safety is mandatory prior to initiation of a clinical trial.
- Surveillance by a Data Monitoring Committee during a study provides ongoing patient safety.
- Presence of a trial run-in period is another measure protecting against selection bias.

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• of interest; •• of considerable interest

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