Clinical Trials – More Than an Assessment of Treatment Effect: LXV Edward Jackson Memorial Lecture

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- PURPOSE: To review the development of clinical trials and demonstrate their value beyond the assessment of the treatment effect.
- DESIGN: Retrospective literature review.
- METHODS: Retrospective literature review.
- RESULTS: There has been a rapid increase in the number of clinical trials in ophthalmology as assessed by the number of ophthalmic publications and the number of ongoing National Eye Institute-(NEI) sponsored clinical trials over the last four decades. The public health significance of the results of these NEI clinical trials goes beyond the demonstration of treatment effects and side effects. From these trials, we learn about the clinical course and risk factors of disease, allowing us to better determine who and when to treat. Furthermore, the collaboration of investigators, as they develop and carry out protocols, facilitates incorporation of new ideas into the practice of medicine.
- CONCLUSIONS: The practice of medicine is increasingly dependent on the results of carefully designed clinical trials. The determination as to whether a new treatment is safe and effective is important, but the additional information we can obtain regarding natural history, risk factors, and patient satisfaction adds immeasurably to our ability to care for our patients. (Am J Ophthalmol 2009;147:22–32. Published by Elsevier Inc.)

Clinical trials have slowly evolved to their current status as the “gold standard” by which we decide if treatments are safe and effective. However, we have an opportunity to learn far more than this from each clinical trial. The dedicated efforts of clinicians and clinic coordinators, as they carefully collect long-term data on the patients in the clinical trial, provide a wealth of information that assists us in the daily care of our patients. We learn about the clinical course of a disease by carefully gathering outcome data on both the treated and the control groups. From this information, we can assess risk factors for the progression of the disease. We can identify “high-risk” patients for whom treatment should be initiated immediately and lower risk patients for whom deferral of treatment might be the best option. The collaboration of clinicians within a trial can help develop and standardize new methods for caring for patients and this collaboration can expand the availability of new technologies. In addition, we have learned to consider the patient’s assessment of the treatment. All this added information, beyond the determination as to whether a new treatment is safe and effective, adds immeasurably to the value of our clinical trials and our ability to care for patients.

The design strategies used for clinical trials are not a new invention. That clinical trial methodology extends back thousands of years is documented in the Book of Daniel in the Bible (Dan. 1). When Nebuchadnezzar, the King of Babylon, besieged Jerusalem, he asked to have some of the exiled Israelites brought to him. They were to be young men, who were free of physical defect and fit for service in the royal court, and included among them were Daniel, Shadrach, Meshach, and Abed-nego. The King allotted them food and wine from the royal table, and this led Daniel to suggest an experiment. Daniel and his friends did not want to be contaminated by the food from the royal table and begged the eunuchs to excuse them from eating the royal food and drink. He proposed what today would be called a “clinical trial” to prove that he could be fit for service without dining at the King’s table. The study groups were defined to be Daniel and his friends, who would eat pulse (nuts and vegetables) and drink water, compared with the young men who were eating at the King’s table. The trial was to last for 10 days and at the end of that time the two groups would be assessed for fairness of countenance. Although ancient, this trial had most of the components of the modern day clinical trial. It had well described treatment groups, although they were not...
randomized, and the treatments, although somewhat lacking in specifics, were distinct. The trial had a specified duration and there was a predefined outcome variable. Some might criticize the trial as being too short and the outcome as too subjective, but notwithstanding these shortcomings, and perhaps not surprisingly, Daniel and his friends were judged to be fairer of countenance at the end of 10 days and they were henceforth allowed to eat pulse and drink water.

Over the succeeding centuries, comparisons of various treatments among groups of patients, such as described in the Book of Daniel, sporadically dot the history of medicine. As noted in Ecclesiastes, there is nothing new under the sun (Eccles. 1.9). One of the most famous of these clinical studies was the trial of limes and other treatments for scurvy among British sailors in 1747.1 Such studies were generally not well organized and the outcomes were often ignored. It took 42 years between Lind's initial observation and the institution of limes aboard ship by the authorities. Today, you can go to the internet and purchase “pulse” to improve your countenance. Apparently some trial results take centuries to be accepted. In general, historical bias and clinical impressions were more important to practitioners than any organized comparisons of treatment groups and this remains true, at least to some degree, today.

In the mid 1940s, Sir Austin Bradford Hill applied the randomized study design, first utilized in agricultural experiments in the 1930s by statistician Ronald Fisher,2 in a groundbreaking randomized clinical trial evaluating streptomycin vs standard care for the treatment of tuberculosis.3,4 In ophthalmology, randomized trials probably date back to the first comparison of oxygen as a treatment for retrolental fibroplasia (retinopathy of prematurity) in 1952.5 By the late 1960s, the rapid development of the randomized clinical trial methodology in medicine coincided with the initiation of the National Eye Institute (NEI). As the NEI director, Dr Carl Kupfer made carefully designed randomized clinical trials a priority for the new Institute and the first such trial was the Diabetic Retinopathy Study.6

Clinical trials in ophthalmology have progressed dramatically over the last four decades. A review of NEI-supported clinical trials documents a dramatic increase in the number of trials underway in any year throughout the first three decades of the NEI with some apparent leveling off in the last decade (Figure 1).7 Although the growth of trials has recently slowed, there has been the new development of clinical trial networks, which have the potential to perform multiple studies, involve a much larger group of clinical trial investigators, and potentially improve clinical trial recruitment, generalizability, and translation.

We also can assess the growth in clinical trials by looking at the number of papers published from clinical trials over the last four decades. The Cochrane Eyes and Vision Group (CEVG) has developed a comprehensive database of eye trial reports.8–10 Since 1940, there have been documented 11,925 eye and vision reports, which may extrapolate to approximately 10,852 individual trials based on previous detailed reviews of samples from the CEVG data set (Scherer R, personal written communication, July 3, 2008). The exponential growth of clinical trial reports is evident in Figure 2. Some of the apparent increase is attributable to the inclusion of non-MEDLINE reports, which include abstracts, but whether these are included or not, the increase over the decades is apparent and parallels the growth of NEI trials, including the possible flattening of the rate in the last decade. From the MEDLINE reported studies, one can assess some characteristics of these trials. Only about 10% are funded by the United States Public Health Service, and about three-quarters are randomized clinical trials. We can also gain an overall view of the most frequent areas studied in clinical trials from details derived from a 10% random sample of the CEVG Specialized Register.11 The studies can be
divided into those for devices and those for drugs; these two categories account for 84% of the trials in the random sample (surgery, anesthesia, and other interventions comprise the rest). Of the ophthalmic device trials, 56% were for contact lenses, spectacles, and other non-surgical devices and 19% were for studies of intraocular devices or prosthetic implants. Of the ophthalmic drug trials, 27% were evaluating treatments for glaucoma and 18% were assessing systemic agents with a broad mix accounting for the remainder.

Given the relative explosion of randomized clinical trials over the last four decades, there must be a general consensus that they provide valuable information for the practice of medicine. However, they are very expensive and time consuming. In 1968, Donald Frederickson, former National Institute of Health (NIH) Director, described them as the “indispensable ordeal”. The trials are no less an ordeal today than they were 40 years ago and they remain extremely expensive. Randomized clinical trials often cost $10,000 to $50,000 per patient per year and some trials are much more expensive than that. This means that trials often cost tens of millions of dollars, with some costing hundreds of millions of dollars. Can these costs be justified? It is hard to put a dollar value on the benefit of thousands of patients receiving the optimal treatment. Although it is difficult and requires many assumptions, one can look at the direct costs of a trial compared with the money saved by applying the study results. Cost analyses of the benefits of using photocoagulation for diabetic retinopathy have demonstrated that the government would save millions of dollars in direct costs if the treatment was widely utilized.

It could be argued that effective treatments, such as photocoagulation for diabetic retinopathy, would eventually be incorporated into clinical practice even without a randomized clinical trial. However, it is easy to forget how much resistance there was to the concept of scatter photocoagulation (pan-retinal photocoagulation) for proliferative diabetic retinopathy (PDR). To many ophthalmologists at that time, scatter photocoagulation of the retina was as controversial as the pattern bombing of North Vietnam. Almost surely without the Diabetic Retinopathy Study (DRS) results it would have taken many additional years before scatter photocoagulation was widely practiced.

The variability of outcome in diabetic retinopathy and other diseases can lead to misinterpretation of apparent treatment effects. Selected cases can appear to do well after a new but ineffective treatment is started, while other cases may do poorly despite initiation of a new and effective treatment. Resolution of this dilemma requires carefully controlled trials to assure that groups of patients do better with treatment than without. The DRS clearly revealed that the clinical trial is the best way to demonstrate treatment effects in complex diseases. Another example comes from the Optic Neuritis Treatment Trial (ONTT), where vision improved on average, with or without treatment. The control group in the clinical trial was necessary to demonstrate that the apparent improvement in vision after treatment was related to the natural history of the disease and not the effect of oral prednisone.

For new drugs, it is not possible to gain approval for their use without demonstrating safety and efficacy to the regulatory agency. This demonstration almost always requires evidence from well designed, adequately controlled, and well conducted randomized clinical trials. However, for “off-label treatments” or surgical approaches, widespread use can occur without clinical trial evidence. In ophthalmology, there are many examples of treatments in widespread use, which eventually were shown to be relatively ineffective by clinical trials, such as decompression surgery for optic neuropathy, sub-macular surgery for neovascular age-related macular degeneration (AMD), oral steroids for optic neuritis, or laser treatment to drusen for intermediate AMD. Similarly, it took a randomized trial to demonstrate that light in the nursery did not increase the risk of retinopathy of prematurity, and that although intravitreal steroids can dramatically reduce retinal thickening, their use alone has more complications and is less effective than focal photocoagulation for diabetic macular edema (DME) two years after treatment.

There are also important clinical questions regarding approved drugs where the government may be the only likely sponsor of a trial. The public health importance of this is demonstrated by the Cardiac Arrhythmia Suppression Trial (CAST). In this trial, two commonly used anti-arrhythmic drugs (encainide and flecainide) actually were associated with increased mortality. Recent examples in ophthalmology are the Comparison of AMD Treatments Trials: Lucentis-Avastin Trial (CATT) or the Diabetic Retinopathy Clinical Research Network (DRCR.net) clinical trial comparing the combination of laser treatment and either Lucentis or intravitreal steroid for DME. The results of these trials will surely have a profound impact in how we treat these diseases in the future.

Even if the value of knowing that treatments are safe and effective were offset by the cost of the clinical trial, the information we can learn above and beyond the treatment effect makes our clinical trials worth the cost and effort we devote to them. An inclusive accounting of this added value, even if limited to NEI-supported clinical trials is beyond the scope of this discussion. However, the following examples demonstrate the various different forms of additional information we gain from clinical trials.

NATURAL HISTORY

Perhaps the most valuable information we receive from clinical trials, beyond what we learn about treatment effects and side effects, is a better understanding of the clinical course or natural history of the disease under study.
The careful follow-up of a cohort of untreated patients or eyes within a randomized trial is often the best available source of such information. When data on the clinical course of a disease assessed in clinical trials can be combined with natural history data available from population-based epidemiology studies the information is enhanced. These two approaches are often synergistic in understanding the natural history of the disease. The population-based studies have the advantage of representing the population in general, while clinical trials enroll a selected patient population that is often enriched in the later stages of disease, thus, providing a better estimate of the rates of progression of disease in this portion of the population at greater risk of functional loss.

An excellent example of this comes from the DRS and the Early Treatment Diabetic Retinopathy Study (ETDRS) combined with data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Based on results from the combination of epidemiologic studies and clinical trials, a severity scale for diabetic retinopathy was developed and validated. As can be seen in Figure 3, with each increasing step of severity on this scale for eyes with moderate to severe non-PDR, there is an increased risk of developing PDR; and the presence of PDR was demonstrated by the DRS to be associated with vision loss. This linkage of the scale with potential functional loss makes it a surrogate outcome variable that can be used in clinical trials. Demonstration that a treatment can slow the progression of this surrogate is sufficient to demonstrate that the treatment would be effective to prevent eventual vision loss. Without this surrogate, it would take decades to show that a treatment could slow functional loss caused by diabetic retinopathy. Using this outcome variable, the Diabetes Control and Complications Trial (DCCT) demonstrated convincingly that tight control of diabetes reduces the risk of retinopathy progression (Figure 4). This beneficial effect was demonstrated across a broad spectrum of diabetic retinopathy severity.

In a similar way, the Age-Related Eye Disease Study (AREDS) investigators, building on natural history information from epidemiologic studies and from the Macular Photocoagulation Study, have created a severity scale for the progression of AMD that should be useful in future trials of treatments designed to slow the progression of AMD (Figure 5). These detailed scales are useful for clinical research, but both the detailed diabetic retinopathy and AMD scales have simplified versions that have
of these times were better correlated with postmenstrual calculated age than “chronological” age.

We learned about a major change in our understanding of the natural history of amblyopia, another major pediatric health problem, from clinical trials done by the Pediatric Eye Disease Investigator Group (PEDIG). From the control group, we now know that improvement of amblyopia with spectacle correction alone can be substantial. This finding has changed treatment practice. It is now common to prescribe spectacles first to see if amblyopia resolves before prescribing additional treatment for amblyopia. The PEDIG studies also demonstrated that spontaneous resolution of infantile esotropia is more common than previously appreciated, and the study identified factors associated with a higher probability of spontaneous resolution, without surgery.

Although not strictly “natural history,” important prospective information related to the course of a disease after treatment can also come from our clinical trials. For example, we learned from the Cornea Donor Study (CDS) that graft success rates are similar from older and younger donor corneas. The five-year cumulative probability of graft survival was 86% in both the <66.0 donor age group and the ≥66.0 donor age group. The study also found that corneal endothelial cell loss is substantial over five years even when the transplant remains optically clear. Half of the successful cases experienced a cell loss of 70% or more and, at five years, more than half had an endothelial cell density less than 800 cells per square millimeter.

From the DRCR.net, we learned that the proportions of patients with vision loss from DME who have improvement in visual acuity (VA) following focal/grid photocoagulation for DME is considerably more than retina specialists had thought, with almost one-third of patients with VA of 20/40 or worse regaining two or more lines of VA two years after treatment.

Finally, long-term follow-up of patients within a trial can provide important information for patients concerning treatment outcome. The ETDRS demonstrated that photocoagulation, and vitrectomy when necessary, can reduce the five-year risk of severe vision loss in persons with PDR from more than 50% to less than 5%. Additional long-term follow-up of a subgroup suggested that more than three-quarters of those survivors with retinopathy severe enough to enter the ETDRS maintained driving VA 15 to 20 years after entering the study.

Our natural history results are not limited to eye findings. The ONTT demonstrated that there was approximately a 50% risk of developing multiple sclerosis within 15 years of an episode of optic neuritis. It also identified specific risk factors associated with developing multiple sclerosis, as well as provided information on the course of vision after an episode of optic neuritis and the apparent high prevalence of subclinical optic nerve dysfunction in the fellow eye of patients with unilateral optic neuritis. If that was not enough, the study further provided...
RISK FACTORS

KNOWING THE NATURAL HISTORY OF A DISEASE IS IMPORTANT, but it is equally important to understand the risk factors associated with disease progression. Many of our clinical trials have provided such information. It is particularly helpful if there is consistency in these risk factors between clinical trials and epidemiologic studies. From a clinical trial, we may learn that a treatment is effective and we learn about the side effects of the treatment. What we often do not learn directly from the trial is “when to treat”. This requires some clinical judgment, balancing the risk of disease progression with the efficacy of treatment and its side effects. The overall clinical course and natural history information as discussed above can be very helpful in making this determination. However, specific risk factor information that helps identify groups at particular risk is also important. For example, data from the diabetic retinopathy clinical trials can be used to define a group of patients at particularly high risk for severe vision loss. These patients have either definite neovascularization of the disc (> 1/4 disc area) or the combination of neovascularization and vitreous hemorrhage. For these subgroups of patients in the DRS, the two year risk of severe vision loss was more than 25%, while for groups with severe non-proliferative or early PDR the risk was less than 11%. The study results led to clinical recommendations to consider photocoagulation for all patients with bilateral severe non-PDR or PDR, but strongly suggested that prompt initiation of treatment was important for most eyes with “high-risk” PDR.

A particularly important risk factor that affects our daily practice comes from the Ocular Hypertension Treatment Study (OHTS). Although not the first to address the issue as to whether central corneal thickness (CCT) was an important risk factor for the development of open-angle glaucoma (OAG), this study demonstrated the clear association of thinner CCT with the risk of developing primary OAG and was instrumental in getting CCT measurement widely incorporated into ophthalmic practice (Figure 7). The study also demonstrated that CCT affects the apparent response to commonly-used medications, including beta-blockers and topical prostaglandin analogs. This concern about CCT is one motivator for the development of new tonometry instruments that are less dependent upon corneal thickness, corneal curvature, and the biomechanical properties of the cornea. In addition to demonstrating the importance of CCT as a risk factor for OAG, the study developed predictive or risk-assessment models, demonstrating that age, intraocular pressure, corneal thickness, cup/disc ratio, and pattern standard deviation, taken as a group, are relatively good predictors of the development of OAG in ocular hypertensive patients. This allows clinicians to separate patients into low-, medium-, and high-risk categories as has been done for diabetic retinopathy and AMD to determine how frequently they should be seen and when treatment should be initiated.

FIGURE 7. Risk factors for the progression from increased intraocular pressure to open-angle glaucoma.
suring VA and visual fields. The clinical trial is usually just part of the process of developing new standard methods. For example, the ETDRS VA charts, commonly used in eye research today, were derived from basic work done by the National Academy of Sciences Working Group No. 39, which was expanded upon by Drs Bailey and Lovie and was eventually incorporated in the VA protocol of the ETDRS (Figure 8).

The methodology of clinical trials has evolved over the years. Because of the varying course of many diseases, it was generally thought that it would be difficult or impossible to evaluate treatments for them in a clinical trial. With the successful completion of the DRS came a spate of trials each building on the experience of the last. The latest innovations in internet methodology have now allowed us to collect data more efficiently and to incorporate more clinical sites as exemplified by the clinical trial networks (PEDIG and DRCR.net) and larger NEI trials such as AREDS 2 and CATT.

We have also learned methods from trials outside the United States. In the Azithromycin for Control of Trachoma Trial, not only was azithromycin shown to be an effective treatment, but it became apparent that one has to treat whole communities, not just cases. Experience was gained with randomization of communities rather than individuals and the results of the study led to ways to improve the delivery of antibiotics at the community level, such as using height sticks to avoid having to weigh children and using village workers rather than medical personnel. The Surgery for Trichiasis, Antibiotics to Prevent Recurrence Trial (STAR) demonstrated a new use of azithromycin to prevent recurrence of trichiasis following surgery. The trial was innovative in that it used performance-based measures rather than academic credentials to certify surgeons.

**EXPAND TECHNOLOGIES**

SOME CLINICAL TRIALS HAVE CHANGED THE WAY MEDICINE is practiced. In order to have enough corneal transplant tissue readily available for all surgeons in the Corneal Donor Study during study enrollment, the eye banks utilized a newly-developed web-based tissue sharing system that increased the cooperation and efficiency of corneal donor placement through out the United States. In addition, the study was able to evaluate variations across eye banks in the measurement of endothelial cell density. By standardizing eye bank techniques for preparing tissue for specular microscopy, the consistency and accuracy of endothelial cell density measurement across eye banks was greatly improved.

Because of the Collaborative Ocular Melanoma Study, the number of eye surgeons evaluating and managing patients with choroidal melanoma across the United States and Canada was dramatically increased. These surgeons took advantage of new methods for standardization of both A- and B-scan ultrasonography, standardization of plaques to serve as the carrier for radioactive iodine seeds, and standardization of surgery for both enucleation and plaque radiotherapy.

**QUALITY OF LIFE/VISION**

As standardized outcome variables have evolved for the development of clinical trials, it has become increasingly apparent that one also needs an overall assessment of a treatment from the patient’s perspective. A questionnaire was developed in the ETDRS to assess the relative subjective differences from a patient’s perspective in the treated and untreated eyes with DME, particularly because of concern regarding the possible problems related to scotomata that might not be demonstrated by visual fields. Interestingly, although the results of the questionnaire were consistent with the overall treatment benefit, as assessed by standardized measurement of best-corrected VA, one particular journal required that these results be omitted from the final publication, because of the subjective nature of the outcome and the lack of masking in the trial. The Prospective Evaluation of Radial Keratotomy Study experienced similar problems. However, they were able to create a psychometric arm of that study that was better designed and their quality of vision results were published. These early experiences have led to the development of the NEI-Visual Function Questionnaire, NEI-Refractive Error Quality of Life Questionnaire, and other standardized approaches to assess patient reported outcome that have become routinely incorporated into government and pharmaceutical industry clinical trials.

**FUTURE DIRECTIONS**

The public health importance of government supported clinical trials is apparent for many reasons. As medicine has moved toward insisting on “evidence based practice,” the results from randomized clinical trials have been designated as the highest level of evidence. This has been incorporated into the methodology used by professional societies as they make recommendations for standard care, such as the American Academy of Ophthalmology’s Preferred Practice Pattern panels. Clinical trials help us determine the best treatments, both medical and surgical. Government-sponsored trials are especially important for treatments that are not regulated by agencies assessing new drugs and devices. They also provide opportunities to evaluate new treatments for rare diseases that will not be assessed by industry and they may be necessary for evaluations of “postmarket” comparisons of approved treatments.

Collaboration is the direction for the future as we strive to solve increasingly difficult clinical questions. An example of this is the collaboration needed to address the explosion of information available from the new approaches to genotyping and sequencing. Genetic epidemiology will require data collection methods that allow for common definitions of phenotype as well as possible risk factors. A start to this process is the initiation of the database of Genotype and Phenotype (dbGaP) at the NIH. This database has been developed to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype. The AREDS was one of the first to download its entire database, along with genotyping of 600 participants using both the Affymetrix and Illumina chips. A publicly available site for phenotype and genotype data is the first step. Investigators will need to develop common definitions so that epidemiologic and clinical trial data can be combined in the search for genetic risk factors as well as their interaction with environmental risk factors.

Only a few examples of the benefits to clinical practice that have derived from clinical trials could be included here. It is apparent that the value of clinical trials goes well beyond the assessment of treatment effect. We learn about the natural history and risk factors of disease, but equally importantly, the collaboration of investigators, as they develop and carry out protocols, facilitates incorporation of new ideas into the practice of medicine. This should increase as we move to the networking of collaborators in clinical research such as evidenced by PEDIG, DCRR.net, AREDS 2, CATT, and other such trials. Support from the vision research community will be necessary to advance the rich tradition of clinical trials in ophthalmology. The rewards from this type of clinical research are well worth the investment. Clinical trials remain the “indispensable ordeal.”

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