Published in final edited form as:

Am J Ophthalmol. 2009 January ; 147(1): 22–32.e1. doi:10.1016/j.ajo.2008.09.013.

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

Frederick L. Ferris III

National Eye Institute, Bethesda, Maryland

Abstract

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.

Imagine what it would be like to be told that you have been selected by the American Academy of Ophthalmology and the American Journal of Ophthalmology, both founded by Dr. Edward Jackson, to be 65th Edward Jackson Memorial lecturer. To be listed among this group of ophthalmologists, from whom we have all have learned so much, and to be associated with Dr. Edward Jackson and his extraordinary contributions to ophthalmology is a special honor. Although Dr. Jackson was not particularly involved in clinical trials during his career, he was devoted to improving the standards of patient care and I have no doubt that he would think it most appropriate to discuss the impact that clinical trials have made to ophthalmology and patient care in his named lecture.

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

Corresponding Author: Frederick L. Ferris III, 10 Center Drive, Building 10 CRC, Room 3-2531, Bethesda, MD 20892-1204; (301) 496-6583; RickFerris@nei.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 ten 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 ten 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 forty-two 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 versus 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 (personal written communication with Roberta Scherer July 3, 2008). The exponential growth of clinical trial reports is evident in Figure 2. Some of the apparent increase is due 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 NIH Director, described them as the “indispensable ordeal.”¹² 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.^{13,14}

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. 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 demonstrated 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.¹⁵

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 AMD, oral steroids for optic neuritis or laser treatment to drusen for intermediate AMD.^{16–18} Similarly, it took a randomized trial to demonstrate that light in the nursery did not increase the risk of retinopathy of prematurity,¹⁹ 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 two years after treatment.²⁰

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.²¹ Recent examples in ophthalmology are the Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT) or the DRCR.net clinical trial comparing the combination of laser treatment and either Lucentis or intravitreal steroid for diabetic macular edema. 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 Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) combined with data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy.^{22,23} Based on results from the combination of epidemiologic studies and clinical trials a severity scale for diabetic retinopathy was developed and validated.²⁴ As can be seen in Figure 3, with each increasing step of severity on this scale for eyes with moderate to severe non-proliferative diabetic retinopathy there is an increased risk of developing proliferative diabetic retinopathy; and the presence of proliferative diabetic retinopathy 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).²⁵ 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,^{26,27} have created a severity scale for the progression of Age-Related Macular Degeneration (AMD) that should be useful in future trials of treatments designed to slow the progression of AMD (Figure 5).²⁸ These detailed scales are useful for clinical research, but both the detailed diabetic retinopathy and AMD scales have simplified versions that have demonstrated clinical utility.^{29,30} The AMD scale is particularly simple to use. One only has to determine whether there are large drusen and/or pigmentary abnormalities in each eye. By adding up the number of these abnormalities one gets a score ranging from 0 to 4. As seen in Figure 6, based on this scale, there is a hundredfold difference in the five-year risk of developing advanced AMD for patients with no risk factors (0.5% risk) compared with those with four risk factors (50%). Information such as this is invaluable in planning patient follow-up and therapeutic intervention.

We have similarly discovered natural history information critical for the care of retinopathy of prematurity (ROP) from data accumulated by clinical trials. A severity scale for retinopathy of prematurity was further developed and verified using data from the ROP trials.³¹ This classification scale has allowed for the development of a coherent set of Neonatal Intensive Care Unit screening examination recommendations.³² We also learned from the Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP) that severe acute ROP without retinal detachment (prethreshold ROP) occurs most predictably at a mean post-menstrual age (gestational age at birth plus duration since birth) of 36.9 weeks, with 90% of cases ranging between 33.6 and 42.0 weeks. This is clinically important because it is more predictive than age since birth and it demonstrates that the train of events of ROP does not begin at birth (into the extrauterine environment) as many had assumed, but rather is on a time-table better related to the moment of conception. The prethreshold time to ROP was confirmed in the Early Treatment for Retinopathy of Prematurity Study (ETROP) where prethreshold ROP occurred at a mean of 36.1 weeks postmenstrual age and involution of ROP occurred at a mean time of 38.6 postmenstrual weeks, with 90% beginning to involute before 44 weeks.³³ These times are important for setting screening guidelines and all 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.^{34,35} 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.³⁶

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 5-year cumulative probability of graft survival was 86% in both the <66.0 donor age group and the ≥66.0 donor age group.³⁷ 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.³⁸

From the Diabetic Retinopathy Clinical Research Network (DRCR.net) we learned that the proportions of patients with vision loss from diabetic macular edema who have improvement in visual acuity following focal/grid photocoagulation for DME is considerably more than retina specialists had thought, with almost one third of patients with visual acuity of 20/40 or worse regaining two or more lines of visual acuity two years after treatment.^{20,39}

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 proliferative diabetic retinopathy from more than 50% to less than 5%.⁴⁰ 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 visual acuity 15 to 20 years after entering the study.⁴¹

Our natural history results are not limited to eye findings. The Optic Neuritis Treatment Trial demonstrated that there was approximately a 50% risk of developing multiple sclerosis within 15 years of an episode of optic neuritis.⁴² It also identified specific risk factors associated with developing multiple sclerosis,⁴² 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.^{43–45} If that was not enough, the study further provided the best published results on steroid side effects in otherwise healthy young adults.⁴⁶

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 ($> \frac{1}{4}$ 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 proliferative diabetic retinopathy the risk was less than 11%,⁴⁷ The study results led to clinical recommendations to consider photocoagulation for all patients with bilateral severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy, but strongly suggested that prompt initiation of treatment was important for most eyes with “high risk” proliferative diabetic retinopathy.

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 6).⁴⁸ The study also demonstrated that CCT affects the apparent response to commonly-used medications, including beta blockers and topical prostaglandin analogs.⁴⁹ 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.⁵⁰ 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.

Methodology

Standardization of methods for measuring outcome variables has been advanced by the methods developed for clinical trials, such as the development of logarithmic visual acuity charts and standardized methods for measuring visual acuity and visual fields.^{51,52} The clinical trial is usually just part of the process of developing new standard methods. For example, the ETDRS visual acuity charts, commonly used in eye research today, were derived from basic work done by the National Academy of Sciences Working Group #39,⁵³ which was expanded upon by Drs. Bailey and Lovie and was eventually incorporated in the visual acuity protocol of the ETDRS (Figure 7).^{54–56}

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 Age Related Eye Disease Study 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.⁵⁷ 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.^{58,59}

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.⁶⁰

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 diabetic macular edema, 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 visual acuity, the 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.⁶¹ 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.^{62,63}

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 "post market" 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 National Institutes of Health. This database has been developed to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype. The Age-Related Eye Disease Study was one of the first to download its entire database, along with genotyping of 600 participants using both the Affymetrix and Illumina chips.⁶⁴ 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, DRCR.net, AREDS2, 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”.

Acknowledgements

A. Funding/Support: Dr. Ferris is receives direct support from the National Eye Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD.

B. Financial Disclosure: A U.S. patent entitled “Nutritional supplement to treat macular degeneration” (Patent No. 6,660,297) was issued on December 9, 2003; Dr. Ferris is one of the inventors. The patent is owned by Bausch and Lomb. Dr. Ferris has assigned his interest in the patent to the U.S. Government and receives government compensation.

C. Contributions to Authors: Dr. Ferris is responsible for preparing the manuscript.

D. Statement about Conformity with Author Information: Retrospective review. All clinical studies discussed had individual IRB approval.

E. Other Acknowledgments: The author would like to thank the following clinical trial investigators for their help in preparing this manuscript: Roy Beck (Jaeb Center for Health Research), Emily Chew (National Eye Institute), Matthew Davis (University of Wisconsin), Kay Dickersin (Johns Hopkins School of Public Health), Donald Everett (National Eye Institute), Stuart Fine (Scheie Eye Institute), Mae Gordon (Washington University), Julia Haller (Wills Eye Institute), Barbara Hawkins (Johns Hopkins School of Public Health), Thomas Hohman (Alcon Labs), Edward Holland (University of Cincinnati), Michael Kass (Washington University), Natalie Kurinij (National Eye Institute), Carl Kupfer (National Eye Institute), M. Cristina Leske (Stony Brook University), Anne Lindblad (The EMMES Corporation), Daniel Martin (Emory University), Robert Murphy (Retina Group of Washington), Earl Palmer (Oregon Health and Science University), Maryann Redford (National Eye Institute), Paul Sternberg (Vanderbilt Eye Institute), George Waring (Emory University), Sheila West (Wilmer Eye Institute) and Scott Whitcup (Allergan Inc).

References

1. Stockman R. James Lind and scurvy. *Edinburgh Medical Journal* 1926;33(6):329–350.
2. Tröhler U. Lind and scurvy: 1747 to 1795. *J R Soc Med* 2005;98:519–522. [PubMed: 16260808]
3. Fisher Ronald A. The Arrangement of Field Experiments. *Journal of the Ministry of Agriculture* 1926;33:503–515.

4. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;2:769–782. [PubMed: 18890300]
5. Patz A, Hoeck LE, de La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. I Nursery observations. *Am J Ophthalmol* 1952;35(9):1248–53. [PubMed: 12976495]
6. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Ophthalmology* 1976;81:383–396.
7. NEI Studies Database: <http://www.nei.nih.gov/neitrials/index.aspx>.
8. Cochrane Eyes and Vision Group Specialized Register
<http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/EYES/frame.html> (accessed Jul 3, 2008).
9. Dickersin K, Manheimer E, Wieland LS, Robinson KA, Lefebvre C, McDonald S. the CENTRAL Development Group. Development of The Cochrane Collaboration's CENTRAL Register of Controlled Clinical Trials. *Eval Health Professions* 2002;25:38–64.
10. Dickersin K, Manheimer E. The Cochrane Collaboration: Evaluation of health care and services using systematic reviews of the results of randomized clinical trials. *Clin Obstet Gynecol* 1998;41:315–331. [PubMed: 9646964]
11. Stephen, Gichuhi; Hawkins, Barbara S.; Dickersin, Kay. Coding of clinical trials and systematic reviews in *The Cochrane Library* using international standards. *Clin Trials* 2007;4:390.
12. Frederickson DS. The field trial: Some thoughts on the indispensable ordeal. *Bull NY Acad Med* 1968;44:985–993.
13. Drummond MF, Davies LM, Ferris FL. Assessing the costs and benefits of medical research: the Diabetic Retinopathy Study. *Soc Sci Med* 1992;34(9):973–981. [PubMed: 1631610]
14. Javitt JC. Cost savings associated with detection and treatment of diabetic eye disease. *Pharmacoeconomics* 1995;8(Suppl 1):33–9. [PubMed: 10159001]
15. Beck RW, Cleary PA, Anderson MA, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. *N ENG J MED* 1992;326:581–8.
16. Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995;273:625, 632. [PubMed: 7844872]
17. Submacular Surgery Trials Research Group. Surgery for subfoveal choroidal neovascularization in age-related macular degeneration: Ophthalmic findings. SST Group N Trial. SST Report no. 11. *Ophthalmology* 2004;111:1967–1980. [PubMed: 15522362]
18. Complications of Age-related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: The Complications of Age-Related Macular Degeneration Prevention Trial. *Ophthalmology* 2006;113:1974–1986. [PubMed: 17074563]
19. Kennedy KA, Fielder AR, Hardy RJ, Tung B, Gordon DC, Reynolds JD. for the LIGHT-ROP Cooperative Group. Reduced Lighting Does Not Improve Medical Outcomes in Very-Low-Birth-Weight Infants. *J Pediatrics* 2001;139:527–31.
20. Diabetic Retinopathy Clinical Research Network. A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema. Forthcoming: *Ophthalmology*.
[http://www.ophsource.org/periodicals/ophtha/article/S0161-6420\(08\)00606-4/abstract](http://www.ophsource.org/periodicals/ophtha/article/S0161-6420(08)00606-4/abstract)
21. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N ENG J MED* 1989;321(6):406–12.
22. The Diabetic Retinopathy Study Research Group. A modification of the Airlie House classification of diabetic retinopathy. Diabetic Retinopathy Study (DRS) Report Number 7. *Invest Ophthalmol Vis Sci* 1981;21(part 2):149–209.
23. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 1991;98(suppl):786–806. [PubMed: 2062513]
24. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS Report Number 12. *Ophthalmology* 1991;98:823–833. [PubMed: 2062515]

25. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329(14):997–986.
26. Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Arch Ophthalmol* 1997;115:741–7. [PubMed: 9194725]
27. Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, de Jong PT, Klaver CC, Klein BE, Klein R. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* 1995;39(5):367–74. [PubMed: 7604360]
28. Davis MD, Gangnon RE, Lee LY, Hubbard LD, Klein BE, Klein R, Ferris FL, Bressler SB, Milton RC. Age-Related Eye Disease Study Group. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No 17. *Arch Ophthalmol* 2005;123(11):1484–98. [PubMed: 16286610]
29. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampik A, Pararajasegaram R, Verdaguer JT. Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110(9):1677–82. [PubMed: 13129861]
30. Ferris FL, Davis MD, Clemons TE, Lee LY, Chew EY, Lindblad AS, Milton RC, Bressler SB, Klein R. Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol* 2005;123(11):1570–4. [PubMed: 16286620]
31. An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity Revisited. *Arch Ophthalmol* 2005;123:991–999. [PubMed: 16009843]
32. Reynolds JD, Dobson V, Quinn GE, Fielder AR, Palmer EA, Saunders RA, Hardy RH, Phelps DL, Baker JD, Trese MT, Schaffer DB, Tung B. for the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002;120:1470–6. [PubMed: 12427059]
33. Reynolds, James D., MD; Dobson, Velma, PhD; Quinn, Graham E., MD; Fielder, Alistair R., FRCOphth; Palmer, Earl A., MD; Saunders, Richard A, MD; Hardy, Robert J., PhD; Phelps, Dale L., MD; Baker, John D., MD; Trese, Michael T., MD; Schaffer, David, MD; Tung, Betty, MS. for the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-Based Screening Criteria for Retinopathy of Prematurity. Natural History Data From the CRYO-ROP and LIGHT-ROP Studies. *Arch Ophthalmol* 2002;120:1470–1476. [PubMed: 12427059]
34. Pediatric Eye Disease Investigator Group. Treatment of Anisometropic Amblyopia in Children with Refractive Correction. *Ophthalmology* 2006;113:895–903. [PubMed: 16751032]
35. Pediatric Eye Disease Investigator Group. Treatment of bilateral refractive amblyopia in children three to less than 10 years of age. *Am J Ophthalmol* 2007;144(4):487–96. [PubMed: 17707330]
36. Pediatric Eye Disease Investigator Group. Spontaneous resolution of early-onset esotropia: experience of the congenital esotropia observational study. *Am J Ophthalmol* 2002;133:109–18. [PubMed: 11755846]
37. Cornea Donor Study Investigator Group. The effect of donor age on corneal transplantation outcome: results of the cornea donor study. *Ophthalmology* 2008;115:620–6. [PubMed: 18387407]
38. Cornea Donor Study Investigator Group. Donor age and corneal endothelial cell loss five years after successful cornea transplantation: specular microscopy ancillary study results. *Ophthalmology* 2008;115:627–32. [PubMed: 18387408]
39. Diabetic Retinopathy Clinical Research Network. Comparison of the modified early treatment diabetic retinopathy study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol* 2007;125(4):469–80. [PubMed: 17420366]
40. Ferris FL 3rd. How effective are treatments for diabetic retinopathy? Commentary *JAMA* 1993;269:1290–91.

41. Chew EY, Ferris FL 3rd, Csaky KG, Murphy RP, Agron E, Thompson DJ, Reed GF, Schachar AP. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology* 2003;110(9):1683–9. [PubMed: 13129862]
42. Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: Final Optic Neuritis Treatment Trial follow up. *Arch Neurology* 2008;65:727–732.
43. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: A final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology* 2008;115:1079–1082. [PubMed: 17976727]
44. Beck RW, Cleary PA, Backlund JC. Optic Neuritis Study Group. The course of visual recovery after optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Ophthalmology* 1994;101:1771–1778. [PubMed: 7800355]
45. Beck RW, Kupersmith MJ, Cleary PA, Katz B. Optic Neuritis Study Group. Fellow eye abnormalities in acute unilateral optic neuritis experience of the Optic Neuritis Treatment Trial. *Ophthalmology* 1993;100:691–98. [PubMed: 8493012]
46. Chrousos GA, Kattah JC, Beck RW, Cleary PA. Optic Neuritis Study Group. Side effects of glucocorticoid treatment: experience of the Optic Neuritis Treatment Trial. *JAMA* 1993;269:2110–12. [PubMed: 8468765]
47. The Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. *Arch Ophthalmol* 1979;97:654–655. [PubMed: 426679]
48. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Kass MA. for the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study. Baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:714–720. [PubMed: 12049575]
49. Brandt JD, Beiser JA, Gordon MO, Kass MA. the Ocular Hypertension Treatment Study (OHTS) Group. Central corneal thickness and measured IOP response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2004;138:717–722. [PubMed: 15531304]
50. Ocular Hypertension Treatment Study Group, European Glaucoma Prevention Study Group. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007;114:10–19. [PubMed: 17095090]
51. Ferris FL, Bailey I. Standardizing the measurement of visual acuity for clinical research studies. Guidelines from the Eye Care Technology Forum. *Ophthalmology* 1996;103:181–182. [PubMed: 8628551]
52. Johnson CA. Standardizing the measurement of visual fields for clinical research: guidelines from the eye care technology forum. *Ophthalmology* 1996;103:186–9. [PubMed: 8628553]
53. National Academy of Sciences-National Research Council Committee on Vision. Report of working group 39: Recommended standard procedures for the clinical measurement and specification of visual acuity. *Adv Ophthalmol* 1980;41:103–148. [PubMed: 7001873]
54. Bailey I, Lovie J. New design principles for visual acuity letter charts. *Am J Optom Physiol Opt* 1976;53:740–745. [PubMed: 998716]
55. Ferris, FLd; Kassoff, A.; Bresnick, GH.; Bailey, I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982;94:91–96. [PubMed: 7091289]1982
56. Ferris FL, Bailey I. Standardizing the measurement of visual acuity for clinical research studies. Guidelines from the Eye Care Technology Forum. *Ophthalmology* 1996;103:181–182. [PubMed: 8628551]
57. Schachter J, West SK, Mabey DH, et al. Azithromycin in control of trachoma. *Lancet* 1999;354:630–5. [PubMed: 10466664]
58. Merbs SL, West SK, West ES. Pattern of recurrence of trachomatous trichiasis following surgery: surgical technique as an explanation. *Ophthalmology* 2005;112:705–709. [PubMed: 15808265]
59. West, SK.; Bedri, A.; Thanh Ton, T.; West, ES.; Mariotti, SP. Final Assessment of Trichiasis Surgeons. Geneva, Switzerland: World Health Organization; 2005. WHO publication WHO/PBD/GET/05.2

60. Cornea Donor Study Group. An Evaluation of Image Quality and Accuracy of Eye Bank Measurement of Donor Cornea Endothelial Cell Density in the Specular Microscopy Ancillary Study. *Ophthalmology* 2005;112:431–440. [PubMed: 15745770]
61. Bourque LB, Cosand BB, Drews C, Waring GO, Lynn M, Cartwright C. Prospective Evaluation of Radial Keratotomy (PERK) Study Group: Reported satisfaction, fluctuation of vision, and glare among patients one year after surgery in the Prospective Evaluation of Radial Keratotomy (PERK) study. *Arch Ophthalmol* 1986;104:356–363. [PubMed: 3954634]
62. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;119:1050–8. [PubMed: 11448327]
63. McDonnell PJ, Mangione CM, Lee P, Lindblad AS, Spritzer KL, Berry S, Hays RD. Responsiveness of the National Eye Institute – Refractive Error Quality of Life (NEI-RQL) instrument to surgical correction of refractive error. *Ophthalmology* 2003;110(12):2302–9. [PubMed: 14644711]
64. database of Genotype and Phenotype (dbGaP):
(http://www.ncbi.nlm.nih.gov/projects/gap/cgi-in/study.cgi?study_id=phs000001.v1.p1)

Biography

Dr. Ferris is the Clinical Director and Director of the Division of Epidemiology and Clinical Applications at the National Eye Institute (NEI). He completed his medical training, internship, residency and retina fellowship at Johns Hopkins. During his 35 years at NEI he has participated in many clinical trials. Notably, he was the co-chairman of the Early Treatment Diabetic Study and the chairman of the Age-Related Eye Disease Study.

Figure 1.

Number of ongoing NEI clinical trials by year. Two curves are presented: all trials and all trials excluding trials from the two NEI clinical trial networks, which have the cost of a single large trial, but generate multiple trials each.

Figure 2.
Number of published ophthalmic reports identified by the Cochrane Eyes and Vision Group by decade.

Figure 3.

Rate of developing proliferative diabetic retinopathy in eyes with four levels of moderate to severe non-proliferative diabetic retinopathy (NPDR) at baseline (Mod. NPDR 1 – level 35; Mod NPDR 2 – level 43; Mod. NPDR 3 – level 47; and Severe NPDR – level 53).

Figure 4.

Cumulative incidence of a sustained change in retinopathy in patients with insulin dependent diabetes mellitus receiving intensive or conventional therapy. A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least three steps from base line that was sustained for at least six months.

Figure 5.
Rates of progression to advanced AMD by baseline AREDS AMD Detailed Severity Score. Advanced AMD is defined as the development of neovascular AMD, central geographic atrophy or both.

Figure 6.

Rates of progression to advanced AMD by baseline AREDS AMD Simple Severity Score. Advanced AMD is defined as the development of neovascular AMD, central geographic atrophy or both.

Figure 7.
Risk factors for the progression from increased intraocular pressure to open angle glaucoma

Figure 8.
ETDRS Logarithmic Visual Acuity Chart