The Pediatric Eye Disease Investigator Group

Michael X. Repka, M.D.

ABSTRACT

Introduction and Background: The Pediatric Eye Disease Investigator Group is a network of pediatric eye care providers undertaking clinical trials with National Eye Institute support. The network includes university- and community-based providers.

Methods: Randomized and observation studies have involved refining the best amblyopia treatment in children from 3 to less than 18 years of age, observation of the behavior of early-onset esotropia, treatment of primary congenital nasolacrimal duct obstruction, and observation of the stability of strabismic angle in esotropia.

Conclusions: To date 16 studies have been undertaken enrolling 5064 children and teens.

INTRODUCTION

The Pediatric Eye Disease Investigator Group (PEDIG) was established in 1997 to create a network of investigators to undertake clinical research into pediatric eye problems. The group was conceived by Roy W. Beck, M.D., Ph.D., in response to the call for large, simple trials from the National Institutes of Health. The research group was created to develop clinical trials exploring common problems in pediatric ophthalmology.

The mid-1990s were an era in which physicians, patients, government, and payers were beginning to look for evidence-based medicine in an effort to control cost and improve quality. Examples are the American Academy of Ophthalmology’s Preferred Practice Patterns, first published in 1992, with revisions ever since, including subjects such as amblyopia, esotropia, and the pediatric eye exam.

By the mid-1990s, hospital- or clinic-based trials had an excellent track record of discovery, but were costly. These trials...
of efficacy were highly controlled with elaborate protocols, a few clinical centers, substantial oversight, and the physicians and the patients were expected to comply precisely with the treatment. About this time experts in clinical trials research were suggesting alternatives to such expensive hospital-based labor-intensive protocols. One suggested approach was the large, simple trial. These trials would typically include community-based investigators recruiting relatively few patients, receiving per patient payment, and simple data collection. The protocols would generally vary from clinical practice only in the masking of the standardized outcome evaluation. More potential clinicians could be investigators who together as a network recruit larger numbers of patients. Such trials were envisioned to answer clinically relevant questions at a reduced cost by moving the recruitment and treatment into the community. The study would evaluate delivery in a community setting, providing evidence of a treatment’s effectiveness when delivered in the manner it would be used outside of a study. This type of delivery would thereby improve the generalizability of the conclusions. A secondary advantage is that a network could run multiple studies at the same time maximizing efficiency. An example of such a collaborative group is the Pediatric Research in Office Settings (PROS) network sponsored by the American Academy of Pediatrics (AAP). The PROS was established in 1986. Among the subjects studied, this group evaluated compliance with the AAP vision screening guidelines.4

STUDY DESIGNS

Our network has used several study designs. Prospective observational studies are very useful when the natural history of a condition is not well understood. The first study undertaken by PEDIG was the Congenital Esotropia Observation Study (CEOS).5 Subsequent observational studies have evaluated the recurrence risk of amblyopia after treatment was discontinued.6

Prospective pilot studies can be undertaken when there is insufficient information to design a proper randomized clinical trial (RCT). These studies are undertaken to determine feasibility of recruitment, the ability of the patient and clinician to follow a protocol, to test study procedures, and to determine a point estimate of a treatment effect when no other data are available. For instance, we were interested in treating patients older than 7 years of age for amblyopia, but we did not know whether there really was an effect or how large that effect might be. A pilot study showed that minimal amblyopia treatment did improve visual acuity.7 In general the results of pilot studies will be of insufficient power to allow a definitive conclusion about the treatment to be studied.

The most commonly performed type of study undertaken by PEDIG has been the randomized clinical trial (RCT). These trials may be divided into efficacy and effectiveness studies. Both use informed consent, randomization, and uniform outcome measures. Efficacy studies are both tightly controlled and monitored with an attempt to achieve 100% compliance with the protocol-determined treatment. These are the classic RCT. Effectiveness trials are controlled and monitored, but use typical methods of encouraging compliance with the randomized therapy. These effectiveness trials are termed “real-world” as they attempt to reproduce what happens in clinical practice. Some have argued that these results will correlate better with treatment outside of a research study.

Randomized trials may test for superiority or equivalence. Trials of superiority are the most common in which the question being asked is whether one method is better than the other. This type of clinical question was posed in our studies of the

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compared hours of patching (2 versus 6, full-time less one versus 6)\textsuperscript{8, 9} or days of atropine (weekend versus daily).\textsuperscript{10} The second type of trial seeks to determine if two treatments are equivalent. Such studies require larger numbers of patients. We used this method in our first RCT, the trial comparing atropine to patching.\textsuperscript{11}

Patients (and their parents) who participate in research studies are generally more knowledgeable and more compliant with treatment than those in the general population. This limitation should be kept in mind in the interpretation of the results. In addition, the patients who decide to enroll may be more homogenous than the general population because of access to care and the time commitment of clinical trial participation.

STRUCTURE OF PEDIG

The PEDIG research group is structured around its different operations. The Data Coordinating Center (DCC) is hosted at the Jaeb Center for Health Research in Tampa, Florida. This DCC is responsible for the coordination of the network. Functions of the DCC include financial agreements, study management, data analysis, and study development functions. Financial management includes applying for grant support, managing research documentation for the National Eye Institute of the National Institutes of Health, distributing payments to investigators, coordinators, and patients. In addition, the DCC helps to maintain the sponsor’s records and credential the investigators for the Investigative New Drug (IND) documentation required by the Food and Drug Administration. An IND is needed whenever a study is conducted for an unapproved drug or for an unapproved indication for an approved drug.

The DCC is responsible for monitoring compliance with protocols by continuous assessment of submitted data. Clinical coordinators within the DCC are available by phone and e-mail to solve problems including patient scheduling, protocol questions, and materials management. Project managers are assigned to individual protocols and work with the planning committee to develop the protocol, design the analysis plan with the steering committee, assist in the data analysis, and help to prepare the manuscript.

An important innovation necessary to allow community-based researchers to be involved in research is to have coverage by an Investigation Review Board (IRB). Many non-university hospitals had done away with such an organization, relying on outside independents such as Western IRB (3535 Seventh Ave. SW, Olympia, WA 98502-5010), which tended to be costly when an individual investigator might recruit just a few patients. In addition, since most pediatric protocols were office-based, there would be a question of whether a hospital IRB would even review such a study. To solve this problem, an independent IRB was established in Tampa, Florida, to review all of the PEDIG protocols.

An informational technology group is also housed within the Jaeb Center. The PEDIG network depends on electronic communication and this staff ensures that clinics have appropriate communications capability including high-bandwidth internet access. In addition, this group has developed and produced a computerized visual acuity platform used in the PEDIG network.\textsuperscript{12, 13} This visual acuity testing platform is being used in other National Eye Institute studies.

The most crucial members of the study group are the investigators and coordinators. An important principle of the group since it was established is that membership is open to all qualified investigators who are interested. To date, 244 investigators from university and community practices have been involved in at least one project. They are free to choose which of the projects they are interested in and become
certified for that project. Our busiest investigators have been from the private practice setting. In part this reflects greater access to the types of clinical problems we have studied and the investigator’s greater flexibility/speed in becoming certified and completing IRB paperwork than the investigators in university settings.

COMMITTEES

There are four types of committees. The executive committee is charged with overall network administration. Functions include determining which protocols will move forward and determining who is qualified to be an investigator in the network. During the lifetime of each study, there is a planning committee, a steering committee, and a number of writing committees. The functions of the planning and writing committees are clear. The steering committee is charged with monitoring the particular study as it is enrolling and following patients, encouraging recruitment among investigators, and monitoring and policing protocol deviations.

COMMUNICATIONS

The internet has improved the ability to collaborate quickly and inexpensively with large numbers of individuals. PEDIG uses e-mail for communications and dissemination of study information to all investigators/coordinators. Each of the committees is in frequent e-mail communication. Certification of coordinators and investigators was initially done on paper forms returned by fax to the DCC, but over the last few years has become completely web-based.14

Where the internet has revolutionized study management is the use of browser-based applications for data entry. This means the source document becomes the electronic file on the server. The “server” computer at the DCC leads the clinical staff through all of the required steps and notes that the visit is complete only when all of the needed data have been entered. This essentially has eliminated data edits because there is real-time validation of the data. The number of protocol violations is also markedly reduced with the switch from paper to web. For this system to work, the data do need to be entered in “real-time” with the patient still present.

Traditional face-to-face technical group meetings of the investigators and coordinators have not been eliminated. In the early years, we did not have such meetings, but there was little sense of involvement in the network even among the large recruiters. This situation has been improved with the implementation of twice yearly investigator group meetings. These meetings have served as a forum to discuss the most recent research findings, to develop the appropriate discussion points for the manuscripts, and to discuss and prioritize new study proposals. In addition, separate monthly investigator and coordinator conference calls are scheduled to update network members about ongoing studies, future studies, and operational details.

OUTCOME MEASURE

The perceived value of clinical trial depends on many factors, but most importantly depends on its outcome measure. An unreliable measure will call a study’s results into question. Most studies will propose to analyze the change in a measure from the time of enrollment to the time of the outcome examination. The same test method should be used at each exam. In studies of amblyopia this has often been overlooked because the patients are aging. However, even using the same technique and optotype at both time points will have the potential biases of learning effect (tested more than once) and age effect (the
There are many optotypes for visual acuity testing available to the pediatric investigator (Allen Pictures, Lea Symbols, fixation preference, isolated letters, surrounded letters, and line letters). In addition there are many methods of encouraging a patient during the testing process and perhaps even some second chances. In a study, the method of testing needs to be the same from center to center or, said differently, standardized. For our amblyopia studies, we selected the single-surrounded HOTV optotype presented randomly because this was available on the Mentor BVAT System. This system was a widely available instrument when we planned the first Amblyopia Treatment Study. To standardize the testing we developed a protocol and certified our testers. As the BVAT instrument became obsolete, we subsequently developed and then automated the visual acuity testing protocols.

Some measures may be sufficiently common and the methods agreed upon that they can be employed with reviews of the technique and certification of an agreed upon level of expertise. For example, the measurement of the angle of strabismus in CEOS and the Esotropia Treatment Study 1.

DEVELOPMENT OF NEW STUDIES

A frequent observation of clinical research is that with each completed project, more questions become apparent. The PEDIG network began with two specific questions: one about the natural history of early-onset esotropia, while a second project sought to determine if atropine was as successful as patching. This led to a series of associated research questions in amblyopia treatment. Recently, studies of nasalacrimal duct obstruction and esotropia have been undertaken.

A new study begins as a brief proposal brought forward by an investigator or developed during discussion at investigator meetings. Each proposal is discussed by the investigator group on monthly conference calls and at the semi-annual meetings of the network. These results lead to a discussion of the importance to the overall PEDIG mission and the costs of the project to the network. If a study is approved by the executive committee, a planning committee is formed.

The planning committee is charged to determine normal clinical practice, investigator interest, feasibility, and to refine the question to be studied. A background, the rationale for the study, and the protocol are then written. Once these are approved, any necessary study procedures are added to the PEDIG Manual of Procedures. Templates for IRB submission are then written and all of the documents are presented to the network leadership and investigators for comment. This often takes several review cycles. In nearly all protocols development there are compromises when multiple investigators are involved. For instance in ATS1 (Patching versus Atropine) the primary outcome at six months was considered too short by those investigators used to atropine treatment, but selected so that a patient who had not improved on their randomized treatment could be switched to another treatment without significant adverse impact. A second compromise allowed amblyopic eyes only from 20/40 to 20/100 inclusive because atropine was not felt to be effective for poorer levels of acuity. In terms of patching, the group had widely varied methods of prescribing patching for this level of amblyopia, from two hours to all waking hours. To undertake the study compromise, we allowed patching from six hours to full-time minus one hour at initiation of treatment, but if the amblyopic eye was not successfully treated by 17 weeks, the children had to
complete a minimum of eight weeks of full-time patching.

Once the protocol is refined, the protocol, manual of procedures, and consent templates are submitted to the Data Safety and Monitoring Committee for review. Some studies are evaluated by an independent scientific review panel selected by the National Eye Institute. Once a study is launched, each project has a steering committee appointed to monitor the progress of the study. Study chairs are selected for each project to have the primary responsibility of communicating with the site investigators.

LIMITATIONS

The PEDIG network is not an appropriate avenue for all (or perhaps even most) clinical research in pediatric ophthalmology and strabismus. Some projects require monitoring or standardization without compromise that is not possible in this model. We design projects with which a majority of our investigators are comfortable. This obviously means there is compromise, but often leads to an approach that is most typical in clinical practice, rather than what is recommended in texts.

The decision to participate cannot be taken lightly. Investigators must have equipoise regarding a particular question to participate. If they do not believe the study question is valid, they must not participate and it would not be ethical to enroll their patients. There is also a time requirement. No matter how easy the web data entry and the DCC make the process of study participation, the process of informed consent must be taken seriously by all involved and cannot be rushed. If there has been a consistent problem for investigators, it has been how to fit the time to properly consent the family into a busy clinical schedule. While some investigators have chosen to fall behind on their office schedule, others have asked the patient and parents to return at another time, and others certainly have not been enrolled.

CONCLUSION

The development of PEDIG has allowed the initiation of sixteen clinical trials examining important issues of amblyopia treatment, nasolacrimal duct obstruction, and esotropia. The investigators, coordinators, and DCC staff of PEDIG have shown that a research network can recruit large numbers of pediatric patients with common eye diseases quickly if there is sufficient DCC coordinator support. Many have been recruited from a community-based setting demonstrating a great interest among clinicians to remain active in research when an opportunity is provided. We are appreciative of the efforts made by the 5064 children and teens (and their families) who have enrolled in our studies of pediatric eye disease (as of 8/1/2007).

REFERENCES


Key words: PEDIG, amblyopia treatment, clinical trials