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Feasibility of a Clinical Trial of Vision Therapy for Treatment of Amblyopia

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Abstract

Purpose—We conducted a pilot randomized clinical trial of office-based active vision therapy for the treatment of childhood amblyopia to determine the feasibility of conducting a full-scale randomized clinical trial.

Methods—A training and certification program and manual of procedures were developed to certify therapists to administer a standardized vision therapy program in ophthalmology and optometry offices consisting of weekly visits for 16 weeks. Nineteen children, 7 to less than 13 years of age, with amblyopia (20/40–20/100) were randomly assigned to receive either 2 hours of daily patching with active vision therapy or 2 hours of daily patching with placebo vision therapy.

Results—Therapists in diverse practice settings were successfully trained and certified to perform standardized vision therapy in strict adherence with protocol. Subjects completed 85% of required weekly in-office vision therapy visits. Eligibility criteria based on age, visual acuity, and stereoacuity, designed to identify children able to complete a standardized vision therapy program and judged likely to benefit from this treatment, led to a high proportion of screened subjects being judged ineligible, resulting in insufficient recruitment. There were difficulties in retrieving adherence data for the computerized home therapy procedures.

Conclusions—This study demonstrated that a 16-week treatment trial of vision therapy was feasible with respect to maintaining protocol adherence; however, recruitment under the proposed eligibility criteria, necessitated by the standardized approach to vision therapy, was not successful.

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A randomized clinical trial of in-office vision therapy for the treatment of amblyopia would require broadening of the eligibility criteria and improved methods to gather objective data regarding the home therapy. A more flexible approach that customizes vision therapy based on subject age, visual acuity, and stereopsis, might be required to allow enrollment of a broader group of subjects.

Keywords

amblyopia; patching; vision therapy; placebo vision therapy; masking

Treatment with patching and/or atropine is effective in improving visual acuity in children with unilateral amblyopia,^{1–7} but reduced visual acuity is not the only visual defect associated with amblyopia. Deficiencies in accommodation,^{8–10} contrast sensitivity,^{11, 12} fixation,^{11, 13, 14} eye movements,^{15, 16} binocular function,^{17–19} motion detection,²⁰ and vernier acuity¹¹ have been reported to occur in amblyopic eyes. Thus, as an adjunct to conventional amblyopia treatment with refractive correction and occlusion, some eye care providers prescribe active vision therapy to specifically address these deficiencies in visual function.^{21–26}

Vision therapy for amblyopia consists of a sequence of visual activities prescribed to facilitate the effects of refractive correction and occlusion by directly treating other aspects of visual function such as accommodation, eye movements, and suppression.^{22–26} There is a clinical impression that active vision therapy can not only speed visual acuity improvement, but may also reduce the likelihood of amblyopia recurrence/regression, especially for anisometropic amblyopia.²⁷ Vision therapy for amblyopia is often administered in the office on a weekly basis by a therapist under the supervision of an eye care provider, and supplemented by similar therapy procedures prescribed to be completed at home to reinforce visual skills. The effectiveness of vision therapy for amblyopia treatment has not been evaluated in randomized clinical trials.

To evaluate the effectiveness of active vision therapy for the treatment of childhood amblyopia, the Pediatric Eye Disease Investigator Group (PEDIG) designed a clinical trial of 7 to <13-year-old children with amblyopia who would be randomized to treatment using 2 hours of daily patching with active vision therapy or to 2 hours of daily patching with placebo vision therapy. Treatment consisted of 16 weekly in-office vision therapy visits with a trained therapist and the use of computer therapy in the office and at home. The primary outcome was the proportion of subjects with 20/25 or better visual acuity in the amblyopic eye as measured using the electronic Early Treatment Diabetic Retinopathy Study protocol (eETDRS©)²⁸ assessed at 17 weeks by a masked examiner. The sample size was determined to be 222 subjects. Because most PEDIG investigators did not offer office-based vision therapy in their practices, the implementation of this protocol would require a significant effort in training therapists to administer the vision therapy in a standardized manner. In addition, there were concerns regarding subjects' willingness to participate in an amblyopia treatment trial that required 16 weekly office visits and whether they would adhere to weekly office visits, the research cost associated with the training of vision therapists and equipment needed for participating clinical sites, and the ability to recruit a sufficient number of eligible subjects. Therefore, an initial "feasibility" phase was implemented at 7 clinical sites.

The primary objective of this phase was to determine the feasibility of a full scale randomized clinical trial, including whether the Investigator group could recruit a sufficient number of eligible subjects and conduct the study according to the proposed protocol. The decision to continue the study (i.e., add additional clinical sites and recruit the full sample

size) was predicated on the success of the feasibility phase of the study. Herein, we report the results of the feasibility phase of this randomized clinical trial of active vision therapy for the treatment of amblyopia.

METHODS

The study, supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health, Bethesda MD, was conducted by the PEDIG at 7 clinical sites (4 optometry-based and 3 ophthalmology-based). Respective institutional review boards approved the protocol and Health Insurance Portability and Accountability Act (HIPAA) compliant informed consent forms. A parent or guardian (referred subsequently as “parent”) of each child gave written informed consent and the children gave assent as required. The study adhered to the tenets of the Declaration of Helsinki and an Independent Data Safety and Monitoring Committee provided study oversight. The study was listed on clinicaltrials.gov (ID NCT00587171).

The specific objectives of the feasibility phase of the trial were to: 1) determine the availability of eligible subjects and willingness of subjects to be randomized to the proposed treatments; 2) determine participant adherence to the treatment protocol (i.e., weekly visits), particularly those assigned placebo vision therapy; 3) test procedures developed to train and certify therapists to administer both active and placebo vision therapy according to protocol; 4) identify possible problems with training and implementation at the clinical sites; 5) evaluate the feasibility of successfully delivering the office-based vision therapy program at the PEDIG sites, particularly those with no prior experience with in-office vision therapy; and 6) determine the success of masking the subjects and parents to their assigned treatment group.

Site and Subject Selection

Clinical sites were selected based on their interest in the study or record of strong recruitment in past PEDIG amblyopia studies. The recruitment goal for the feasibility phase of the trial was 45 subjects over a 1-year period, with each site enrolling 6 to 7 subjects, but not more than 10 per site, to allow all sites to gain experience with the protocol. Major eligibility criteria included: age 7 to <13 years; amblyopia associated with anisometropia, strabismus, or both; visual acuity 20/40 to 20/100 in the amblyopic eye and 20/25 or better in the fellow eye; interocular visual acuity difference of 3 or more logarithm of the minimum angle of resolution (logMAR) lines; at least 800 seconds of arc on the Randot Preschool Stereoacuity test; single vision spectacles (if needed) worn for at least 16 weeks or until amblyopic eye visual acuity was documented to be stable (defined as 2 consecutive visual acuity measurements by the same testing method at least 4 weeks apart with no improvement of 1 logMAR line); no previous vision therapy or orthoptics; and daily access to a computer (internet access not required). Constant strabismus at near at the time of the eligibility examination was an exclusion criterion. Table 1 provides a complete listing of eligibility and exclusion criteria. Eye patches, therapy visits, and vision therapy equipment including the computer program, were provided free of charge to the subjects.

Randomization and Treatment Protocols

After informed consent was obtained and eligibility confirmed, participants were randomly assigned with equal probability to receive either active vision therapy or placebo vision therapy using a master randomization list with a permuted block design stratified by site. The treatment regimen for both treatment groups was 2 hours of daily patching of the non-amblyopic eye during which 30 minutes were to be devoted to performing near activities and 30 minutes to computerized home therapy, and a weekly 45-minute in-office vision

therapy session with a therapist. Near activities were the same in both groups and consisted of activities performed within arms' reach using eye-hand coordination such as crafts, coloring, video games, written homework or reading. Subjects in both groups were scheduled for 16 consecutive weekly in-office therapist-supervised therapy sessions. The treatment regimen difference between the two groups was that the active group performed active vision therapy procedures during the in-office sessions as well as for the computerized home therapy, whereas the control group performed placebo vision therapy procedures in the office and at home.

All subjects and their parents were masked to treatment assignment and every attempt was made to maintain masking during the trial. The active vision therapy procedures consisted of standard accommodative amplitude and facility, vergence (e.g., free-space fusion cards, vectographs, computerized therapy), and anti-suppression (e.g., Brock string, anaglyphic drawing) therapy procedures. All vergence activities required subjects to have normal peripheral sensory fusion and some required appreciation of random dot stereopsis. The home therapy activities for the active therapy group required subjects to spend a total of 30 minutes on computer-based programs including Amblyopia iNet and HTS (HTS Inc., Gold Canyon, AZ). The in-office placebo therapy included visual perceptual activities such as parquetry blocks and the Visual Information Processing Skills (VIPS) component of the Computer Aided Vision Therapy (CAVT) program (Bernell, Mishawaka, IN). These activities were performed with both eyes open instead of with the nonamblyopic eye patched and lens flippers with plano lenses, yoked prism, or neutral density filters were used. Placebo home therapy consisted of 30 minutes of computer therapy with a version of the Amblyopia iNet program, in which the initial target size corresponded to 20/200 and automatically decreased to 20/100 at the 8-week interval. Objectives and goals were established for each procedure in both treatment groups to motivate subjects to engage in the activities. Therapists were instructed to encourage all subjects regardless of treatment assignment. A copy of the in-office active and placebo vision therapy Manuals of Procedures designed for this study can be downloaded at <http://pedig.jaeb.org/Studies.aspx?RecID=35>.

Training/Certification of Therapists & Quality Assurance

The Manual of Procedures specified that each clinical site have at least one certified therapist whose qualifications were being an optometrist, ophthalmologist, orthoptist, occupational therapist, or vision therapist. Training and certification procedures for all therapists were to: review the Manual of Procedures; watch a DVD-based training program that was developed specifically for the study; successfully complete a written examination; demonstrate proficiency with the in-office vision therapy procedures (both active and placebo) at a study training and certification session; and submit treatment progress reports for 2 test patients. Any therapist not having a minimum of 60 hours of experience with in-office vision therapy in the prior year or unable to attend the study certification session was initially given provisional certification upon fulfillment of all other criteria; full certification status was conferred after a Steering Committee member observed the therapist administering in-office vision therapy per protocol to study participant(s). Additional quality assurance measures included a therapy session evaluation at a site visit performed during the course of the study and review by a Protocol Chair of the therapists' notes from all completed vision therapy sessions to ensure that the treatment protocol was followed appropriately.

A priori, it was determined that the ability to train therapists successfully would be measured by the number of errors during the vision therapy phase occurring during the study. Errors were defined as subjects receiving non-assigned vision therapy or advancing through the phases of vision therapy more quickly or slowly than specified by protocol. A Protocol

Chair identified vision therapy-related deviations after review of the weekly in-office vision therapy forms completed by the therapists.

Adherence with Home Vision Therapy and Patching

At each of the weekly follow-up visits, the therapists reviewed the subject's written log of the number of hours spent patching and doing computer activities each day, and inquired about the subject's adherence to the home therapy and patching. For subjects who had internet access at home, the therapist was instructed to review an on-line log of the computerized activities performed each day at home, automatically recorded by the computer program and uploaded to a protected database each night. Subjects who did not have home internet access received instructions to copy the log files onto a USB drive and bring it to the weekly in-office visit for review. Time spent doing general near activities while patching was not monitored. Adherence to patching and home therapy was scored separately (excellent when 76–100% of prescribed treatment completed, good 51%–75%, fair 26%–50%, and poor 25% or less). Adherence determination was completed before the subject's visual acuity was measured.

Masking Assessment

During the initial verbal consent process, and as part of the written informed consent, parents and subjects were informed that at each office visit a therapist would treat the child with active vision therapy or activities that were not believed to help his or her vision (control therapy). At the 17-week outcome visit, the therapist independently queried both the subjects and parents regarding which treatment group they thought they or their child was assigned by asking the child "what treatment do you believe that you received?" when the parent was not present, and asking the parent "what treatment do you believe your child received?" when the child was not present. Masking of subjects and parents was defined as successful if, at the conclusion of the study, the proportion of subjects (and respective parents) able to correctly identify the treatment assignment was statistically not different from or less than predicted by chance (50%). This corresponded to less than 30 (67%) subjects/parents identifying the treatment assignment correctly as the criterion for successful masking based on a sample size of 45.

RESULTS

Recruitment and Retention

Between April 2008 and March 2009, 19 subjects (9 with anisometropic, 2 with strabismic, and 8 with combined mechanism amblyopia) were enrolled at 7 sites (14 from optometry-based and 5 from ophthalmology-based sites); 9 were randomly assigned to active vision therapy and 10 were assigned to placebo vision therapy. One site recruited 10 subjects; 3 sites recruited 2 subjects each, and the remaining 3 sites each recruited 1 subject. One subject's parents requested their child be dropped from the study after randomization. Another subject completed 12 weeks of vision therapy, but did not complete the 17-week outcome visit. All other subjects completed the study.

Based upon reports from the investigators on monthly conference calls, recruitment was limited largely by the stringent eligibility criteria, including the combined requirements of at least 800 seconds of arc of random dot stereopsis at near on the Randot Preschool Stereotest, visual acuity in the amblyopic eye of 20/40 to 20/100, and the minimum age of at least 7 years. In addition, sites were requested to document all children who were screened for the study for an approximate 2-month time period (actual period varied by site depending on time of IRB approval). During this period, there were 6 children who were eligible but failed to enroll, 140 children with amblyopia who were not eligible, and 4 children who were

enrolled. The most frequent reasons for failure to enroll of a eligible child were living too far from the site and unwillingness to wear spectacles/poor compliance with spectacles each reported for 2 children. The most frequent reasons for ineligibility were visual acuity not between 20/40 and 20/100 (54 (39%) children), intraocular difference of less than 3 lines (30 (21%) children), age younger than 7 years or older than 12 years (26 (19%) children), Randot near stereoacuity less than 800 arc seconds (25 (18%) children), and constant strabismus at near (12 (9%) children; percentages sum to more than 100% as some children had multiple reasons for ineligibility). Other reasons for ineligibility applied to less than 3% of children. We did not identify any issues related to specific sites that affected recruitment.

Subjects in each group completed a similar number of the 16 weekly in-office vision therapy visits. On average 2.5 treatment visits were missed per subject for an overall completion rate of 85% with those in the active treatment group having more missed office vision therapy visits compared to those in the placebo group (3.0 vs. 2.0 visits). The proportion of subjects completing the 17-week masked outcome examination was not different between the active (89%) and the placebo (90%) vision therapy groups.

Protocol Adherence

Two major protocol deviations were noted during the 256 treatment visits of the trial. One placebo group subject received active vision therapy at the first in-office visit. Another subject was initially given the incorrect home therapy computer disk; however, this was discovered before the subject used the program, and the correct program was subsequently provided to the subject. In addition, there were 4 instances where the in-office vision therapy was not fully completed at that visit because of time constraints. There was one instance where a subject was moved into the second phase of the vergence therapy despite not meeting the criteria for phase one.

Adherence with Home Vision Therapy

Home adherence with the computer program could not be objectively assessed because only about 50% of subjects reported their results online or brought their data-storage devices to study visits. Participant adherence to the prescribed home therapy based on the written logs (completed by a parent), and discussion with the parent was judged subjectively by therapists to be excellent in 88%, good in 12%, fair in 0%, and poor in 0% of subjects assigned to active vision therapy. For the placebo vision therapy group, adherence was judged to be excellent in 70%, good in 20%, fair in 10%, and poor in 0% of subjects.

Subject Masking

At the 17-week outcome visit, 100% (8 of 8) of those subjects assigned to active vision therapy and 67% (6 of 9 subjects) of those assigned to placebo vision therapy reported that they thought they were assigned to the active vision therapy regimen. This corresponded to 65% (95% confidence interval (CI): 38–86%) of subjects correctly identifying their treatment assignment. Fifty percent (4 of 8) of the parents of those assigned to active vision therapy and 55% (5 of 9) of the parents of those assigned to placebo vision therapy reported that they thought their child received the active vision therapy, corresponding to 47% (95% CI: 23–72%) of parents correctly identifying their child's treatment assignment. The overall percentage of correct guesses was not statistically different from 50% for either subjects or parents; however, as the full feasibility phase sample size was not reached, the confidence interval on this percentage was wider than planned, and we were unable to reach a definitive conclusion regarding success of masking.

DISCUSSION

This feasibility study was performed to evaluate potential difficulties in conducting a proposed randomized clinical trial to evaluate the effectiveness of a 16-week office-based regimen of active vision therapy for the treatment of childhood amblyopia. Experience from this feasibility study, using the study design and treatment regimens developed for the intended clinical trial, was to be used to identify any issues related to recruitment, retention, certification of therapists, adherence with study visits and home-based treatment, and the masking of participants and their parents. The results of this study showed that once enrolled into this multi-center treatment trial of in-office vision therapy for the treatment of amblyopia, few subjects missed study visits and most completed the entire 16-week treatment program. Also, there was good adherence to the prescribed weekly in-office vision therapy. However, both recruitment and the ability to monitor adherence objectively with computerized home therapy were problematic.

The recruitment goal of 1 subject per month per site was met by only 1 of the 7 clinical sites, with total recruitment reaching only 42% of the goal. Thus, the full-scale randomized clinical trial was deemed to not be feasible based on insufficient recruitment. The reason for insufficient recruitment was largely due to the combined eligibility criteria for visual acuity, stereoacuity, and age. This was the first PEDIG amblyopia study with these eligibility criteria; in particular, no previous PEDIG amblyopia study had a minimum stereoacuity requirement. Many children whose visual acuity and/or intraocular difference were not in the eligible range had amblyopic eye visual acuity that was better than 20/40 following treatment with spectacles alone. These children would not be the best candidates for an amblyopia treatment trial due to limited room for further improvement. It was thought that allowing children with visual acuity worse than 20/100 would require significant changes to the treatment protocol. This would have significantly increased sample size if those subjects were treated and analyzed as a separate cohort. As we learn more about children with severe amblyopia and how they respond to traditional therapy there could be justification to include subjects with poorer visual acuity. While recruitment might have benefited if a less stringent stereoacuity requirement had been used, presence of random dot stereopsis was considered necessary because many of the office-based active vision therapy procedures for vergence and anti-suppression required fusion and stereopsis to perform the task. The lower age limit of 7 years was specifically chosen as children less than 7 years old often have difficulty understanding many of the vision therapy procedures. The upper age limit was based upon a previous Amblyopia Treatment Study,⁷ which showed less improvement for children >12 years than for younger children with conventional treatment of occlusion and/or atropine. We were attempting to maximize the benefit of vision therapy, if it existed. If subjects with less than 800" of stereopsis and/or age <7 years had been included, modifications to the active vision therapy protocol that allowed for the vision therapy to be customized based on the subject's age and stereoacuity would have been necessary. For this initial study, we decided to adopt more stringent criteria for stereoacuity and age to allow for a uniform approach to the active vision therapy program. Future studies may need to consider a more flexible approach, customized according to subject age, visual acuity, and stereopsis that would allow a broader range of children with amblyopia to be enrolled. However, a more flexible approach to the vision therapy treatment protocol would complicate training and certification and could conceivably result in increased variation in treatment effect.

There were also difficulties with the method used to objectively monitor the computerized home therapy. A number of subjects without internet access who were instructed to store their computer therapy performance on USB drives and bring the drives to their vision therapy appointments either did not understand how to download the computer therapy performance to USB devices or did not bring the devices to the treatment visits. This made it

impossible to obtain adequate data regarding computerized home therapy adherence and performance. For future studies that use computerized home therapy with internet monitoring either as an adherence or an outcome measure, internet access to facilitate documentation of computerized home therapy performance should be required.

CONCLUSIONS

This feasibility study demonstrated that amblyopic children aged 7– <13 years can adhere to 16- weeks of in-office vision therapy program for amblyopia treatment and that therapists can be trained to administer vision therapy in a standardized manner. However, a full-scale randomized trial proved not to be feasible because of our inability to recruit a sufficient number of eligible subjects in a reasonable time frame. Successful completion of a randomized clinical study of in-office vision therapy for the management of amblyopia would require modifications to the eligibility criteria and employment of improved methods to gather the objective data from the computerized home therapy treatments.

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The Pediatric Eye Disease Investigator Group

Clinical Sites

Sites are listed in order by number of subjects enrolled into the study. Personnel are listed as (I) for Investigator, (C) for Coordinator, (VA) for Visual Acuity Tester, and (VT) for Vision Therapist.

Bascom Palmer Eye Institute, Miami, Florida (10): Susanna Tamkins, (I); Mariana Nunez, (C); Eva Olivares, (C); Raynold Crespo, (VA); Yaidy Exposito, (VA); Sonia Fernandez, (VA); Shannon Hooker, (VA); Lidia Salinas, (VA); Adam Perlman, (VT)

Family Eye Group, Lancaster, Pennsylvania (2): David Silbert, (I); Noelle Matta, (C); Darelene Crick, (VA); Debra Hazel, (VT)

Casey Eye Institute, Portland, Oregon (2): Allison Summers, (I); Kimberley Beaudet, (C); Yelena Bubnov, (VA); Pamela Berg, (VT); Dusty Gronemyer, (VT)

Indiana University School of Optometry, Bloomington, Indiana (2): Don Lyon, (I); Kristy Dunlap, (C); Jonathan Bradley, (VA)

Pediatric Ophthalmology of Erie, Erie Pennsylvania (1): Nicholas Sala, (I); Benjamin Whitling, (I); Rhonda Hodde, (C); Jeanine Romeo, (C); Cindy Tanner, (VA); Benjamin Whitling (VT)

University of Alabama at Birmingham School of Optometry, Birmingham, Alabama (1): Kristine Hopkins, (I); Michael Hill, (C); Tiffany Rhyne, (VA)

Southern College of Optometry, Memphis, Tennessee (1): Kristin Anderson, (I); Kelly Dasinger, (C); Janette Dumas, (VT)

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Table 1**Study eligibility and exclusion criteria.**

Eligibility Criteria
1. Age 7 to <13 years.
2. Amblyopia associated with anisometropia, strabismus (comitant or incommittant), or both [*] .
3. No constant strabismus at near.
4. Visual acuity, measured using the eETDRS© protocol ²⁸ on the Electronic Visual Acuity Tester (EVA) ²⁹ meeting the following criteria: <ul style="list-style-type: none"> • Best-corrected visual acuity in the amblyopic eye between 49 and 71 letters inclusive (20/40 to 20/100 inclusive) • Best-corrected visual acuity in the sound eye 79 or more letters (20/25) • Inter-eye acuity difference 15 or more letters (3 logMAR lines) (i.e., amblyopic eye acuity at least 3 lines worse than sound eye acuity)
5. Single vision spectacles, if needed, worn for at least 16 weeks or until visual acuity documented to be stable (bifocals not allowed).
6. Near stereoacuity of 800 seconds of arc or better on the Randot Preschool Stereoacuity test.
7. No previous home-based, office-based or computerized vision therapy or orthoptics.
8. Previous or current amblyopia treatment with spectacles, contact lenses, patching, or atropine is permitted. At the time of enrollment the patient must be: <ul style="list-style-type: none"> • currently patching for 2 hours per day, <i>or</i> • ready to be switched to 2 hours per day of patching from another patching dose or from atropine, <i>or</i> • not currently on treatment (other than spectacles or contact lenses) and ready to initiate patching for 2 hours per day.
9. No known skin reactions to patch or bandage adhesives.
10. Cycloplegic refraction within 6 months prior to enrollment.
11. Ocular exam within 6 months prior to enrollment revealing no ocular cause for reduced visual acuity.
12. No developmental disability, mental retardation, or learning disability diagnosis that in the investigator's judgment would interfere with treatment.
13. Children with attention deficit hyperactivity disorder (ADHD) may be enrolled if the investigator feels that the patient could still properly perform the therapy activities.
14. No myopia more than -6.00 D spherical equivalent in the amblyopic eye.
15. No prior intraocular or refractive surgery.
16. Parent does not anticipate relocation outside area of active study site within the next 5 months.
17. Patient and parent are willing to accept randomization and be available for 17 consecutive weeks of office visits and follow up.
18. Siblings of patients already enrolled in this study, and children of ophthalmologists, optometrists, orthoptists, and vision therapists are excluded.
19. Subject must have access to a computer on a daily basis.

^{*} Subjects with strabismus or combined-mechanism etiology for amblyopia cannot have constant strabismus at near at the time of the eligibility examination.

^{**} Electronic Early Treatment Diabetic Retinopathy Study protocol.