The articles that follow are part of an ongoing series that aims to review collaborative prospective studies supported by the National Eye Institute. The first article, written by investigators, will remind readers of the rationale, goals, methods, findings, and recommendations. The second article, written by an expert who did not participate in the investigations, will offer a constructive critique and attempt to estimate the impact of the study on the practice of ophthalmology.

Impact of the Cryotherapy for Retinopathy of Prematurity Randomized Clinical Trial

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The true impact of the Cryotherapy for Retinopathy of Prematurity (ROP) randomized trial, or CRYO-ROP trial as it came to be known, cannot be measured apart from the development of the international classification of ROP (ICROP), which served as the backbone of the trial's organization. The trial served as a necessary and sufficient test of the validity of the classification itself. Both were validated by the exercise.

A brief overview of the background of the ICROP is in order to understand how closely entwined the two were and how both were born in response to the upsurge of ROP following a more liberal policy of oxygen use in the decade of the 1960s and the sporadic reports of the beneficial effects of photocoagulation and cryotherapy (coming from Japan and Israel primarily). The need for a new classification became obvious because studies had shown in previous decades that spontaneous regression of ROP indeed occurred. A better way of describing the eyes that truly needed treatment was required to separate a true response to therapy from the natural history of the disease itself. In answer to the need, some 23 members from 11 countries with an interest in ROP assembled in Calgary, Alberta, Canada, in 1981 to map out a rough sketch of a classification system that they agreed to use for a year without publication. The group then reconvened on the campus of the National Institutes of Health, Bethesda, Maryland, to finalize the document, which was published in 1984.

The direct results of these efforts were the conception, planning, and implementation of the Cryotherapy for ROP randomized clinical trial of cryotherapy against observation (no treatment). A group of ophthalmologists from the United States intimately involved in the development of knowledge of ROP and its classification, among them Earl Palmer, MD, the study's principal investigator, David Schafer, MD, Graham Quinn, MD, Dale Phelps, MD, myself, and others, put together the manual of procedure. In this effort, we were joined by Robert Hardy, PhD, professor of epidemiology and biostatistics at the School of Public Health, University of Texas, Houston, who lent design and biostatistical expertise and served as study coordinating center principal investigator during this and subsequent studies. The study manual of procedure outlined in exquisite detail every step in the selection of eligible infants, examining technique, diagnosis of the disease, threshold for treatment, technique of treatment, and follow-up of the infant's treated eye. Because the disease was most often symmetrical in patients (>80%), one eye served as the treated eye and the other as its control. The threshold for treatment was greater than 5 clock hours of grade 3 ROP in zone 1 or 2 accompanied by plus disease—defined for the study as dilated and tortuous veins and arteries of the posterior pole vessels. Twenty-three centers were enrolled in the study and their principal investigators were trained in the study protocol, applying ICROP to the disease as they examined premature infants of birth weight less than 1251 g and accurately diagnosing ROP and its severity. After careful peer review, the National Eye Institute fully supported the study and subsequent follow-up of the enrolled infants. The study compared treatment with cryotherapy to the avascular retina for threshold ROP vs observation and no treatment for threshold disease in the opposite eye. Subjects were randomized by eye when the level of ROP was equal in both eyes and by patient when one eye was at the threshold but the other was not. Unfavorable outcome was defined as a total retinal detachment or a retinal fold through the macula destroying central vision. The results, both anatomical and later functional, were positive for cryotherapy. The finding of an unfavorable outcome in the treated eye was reduced by 50% (to approximately 25%) over its nontreated control (unfavorable outcome in approximately 46%). Some 291 premature infants were entered in the trial. At that point, the trial was stopped as it became clear that even if all future infants needed to attain sample size had failed cryotherapy, the study results would not be reversed. The infants enrolled in the study have been carefully followed up for 15 years. And although the visual results have not been as striking as had been hoped, they have nevertheless maintained a statistically significant edge over the results in the untreated eye.

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Cryotherapy proved to be far less successful in zone 1 disease than in zone 2 disease, where fortunately greater than 75% of the disease occurs. It is important to note that unfavorable outcomes as stage 5 (total retinal detachment) outnumbered stage 4B (a retinal fold extending through the macula) by a ratio of 13 to 1. The treated unfavorable results were far more common proportionately in zone 1 disease than in zone 2 disease.

The results of this study proved for the first time the availability of a treatment that improved the outlook for vision significantly over the natural history of the disease. The results of the study were quickly adopted both in the United States and worldwide as the standard of care, a tribute to the meticulous planning and execution by the investigators involved in carrying it out. Treatment took a further step forward when the indirect diode laser became available and was shown in a number of observational studies to be as effective as cryotherapy and easier in application for the infant and therapist. The CRYO-ROP trial proved to be the template for studies to follow. It also furnished a cadre of ophthalmologists trained in the design and implementation of randomized trial methods and the application of the methods to other problems in pediatric ophthalmology as they arose. It stands as one of the most successful trials undertaken with support of the National Eye Institute.

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REFERENCES


Evaluating the Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP)

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The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP) remains one of the largest investigations ever organized for a pediatric ophthalmic disease. Spanning more than 20 years so far, and involving hundreds of ophthalmologists, neonatologists, photographers, visual acuity testers, and other investigators in 23 clinical centers across the United States, this gargantuan effort has produced high-quality data about the benefits of treatment of retinopathy of prematurity (ROP) with peripheral retinal ablation as well as the natural history of ROP and the development and measurement of visual function in young children with developmental and visual impairment. In addition, this trial led to innovations in the design and organization of randomized interventional trials that have gained wide acceptance and application in other fields.

What is the best measure of the success of a clinical trial? Formally, trials must be judged first on the ability to achieve the prospective goals of the investigation, generally a question of benefit and safety of the intervention being tested. The quality of the information measured, including its statistical measurement and clinical relevance; the number and quality of publications produced from the data and their subsequent citation; the development of new tools for future clinical research and patient care; and secondary trials founded on the initial results are also important measures of the influence of a clinical investigation. By all these measures, CRYO-ROP has been highly successful, both in achieving its formal goals as well as developing information to support a new understanding of ROP and the development of visual impairment in young children.

Ultimately, however, the most important measure of the impact of a clinical investigation is its influence on the clinical practice of medicine. CRYO-ROP changed tremendously the way we treat ROP from the previously highly variable strategies, including everything from non-intervention to treatment of even mild cases, to the current nearly universal application of peripheral retinal ablation at specific levels of severity based on evidence from this and subsequent randomized trials. Despite the evo-