

PHOTODISC

# Changing Current Practice

## Implementing Large Multicenter Trials for a Rare Condition

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Eye centers throughout the United States can provide reliable diagnosis of choroidal melanoma and high-quality standardized treatment as a result of the extensive standardization, training, and recruitment efforts of the Collaborative Ocular Melanoma Study.

Implementing a randomized clinical trial for a rare or uncommon condition requires substantial changes in current clinical practice. Patient referral patterns may have to be changed, and evaluation and treatment procedures must be standardized across multiple clinical sites. When a new treatment is found to be effective based on a clinical trial, it is more likely to be accepted if it can be delivered in a high-quality manner by other physicians beyond those who participated in the trial. The Collaborative Ocular Melanoma Study (COMS), a set of trials initiated in 1986 to investigate treatments of choroidal melanoma, is a case in which this goal was achieved.

### Background of the study

Choroidal melanoma is an eye cancer with an incidence of only 1600–2000 new cases per year in the United States.<sup>1</sup> Before the 1980s, removal of the eye (enucleation) was the standard management, although a few centers with the requisite technology and expertise offered various eye-preserving treatments.<sup>2–7</sup> These highly individual-

ized treatment methods had not been evaluated in controlled clinical trials.

Some physicians were skeptical that it would be possible to reliably diagnose choroidal melanoma and adopt uniform treatment protocols that would be followed across multiple centers and investigators. Others doubted that a trial could enroll a sufficient number of subjects. However, the question of treatment efficacy relative to enucleation would remain unanswered without a randomized clinical trial. Because size of the tumor has been correlated with prognosis for both survival and vision, investigators proposed two randomized clinical trials, one for subjects with large tumors and one for subjects with medium tumors.

The two COMS randomized trials enrolled two groups of subjects: one group with medium-sized choroidal melanoma, equally randomized between enucleation and I-125 brachytherapy, and another group with large choroidal melanoma, equally randomized between enucleation and pre-enucleation external beam radiation therapy (PERT). In all,

between 1986 and 1998, investigators at 41 COMS clinical centers in the United States and two centers in Canada evaluated more than 8700 patients with choroidal melanoma. Of these, 2320 subjects were randomized, treated, and followed for the primary outcome, survival.

The COMS design and methods have been published previously.<sup>8</sup> Descriptions of subject characteristics<sup>9,10</sup> and initial mortality findings<sup>11,12</sup> also have been published. In this report, we describe the selection of clinical centers, coordinated recruitment procedures, certification of personnel, diagnostic accuracy and standardization of treatment delivery across centers, and the impact of these mechanisms on current practice.

### Selection of clinical centers

Before the COMS, ophthalmologists typically referred patients with an eye lesion to one of a few ocular oncologists for further evaluation and treatment. In 1986, in an attempt to address the unanswered question of treatment efficacy, the National Eye Institute invited ophthalmol-

ogists throughout the United States to submit proposals to organize and direct clinical centers that would participate in the evaluation, treatment, and follow-up of patients in the COMS. The multidisciplinary nature of the COMS interventions required collaboration of two groups of medical specialists within each center: ophthalmologists and radiation oncologists. Important criteria for center selection were:

- The investigator's qualifications in ophthalmology
- The investigator's previous experience with clinical trials
- An existing or possible collaboration with a department of radiation oncology and physics
- A stated commitment to the study
- Demonstrated subject recruitment potential.

Applicants documented availability of required personnel, equipment, and facilities and the number of potentially eligible subjects with choroidal melanoma they

study. The median time from the initial site visit to first enrolled subject was 56 days, with a range from 7 to 162 days.

The initial COMS clinical centers in the United States were located predominantly on the East or West Coasts or in the Midwest. They represented a variety of settings, including university medical centers, large and small teaching hospitals, and private practices. By 1992, additional clinical centers were added in geographic areas not represented well by the earlier COMS centers, for a final total of 41 sites in the United States and two in Canada.<sup>13</sup> The Coordinating Center conducted additional training meetings as these centers were added. In addition to initial site visits, Coordinating Center personnel made site visits to each clinical center every 1–3 years and annually contacted clinical center coordinators between visits.

As another aspect of quality assurance and training, all key personnel in each clinical center were certified for their study roles and responsibilities: clinic

order for the COMS to succeed. During the early years of the study, the primary focus was to encourage referral of patients with newly diagnosed choroidal melanoma to COMS clinical centers. Investigators publicized the COMS at both local and national levels. The COMS Chairman's Office, with assistance from investigators at the Coordinating Center and other resource centers, centrally prepared and managed educational materials for both patients and physicians. These comprised

- A 20-page Guide for Patients with descriptions of the eye and choroidal melanoma, COMS, and patient considerations regarding clinical trials, accompanied by illustrations and a glossary
- An informational videotape regarding the COMS clinical trials for patient viewing before consent
- A standard slide set to facilitate presentations at local and national medical and scientific meetings
- A large informational exhibit for display at local and national meetings
- A glossy brochure that described the COMS design and listed the names and locations of clinical centers, suitable for specialty mailings and distribution at meetings
- Colorful plastic Rolodex cards, one with names and telephone numbers of COMS investigators and another with an 800 telephone number for calls to the COMS Coordinating Center for information on how to refer a patient
- Postcards with a color fundus photograph of the interior of the eye that showed an ocular melanoma, for mailings to referring physicians
- An informational Web site with an email address and provisions for email query and response
- Courses at national ophthalmology meetings that focused on choroidal melanoma and the COMS.

At the local level, principal investigators sent personalized letters to potential referring physicians, and held Saturday morning conferences and continuing medical education courses for local physicians.

At annual meetings of study personnel, the study leadership held recruitment workshops to permit discussion, role-playing, and problem solving. They invited investigators from centers with high accrual rates to discuss their experience

## Study leaders recognized the need to promote new patient referral patterns in order for the COMS to succeed.

had seen annually in recent years at their center or associated institutions. By July 1986, the National Eye Institute had selected medical teams at 27 clinical centers in the United States and one in Canada to participate in the COMS.

### Training and certification

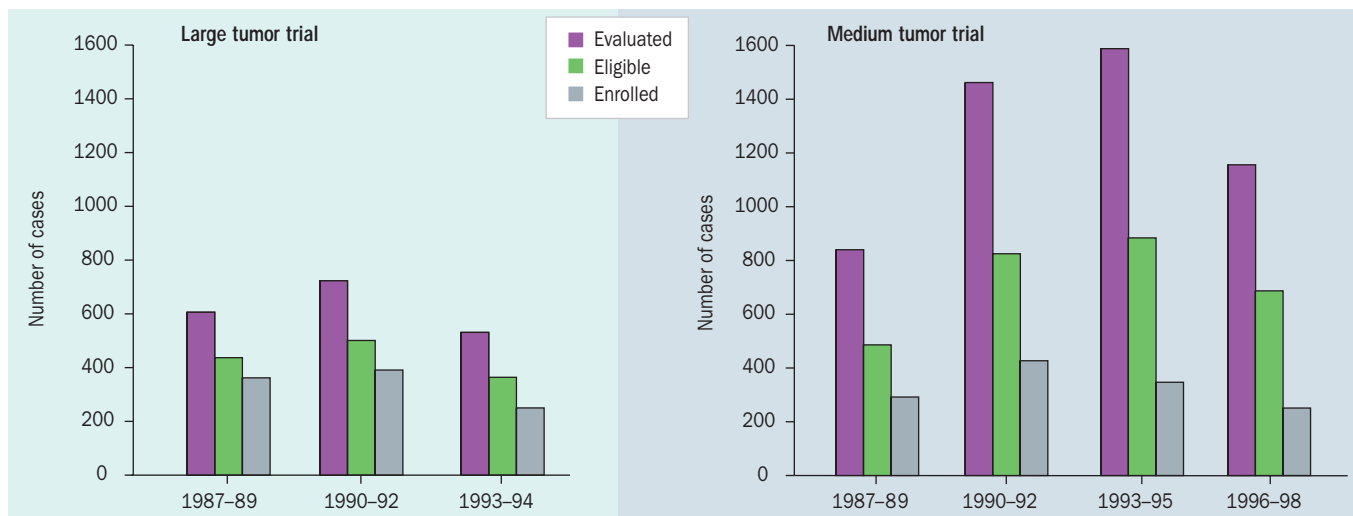
Many of the teams selected did not have extensive experience in treating patients with choroidal melanoma. Before study initiation, the COMS Coordinating Center and the COMS Chairman's Office organized and conducted a central orientation and training meeting to ensure that site personnel understood design and protocol issues and to review standard procedures adopted for the COMS. All COMS personnel from the 28 centers, approximately 350 individuals, attended a three-day orientation and training meeting in July 1986. Subsequently, key Coordinating Center personnel and other study leaders conducted an initial site visit to each clinical center to review the centers' facilities, equipment, and implementation of the

coordinator, ophthalmic echographer, ophthalmic surgeon, following ophthalmologist, pathologist, retinal photographer, radiation oncologist, radiation physicist, and visual acuity examiner. Certified individuals demonstrated understanding of study design, protocol, completion of assigned procedures and related data forms. Time allocation to COMS responsibilities by clinic coordinators was reported in a previous article in this magazine.<sup>14</sup>

In long-term trials, there is considerable turnover of personnel and a heightened need for an ongoing training and certification program to enhance protocol compliance and standardization. During the first nine years of the COMS, 506 of 1265 certified individuals left their positions.<sup>15</sup> By the end of study recruitment, more than 2000 individuals had been certified in the COMS.

### Recruitment procedures

From the outset of the COMS, the study leadership recognized the need to promote new patient referral patterns in



**Figure 1.** Evaluation and enrollment of subjects over time in both trials.

and share advice. Periodically, either by mail or telephone, the study chairman contacted individual investigators to discuss reasons that some eligible patients did not enroll.

### Diagnostic accuracy

Before 1986, the reported misdiagnosis rate for choroidal melanoma ranged from 2.7 to 39.7%.<sup>16</sup> COMS investigators developed a standard evaluation procedure that included multiple diagnostic methods: clinical examination, standardized echography, fundus photography, and fluorescein angiography of the eye and tumor. Echograms were reviewed centrally for consistency with the diagnosis. In addition, a committee of ocular pathologists reviewed the histopathology of all eyes removed in the COMS. Over 99% of 1650 subjects who enrolled and subsequently had their affected eyes removed had a histopathologic diagnosis of choroidal melanoma.

### Standardization of treatment

Most clinical centers selected for the COMS did not have extensive experience in treating choroidal melanoma prior to the COMS. Standardization and training in the treatment protocols were critical. The COMS Manual of Procedures<sup>17</sup> includes the description of the standardized treatment protocols developed for the COMS. A resource center, the Radiological Physics Center, was established in Houston. Personnel from the Radiological Physics Center certified all individuals associated with treatment planning at all COMS clinical centers. In addition,

they visited initially and periodically thereafter to review procedures and equipment. The Radiological Physics Center and the COMS principal radiation oncologist monitored adherence to the treatment protocol and reviewed treatment planning and delivery documents for each subject assigned to radiotherapy.

Compliance with the radiotherapy protocols was high. In the large tumor trial, of 497 subjects assigned to PERT, 491 (99%) were treated as assigned. With respect to duration of treatment, only three (1%) received treatment over a period longer than the eight days prescribed by the COMS protocol. More than 90% of subjects received the total dose of 20 Gy; 93% had a daily dose fraction of 4 Gy. In 459 subjects (93%), the overall compliance was per protocol. In the medium tumor trial, 650 of 657 eyes assigned to I-125 brachytherapy received protocol treatment. An acceptable dose to the prescription point was achieved in 94%. Overall compliance was per protocol in 592 (91%) of subjects treated. Similarly, there was high compliance with the enucleation protocol. The affected eye was removed in the protocol time frame of four weeks from enrollment in 646 (99%) of eyes assigned to enucleation in the medium tumor trial and in 976 (98%) of 1003 eyes in the large tumor trial.

Treatment crossover was an early concern in the COMS. It was anticipated that 1% of patients would have opted for treatments other than their randomized assignments. However, the treatment crossover rate was lower than anticipated for both trials (<1% and 1.6% in the large

and medium tumor trials, respectively).

### Changes in practice

When the COMS began in 1985, the study leaders recognized the challenges associated with its undertaking. However, between 1987 and 1998, investigators at the 43 COMS clinical centers evaluated a large fraction of all newly diagnosed cases of choroidal melanoma. A total of 6906 subjects with medium or large choroidal melanoma were evaluated for one of the COMS randomized trials. Under the assumption that 2000 new cases of choroidal melanoma are seen each year by ophthalmologists in North America, it was estimated that approximately 800 of the tumors would be of medium size and 600 of the tumors would be large. Over 11.5 years of enrollment of subjects with medium tumors, 9600 subjects would be expected: 5046 (53%) were evaluated at a COMS center. Similarly, over the eight years of accrual of subjects with large tumors, 1843 (38%) of the 4800 expected cases were evaluated by COMS ophthalmologists. Thus, almost 50% of all subjects with newly diagnosed choroidal melanoma of eligible sizes were evaluated at COMS clinical centers after recruitment was initiated. Figure 1 depicts patterns in evaluation and enrollment of subjects over time in both trials.

Evaluation and treatment of choroidal melanoma has become routine at COMS centers. For enrolled COMS patients, diagnostic accuracy was excellent<sup>16</sup> and adherence to treatment protocol was high. High-quality delivery of both radiation treatment and enucleation via a stan-



standardized protocol is now routine at these centers. As a result, most patients diagnosed with choroidal melanoma have treatment alternatives available in centers reasonably close to where they live that were not available previously.

Sixteen years later, the efforts of all COMS investigators have culminated in preparation of many manuscripts to summarize and disseminate the data regarding the primary and secondary outcomes of interest in the two randomized trials as well as numerous ancillary studies, including an observational study of time to tumor growth and mortality of subjects with small tumors<sup>18,19</sup> and a concurrent COMS Quality of Life Study.<sup>20</sup> Most important, future patients with suspected choroidal melanoma will have easier access to reliable evaluation and diagnosis and more options for high-quality treatment for this rare condition.

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## COMS controversy

While preparing this manuscript for publication, the editors became aware of a controversy over the design of the COMS. Readers who would like to learn more about it may refer to a letter published in the May 2002 issue of *Archives of Ophthalmology*, which can be found online at [archophth.ama-assn.org/issues/v120n5/full/elt0502-1.html](http://archophth.ama-assn.org/issues/v120n5/full/elt0502-1.html).