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The Complications of Age-Related Macular Degeneration Prevention Trial study group

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# The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology

*The Complications of Age-Related Macular Degeneration Prevention Trial study group*<sup>1</sup>

**Background** The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) is a randomized clinical trial to evaluate whether prophylactic laser treatment to the retina can prevent the complications of the advanced stage of Age-Related Macular Degeneration (AMD), the leading cause of irreversible blindness.

**Methods** CAPT is conducted in 23 clinical centers and in three central resource centers. The primary outcome measure is change in visual acuity; secondary outcomes include the incidence of complications of AMD, changes in other measures of visual functioning and vision-related quality of life. In total, 1052 patients with two high-risk eyes were enrolled. One eye was randomized to receive laser treatment and the other eye to observation. All patients were treated immediately after randomization and again at 12 months, dependent on clinical status. All patients are followed via study visits and telephone calls for a minimum of five years. Study visit procedures include established tests of visual function conducted by examiners masked to the treatment assignment of each eye, a biomicroscopic examination by CAPT ophthalmologists, and photographs of each eye taken according to protocol and assessed by masked graders in a centralized Photograph Reading Center.

**Results** This paper describes the CAPT study, including study rationale, operational structure, and measures implemented to ensure standardization of assessments, adherence to protocol, quality assurance, and maintaining follow-up. Several features related to study design and procedures that are specific to CAPT are highlighted, including clinic selection and judgements regarding patient eligibility.

**Conclusions** An intervention that can reduce the risk of advanced AMD by 30% in the eyes of people with two high-risk eyes may halve the rate of bilateral blindness from AMD. It would also yield substantial savings in expenditures devoted to treating advanced AMD and the disability it causes, and enhance the quality of life for people at risk. *Clinical Trials* 2004; 1: 91–107. [www.SCTjournal.com](http://www.SCTjournal.com)

The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) is a multi-centered randomized clinical trial to evaluate whether prophylactic low-intensity laser treatment to the retina can prevent the complications of the advanced stage of Age-Related Macular Degeneration (AMD), a stage that usually causes severe irreversible vision loss. CAPT is conducted in 23 clinical centers and three resource centers and is funded by the National Eye Institute.

## Background

The macula is the part of the retina that is responsible for central visual functioning. Age-related macular degeneration is the leading cause of irreversible blindness among people over age 50 years in the USA and other western countries [1–6]. Approximately 230 000 Americans are believed to be legally blind due to AMD [1] and approximately 1.7 million people in the USA have

<sup>1</sup>A listing of the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) study group is appended at the end of the manuscript.

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one or both eyes affected by the late stage of AMD [7]. In the USA alone, the direct cost of illness associated with AMD is conservatively estimated at \$10 billion annually [8]. Because the incidence of AMD rises sharply with age, these numbers will multiply as the American population over the age of 65 years increases.

Approximately 90% of people with AMD have the early or intermediate stage of the disease, characterized by clinically visible, yellowish deposits (drusen) under the macula [6]. These stages of AMD are associated with good visual acuity, but problems with night vision, contrast sensitivity (the ability to discern subtle degrees of grayness) and the need for bright light for reading. Eyes progress to advanced AMD with the development of choroidal neovascularization (CNV), serous detachment of the pigment epithelium and geographic atrophy involving the center of the retina. Approximately 90% of AMD-related blindness is attributable to CNV [2,9,10]. Serous pigment epithelial detachment (PED) and CNV are also referred to as “wet” or exudative AMD because of abnormal leakage of blood and other fluids.

### Risk factors for developing advanced AMD

Most risk factors for developing advanced AMD cannot be modified. The strongest risk factors are numerous large drusen and the presence of neovascular disease in the contralateral eye [11–13]. Other established risk factors are older age, non-Hispanic white race, family history of the disease, and cigarette smoking. The latter is the only potentially modifiable risk factor. Although daily high doses of oral anti-oxidants and zinc can reduce the risk of developing advanced AMD among high-risk people, the risk of vision loss from AMD remains high [14]. Furthermore, these supplements are associated with some side effects and are contraindicated for some people.

### Current treatments for neovascular AMD

Current treatments for neovascular AMD include thermal laser photocoagulation [15–18] and ocular photodynamic therapy with verteporfin (Visudyne®) [19–21]. Although treated patients experience less visual acuity loss than untreated patients, the treatments are effective only in selected cases, the benefit is modest, and the need for multiple treatments is high. More importantly, about half of all neovascular lesions are not amenable to either treatment [22].

Since the 1970s, clinicians have reported that laser photocoagulation causes drusen to disappear.

However, studies of the effects of laser treatment on preventing vision loss from advanced AMD have shown inconsistent results and have been based on relatively small numbers. The aim of the CAPT study is to provide a comprehensive evaluation of laser treatment for patients with two eyes at high risk for vision loss from AMD.

### Potential impact of the CAPT study

People over the age of 65 years, the group most at risk for advanced AMD, represent the fastest growing proportion of the American population. The US Census Bureau projects that by 2020, there will be more than 53 million people aged 65 years or older [23]. Thus, the estimated value of 200 000 cases per year of CNV in either the first or second eye [24] is likely to rise dramatically. A treatment that can prevent the progression of AMD would have tremendous impact on millions of people at risk. According to one estimate, an intervention that reduced the risk of developing CNV by 30% in eyes of people with bilateral large drusen could halve the rate of bilateral blindness from AMD [25]. Identification of an intervention that is as noninvasive, painless, and free of systemic adverse effects as the CAPT laser treatment, would have a major public health benefit and would yield substantial savings in expenditures devoted to treating advanced AMD and addressing the disability caused by this disease.

### Impact of the pilot study for CAPT

The conduct of a pilot study, the Choroidal Neovascularization Prevention Trial (CNVPT), had a major impact on the ultimate design of CAPT. The CNVPT was initiated to establish the effects of laser photocoagulation in reducing drusen and to confirm the short-term safety of laser treatment. The CNVPT was designed with the structure intended to be used in CAPT. The CNVPT consisted of two separate clinical trials operating under a common protocol with regard to treatment and evaluation of outcomes [26]. The Bilateral Drusen Study was designed for patients with large drusen in both eyes and no advanced AMD in either eye. In total, 156 bilateral drusen patients had one eye randomly assigned to receive unmasked laser treatment and the other eye assigned to usual care (observation). The Fellow Eye Study was designed for patients with neovascular AMD in one eye and a second eye with large drusen and no neovascular AMD. In this study, 120 patients were randomized to receive either treatment or observation in the eye with only drusen (the fellow eye).

The CNVPT provided the basis for several important decisions about the design of CAPT:

- Among Fellow Eye Study patients, there was a higher rate of CNV development in treated eyes compared to observed eyes by one year; however, there was no difference between treatment groups in visual acuity. Concern that laser treatment to fellow eyes would be harmful to patients in the long term caused the Fellow Eye Study for CAPT to be dropped.
- Among Bilateral Drusen Study patients, the risk of developing CNV was relatively low and similar between treatment groups. Plans for a Bilateral Drusen Study in CAPT were retained.
- Laser treatment reduced the area and number of drusen in the majority of eyes, both in areas of direct treatment and areas remote from the treatment [27]. The remote effect of the laser burns was a key consideration in the specification of the placement of burns in the CAPT laser treatment protocol.
- The incidence of CNV in treated eyes was greater for eyes with more intense laser burns [28]. The specification of burn intensity in the CAPT laser treatment protocol was reduced below the level specified in the CNVPT.
- Drusen reduction was associated with small improvements in visual acuity. Although not all eyes had reduction in drusen, this beneficial effect of treatment on visual acuity contributed to the rationale for proceeding with evaluation of laser treatment in CAPT even though the results of the Fellow Eye Study raised concerns about the long-term safety of treatment [27].
- There were no immediate complications among the 215 eyes assigned to laser treatment. This fact

was used in planning the follow-up schedule for CAPT. Clinical investigators were comfortable with the plan to not require an examination until three months after treatment.

These findings, in concert with reports of treatment benefit from other small pilot clinical trials [29–32] provided the basis for the CAPT study.

## Study design

### Overview

Enrollment opened on May 1 1999 and closed on March 31 2001. A total of 1052 participants age 50 years and older with at least 10 large ( $\geq 125$  microns in diameter) drusen in each eye and no evidence of CNV or serous PED on fluorescein angiography were enrolled. (Fluorescein angiography is essential in determining whether neovascular AMD is present.) One eye was randomly assigned to laser treatment and the other eye to observation. At 12 months, treated eyes that still had many drusen were given additional laser treatment. Follow-up will continue until the last patient enrolled has been followed for five years. By this time, approximately half of the patients will have been followed for six years.

### Study aims (Table 1)

The primary outcome measure of CAPT is change in visual acuity. Secondary outcomes include the incidence of complications of AMD, changes in other measures of visual functioning and vision-related quality of life. As each participant has one

**Table 1** CAPT design summary

Feature	CAPT criteria
Objective	Evaluate low intensity laser treatment in preventing vision loss from AMD
Major eligibility criteria	$\geq 10$ large drusen in each eye Visual acuity $\geq 20/40$ in each eye
Randomization unit	Eye within person
Treatments	Laser treatment <ul style="list-style-type: none"> <li>• Initial: 60 barely visible burns, grid pattern</li> <li>• Re-treatment at 12 months: 30 barely visible burns, focal treatment</li> <li>• Dependent on resolution of drusen</li> </ul>
Outcome measures	Observation
Primary	Change in visual acuity
Secondary	Incidence of CNV, PED, GA* Contrast threshold Reading (critical print size) Quality of life (NEI-VFQ-25)
Descriptive measures	
Sample size	1000 people (2000 eyes)
Length of follow-up	Five to six years

\*CNV = choroidal neovascularization; PED = pigment epithelial detachment; GA = geographic atrophy.

eye assigned to treatment and one eye assigned to observation, no direct data on the impact of treatment on quality of life can be obtained from CAPT. However, changes in quality of life measures that are associated with changes in visual functioning will be described.

### Patient eligibility

All eligible patients must have been at least 50 years of age, available for five years of follow-up, and signed a patient consent form approved by the CAPT Coordinating Center and local Institutional Review Board (Table 2). Both eyes had to meet all ocular eligibility criteria.

Prior to enrollment, all candidates had an ophthalmological examination and underwent visual function testing. Eligibility of eyes was initially assessed by the CAPT certified ophthalmologist at each clinical center based on the clinical examination and review of a fluorescein angiogram of each eye taken according to the CAPT protocol.

CAPT was designed to allow ophthalmologists to make initial eligibility assessments rather than confirming eligibility through review of photographs by the CAPT Reading Center before enrollment. Investigators were interested in the effects of laser treatment as it would likely be applied

clinically if it were shown beneficial. Departures from ocular eligibility criteria by selected retinal specialists were expected to be minor. However, to monitor the frequency and magnitude of such departures, the Reading Center assessed, after enrollment and without knowledge of which eye was assigned to treatment, compliance with the ocular eligibility criteria as judged from photographs. Upon request, the CAPT Reading Center provided a prerandomization review of patient eligibility in borderline cases in which the clinical center was uncertain about patient eligibility.

Among the 1052 patients, 182 (17%) were later determined by the Reading Center to be ineligible. Ninety-three of the ineligible patients had minor departures from the eligibility criteria, meaning they had fewer than the requisite 10 large drusen, but the area of drusen was equivalent to the area of 10 large drusen. Another 89 patients were "unequivocally ineligible" because they had too few drusen or had another disease that rendered them ineligible, or both. The primary analysis to evaluate the effect of treatment will include all enrolled patients, regardless of departure from eligibility criteria. However, the impact of the departures on the direction and magnitude of treatment benefit will be examined to determine if strong cautionary notes about treating only patients who meet the eligibility criteria exactly are warranted.

**Table 2** CAPT patient eligibility criteria

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Patient inclusion criteria

- Age  $\geq 50$  years
- Signed informed consent form
- Available for 5 years of follow-up

Eligibility criteria for each eye

- 10+ large drusen ( $>125$  microns) within 3000 microns of the foveal center
  - Visual acuity of 20/40 or better (ETDRS equivalent)
  - No evidence of exudative AMD
  - No serous PED of any size
  - No geographic atrophy within 500 microns of the foveal center
  - Total area of geographic atrophy within 3000 microns of the foveal center must be  $\leq 1$  MPS Disc Area
  - No macular edema or signs of diabetic retinopathy more severe than 10 red dots (microaneurysms or blot hemorrhages)
  - No retinal changes related to high myopia and no myopic correction greater than 8.00 diopters spherical equivalent (sphere +  $\frac{1}{2}$  cylinder)
  - No progressive ocular disease likely to affect visual acuity within the next 5 years
  - No lens extraction or implantation within the last 3 months
  - No capsulotomy within the last 3 days
  - No vitrectomy within the last 12 months
  - No LASIK surgery within the last 12 months or if the presurgical refractive error was  $<8$  diopters of myopia or there are pathologic retinal changes related to high myopia
  - No nevus  $>2$  disc areas within 3000 microns of the foveal center or with fluid or leakage on fluorescein angiography
  - Disc and macula color photographs and fluorescein angiogram within 28 days of randomization
  - No lens or other media opacity that would preclude good fundus photography or angiography within the next 5 years
  - No current use or history of using macular affecting drugs
-

## Description of the intervention

All patients were treated immediately after randomization and, if there had not been sufficient resolution of drusen, again at 12 months.

### Initial treatment

Initial treatment consisted of 60 barely visible burns in a grid pattern within an annulus between 1500 and 2500 microns from the center of the macula

(the fovea). Fifteen burns were applied per quadrant (Figure 1).

### Treatment at 12 months

Additional treatment was performed at 12 months if 10 or more drusen  $\geq 125$  micron diameter (or an equivalent area) remained in the treated eye within 1500 microns of the foveal center. During re-treatment, 30 burns were administered in the 1000–2000 microns annulus centered on the fovea, and drusen were treated directly. If all drusen

#### Initial treatment session

- **Number:** 60
- **Wavelength:** Green
- **Intensity:** Light intensity, 0.1 sec duration (barely visible, not white lesion)
- **Spot size:** 100 micron spot size
- **Configuration of burns** – grid; 15 burns per quadrant; avoiding retinal blood vessels
- **Location** - Burns should be placed:
  - 360 degrees, **around the foveal center**
  - No closer than 1500 microns from foveal center
  - No farther than 2500 microns from foveal center

**Treatment at 12 months** if  $\geq 10$  CAPT drusen ( $>125$  microns) or an area of drusen ( $>63$  microns) equivalent to the area of 10 CAPT drusen within 1500 microns of the foveal center.

- **Number:** 30
- **Wavelength:** Green
- **Intensity:** Light intensity, 0.1 sec duration (barely visible, not white lesion)
- **Spot size:** 100 micron spot size
- **Configuration of burns** – direct treatment of up to 30 remaining drusen; remainder of 30 burns after drusen treated are to be evenly spaced through the annulus of treatment, avoiding retinal blood vessels and areas of previous treatment (a frame from the 12 month angiogram is used to identify burns from the initial treatment)
- **Location** - Burns should be placed:
  - No closer than 1000 microns from foveal center
  - No farther than 2000 microns from foveal center

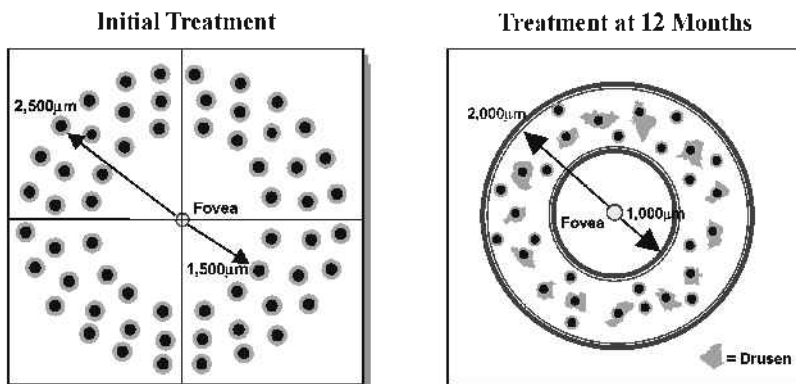


Figure 1 Summary of CAPT laser treatment.

within the annulus could be treated with less than 30 burns, the remainder of the burns was applied evenly within the treatment annulus, avoiding retinal vessels and any previous burns. Additional treatment was not performed if neovascularization or any other complication of AMD had developed in either eye.

The treatment annulus at 12 months was closer to the foveal center than the initial CAPT treatment because of results from the pilot study. In CNVPT, the degree of drusen resolution decreased with distance from the treatment burns. The CNVPT patients were more likely to have a small increase in visual acuity when drusen close to the fovea resolved. However, direct treatment too close to the foveal center may have a deleterious effect on visual acuity or visual field. The initial treatment location was viewed by clinical investigators as generously outside the area where treatment burns could harm vision. If the initial treatment did not cause sufficient resolution of drusen, it was thought that placing burns 500 microns closer might stimulate resolution of foveal drusen.

Retreatment eligibility decisions were made by the ophthalmologist at each clinic during the 12-month visit. If no treatment was performed during this visit and the Reading Center later determined that the patient was eligible for additional treatment, the ophthalmologist was encouraged to recall the patient for treatment within 18 months of randomization.

## Outcome measures

### Primary outcome measure

Visual acuity was chosen as the primary outcome measure to assess the effectiveness of CAPT treatment because this measure incorporates the potential beneficial effects of treatment, and addresses the major disability resulting from all forms of advanced AMD. Specifically, the proportion of eyes with a loss of three or more lines (on a standardized eye chart) of visual acuity at five years is used as the primary comparison of treated and untreated eyes. A binary classification of change in visual acuity was chosen for several reasons. Patients with only drusen typically have little change in vision over time; however, development of advanced AMD is usually associated with large losses in vision. Thus, the distribution of change in visual acuity is expected to be highly skewed or possibly bimodal, making use of the mean or median number of lines changed undesirable. In addition, a change of three lines substantially exceeds the test–retest variability in AMD patients [33]. Finally, a change of three lines corresponds to needing to double the size of letters

in order to be able to identify them; such a change is believed to be clinically significant.

Best corrected visual acuity and the other measures of visual function are assessed by CAPT-certified Visual Function Examiners who are masked to the treatment assignment of each eye. For all tests of visual function, each eye is tested separately while the untested eye is occluded. Prior to testing, a standardized CAPT refraction is performed. CAPT protocol follows the procedures developed for the Early Treatment Diabetic Retinopathy Study [34] as adapted for the Age-Related Eye Disease Study [35]. Distance for CAPT testing is 3.2 m (10.5 ft), moving to 1 m if the patient is unable to read 16 letters on the charts. The range of visual acuity that can be measured is 20/12 to 20/800. This information and the data from all other vision testing are recorded on CAPT data collection forms.

### Eye-specific secondary outcome measures

#### *The incidence of complications of AMD*

- The incidence of the complications of AMD (CNV, geographic atrophy, and serous pigment epithelial detachment) provides a direct measure of the effectiveness of the laser treatment in preventing the late complications of AMD, independent of visual function.
- The diagnoses of CNV and serous PED are based on color stereo fundus photographs and confirmed with fluorescein angiography. Color photographs confirm the development of geographic atrophy. CAPT-certified photographers take all photographs and angiograms, all of which are sent to the CAPT Reading Center for evaluation.

#### *Contrast threshold*

- Contrast threshold can be “independent” of visual acuity among patients with AMD because it does not necessarily change in the same direction as visual acuity [18]. In addition, contrast sensitivity is of interest because it is an independent predictor of the ability of AMD patients to perform several tasks of daily living [36,37]. Contrast thresholds may worsen because of damage by the laser or may improve as drusen resorb.
- CAPT uses the Pelli and Robson chart [38] to assess contrast sensitivity annually. The chart consists of equally sized letters in groups of three that range from high contrast to low. The contrast of triplets of letters decreases logarithmically. Results of the test are scored as the total number of letters read.

*Critical print size for reading*

- Critical print size for reading will be compared between the treated and untreated eyes to expose functional changes that are not detected by the less “real world” tests of visual acuity and contrast threshold. The critical print size is determined as the print size at which the patient’s reading speed decreases.
- The MN Read charts [39] are used to determine critical print size. The charts are printed with 19 sentences of decreasing print size. The reading test is administered at the initial visit and repeated at the 36-month and 60-month follow-up visits.

**Patient-specific secondary outcome measure***Vision-related quality of life*

Vision-related quality of life (QOL) is assessed using the NEI-VFQ-25, an instrument developed under sponsorship by the National Eye Institute for use in populations with visual impairment [40]. The instrument has been extensively field tested in populations that included patients with AMD.

At the initial visit, the NEI-VFQ was self-administered by all participants. Because only 6% of participants are expected to have bilateral advanced AMD by the end of the study, we anticipate that at month 60, when QOL is reassessed, the vast majority of participants will be able to again self-administer the instrument during their final clinic visit. Participants who are unable to do so will

be asked to complete it by having a trained telephone interviewer call them at home.

**Randomization**

Randomized treatment assignment schedules were generated for each clinical center using a permuted block method with randomly chosen block size. The clinic co-ordinator faxed a completed eligibility checklist to the Co-ordinating Center. Immediately before CAPT treatment, the Clinic Co-ordinator and enrolling Ophthalmologist telephoned the Co-ordinating Center to review the eligibility checklist and to obtain the next sequential treatment assignment for that clinic. Both the ophthalmologist and the coordinator verbally confirmed the eye assigned treatment. Only one of 1052 patients refused treatment after the randomized assignment and there were no instances when the wrong eye was treated.

**Patient visits, examinations and management**

CAPT protocol requires study visits and telephone contacts for a minimum of five years after enrollment and treatment (Table 3 lists the visit schedule and required procedures). A description of these visits follows.

**Initial visit**

During the initial visit, all candidates were evaluated for eligibility and eligible and consenting

**Table 3** CAPT follow-up and procedures schedule

	Follow-up month														
	IV	3	6	12	15 <sup>a</sup>	18	24	30	36	42	48	54	60	66	72
History	X	X	X	X	X	T	X	T	X	T	X	T	X	T	X
Refraction	X		X	X			X		X		X		X		X
Visual acuity	X	X <sup>b</sup>	X	X	X <sup>b</sup>		X		X		X		X		X
Contrast	X		X	X			X		X		X		X		X
Reading	X								X				X		
QOL assessment	X												X		
Ophthalmologic exam	X	X	X	X	X		X		X		X		X		X
Color stereo photography															
Disc	X														
Macula	X		X	X			X		X		X		X		X
Fluorescein angiography	X			X			X		X		X		X		X
Laser treatment	X			X <sup>a</sup>											

IV, denotes “initial visit”.

X, denotes a procedure in a CAPT clinic.

T, denotes a telephone call.

<sup>a</sup>Required only if 10 or more drusen remain at FV12.

<sup>b</sup>Visual acuity measurements at safety check visits do not need to have protocol refraction.



patients were given a randomized treatment assignment as noted above. CAPT treatment was performed immediately. A color photograph of the treated eye was also taken within 48 hours after treatment, usually immediately after treatment. Post-treatment photographs were reviewed by Reading Center graders to assess compliance with the CAPT treatment protocol in regard to laser burn intensity and location in the retina.

### Follow-up visit

Visits consisting of vision testing, clinical examination, and photography are scheduled for six months and then annually through 60 months for patients enrolled after 31 March 2000 and through 72 months for patients enrolled earlier. Safety check visits are scheduled three months after each CAPT treatment to assess whether laser treatment has induced any adverse effects. Ophthalmologists may see CAPT patients more frequently than the study mandates if they believe additional visits are clinically indicated.

### Telephone calls

Telephone calls are made by the clinic co-ordinator midway between annual visits to maintain contact with the patient and to elicit information on any change in vision that the patient might be experiencing since the last examination. If any are reported, patients are encouraged to have an examination at the CAPT clinic.

### Procedures when patients develop advanced AMD

CAPT policy specifies that CAPT patients who develop CNV or any other ocular condition be counseled with respect to available treatment options as any other patient would be. In addition to ethical considerations, treating patients for advanced AMD provides a more realistic estimate of the incremental benefit, or harm, of prophylactic treatment. The type of treatment is recorded and all patients continue follow-up for both eyes, whether they receive treatment or not.

Neovascularization discovered by the CAPT ophthalmologist is documented on special forms, color photographs, and a fluorescein angiogram, whether the neovascularization is detected at a regularly scheduled visit or a nonscheduled visit. If the Reading Center detects CNV that the CAPT ophthalmologist has not detected, the Reading Center notifies the clinical center, instructing the ophthalmologist to review the patient's photographic materials and to respond to the

Reading Center with respect to the ophthalmologist's interpretation regarding presence of CNV. If the ophthalmologist agrees that CNV is present, the patient is asked to return to the clinical center to discuss treatment options. If the ophthalmologist disagrees that CNV is present, the disagreement is noted. Reading Center judgements regarding development of CNV prevail for data analysis purposes.

### Clinical center/Reading Center agreement on the need for treatment at 12 months

The CAPT ophthalmologist determined whether the patient was eligible for additional CAPT treatment. The Reading Center subsequently made an independent determination. When clinical centers did not treat patients the Reading Center judged appropriate for treatment, the Reading Center alerted the clinic staff and encouraged them to have the patient return for treatment. The clinical centers and Reading Center agreed for 846 patients (84%). Among the 166 patients for whom different determinations about treatment eligibility were made, there were 133 patients judged eligible for treatment by the Reading Center but who were not treated. The Reading Center alerted the clinic staff and encouraged them to have the patient return for treatment. These letters have proven very effective, as the 107 letters sent to the clinical centers have resulted in 92 additional CAPT treatments (86%). There were 33 patients who received additional treatment at 12 months who either had too few drusen to qualify for treatment or had developed CNV or other conditions that would disqualify them for treatment.

### Masking

To control bias, Visual Function Examiners are masked to the treatment status of each eye. At each follow-up visit, both the clinic co-ordinator and the examiner remind the patient not to reveal which eye was treated. If, despite these efforts the examiner is unmasked to treatment, it is noted on the data collection form. Staff of the Reading Center are similarly masked to treatment when evaluating baseline photographs. However, despite the light burn intensity mandated by the CAPT treatment protocol, treatment burns are typically visible on angiograms and color photographs taken during follow-up visits.

### Reports from other trials

About six months after the close of CAPT enrollment, the Age-Related Eye Disease Study group

reported that high-dose supplementation of anti-oxidants and zinc reduced the risk of AMD progression and visual acuity loss among patients with the most high-risk eyes [14]. A letter signed by the CAPT study Chairman and the local clinical center principal investigator was sent to all CAPT participants alerting them to these results. At all annual visits, CAPT patients are asked about their daily use of anti-oxidants, zinc and lutein (another supplement with as yet unproven benefits for macular health). If patients do not bring their supplement bottles with them to the visit, the clinic co-ordinator telephones them later at home and asks them to read the dosages listed on the bottle. These data will be included in secondary analyses of data.

### Definition of adverse events

Unexpected negative outcomes that may be associated with the laser treatment are classified as adverse events. Development of conditions that are expected in the natural course of patients with age-related macular degeneration (such as CNV and GA) is not considered an adverse event.

CAPT adverse events were classified as occurring at the time of treatment or during follow-up. Adverse events occurring during treatment were defined as:

1. Treatment applied too close to the center of the fovea.
2. Hemorrhage reported at the time of treatment by the treating ophthalmologist or observed by Reading Center graders on post-treatment color photographs.
3. A break in Bruch's membrane (a thin layer of tissue between the choroid and the retina) at the time of treatment as evidenced by blood or pigment and reported by the treating ophthalmologist.

No adverse events occurred during treatment. A CAPT adverse event during follow-up is defined as a loss of six or more lines (30 letters) of visual acuity from baseline on the ETDRS chart without the development of CNV, serous PED, GA, or cataract.

### Study organization

The organizational structure of CAPT follows the National Institutes of Health (NIH) guidelines and includes an Operations Committee, an Executive Committee, and a Data and Safety Monitoring Committee. The Executive Committee, which meets twice annually, provides the major scientific leadership of CAPT, including granting approval for ancillary studies, abstracts, presentations, and

papers; approving changes in the CAPT protocol; and providing general study advice.

The Data and Safety Monitoring Committee (DSMC) meets twice each year. A Medical Monitor chosen from among the Committee members reviews updated reports of possible adverse events on a monthly basis. The Investigative Group, which is comprised of all CAPT-certified staff from all clinical centers, the three resource centers, and the representative from the National Eye Institute, meets annually to review the progress of the study and to solve problems that have arisen in carrying out the protocol.

### Selection of clinical centers

The process for selecting CAPT clinical centers differed from the process used for many NIH-funded trials. The Study Chair's grant application documented that a large number of investigators were interested in participation in CAPT; however, applications for individual clinical centers were not submitted concurrently. Upon approval of funding in June 1998, the NEI charged the Study Chair and Co-ordinating Center with overseeing the solicitation and selection of 20–25 clinical centers. The intention was to accelerate the process relative to announcing a request for proposals and reviewing applications on the standard grant cycle.

On 23 July 1998, the Co-ordinating Center sent to the 1200 members of three professional organizations for retinal specialists a letter outlining the trial design and a request for letters of interest. In mid-August, the Co-ordinating Center distributed to the 175 investigators who expressed interest, a more detailed description of the trial, including proposed funding levels, and detailed instructions on preparing an application. The criteria for selection and the weight of each criterion also were provided: recruitment potential (30%), background and qualifications of the personnel (25%), ability to retain patients for five years (20%), presence of qualified personnel for every study role and of required facilities and equipment (15%), and ability to submit accurate data collection forms in a timely manner (10%). No budgetary information was required. In total, 75 investigators submitted applications by September 30. On October 16 1998, a selection committee composed of the Study Chair, Director of the Coordinating Center, two senior clinical research investigators external to CAPT, and an NEI representative met to select the top 25 clinical centers. Each application was scored by two members of the committee and the full committee discussed the 48 centers that were in the top half on at least one reviewer's list. Applications were ranked and the investigators of the top 25 were invited to

provide budget proposals by November 30 1998. The NEI approved 24 of the applications for funding on December 17 1998. Thus, the process for soliciting applications took three months and the period between submission of applications to notification of award funding was 2.5 months.

## Quality assurance

Quality assurance within CAPT is implemented through a variety of standardization, training and quality control procedures.

### Standardization of procedures and assessments

The CAPT study incorporates several measures to ensure standardization of assessments. These include the use of a common protocol for eligibility, examination, treatment, and follow-up of all patients in all clinical centers, central treatment allocation, standardized data collection forms, central processing of data, and central grading of photographs and fluorescein angiograms for eligibility, adherence to treatment protocol, and follow-up status.

Standardization of CAPT photograph interpretation is essential for an accurate assessment of study eye follow-up status. The CAPT Reading Center's Quality Assurance System involves the regrading of a predetermined set of photographs of 25 patients to test for reliability of the grading scheme, the reproducibility of each reader, and to monitor for reader "drift" in interpretation. Three times annually, each reader reviews this set of photographs without access to previous gradings.

The Quality Assurance System has yielded excellent reliability for most aspects of the grading scheme and reproducibility of the graders. Less than reliable results for one aspect of the grading scheme led to an alternative method of grading. For another less reliable aspect of the grading with no alternative grading method, interpretation of the data will be performed with caution. If a grader is not reproducible or drift is detected, retraining will be initiated until the grader demonstrates consistency. If the drift continues, regrading would be considered. The results of the regradings are reviewed by the Data and Safety Monitoring Committee.

### CAPT staff training and certification program

The Co-ordinating Center and Reading Center developed certification programmes for each CAPT role. In addition to exhibiting knowledge in

CAPT design and rationale via a written assessment, each individual demonstrated proficiency in performing specific CAPT protocols as appropriate.

All CAPT visual function examiners are recertified semi-annually, a process that includes a fellow CAPT examiner or the clinic co-ordinator observing the examiner perform the protocol or examiners replicating the examination on a single patient. In addition, the protocol monitor observes all examiners during site visits. The performance of CAPT photographers is monitored by the Reading Center, which grades the quality of CAPT photographs. Photographers who do not submit CAPT photographs at least once in 12 months must submit photographs for recertification.

### Site visits and telephone calls

All CAPT centers were visited within a few months of the initiation of patient recruitment and are revisited biennially. Visits can occur with greater frequency if warranted by performance concerns or if requested by the center. A written summary of the visit is prepared by the monitor and sent to the clinic co-ordinator, principal investigator, and members of the Clinic Monitoring Committee. A telephone call between the protocol monitor and clinic co-ordinator occurs quarterly to ensure that progress is being made in any problem areas of performance (if any), and to address any other study issues.

### Clinic performance reports

The Clinic Monitoring Committee meets quarterly and individualized clinic performance reports are developed and distributed to the principal investigator and clinic co-ordinator at each center. Tables that allow each center to compare their performance with their colleagues at other centers accompany each individualized report.

### Data quality assurance

Every month, the Co-ordinating Center sends to clinic co-ordinators a list of expected study visits within the coming month. This aid serves as a reminder for coordinators to ensure that their patient visits are scheduled within the visit windows, and to remind patients of approaching scheduled appointments. Included in these lists are special instructions to assist clinic staff. For example, if the Reading Center previously determined that an eye was not eligible for additional treatment, this information was noted on the list

that reminded the co-ordinator of that patient's expected 12-month visit.

Data from the original data collection forms are entered into the CAPT database using Microsoft ACCESS. Each month a 5% random sample of forms is selected for quality assurance checking. During this process, a two-person team of Co-ordinating Center staff checks all entered data against the original data collection forms after data editing has been completed. If this procedure were to identify an unacceptably high residual error rate (more than 15 errors per 10 000 keystrokes), CAPT policy requires that all aspects of data management will be reviewed.

Extensive editing of the data for completeness and consistency results in the generation of edit queries that are sent to the clinical centers weekly. All edit queries are tracked to ensure that all outstanding issues are resolved.

The CAPT Reading Center also checks a 5% random sample of forms each month to compare data on the Reading Center forms with the data entered into the Reading Center database. To ensure the quality of Reading Center gradings of CAPT photographs, two photographic readers independently grade the photographs, with discrepancies openly adjudicated. Only the adjudicated findings are recorded and data entered.

The quality of the data entry has been high. Since CAPT's inception through June 2003, there was an average of 1.5 keystroke errors per 10 000 keystrokes, and 0.75 errors per 1000 data fields. The Reading Center data entry has also been excellent; there is an average of 5.3 keystroke errors per 10 000 keystrokes, and 1.1 errors per 1000 data fields.

## Sample size considerations and analysis issues

### Sample size

The required sample size was calculated to compare the proportion of treated and observed eyes with a loss of visual acuity of three or more lines at five years after enrollment into CAPT. The proportion of eyes with visual acuity loss at five years in the observed group was assumed to be 15%. This estimate was based on the assumption that the majority of visual acuity loss would be secondary to the development of CNV. Data from the Macular Photocoagulation Study showed that unless CNV developed, there was no large loss of visual acuity in the second eye of patients enrolled in the clinical trial because of CNV in first eye [41]. Additionally, it was assumed that 75% of the eyes with CNV would have a loss of three or more lines by five years after the enrollment, again based on the data from the

Macular Photocoagulation Study. An annual rate of 4% was consistent with the rate of CNV development in a previous study of patients with bilateral large drusen [13] and with an appropriately weighted average of the observed rates of CNV in the Age-Related Eye Disease Study (from communication with Anne Linblad, PhD, at the AREDS Coordinating Center). The correlation between the eyes of a patient for development of CNV was derived from a model assuming independent development of CNV in treated and observed eyes until development of CNV in one eye of a patient, after which the increased rate of CNV for fellow eyes was applied to the contralateral eye. The minimal treatment effect of interest was defined as a 30% relative reduction, or a five-year incidence of loss of visual acuity of 10.5%. Finally, assuming loss of 16% of patients because of death and loss to follow-up, a two-sided Type 1 error level of 0.05, and 90% statistical power yielded a required sample size of 1000 patients, or 2000 eyes [42].

### Data analysis

Data analyses are conducted using standard statistical techniques for comparing two paired groups (McNemar test for equality of proportions, paired *t*-test, Wilcoxon signed rank test), multiple logistic and linear regression with correlated data [43–45] and proportional hazards modeling with correlated data [46–48].

Data analysis for the primary outcome will be a comparison of the observed proportions with a loss of three or more lines of visual acuity at the five-year visit using the McNemar test for correlated proportions. Although visual acuity data from all visits will be examined for the purposes of data monitoring, the main question to be answered by CAPT concerns the long-term effect of this candidate prophylactic treatment. Data from the first four years of follow-up will provide information on the lag time between treatment and any beneficial effect. Cumulative incidence of a three-line loss in visual acuity can be misleading in that some eyes have true, small fluctuations that may cause measurement of a three-line loss at one visit but not the next. In addition, measurement error may cause a one-time loss of three lines. With multiple visits, the five-year estimated cumulative incidence rate would overestimate the true proportion of eyes with a three-line loss in visual acuity. Due to the considerable quality monitoring in CAPT, dropout rates were expected to be low. With a median of three years of follow-up, the missed visit rate, exclusive of those attributable to patient death, was less than 2%. Should missing data be more of a source of possible bias in the comparison of

proportions at five years, multiple imputation methods and other approaches to assessing the impact of missing data will be used [49].

Although the CAPT Data and Safety Monitoring Committee recognizes that the primary questions concern long-term effects of treatment, they have specified guidelines following the O'Brien and Fleming approach [50], as expanded by Lan and DeMets [51,52], as a basis for discussion of early release of the data because of treatment efficacy. For this purpose, longitudinal data analysis techniques, specifically the general estimating approach to repeated measurement over time, will be employed [44,53].

The cumulative incidence of advanced AMD (CNV, serous PED, and GA) will be analysed with survival analyses methods for correlated data. The proportion with only CNV will also be analysed separately as it is expected to be responsible for the great majority of loss of vision.

Change in contrast threshold and in critical print size are examined as continuous variables using the mean as the main summary measure, unless inspection of the distribution of data shows highly non-normal data. If so, nonparametric and categorical summary measures and analyses are used. The absolute and change in overall NEI-VFQ-25 scores will be analysed using continuous data techniques, and longitudinal data analysis techniques will be used to describe the pattern of scores over time.

## Discussion

Many of the methodologic features of CAPT are common to most multicenter clinical trials sponsored by the National Institutes of Health. Some of the features of special interest in CAPT are:

- The CNVPT pilot trial provided valuable information on patient selection, safety, and effects of treatment on drusen resolution. Many aspects of CAPT were strongly influenced by the experience in the CNVPT. This large pilot study, however, was supported, for the most part, by the individual participating centers led by investigators who were very interested in the research question. Such pilot studies are not generally feasible.
- The decision for individual CAPT ophthalmologists to determine the eligibility of patients without confirmation by the Photograph Reading Center before randomization resulted in 9% of patients with minor departures from the ophthalmic eligibility criteria and more serious departures in an additional 8%. CAPT ophthalmologists are retinal specialists who received

instruction on eligibility criteria as part of their certification and received feedback whenever a patient did not meet the criteria. While these departures may erode the statistical power of the study, the overall results will be more representative of the true impact of treatment in practice than results from a trial with confirmation of eligibility by a central reading center before enrollment.

- The approach to selection of clinical centers used in CAPT was efficient and swift compared to alternative approaches. Submission of a large number (approximately 75) of full applications for clinical centers concurrent with the main application for the trial was discouraged by NEI staff because of the effort that would be expended at clinical centers and the review process if the main application required revision and resubmission. However, waiting until the National Advisory Eye Council approved the trial in June 1998 to request applications would have delayed awarding of funding until July 1999 under the standard grant review cycle. The accelerated process allowed an orientation and training meeting to be held in January 1999, at least six months earlier than possible under the standard review cycle. In addition, because detailed budget applications were only required from the 25 clinical center finalists, the process was further streamlined. With the centers selected, patient recruitment was completed two months early and the missed visit rate during a median of three years of follow-up has been 2%. This provides evidence that this method can provide selection of centers capable of a high level of performance.

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