Chapter 10

DESCRIPTION OF INTERVENTION

10.1 INTRODUCTION

All participants enrolled during the Qualifying Visit will take part in a one-month run-in period of taking placebo tablets. The tablets for the run-in period will be packaged in bottles each containing 56 tablets. The bottles will be labeled as illustrated in Exhibit 10-1.

The design of the AREDS clinical trial of AMD includes a primary study of 3,600 participants with age-related macular changes (AMD Categories 2, 3, and 4) who will be randomized in a 2^2 factorial design, with 25 percent probability to each of four treatments: placebo, zinc, antioxidants, and antioxidants plus zinc. The last three treatments will be provided as high-dose dietary supplements. To study the effect of high-dose antioxidants on the development and progression of cataract, 1,000 additional participants, without evidence of age-related macular changes (AMD Category 1) will be randomized with 50 percent probability into two groups: control and antioxidants. The tablets for the clinical trial will be packaged in bottles each containing 92 tablets. The bottles will be labeled as illustrated in Exhibit 10-2. In the Fall of 1998, an expiration date of 4 years beyond the manufacturing date was added. The AREDS code identifies the bottle number assigned by the Coordinating Center to correspond with a tablet type. A description of the design of the clinical trials of AMD and cataract is provided in Section 3.4. A full description of the intervention and expected toxicities are provided below.

10.2 DESCRIPTION OF INTERVENTION

AREDS investigators will be studying the effects of high doses of the mineral zinc and of the vitamins C, E, and beta-carotene which is converted into vitamin A in the body. The study medications are not Kosher. Each tablet contains some lactose as indicated in the formulation description below, but contain no other sugars. Although the tablets contain some sodium the amount is negligible (about .36mg/tablet). The placebo tablets supplied for the run-in period will be labeled Trial Medication: Week 1--Week 4. The study medication tablets supplied for the clinical trial (placebo, antioxidants, and zinc) will be labeled Study Medication. The study medication tablets will be identical in appearance, size, smell, and taste. The formulation of the tablets is provided below in terms of the recommended dietary allowance (RDA).

Placebo (Trial Medication and Study Medication): Contains no vitamins or minerals and no active substances other than lactose (1/4 the amount in an 8 ounce glass of milk).

Vitamin only:

- Vitamin C, about 8 times the RDA
- Vitamin E, about 50 times the RDA
- Beta-carotene, about 3 times the RDA for vitamin A
- Less than 1/25 of the lactose in an 8 ounce glass of milk.

Mineral only:

- Zinc, about 5 times the RDA.
- Copper, about the estimated safe and adequate daily dietary intake.
- 1/4 the lactose in an 8 ounce glass of milk.

Vitamin and mineral:

- All the above vitamins and minerals.
- Less than 1/25 of the lactose in an 8 ounce glass of milk.

In addition, participants who wish to take a multivitamin and mineral supplement will be provided with Centrum®.

10.3 EXPECTED TOXICITIES

The study supplements have much higher doses of vitamins and minerals than the RDA. The vitamin and mineral components used in the AREDS tablets are available in various concentrations in other marketed, over-the-counter, multivitamin and mineral products. Although these doses are believed to be safe, even in addition to a multivitamin and mineral tablet, it is possible that some participants may experience adverse effects. Each tablet contains some lactose. Although unlikely, some persons who are lactose intolerant may not be able to tolerate the tablets. A summary of other possible effects associated with each of the supplements is provided below:

10.3.1 Placebo

No adverse experiences are expected with either the placebo supplied for the run-in period (Trial Medication) or the placebo supplied for the clinical trial (Study Medication). The placebo will have no nutrients or any other active substances.

10.3.2 Antioxidants

Vitamin C. No side effects are expected at the dose that will be given. Persons who have had oxalate kidney stones or hemochromatosis (an iron disorder), are not eligible to participate in AREDS, and should not take this large a dose.

Vitamin E. Side effects of high doses of vitamin E are rare and unlikely to occur among participants in AREDS. The possible side effects include extreme fatigue, muscle weakness, blurry vision, and decreased thyroid gland function. The effects of vitamin E, at a dose lower than in AREDS, on lung cancer development was tested in a randomized study of 29,000 male cigarette

smokers in Finland.[1] No effect on lung cancer was found, but those taking vitamin E had fewer cases of prostate cancer. Although participants supplementing with vitamin E were observed to have more cases of hemorrhagic stroke than those not taking vitamin E, they had fewer cases of other kinds of stroke. Overall there was no increase in stroke. In people who do not have enough vitamin K, high doses of vitamin E may slow the time it takes for blood to clot. Persons taking prescription blood-thinning medications should check with their medical doctor before enrolling in AREDS.

Beta-carotene. In doses much higher than the study dosage some people find that their skin turns yellowish. The skin returns to a normal color when the dose is lowered. No problems are expected at the dosage to be used in this study. The effects on lung cancer of beta-carotene at a somewhat higher dose than used in AREDS was also tested in the Finnish study of 29,000 male cigarette smokers.[1] The study found no benefits and an increase in lung cancer for people taking beta-carotene. The number of new lung cancer cases per 1,000 smokers per year was about 6 for those taking beta-carotene and about 5 for those not taking beta-carotene. There was also a somewhat smaller increase in the risk of heart disease and of total mortality in those taking beta-carotene.

The results of the Beta-Carotene and Retinol Efficiency Trial (CARET)[2], which followed over 14,000 current and former heavy smokers, also found an increased risk of lung cancer and mortaility for participants taking beta-carotene at a higher dose than used in AREDS. After four years of followup in CARET, participants taking beta-carotene (along with vitamin A) had 24% more lung cancers and 17% more deaths than the control group.

In contrast, the Physician's Health Study[3], which followed over 22,000 male physicians (11% of whom were smokers) for 12 years, found no increased risk of cancer, cardiovascular disease, or mortality for participants taking beta-carotene at a much higher dose than used in the Finnish Study or CARET.

10.3.3 Zinc and Copper

Copper deficiency leading to anemia has been reported when high levels of zinc are given. For this reason, some copper will be added to the zinc plus antioxidants and zinc tablets. It is expected that this addition will prevent anemia. A decrease in high density lipoproteins (HDL), the beneficial or "good" part of the cholesterol measurement, in the blood has been observed in some persons taking about twice the dose of zinc that will be used in AREDS. Some zinc compounds can cause stomach upset, but the form chosen for AREDS is less likely to do this.

10.4 REFERENCES

1. The Alpha-Tocopherol, Beta-Carotene Prevention Study Group: The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029-35, 1994.

2. Omenn GS, Goodman GE, Thornquist MD, et al.: Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 334:1150-5, 1996.

3. Hennekens CH, Buring JE, Manson JE, et al.: Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 334:1145-9, 1996.

Exhibit 10-1. EXAMPLE OF BOTTLE LABEL FOR TRIAL MEDICATION TABLETS

AGE-RELATED EYE DISEASE STUDY (AREDS)

56 TABLETS LOT 12345

TRIAL MEDICATION
Week 1 --- Week 4

DIRECTIONS: Take two (2) tablets each morning with food and two (2) tablets each evening with food.

NOTE: Return unused medication to your physician.

NOTE: Store at room temperature.

CAUTION: Limited by Federal (USA) Law to Investigational Use.

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EXHIBIT 10-2. EXAMPLE OF BOTTLE LABEL FOR TABLETS TO BE USED IN THE CLINICAL TRIAL

AGE-RELATED EYE DISEASE STUDY (AREDS)

92 TABLETS LOT 12345
EXPIRES: 03/06

STUDY MEDICATION

AREDS CODE

01

DIRECTIONS: Take two (2) tablets each morning with food and two (2) tablets each evening with food.

NOTE: Return unused medication to your physician.

NOTE: Store at room temperature.

CAUTION: Limited by Federal (USA) Law to Investigational Use.

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