ABSTRACT

Arriving at a decision for early termination of a treatment group or of an entire clinical trial, due to either beneficial or adverse results, is a complex process. It may involve, among other things, the need to (1) determine whether the observed treatment differences are likely to represent real effects and are not due to chance; (2) weigh the importance of different response variables, some possibly trending in favor of the treatment and some against it; (3) adjust for differences in distributions of baseline characteristics among the treatment groups; (4) discern possible biases (due to the study not being double-blind) in the medical management of patients or in the diagnosis of events; and (5) evaluate treatment effects in subgroups of the study participants. Experiences from the Coronary Drug Project in making decisions for early termination and for non-termination of treatment groups are described.

INTRODUCTION AND BACKGROUND

By 1960 evidence had accrued linking elevated blood lipid levels with increased incidence of coronary heart disease (CHD). At the same time the pharmaceutical industry was developing drugs that were effective in reducing blood cholesterol in persons with hyperlipidemia. The time had come to assess whether reduction of lipid levels would be effective in the treatment and possible prevention of CHD. In November 1960 the National Advisory Heart Council asked Dr. Robert Wilkins, a Council member, along with National Heart Institute (now National Heart, Lung, and Blood Institute (NHLBI)) staff to explore the desirability, feasibility, and methodology of a controlled clinical trial of cholesterol-lowering drugs. The ultimate develop-
ment and funding in 1966 of the Coronary Drug Project (CDP) from this initiative makes a fascinating story in itself, but is beyond the scope of this book.

**PROTOCOL DESIGN**

The CDP was a randomized, double-blind, placebo-controlled clinical trial of the efficacy and safety of five lipid-modifying agents in men with previous myocardial infarction (MI). The drugs were mixed conjugated equine estrogens at two dosage levels (2.5 and 5.0 mg/day), clofibrate (1.8 g/day), dextrothyroxine (6.0 mg/day), and nicotinic acid (3.0 g/day). All these and a lactose placebo (3.8 g/day) were dispensed in identical-appearing capsules (9 per day at full dosage). The primary outcome variable was all-cause mortality, with secondary outcomes of cardiovascular death, CHD death, recurrent non-fatal MI, coronary incidence (i.e., CHD death or definite non-fatal MI), stroke, and others.

From March 1966 to October 1969, a total of 8,341 patients were recruited at 53 Clinical Centers—about 1,100 in each of the five drug groups and 2,789 in the placebo group. (The 2.5:1 ratio of patients in the placebo group relative to each drug group was designed to minimize the total sample size while achieving a specified power relative to each of the five drug-placebo comparisons. To qualify for the CDP, a prospective participant had to be a male aged 30 to 64 years with electrocardiogram-documented evidence of an MI’s occurring not less than three months previously. Patients were followed with clinic visits and examinations every four months for a minimum of 5 and a maximum of 8.5 years per patient. The scheduled conclusion of patient follow-up took place during the summer of 1974.

**DATA MONITORING EXPERIENCE**

The CDP may have been the first clinical trial to have an external monitoring committee. However, even the CDP did not have such a committee from the outset. During the first two years of the study, reports on data, including mortality, morbidity, and side effects by treatment group, were presented to the entire CDP investigator group at its semiannual meetings. For the two investigator group meetings in 1967, the results were presented with the treatment groups identified by the letters A through F. We may snicker at the naivety and lack of wisdom of the CDP leadership with regard to sharing treatment group data with the study investigators, but in those days there was no precedent for any other approach. The philosophy changed when Dr. Thomas Chalmers wrote a letter dated October 31, 1967,