Rationale and Historical Development of Clinical Trials for Primary Prevention of Cardiovascular diseases in The United States

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The United States, similar to other Western industrialized countries, experienced a post-war epidemic of atherosclerotic and hypertensive cardiovascular disease, chiefly coronary heart disease (CHD), Based on observational epidemiologic studies conducted beginning 50 years ago, a program of large-scale clinical trials aimed at primary prevention has been undertaken over the past 25 years by the National Heart, Lung and Blood Institute (NHLBI). Together with similar trials conducted primarily in Europe and with secondary prevention trials, much knowledge has been gained about 1) the effectiveness of various preventine and therapeutic-interventions, and 2) the methods of designing and conducting trials.

The trials have tested interventions aimed at reducing the three major CHD risk factors: high blood pressure, high blood cholesterol, and cigarette smoking. More recently, trials have targeted the thrombotic process, and a few trials supported by other NIH units have studied interventions in diabetes mellitus. Results of these trials, viewed in the context of other evidence both from trials and other kinds of research, have provided a solid foundation for national and international efforts to control cardiovascular diseases. On the other hand, many new questions have arisen:

- What are the respective roles of pharmacologic and lifestyle (nonpharmacologic) methods of treating hypertension?
- Do particular classes of antihypertensive drugs have any advantage in preventing coronary, cerebrovascular, or renal disease?
- Does cholesterol-lowering, particularly with drug treatment, reduce total mortality?
- What are optimal dietary approaches for treating dyslipidemias?
- Do anti-oxidant vitamins prevent CHD?

- Can lifestyle modification, particularly at a population level, reduce the development of risk factors themselves ("primordial prevention")?

Most of the previous intervention issues in primary prevention could be addressed reliably only with large sample sized, so that extensive experience has been accumulated on the design and conduct of multicenter trials. These large and expensive enterprises require, first and foremost, careful formulation of the research question(s), including wide consultation with experts and advisors. Then, groups of investigators need to be assembled, either on the initiative of non-government senior scientists, or more commonly, through a solicitation Issued by NIH. After a protocol is fully developed and reviewed, study implementation proceeds, with technical and logistical support through one or more separately funded coordinating and central core units. Trials are also monitored by independent advisory boards (elsewhere called "ethics committees"). Upon successful implementation of subject recruitment and followup, the accumulated data can then be analyzed and disseminated to the scientific, clinical, and public health community. Finally, attention is devoted to ensuring appropriate transfer of relevant findings, as well as scrutiny of the results for future research needs.