ELSEVIER

Foreword

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INTRODUCTION

With an enrollment of 161,809 participants at 40 clinical centers, the Women's Health Initiative (WHI) is the largest and most comprehensive set of women's health studies ever conducted. Scientifically, the WHI is supported by a long history of developmental work, including epidemiologic and animal studies, and feasibility and intermediate endpoint trials in key areas of women's health. Societally, the existence of this program is testament to the powerful interest in and need for definitive research in the health concerns of postmenopausal women.

The history and rationale for the WHI have been described previously (1,2). National Institutes of Health (NIH) Director Bernadine Healy initiated the program in 1991 and obtained funding from Congress beginning in 1992. A multi-institute planning group of NIH scientists evaluated the most pressing health needs of older women, considered the most promising interventions to be tested, and developed the framework for the study. At critical junctures, input was sought from non-NIH scientists and from the public. For design purposes, the planning group identified cardiovascular disease, breast and colorectal cancer, and osteoporotic fractures as the primary outcomes of interest. However, it was decided that the planned studies should not focus narrowly on these outcomes, but should assess the impact of the prevention therapies on overall health. The study plan was developed into requests for contract proposals for the Clinical Coordinating Center and the Clinical Centers. The Clinical Coordinating Center was funded in the fall of 1992, and the first set of 16 clinical centers was funded in the spring of the following year. The Clinical Coordinating Center investigators drafted the first version of the protocol, which was subsequently refined by investigators from the Clinical Centers. In early 1993, the investigators drafted the first elements of the Manual of Operating Procedures, and by the fall of 1993 enrollment of participants had begun. Recruitment and clinic visit procedures were refined based on the early experience in the first set of Clinical Centers and prior to the engagement of the second set of 24 clinical centers in 1995. Recruitment goals having been met, enrollment ended in 1998.

At its inception, the WHI was administered from the Office of the Director at the NIH. This unusual situation came about because of the Director's interest in the study and because the aims of the program cut across boundaries within the NIH. However, by 1997 the program had been well established and it became clear that the National Heart, Lung, and Blood Institute (NHLBI) would be a more appropriate home for this research program. Accordingly, the program was moved to the Office of the Director at the NHLBI, while maintaining the links with staff from other NIH institutes.

This report highlights the achievement of the recruitment goals. In fact, the original goal of 57,000 participants for the WHI Clinical Trial was increased to 67,000 because of a significant protocol modification (see the article in this issue entitled "WHI Postmenopausal Hormone Trials") together with experience that relatively few women were enrolling in both the dietary and hormone trials. The new goal was exceeded with a final enrollment of 68,133 participants in the Clinical Trial. The original estimate was that 100,000 women initially screened for the Clinical Trial would enter the WHI Observational Study. Early experience indicated that the Observational Study would become oversubscribed rapidly, at some cost to Clinical Trial enrollment. Thus, enrollment targets for the Observational Study were scaled back for much of the recruitment period and were increased again in the final months once it was clear that the Clinical Trial target would be met. Enrollment into the Observational Study was stopped at 93,676 so that the study could turn its attention to the next priority: adherence, retention, and outcomes ascertainment in the Clinical Trial. The fulfillment of recruitment goals was possible because of the strong commitment of many investigators and staff, and the willingness of so many women to offer their time, experience, and energy to this endeavor.

As important as overall recruitment goals were, it was equally important that women from minority groups were adequately represented in the study population. Efforts were made to assure that meaningful numbers of Black, Hispanic, Asian/Pacific Islander and American Indian women were enrolled in the WHI. The final numbers reflect minority representations close to or at the proportions found in the U.S. population of women in the age range studied. This promotes the generalizability of the findings,

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and allows for informative subgroup analyses. In the Clinical Trial, the statistical power for the primary outcomes is predicated on the size of the entire cohort, but various prespecified subgroup analyses will be performed to examine the consistency of findings across subgroups. For intermediate outcomes, including blood biomarkers, the minority subgroups are oversampled to improve the statistical power to measure the impact of the study treatments on risk markers. Because of the large numbers in the Observational Study, there will be ample opportunity to perform within-group analyses examining the relationship of risk factors to important clinical outcomes such as heart disease, breast and colorectal cancer, and osteoporotic fractures. To the best of our knowledge, the WHI is not only the largest and most comprehensive study of women to date, it is also the largest and most comprehensive study of minority women.

The primary objective of this issue is to describe the baseline characteristics of participants in the WHI Clinical Trial and Observational Study. The secondary objectives are to document methods that are critical to understanding study findings and to provide guidance and insight from the WHI experience to investigators and funding agencies embarking on similar large multicenter studies. Separate articles are devoted to the Clinical Trial components testing three prevention strategies: postmenopausal hormones, low-fat dietary modification, and calcium/vitamin D supplementation. Another article is devoted to the large Observational Study. These descriptions of the methods and baseline characteristics of participants are introduced by articles on recruitment strategies and on the implementation of the study design, including data management and quality assurance procedures. Finally, there is a description of the methodology used for ascertaining and classifying clinical outcomes. This issue does not describe the WHI Community Prevention Study, which will be reported elsewhere.

The data presented herein include: (1) data obtained from WHI participants during the screening and enrollment process; (2) laboratory results obtained from specimens collected during screening and subsequently analyzed; and (3) limited year 1 data to address methodologic issues in the screening data (see Ritenbaugh's article in this issue entitled "WHI Dietary Modification Trial"). Simple descriptive statistics are provided to document the observed distributions. No adjustments for age, race, or other factors were incorporated, though many of the displays provide tabulations by these important design factors. Each article presents the baseline data critical for understanding how that study component is positioned to address the targeted hypotheses. Comparisons across study components are not considered inherently meaningful because of the separate eligibility requirements; however, an extensive display of the information by race and ethnicity for the Clinical Trial and Observational Study is provided (see the appendix to Hays' article entitled "Recruitment Methods and Results"). The WHI Observational Study baseline dataset will be available at http://www.nhlbi.nih.gov/resources/index.htm in December 2003.

What about the future of WHI? Four years after the end of recruitment, the investigators and staff are fully engaged with meeting the challenges of adherence, retention, and outcomes. Laboratory analyses of risk markers are well underway, and analyses of the major trial outcomes are routinely conducted and reported to an independent data and safety monitoring board. The database on exposures and outcomes already allows WHI investigators to rapidly and more completely examine issues that have been raised by smaller studies. The parallel conduct of the Clinical Trial and Observational Study will make WHI an important laboratory for examining the strengths and weakness of observational studies in evaluating potential intervention strategies.

Several ancillary studies are underway or are being planned. The largest ancillary study is the WHI Memory Study, which examines the effect of postmenopausal hormones on the incidence and progression of dementia, including Alzheimer's disease. A second large ancillary study will examine the effects of hormone use on macular degeneration. Other ancillary studies in various stages of development will use the blood and DNA resource in the Observational Study together with questionnaire data to refine information about known risk factors, and to discover new risk factors for the more important diseases of postmenopausal women.

Of course, the major contribution of the WHI lies somewhat further in the future, when the trials are completed. At that time, definitive answers will be given to questions that have vexed the medical profession and the public alike. For example, is long-term hormone use beneficial? Will a low-fat eating pattern prevent cancer? And how effective is calcium and vitamin D for preventing fractures? Finally, will these commonly promoted but unproven prevention treatments have an effect on overall health and well-being? The investigators and participants in this unique venture are hopeful that the answers will benefit the daughters and granddaughters of the trial participants, as well as the current generation of women who are in the postmenopausal stage of life.

APPENDIX: ACKNOWLEDGMENTS

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