SECTION 1

INTRODUCTION TO WOMEN'S HEALTH INITIATIVE: CLINICAL TRIALS AND OBSERVATIONAL STUDY

INTRODUCTION

The health of women has extraordinary medical, social, and economic implications, as well as being of personal interest to women making choices about healthy behaviors. Too little research has focused on health issues unique to, or more common for, women, particularly chronic diseases in mature women. These conditions—cardiovascular disease, cancer, and osteoporosis—are the leading causes of mortality, morbidity, and declining quality of life. Thus, in 1991 the Director of the National Institutes of Health (NIH) announced the development of a research program to address these issues. This program, entitled the Women's Health Initiative (WHI), is composed of three studies: a Clinical Trial (CT), an Observational Study (OS), and a community-based study. For efficiency, the CT and OS have been combined into one program. This manual, *Vol. 2 - Procedures* describes Clinical Center (CC) operations and procedures for the CT and OS components.

1.1. Overview

One of the Women's Health Initiative's goals is to evaluate preventive approaches to cancer, cardiovascular disease, and osteoporotic fractures. The three approaches used in WHI are a low-fat eating pattern, hormone replacement therapy, and calcium and vitamin D supplementation. These interventions will be tested in a large clinical trial of postmenopausal women. The recruitment and screening of large numbers of women for the CT also affords a unique opportunity for observational studies of disease predictors (the OS).

The CT and OS will direct particular attention to the recruitment and study of minorities and medically-underserved segments of the population in a culturally sensitive manner. The information derived from these studies will be relevant to all women regardless of race, culture, or economic status.

The CT and OS are integrated into a single program to improve scientific and fiscal efficiency.

1.1.1. Clinical Trial

The CT is designed to address the major causes of mortality and morbidity in postmenopausal women, namely coronary heart disease, breast and colorectal cancer, and osteoporotic fractures. Cardiovascular disease is the most common cause of mortality in older women, accounting for 29 to 48 percent of all deaths in the age range of 50 to 79. Both absolute rates and proportional mortalities from these causes increase steeply with age. Among the cancers, breast cancer is the second most common cause of death. Even though breast cancer rates increase with age, the proportional mortality from this disease is slightly higher at younger ages. Colorectal cancer is the third most common cause of death among the cancers and the second most common incident cancer. Incidence and mortality rates of colorectal cancer increase with age. Fractures account for considerable morbidity, fragility, and loss of independence. Annual fracture incidence rates also increase with age.

The goal of the CT is to test whether or not treatments reduce the incidence of disease and subsequent morbidity and mortality. The CT is a controlled clinical trial of preventive treatments in women ages 50 to 79 years. There are three main components: hormonal replacement therapy (HRT), dietary modification (DM), and calcium/vitamin D (CaD) supplementation. The primary goal of the HRT component is to determine whether estrogen or estrogen plus progestin reduces the rate of coronary heart disease in comparison to placebo. The primary goal of DM is to determine whether or not following a low-fat eating pattern is associated with a lower rate of breast cancer and colorectal cancer. The primary goal of CaD is to learn whether or not calcium and vitamin D supplements reduce the rate of hip fracture as compared to placebo. The sample sizes chosen are large enough to test each treatment with confidence. The treatments will be tested in a partial 3 x 2 x 2 factorial design to reduce the total number of participants required. Women may participant in one, two or all three components of the CT depending upon their interest in and eligibility for each individual component.

1.1.2. Observational Study

There is a general recognition that few older women have been studied longitudinally and that major questions about prediction of chronic disease in postmenopausal women remain. This initiative, with its CT and OS, presents an opportunity to accumulate a large cohort of women, to follow them, and to determine the predictors and biological markers of disease. Integration of the findings of the OS and CT components is an efficient and effective way to achieve the following objectives:

- Screen women for participation in the CT.
- Develop risk-factor analyses for cardiovascular disease, cancer, and osteoporosis.
- Conduct surveillance of deaths and incidence of cardiovascular disease (especially coronary heart disease and stroke), cancer, and fractures. Assess psychosocial, including quality of life, changes over time.
- Use the case-control approach to study the link between subclinical markers and clinical disease.

1.2. Time Table for the Clinical Trial and Observational Study

Phase 1 - Vanguard Clinical Centers (16)		
Phase 1A - Protocol Development	09/30/92 - 05/31/93	(8 months)
Phase 1B - Training	06/01/93 - 08/31/93	(3 months)
Phase 1C - Vanguard Recruitment and Follow-Up	09/01/93 - 01/31/95	(17 months)
Phase 2 - Additional Clinical Centers (24)		
Phase 2A - Training	09/30/94 - 01/31/95	(4 months)
Phase 2B - Recruitment	02/01/95 - 08/31/96	(19 months - VCCs)
	02/01/95 - 01/31/98	(3 years - Other CCs)
Phase 2C, 2D - Follow-Up and Closeout Visits	09/01/96 - 03/30/05	(8 years, 7 months - VCCs)
	02/01/98 - 03/30/05	(7 years, 2 months - Other)
Phase 2E - Closeout Data	04/01/05 - 09/14/05	(5.5 months)
Phase 2F - Data Analysis	09/15/05 - 09/29/07	(2 years, 0.5 months)

1.3. WHI Manuals

The design and implementation of the WHI, as captured in the study Protocol, policies, procedures, interventions, and data collection instruments are described in the WHI Manuals. The primary function of these manuals is to provide common training and reference materials across all participating WHI organizations as a way of assuring the quality of the study. Each operational unit is responsible for developing its own manual describing the policies and procedures specific to that unit.

The WHI Manuals are contained in several volumes. The allocation of topics to volumes was based on the WHI staff members who would most use the various sections.

Volume 1 - Study Protocol and Policies: This manual contains the Protocol for the CT and OS, the committee structure and the policies governing the scientific conduct of the study. As this is a document written for and by WHI Investigators, procedural aspects of the study that are performed by Investigators (e.g., outcomes classification) are included in this manual.

Volume 2 - Procedures: This manual describes all CC procedures and guidelines for operations other than Nutrition Intervention. As the primary CC training and reference source, this manual serves as the standard by which CC operations are assessed. Procedures that are designated as Required in the section heading must be followed to adhere to the protocol, for consistency, and for participant safety.

Volume 3 - Forms: All standardized study forms are displayed in the Forms Manual in numerical order. Accompanying each form is a detailed set of instructions describing who completes the form, when and how each data item should be coded, and what should happen to the form when completed.

Volume 4 - Dietary Modification Intervention: The Dietary Modification (DM) Intervention Manual consists of two parts: the Group Nutritionist Manual and the Participant Manual. The Group Nutritionist Manual describes the procedures for carrying out the intervention sessions for the DM component. The Participant Manual contains information pertinent to each intervention session.

Volume 5 - Data System: This is a user's manual for the WHI computing system. Information is provided on the general hardware and software used as well as the specific WHI database, WHILMA.

Volume 6 - DXA Quality Assurance Manual for Hologic QDR-2000 Bone Densitometer: This is a user's manual for the WHI Bone Density Clinical Centers. This manual is intended as a supplement to the Hologic User's Manual.

Volume 7 - Quality Assurance: This manual provides procedures and checklists for Clinical Center QA Activities.

1.4. Study Communication

1.4.1. Lines of Communication

The success of any multi-center study depends heavily on the quality of communications. As the number of participating individuals and institutions increase, so does the need for formal channels and efficient, reliable means of communication. This version of the WHI Manual describes the current organization and procedure. Spring of 1995 will be the advent of new organizational structure and modified procedures. The current status is described here to avoid confusion. The study organization and committee structure provides the foundation for communications. Protocol, policy, or procedural issues or problems identified by any study personnel can be brought to the attention of an appropriate committee member or a designated Clinical Coordinating Center (CCC) representative. Staff groups have been identified for the clinic managers, clinic practitioners, data coordinators, lead nutritionists and recruitment coordinators. Regular conference calls for these staff groups, as well as the principal investigators, provide an opportunity for all staff to bring concerns and problems up for discussion, resolution and dissemination. These issues are initially brought to the Management or Executive Committee for consideration and/or may be referred to one of the Subcommittees of the Executive Committee for further development and consideration. Issues not clearly falling on a particular subcommittee will be assigned by the Management Committee. It is the responsibility of the subcommittees to evaluate any concerns and make recommendations to the Executive Committee for final approval.

As a body governed by committees, the minutes of each committee meeting or conference call will serve to document the course of the study. Minutes from all committee meetings or conference calls should be submitted to the CCC within one week of the meeting. All such minutes will be made available upon demand, eventually through a computer bulletin board. However, to limit the flood of paper, routine distribution will be limited. Minutes from the Management Committee will be regularly provided to the Executive Committee. Minutes from all Executive Committee meetings and calls will be routinely circulated to the PI from each institution and one designated clinic manager. Minutes from the Investigator's Committee meetings will also be provided to all PIs and clinic managers.

From time to time, the CCC will issue bulletins describing changes to study policies, procedures, or forms. These bulletins are intended to modify the existing WHI Manuals until an updated version of the manual is printed. These bulletins should be reviewed with all appropriate staff and added to the appropriate appendix of each manual when received.

Routine questions of study operations should be directed to the CCC (including the Regional Resource Center [RRC] which functions as a part of the CCC). Contact staff for each function will be identified on an ongoing basis. Please note the hours and days of coverage, including CCC institutional holidays.

CCC (FHCRC) Holidays:

January	1	New Year's Day
		Martin Luther King Day (Monday)
February		President's Day (Monday)
May		Memorial Day (Monday)
July	4	Independence Day
September		Labor Day (Monday)
November	11	Veteran's Day
		Thanksgiving (Thursday)
		Day After Thanksgiving (Friday)
December	24	Christmas Eve (or December 26)
	25	Christmas Day

1.4.2. Methods of Communication

The WHI will take full advantage of available means of communications: meetings, conference calls, personal calls, facsimile transmission (fax), regular and express mail, and electronic mail (eMAIL). The availability of a

standardized computing environment and eMAIL makes eMAIL the first choice for all but the most urgent communications. The advantages of eMAIL are speed, accuracy, reliability of communications, simplification of documentation, and cost, given the existence of the WHI network.

Electronic Mail

All WHI personnel with access to the WHI network will be given a unique user identifier. This ID and a user-defined password will be required for accessing the network and participating in the electronic messaging system. Each user will be able to send and receive messages throughout the network, store, and retrieve them electronically, and access messages for general dissemination (e.g., minutes from meetings). Groups of WHI personnel, as defined by interests or responsibilities (e.g., nutrition interventionists, lead data coordinators, subcommittees or the Executive Committee) will be established as an entity within the eMAIL system to facilitate quick and comprehensive addressing and distribution.

Access to WHI eMAIL is desirable for all affiliated institutions and individuals. Budget limitations may limit the ability of the system to reach all WHI staff. Groups not explicitly funded for access, such as various CCC subcontractors and other NIH collaborating offices will be added if funding is identified. Priorities will be based on data flow and communication needs. EMAIL connections, such as Internet, have been made available on a broad basis especially for communications with these groups. The Internet address of all WHI users is based on the CCC maintained gateway and is of the form: user name %or@hub.fhcrc.org.

Inquiry Reporting System

The eMAIL system will be used for routine inquiries between the CCs and the CCC. A paper version, *Form 171 - Inquiry Form*, may also be used if necessary.

The Inquiry Form provides a standard format for the CCs to ask questions of the CCC. The Inquiry Form allows the CC to describe problems and ask questions about any aspect of study procedures, policies, and forms.

CCs should take the following steps before completing a CC Inquiry Form:

1. Consult *Vol. 1 - Protocol*
2. Consult *Vol. 2 - Procedures* or other volumes of the WHI manuals.
3. Ask the Clinic Manager or other supervisor.
4. Ask the Principal Investigator or other Investigator.

If the question cannot be answered, the CC should complete an Inquiry and send it to the CCC. If the question is urgent (for example, involving a safety issue or randomization, being unable to dispense medication or other critical matters), the CC should call the CCC for a quicker response.

The CCC records an answer on the form and returns the Inquiry to the CC. Questions and answers recorded on the Inquiry Form are used to update the WHI Manuals or other relevant study manuals.

If an Inquiry from one CC results in a change or clarification of a procedure applicable to other CCs, the CCC issues a bulletin to all CCs. In addition, a copy of each answered Inquiry that pertains to all CCs is forwarded to each CC.

Issue Action Log

As a subset of the Inquiry Reporting System, some issues raised may require a change in protocol, study policy or procedure. Such issues may be referred to a subcommittee of the Executive Committee or Management Committee for further development and approval. Tracking of these activities, as well as the

review and approval steps within the study organization, the Data Safety and Monitoring Board, and the Director of NIH, is done with the *Issue-Action Log*.

Telephone Calls

Telephone calls are necessary to maintain rapport between individuals and to provide a forum for a "real-time" discussion. The number of participating CCs makes the number of calls received at the CCC or the Program Office potentially overwhelming unless there is discretion in their use. It is recommended that CCs establish logs of long-distance calls to the CCC and NIH to monitor their own activity.

Mail

Regular and express mail will be used to ship supplies and larger documents. Note that express mail addresses for some institutions, including the Program Office and the CCC, are different from the regular US Mail address. It is recommended that you do not send items to the Program Office by regular mail because of delays in the internal mail system at NIH.

WHI Directory

A directory of all WHI investigators and staff addresses, telephone and fax numbers are provided through the CCC. The directory is updated and distributed to all WHI personnel on a regular basis.

1.5. Contact with Primary Care Physicians

The intent of WHI is to avoid interfering with the participant's relationship with her usual source of medical care. The WHI CCs will not provide regular medical care for participants. Each CC will have a referral system for women who do not have their own physician.

Community Relations

It will be advantageous to each CC to have familiarized local physicians and medical associations about the WHI CC activities. Articles in local professional publications, presentations at local meetings, and a mailing of informational materials to the women's primary care physicians should be considered. A standard set of slides describing WHI will be provided to each CC. These may be useful for presentations to local professional or lay groups.

Providing Information to Help Them Advise Their Patients About Participation

Sometimes a potential participant will want to talk with her primary physician regarding the study and whether or not she should participate. This will occur, for example, if a woman is currently using hormone replacement therapy at the first contact. Provide her with information to take to her primary physician and ask her to visit her primary physician and discuss whether or not she can discontinue her present hormone regime. Her primary physician may also call the CC for information about the study. Each CC should decide upon a contact person(s) who will talk with these physicians. The contact person(s) should be very knowledgeable about the study and able to answer the physician's questions in detail.

Obtaining/Confirming Medical History

To avoid unnecessary duplication of services, some information about a participant's medical history (e.g., results of last mammogram) and some diagnostic study results may need to be requested from her physician. Such requests for information should be accompanied by a medical release form signed by the participant (see *Section 4.2.4.3. - Initial [Screening] Informed Consent*).

Reporting/Advising on CC-Detected Medical Conditions (Alerts)

To prevent duplication of service and subsequent charges and inconvenience or increased risk to a CT participant from repeating a procedure, results of the following procedures will be forwarded to the participant's primary physician:

- Mammography
- Pelvic Exam
- Pap Smear
- Endometrial Aspiration
- Transvaginal Endometrial Ultrasound

Community physicians and WHI participants should be informed that the CCs will not be measuring cholesterol or performing any blood tests that would replace the woman's routine medical care. Inform both the participant and her personal health care provider that the WHI CC is not measuring or monitoring cholesterol levels or other biochemical markers, unless the CC has made arrangements for this on an ongoing basis.

Results of other WHI measures and studies (such as CBC, ECG, bone density) will be provided to the participant or her primary physician if they indicate possible underlying serious problems. See *Section 4.3.4.4. - Procedures* for WHI alert values for procedures and measurements.

Some CCs may want to refer other measurements and procedure results to the participant's primary physician. Follow your CC's guidelines regarding additional alerts and referrals to primary physicians.

Coordinating Adverse Effect Monitoring and Management

The need to coordinate the monitoring and management of adverse effects (e.g., vaginal bleeding) may require coordination with a participant's physician(s) particularly if the physician has reported these effects to the CC. Participants in the HRT component of the CT will require such coordination more often than other CT participants (see *Section 5.4. - Managing Symptoms* and *Section 5.5. - Major Health Problems*). All physicians' requests for information should be handled in a professional manner.

Obtaining Outcome Information

Some information about outcomes may be ascertained through the participant's physician(s). Contacts to obtain this information should be courteous, professional, and as brief as possible.

Section 1
Introduction to WHI

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