Women's Health Initiative
Clinical Trial and Observational Study

Annual Progress Report

September 1, 1994 to August 31, 1995

Prepared by
WHI Clinical Coordinating Center
Fred Hutchinson Cancer Research Center

Ross Prentice, Principal Investigator

Funded by National Institutes of Health Contract No. N01-WH-2-2110

December 1, 1995

WHI Annual Progress Report

Contents Page

by stage of screening variable among CCs. (3) CCs are not required to enter data on known ineligible women. This causes the recruitment yields to be overestimated and the screening activities and exclusion rates to be underestimated.

2.2 Recruitment Goals

In the initial planning, NIH anticipated that 45 CCs would be funded in two phases. In the second phase of competition only 24 sites were finally selected resulting in a total of 40 CCs. Recruitment goals and budgets were based on 45 clinics however, so the program is addressing this shortfall by asking existing clinics, particularly VCCs, to consider recruiting beyond the original goals. Six VCCs have offered to do enhanced recruitment and were awarded the additional funds to support this activity in Spring 1995. The additional recruitment at these six clinics is equivalent to 2.5 clinics in the second phase (See *Table 2.1 - Enhanced Recruitment Sites*). Two other VCCs are negotiating for enhanced recruitment and the NIH has solicited proposals from the NCCs, due December 1995, to meet the remaining goals.

Table 2.1
Enhanced Recruitment Sites

	Increase		Comments
Pawtucket	75%		
La Jolla	50%		Reduced minority recruitment goal.
Brigham & Womens	50%		
Minneapolis	25%		
Memphis	25%		Offered additional minority recruitment
Birmingham	25%		Continued minority recruitment goal of 60%. Bone Density measures not required on additional participants.

For the initial six clinics named, the enhanced screening goals were phased in over the 3 months from February to April 1995 with corresponding randomization and enrollment goals implemented on April 1, 1995.

The change in the HRT design resulted in an additional change in recruitment goals (total of 27,500 versus 25,000 women to be randomized) and these were also implemented in April for all CCs.

2.3 Progress

VCC recruitment into the CT officially opened September 1, 1993. OS enrollment at VCCs was delayed until September 1, 1994 at which time the study obtained clearance from the Office of Management and Budget to begin OS accrual. Recruitment into both the CT and OS components officially began in NCCs on February 1, 1995.

Figure 2.1 - Cumulative DM and HRT Randomization and Goals compares recruitment progress to date by both cumulative and monthly goals. As of August 31, 1995, 5055 women

had been randomized to HRT (64% of cumulative goal) and 11,476 women had been randomized to DM (80% of goal). In the last four months accrual has proceeded at 47% of monthly goal for HRT and 63% for DM. These reductions are due in large part to the graduated achievement of full recruitment goals at the NCCs.

Table 2.2 - Randomization Activity by Clinic Group, Study Component and Month displays HRT and DM randomization activities separately for VCCs and NCCs. Though the pace of studywide recruitment to both components has increased in the last few months, the acceleration is attributable to the addition of the NCC activities.

VCCs as a group have experienced a drop in recruitment of approximately 47 HRT and 84 DM randomizations per month. This has occurred despite the fact that enhanced recruitment was initiated at six VCCs increasing the corresponding goals by 97 and 78 during this period. Thus the VCC monthly accrual rate is now at 59% of goal for HRT and 77% for DM. The variation between clinics in achieving goals continues to be large, ranging from 49% to 129% of goal for HRT and 61% to 101% for DM. Related clinic performance issues are discussed in *Section 8 - Clinical Center Performance Monitoring.*

In August NCCs recruited 52% of their monthly goal for HRT and 71% of goal for DM, bringing them to 42% and 57% of their respective cumulative goals for HRT and DM. Initial indications suggested that NCC recruitment would proceed at a faster rate than was observed in VCCs but the data no longer support this. A few NCCs have succeeded in meeting or even surpassing the goals but the majority are experiencing many of the same start-up delays observed among VCCs. Given their two month shorter interval from funding to recruitment start-up, this still suggests that NCCs as a whole have made progress toward a somewhat earlier start-up. The variation in NCC performance is large; for HRT recruitment the range is 0% to 153% of cumulative goal; for DM the range is 15% to 109%. See *Section 8 - Clinical Center Performance Monitoring* for more discussion of clinic specific issues.

Accrual into CaD officially began in VCCs on June 15, 1995. This eight month delay, brought on by the difficulty in obtaining CaD preparations, results in a small loss in person years of follow-up relative to the design. Only about 3% of the potentially eligible sample (that is, CT participants due for their one year follow-up visit) were available for randomization before that time. These participants will be invited to participate at their next annual visit to minimize the potential loss.

With just over two months of active recruitment, *Table 2.3 - CaD Randomization Activity and OS Enrollment Activity by Clinic Group and Month* indicates that 896 women are randomized to CaD, 67% of the cumulative design goal and 61% of those randomized to CT during this period one year earlier. The CaD power calculations assume that 70% of CT participants will be accrued into CaD. The current experience is quite limited but still somewhat lower than expected. Further monitoring of CaD accrual is needed to assess the accuracy of the design assumptions.

OS enrollment in both VCCs and NCCs has progressed well in the last year, reaching 85% of cumulative goal in VCCs and 81% in NCCs (see *Table 2.3 - CaD Randomization Activity and OS Enrollment Activity by Clinic Group and Month*). The study continues to emphasize

CT recruitment over OS; CCs are advised to give priority to scheduling screening visits for potential CT participants.

2.4 Recruitment Yield

2.5 Exclusions

Available data on reasons for CT exclusions can be given only a limited interpretation because of missing data on ineligibles.

The primary reason for excluding age-eligible women from HRT is lack of interest or willingness to be randomized, accounting for approximately 78% of the HRT exclusions. Other exclusions accounting for 1% or more (where a woman can be excluded for multiple reasons) include: not postmenopausal; cancer; clinical assessment of ability to participate; logistical issues; history of DVT; BMI; using hormones to treat osteoporosis; and currently randomized in another study.

The primary reason for excluding women from DM is dietary fat intake, accounting for 48% of the women excluded. Other prevalent exclusions are: lack of interest; large number of meals eaten away from home; cancer; clinical assessment of ability to participate; logistics; not postmenopausal; BMI; and currently randomized in another study.

Table 2.4 - Reasons for Refusing/Revoking Consent provides further detail on reasons for refusing consent for each consent process (Screening, HRT and DM). See *Form 11 - Consent Status* for the list of reasons for refusing or revoking consent. (Revoking consent in this setting means the woman initially signed a consent and later decided not to participate.) Overall, 86% of women at VCCs and 91% at NCCs asked to sign the screening consent have agreed to do so; 32% and 35% of women offered HRT participation at VCCs and NCCs respectively have signed their HRT consents. Similarly 69% of VCC women and 77% of NCC women offered DM participation have signed the component-specific consents. The higher proportion observed at NCCs to date is likely an early volunteer effect.

Among those women who attend a clinic visit but do not consent to screening procedures, commonly reported reasons for not participating include personal issues, study limitations and travel issues. For HRT the primary reasons were study limitations, treatments, and worries about symptoms, procedures or risks, and "other." For DM, personal issues, study limitations, and travel were the most frequently identified reasons. The reasons cited do not vary substantially between VCCs and NCCs. They have remained quite consistent over time except for some small changes associated with the procedures for collecting this information.

2.6 Issues

The challenges of recruiting women into WHI are large and multifaceted. From the perspective of a potential study participant, WHI is complex in its multiple components and their associated entrance criteria, its many required forms and procedures, and even in its hypotheses. In particular, the objective of weighing potential benefits and risks of HRT is especially difficult to understand and possibly accept.

From the clinic viewpoint, recruitment into HRT is difficult because of the strong opinions already formed by some in the medical community in favor of the benefits of HRT and because of some women's strong feelings either for or against HRT, presumably formed by prior experience. Recruitment into DM is a challenge because of the large number of women (currently 45%) who are screened out by the food frequency questionnaire in order to assure the control group on average consumes a diet slightly higher in fat than the general population. This creates a large processing burden for CCs. The low interest in HRT and eligibility for DM imply that a very large population base is required.

Clinic burden represents another important constraint to recruitment flow. Currently, VCCs are conducting follow-up activities every six months on a large number of women while simultaneously recruiting into HRT and DM and recently adding recruitment into CaD and OS. The complexity of the protocol, including many component specific procedures and subsampling, requires a very high degree of organization and efficiency in the clinic to meet these goals.

The problems of recruitment are considered a high priority by the study leadership and are discussed frequently in the governing committees. These have spawned several initiatives that are being pursued, the most visible of which is the enlistment of a public relations firm, Porter-Novelli, to assist in a national recruitment and public awareness campaign. To date Porter-Novelli has made several contributions:

- Revised the consent video.
- Conducted focus groups to learn current understanding of WHI among participants.
- Participated in training of Recruitment Coordinators at the AGM.
- Consulted on press releases in response to recent publications on HRT.
- Made contact with national organizations and media on behalf of WHI (e.g., AARP, editors of women's magazines).
- Developed press packets for local use.
- Produced a 10 minute recruitment video specifically targeting women over 65 and minorities.
- Coordinated WHI activities generated by Dr. Bernadine Healy's recent book release and tour.

Minority Recruitment Strategies

Considerable attention is being given to recruitment of minorities. The WHI is committed to being representative of postmenopausal women in the United States from all major ethnic groups, and to the inclusion of women at all levels of education and socioeconomic status. Ten of the 40 CCs (Pool 1) were funded to specifically to recruit at least 60% of their participants from specific ethnic groups. In addition, several of the remaining 30 CCs are actively recruiting and retaining ethnic minorities.

Since there is diversity among centers and each CC must conduct its program within the constraints of its institution and environment, a variety of approaches have been used to accomplish these goals. The common denominator is, however, that in all cases the strategies are tailored toward the community. The most successful clinics have been those who work closely with representatives from the community that is being targeted.

The following is a summary of the strategies employed to date:

1. Recruitment

The majority of recruitment of minority participants is conducted through personal contact. Recruitment by mail is generally only successful if it is targeted, personal and accompanied by community publicity. The strategies which are most successful involve individual recruiters, preferably who represent the community, attending local fairs, gatherings, churches, and community organizations, presenting information about the study and individually interviewing potential participants. Enrolled participants have assisted in recruiting. A woman who has had a pleasant and successful visit is often willing to recruit friends or relatives. Some clinics use incentives to encourage recruitment by enrolled participants.

2. Conduct of the Clinical Examination

Essential to the recruitment and retention of minority participants is personal contact at the time of the clinic examination by clinic staff who truly make an effort to make the participant feel welcome. The participant is assisted with forms, in the case of low literacy participants or in other cases where the participant is inexperienced or apprehensive about the forms or other procedures. Forms are not generally mailed out unless they are preceded by a personal explanation, either in person or by phone call. Study forms have been translated into Spanish, and Spanish speaking staff are available. Transportation can often be a problem and clinical staff assist in advising participants about forms of transportation; in some centers participants are reimbursed for transportation.

3. Manpower

It is important that investigators at all levels of the study are representative of the targeted minority community. The Women's Health Initiative is exploring sources of funding to provide more opportunities for minority investigators. Clinic staff, managers and recruiters in the Pool 1 CCs represent the community and are often known by participants. It must also be recognized that the inclusion of minority participants often takes extra manpower. This is because of the need for personal recruiting as well as the need for devoting extra time during clinic visits to establish a rapport with the participants. Manpower has been a major problem given the restrictive funding for this study. Several centers have devised innovative ways to obtain volunteer manpower from community organizations or interested participants who may be retired and have free time.

4. Publicity

Publicity efforts have been focused on the minority communities. Individual centers have placed ads in community periodicals and on local radio stations. Porter-Novelli is also working to provide national media coverage aimed towards minority participants and to supply press packets which can be used by the local centers. Endorsement of the study by community members is extremely important; this needs to be done at the local level.

5. Incentives

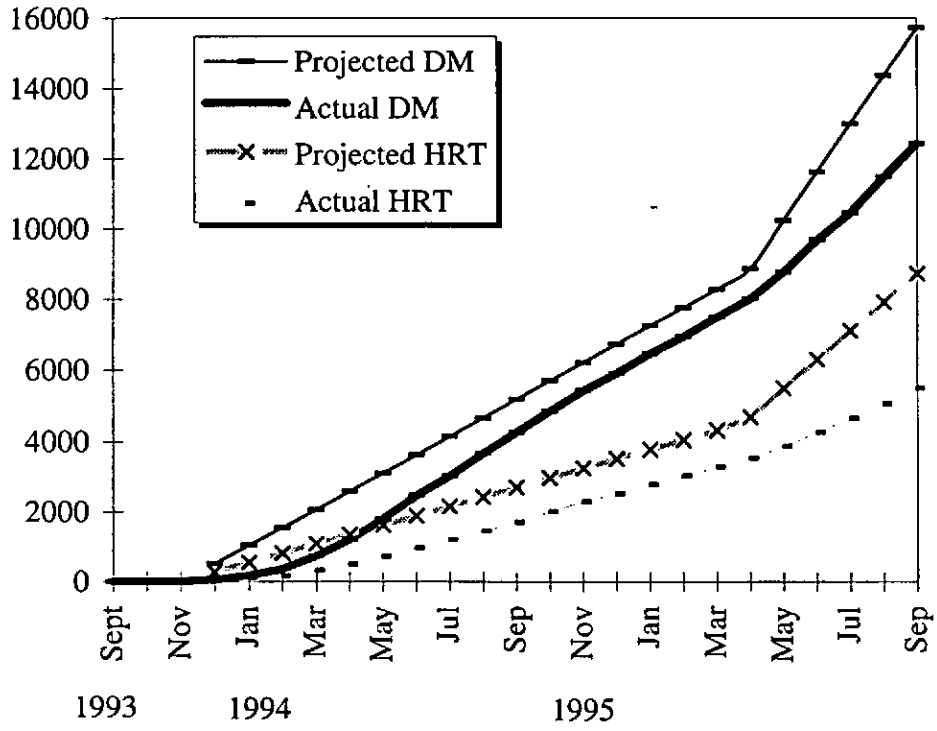
It has been the experience of many of the investigators that the incentives that are given to participants at various visits and milestones in the study are an important component to recruiting and retention. The investigators are working on ways to maximize our ability to bond women to the study, which will include judicious use of incentives, particularly for retention. These incentives do not need to be large, but it is important to have a variety and for the incentives to change as the study progresses.

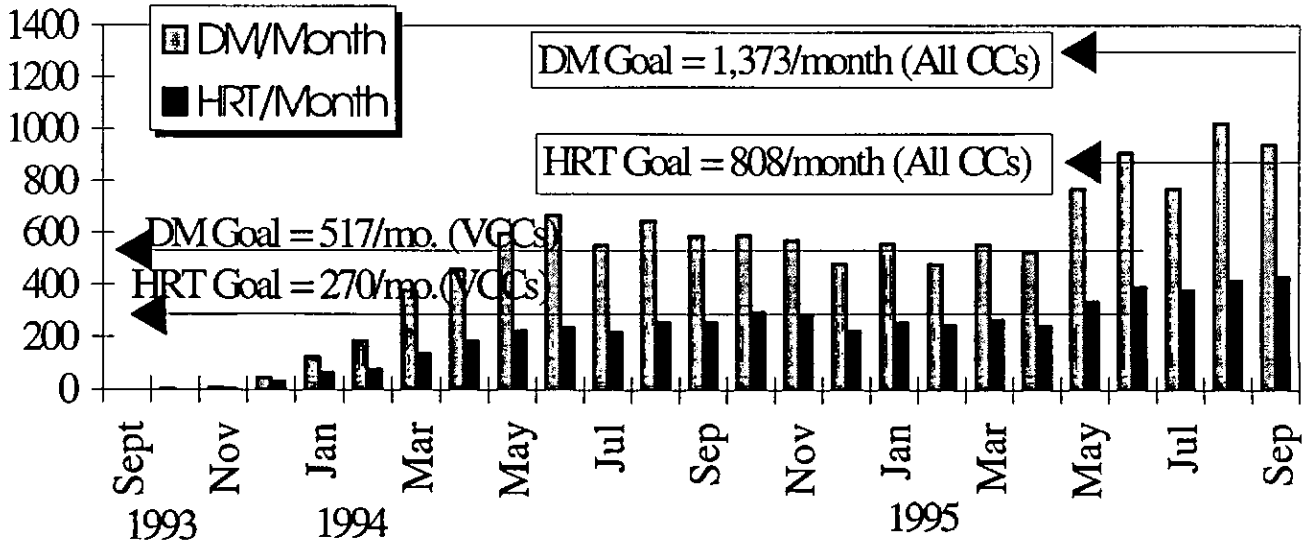
6. Concern for the Welfare of the Participant

It is more likely that the minority participant will not be integrated into a satisfactory healthcare system. While the WHI clinics are not structured to provide medical care, they provide counseling to the participant concerning health problems and assistance in obtaining referrals and care when issues are uncovered during the course of the study. This includes assisting participants in enrolling for healthcare programs for which they might be eligible and serving as a resource for advice concerning health matters. Information concerning various aspects of health are often provided to participants at the end of the clinic visits. These also serve as incentives. Some centers have a local newsletter which not only keeps participants informed about the study progress, but also serves as an additional resource for information on health.

The WHI continues to focus its efforts in recruiting minority participants. The Special Populations Subcommittee is currently compiling information on problems encountered to date and is developing a list of solutions and suggestions in order to enhance both recruitment and retention efforts in minority communities.

Figure 2.1
Cumulative DM and HRT Randomization and Goals





Data as of August 31, 1995

Table 2.2
Randomization Activity by Clinic Group, Study Component and Month

Data As Of: 08/31/95

Clinic Group: VCC

		HORMONE REPLACEMENT THERAPY RANDOMIZATIONS					DIET MODIFICATION RANDOMIZATIONS					TOTAL CLINICAL TRAIL RANDOMIZATIONS					
Year	Month	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	CT Number	CT Cum Number	HRT/DM Number	HRT/DM Cum #	Pct Overlap	Pct Cum Overlap
1993	September	0	0	0.0	0.0	0.00%	0	0	0.0	0.0	0.00%	0	0	0	0	0.00%	0.00%
	October	0	0	0.0	0.0	0.00%	1	1	0.0	0.0	0.00%	1	1	0	0	0.00%	0.00%
	November	3	3	0.0	0.0	0.00%	7	8	0.0	0.0	0.00%	8	9	2	2	25.00%	22.22%
	December	30	33	269.4	269.4	12.25%	45	53	517.2	517.2	10.25%	62	71	13	15	20.97%	21.13%
1994	January	65	98	269.4	538.7	18.19%	125	178	517.2	1034.3	17.21%	166	237	24	39	14.46%	16.46%
	February	77	175	269.4	808.1	21.66%	186	364	517.2	1551.5	23.46%	235	472	28	67	11.91%	14.19%
	March	137	312	269.4	1077.4	28.96%	379	743	517.2	2068.7	35.92%	451	923	65	132	14.41%	14.30%
	April	186	498	269.4	1346.8	36.98%	458	1201	517.2	2585.9	46.44%	560	1483	84	216	15.00%	14.57%
	May	226	724	269.4	1616.2	44.80%	598	1799	517.2	3103.0	57.98%	737	2220	87	303	11.80%	13.65%
	June	240	964	269.4	1885.5	51.13%	668	2467	517.2	3620.2	68.15%	806	3026	102	405	12.66%	13.38%
	July	223	1187	269.4	2154.9	55.08%	552	3019	517.2	4137.4	72.97%	671	3697	104	509	15.50%	13.77%
	August	260	1447	269.4	2424.2	59.69%	646	3665	517.2	4654.5	78.74%	799	4496	107	616	13.39%	13.70%
	September	260	1707	269.4	2693.6	63.37%	588	4253	517.2	5171.7	82.24%	745	5241	103	719	13.83%	13.72%
	October	295	2002	269.4	2963.0	67.57%	590	4843	517.2	5688.9	85.13%	763	6004	122	841	15.99%	14.01%
	November	288	2290	269.4	3232.3	70.85%	572	5415	517.2	6206.1	87.25%	750	6754	110	951	14.67%	14.08%
	December	226	2516	269.4	3501.7	71.85%	482	5897	517.2	6723.2	87.71%	613	7367	95	1046	15.50%	14.20%
1995	January	256	2772	269.4	3771.0	73.51%	557	6454	517.2	7240.4	89.14%	715	8082	98	1144	13.71%	14.15%
	February	247	3019	269.4	4040.4	74.72%	479	6933	517.2	7757.6	89.37%	637	8719	89	1233	13.97%	14.14%
	March	264	3283	269.4	4309.8	76.18%	541	7474	517.2	8274.7	90.32%	704	9423	101	1334	14.35%	14.16%
	April	213	3496	366.6	4676.3	74.76%	411	7885	595.6	8870.3	88.89%	553	9976	71	1405	12.84%	14.08%
	May	221	3717	366.6	5042.9	73.71%	467	8352	595.6	9465.9	88.23%	608	10584	80	1485	13.16%	14.03%
	June	214	3931	366.6	5409.5	72.67%	494	8846	595.6	10061.5	87.92%	627	11211	81	1566	12.92%	13.97%
	July	190	4121	366.6	5776.1	71.35%	385	9231	595.6	10657.1	86.62%	508	11719	67	1633	13.19%	13.93%
	August	189	4310	366.6	6142.7	70.17%	469	9700	595.6	11252.7	86.20%	603	12322	55	1688	9.12%	13.70%

WHIP1108 1.2

Table 2.2 (continued)

Data As Of: 08/31/95

Clinic Group: NCC

		HORMONE REPLACEMENT THERAPY RANDOMIZATIONS					DIET MODIFICATION RANDOMIZATIONS					TOTAL CLINICAL TRAIL RANDOMIZATIONS					
Year	Month	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	CT Number	CT Cum Number	HRT/DM Number	HRT/DM Cum #	Pct Overlap	Pct Cum Overlap
1995	February	0	0	0.0	0.0	0.00%	0	0	0.0	0.0	0.00%	0	0	0	0	0.00%	0.00%
	March	4	4	0.0	0.0	0.00%	13	13	0.0	0.0	0.00%	16	16	1	1	6.25%	6.25%
	April	31	35	0.0	0.0	0.00%	113	126	0.0	0.0	0.00%	131	147	13	14	9.92%	9.52%
	May	115	150	444.4	444.4	33.75%	301	427	775.8	775.8	55.04%	388	535	28	42	7.22%	7.85%
	June	176	326	444.4	888.9	36.67%	413	840	775.8	1551.5	54.14%	535	1070	54	96	10.09%	8.97%
	July	189	515	444.4	1333.3	38.62%	384	1224	775.8	2327.3	52.59%	514	1584	59	155	11.48%	9.79%
	August	230	745	444.4	1777.8	41.91%	552	1776	775.8	3103.0	57.23%	724	2308	58	213	8.01%	9.23%

WHIP1108 1.2

Table 2.3
CaD Randomization Activity and OS Enrollment Activity by Clinic Group and Month

Data As Of: 08/31/95

Clinic Group: VCC

		CALCIUM AND VITAMIN D SUPPLEMENTATION RANDOMIZATIONS					OBSERVATIONAL STUDY ENROLLMENTS				
Year	Month	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal
1994	September	0	0	0.0	0.0	0.00%	25	25	0.0	0.0	0.00%
	October	0	0	0.0	0.0	0.00%	148	173	0.0	0.0	0.00%
	November	0	0	0.0	0.0	0.00%	374	547	0.0	0.0	0.00%
	December	0	0	0.0	0.0	0.00%	500	1047	1077.4	1077.4	97.17%
1995	January	0	0	0.0	0.0	0.00%	621	1668	1077.4	2154.9	77.41%
	February	0	0	0.0	0.0	0.00%	982	2650	1077.4	3232.3	81.98%
	March	0	0	0.0	0.0	0.00%	1091	3741	1077.4	4309.8	86.80%
	April	0	0	0.0	0.0	0.00%	1037	4778	1240.7	5550.4	86.08%
	May	0	0	0.0	0.0	0.00%	1199	5977	1240.7	6791.1	88.01%
	June	118	118	0.0	0.0	0.00%	1010	6987	1240.7	8031.8	86.99%
	July	298	416	673.5	673.5	61.77%	880	7867	1240.7	9272.5	84.84%
	August	480	896	673.5	1347.0	66.52%	1110	8977	1240.7	10513.1	85.39%

Clinic Group: NCC

		CALCIUM AND VITAMIN D SUPPLEMENTATION RANDOMIZATIONS					OBSERVATIONAL STUDY ENROLLMENTS				
Year	Month	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal	Number	Cum. Number	Goal	Cum. Goal	Pct Cum Goal
1995	February	0	0	0.0	0.0	0.00%	22	22	0.0	0.0	0.00%
	March	0	0	0.0	0.0	0.00%	234	256	0.0	0.0	0.00%
	April	0	0	0.0	0.0	0.00%	481	737	0.0	0.0	0.00%
	May	0	0	0.0	0.0	0.00%	932	1669	1616.2	1616.2	103.27%
	June	0	0	0.0	0.0	0.00%	1194	2863	1616.2	3232.3	88.57%
	July	0	0	0.0	0.0	0.00%	1039	3902	1616.2	4848.5	80.48%
	August	0	0	0.0	0.0	0.00%	1345	5247	1616.2	6464.6	81.16%

WHIP1138 1.1

Table 2.4
Reasons for Refusing/Revoking Consent

Data as of: 08/31/95

Clinic Group: VCC

Consent Form Summary

Consent Name	Forms	Signed	%	Refused	%	Revoked	%	Unanswered	%
SCREENING CONSENT	35986	31210	86.73	3466	9.63	1285	3.57	25	.07
HRT CONSENT	17839	5735	32.15	8902	49.90	3177	17.81	25	.14
DMT CONSENT	17937	12395	69.10	2302	12.83	3219	17.95	21	.12

	Screening Consent		HRT Consent		DM Consent	
Reason Group	Refused/Revoked Count	Refused/Revoked Percent	Refused/Revoked Count	Refused/Revoked Percent	Refused/Revoked Count	Refused/Revoked Percent
CONFLICTS	114	2.40	418	3.46	47	0.85
CONTACTS	172	3.62	13	0.11	222	4.02
LIMITATIONS	304	6.40	3398	28.13	631	11.43
LOST CONTACT/DIED	14	0.29	5	0.04	14	0.25
OTHER	1330	27.99	1845	15.27	1138	20.61
PERSONAL	1672	35.19	423	3.50	1373	24.87
PROCEDURES	34	0.72	26	0.22	84	1.52
REASON NOT GIVEN	415	8.74	1292	10.70	933	16.90
REFUSAL	760	16.00	352	2.91	291	5.27
TRAVEL	360	7.58	140	1.16	418	7.57
TREATMENTS	159	3.35	1863	15.42	49	0.89
WORRIES	89	1.87	1363	11.28	21	0.38

WHIP1106 1.1

Table 2.4 (continued)

Data as of: 08/31/95

Clinic Group: NCC

Consent Form Summary

Consent Name	Forms	Signed	%	Refused	%	Revoked	%	Unanswered	%
SCREENING CONSENT	14786	13501	91.31	1058	7.16	222	1.50	5	.03
HRT CONSENT	4299	1490	34.66	2512	58.43	295	6.86	2	.05
DMT CONSENT	4214	3260	77.36	606	14.38	342	8.12	6	.14

	Screening Consent		HRT Consent		DM Consent	
Reason Group	Refused/Revoked Count	Refused/Revoked Percent	Refused/Revoked Count	Refused/Revoked Percent	Refused/Revoked Count	Refused/Revoked Percent
CONFLICTS	14	1.09	45	1.60	0	0.00
LIMITATIONS	39	3.05	601	21.41	82	8.65
OTHER	264	20.63	95	3.38	77	8.12
PERSONAL	369	28.83	50	1.78	159	16.77
PROCEDURES	8	0.63	1	0.04	15	1.58
REASON NOT GIVEN	144	11.25	370	13.18	185	19.51
REFUSAL	121	9.45	31	1.10	20	2.11
TRAVEL	87	6.80	20	0.71	47	4.96
TREATMENTS	33	2.58	345	12.29	11	1.16
WORRIES	4	0.31	68	2.42	4	0.42

WHIP1106 1.1

3. Baseline Characteristics

3.1 Design Parameters and Study Goals

The randomization scheme for WHI is based on a randomized permuted block algorithm, stratified by CC site, by age category (50-54, 55-59, 60-69, 70-79) and, for HRT, by hysterectomy status. The change in the design of the HRT as described in the previous report eliminated the unopposed estrogen arm from women with a uterus and increased the HRT sample size from 25,000 to 27,500. Women with an intact uterus are now randomized to PERT or placebo in a ratio of 1:1. Women post-hysterectomy are randomized to ERT or placebo, as before, though the randomization ratio has been adjusted to 1:1. The change in the randomization ratios was made to preserve power since we no longer envision pooling any treatment arms across hysterectomy strata for the primary analyses. To aid in balancing the power of the ERT vs. placebo and PERT vs. placebo comparisons, a target hysterectomy rate of 45% has been set. Formerly, randomization ratios were defined as 30:28:42 for ERT:PERT:placebo in HRT. The randomization ratio for DM is 4:6 for Intervention:Control.

Figure 3.1 - Partial Factorial Design shows the current number in each component. The number originally randomized to ERT and subsequently transitioned to PERT are shown in parentheses under the now closed ERT arm.

Figure 3.1
Partial Factorial Design

Number of women in each cell of the partial factorial design.

			HRT		
			Intact Uterus		Not Randomized
			Yes	No	
			3,320 (331)	2,066	9,575
DIET	Intervention	4,600	536 (79)	300	3,843
DIET	Control	6,876	701 (52)	495	5,732
DIET	Not Randomized	3,154	2,083 (200)	1,271	—
		14,630			

There is still a notable imbalance in the number assigned to each HRT arm as a result of the original design allocations. This imbalance should eventually be small but we will adjust for this change in design in the primary analyses by stratification on randomization date (prior to December 16, 1994).

Of the 11,476 women randomized into DM, 4,600 (40%) are randomized to the Intervention arm.

An additional monitoring concern for this study is the enrollment into CaD. While our experience to date is quite limited, we are nonetheless concerned to see whether existing randomization assignments will be balanced with respect to CaD participation. This is of particular interest for the DM component where the treatment is unblinded and the controls are given little in the way of tangible benefits for participation.

As a simple measure of bias in CaD participation associated with treatment arm, we classified the 896 women enrolled in CaD by their DM randomization assignment. Currently 38% of those enrolled in both CaD and DM are randomized to DM Intervention and 62% to DM control. Ideally these rates would be 40% and 60%. This discrepancy is not large but deserves further monitoring.

Age and, for HRT, hysterectomy status are important design factors in determining the required sample size for the CT. *Figure 3.2 - Age Distribution by Study Component and Hysterectomy Status* displays the distribution of age and hysterectomy status by study component. Note that the target age distribution for each component is 10%, 15%, 45% and 25% for the age categories 50-54, 55-59, 60-69, and 70-79, respectively. For HRT, the proportion of randomized women having had hysterectomies at baseline has been modified to reflect the redesign of HRT; the new target is 45%.

The study continues to experience a deficit in the oldest age category; only 17% of HRT participants and 14% of DM participants are 70-79 years of age. This represents a slight improvement from the 16% and 13% levels reported previously. With respect to uterine status, 41% of women randomized to HRT have had hysterectomies. While there is some variability in the degree, these trends are uniform across VCCs. At the August 2, 1994 Executive Committee meeting, VCCs were asked to begin targeting older women through preferential recruitment and screening of these women. In addition, a policy for monitoring and closing recruitment within design cells was also adopted in January 1995. Specifically, CCs reaching 85% of their total recruitment goal within a cell will be asked to stop further recruitment into that cell with the following exceptions: women currently in the screening pipeline may be randomized; minority women may always be recruited; a woman eligible for both HRT and DM may be randomized into both as long as one of these study components is open for her age category. In March 1995, seven VCCs were notified that they were to stop further recruitment into the 50-54 year old age category for DM and a subset of these were also to asked to discontinue accrual into HRT in this age group. Subsequently, other VCCs have been asked to stop recruitment of younger women, however the need to enhance recruitment efforts to the level of 2.5 full clinic equivalents has spurred a re-evaluation of this approach.

Race and ethnicity goals have been defined to assure the study's ability to address particular questions in minority populations. The study-wide goal is to recruit 20% of the WHI population from racial and ethnic minorities (as compared to the 1990 U.S. Census figure of 17%). To achieve this goal, CCs were awarded in two pools: Pool 1 CCs are obliged to recruit 60% of their enrollees (for CT and OS) from racial and ethnic minorities; Pool 2 CCs are asked to recruit minorities in proportion to their local population. Among VCCs, four Pool 1 clinics were named, each with a particular minority population focus: Atlanta (Black/African American); Birmingham (Black/African American); La Jolla (Hispanic); and

Tucson (Hispanic and Native American). There are six NCCs identified as Pool 1 clinics: Chicago-Rush (Black/African American); Detroit (Black/African American); Honolulu (Asian/Pacific Islander); Medlantic (Black/African American); Miami (Hispanic); San Antonio (Hispanic).

Race and ethnicity are determined by self-report on *Form 2/3 - Eligibility Screen* in accordance with the U.S. Census defined categories. *Figure 3.3 - Distribution of Race and Ethnicity* presents the distribution of race and ethnicity among all women randomized or enrolled to WHI by CC group and funding category (Pool 1 or 2).

Among Pool 1 VCCs, 26% of currently recruited women are from racial or ethnic minorities, with most of these being either Black/African American (16%) or Hispanic (7%). Among Pool 2 VCCs, minority women represent 8% of the accrued population. Among NCCs, Pool 1 sites have recruited 49% of their enrollees from racial or ethnic minorities, 21% Black/African American, 18% Asian/Pacific Islander and 8% Hispanic. Pool 2 NCC clinics have also recruited over 9% minorities. The minority recruitment rate is over 13% overall, and shows a modest increase (2%) in the last six months.

The Special Populations Advisory Committee is working with Pool 1 centers, the CCC, NIH and Porter-Novelli to facilitate greater recruitment of minority and lower SES women as well as those over age 70. (See *Section 2.4* for more detail).

3.2 Selected Baseline Predictors

To further characterize the recruited population, *Table 3.1 - Baseline Characteristics by Study Component* present the comparisons of selected baseline variables by study component.

- Demographic: race/ethnicity; marital status; income; education.
- General Health History: ever smoker; alcohol consumption.
- Breast Cancer risk factors: menarche; parity; age at first pregnancy; history of breast biopsy; family history of breast cancer; oophorectomy status.
- CHD risk factors: history of angina and MI; diabetes; current use of anti hypertensive medications and cholesterol lowering medications, family history of MI (males and females) before age 55 and at any age.

Table 3.2 - Physical Measures by Study Component shows the similar study component distributions for height, weight, body mass index, and systolic and diastolic blood pressures.

The differences between the two HRT cohorts defined by uterine status are of interest for study power considerations. HRT participants with a uterus tend to be of lower SES, more likely to have ever smoked, and more frequently report other key CHD risk factors (history of angina, MI and diabetes, on antihypertensive medications and some family history of MI). The concern in examining these factors is that the power for the comparisons within these cohorts is a function of the CHD event rate and differences in baseline risk factors may suggest differential event rates. If the women with a uterus indeed show a lower CHD risk profile, it may become necessary to adjust the planned size of these cohorts to preserve the

power of this treatment comparison. These discussions should occur over the next year as the estimates become more robust.

Figure 3.2
Age Distribution by Study Component and Hysterectomy Status

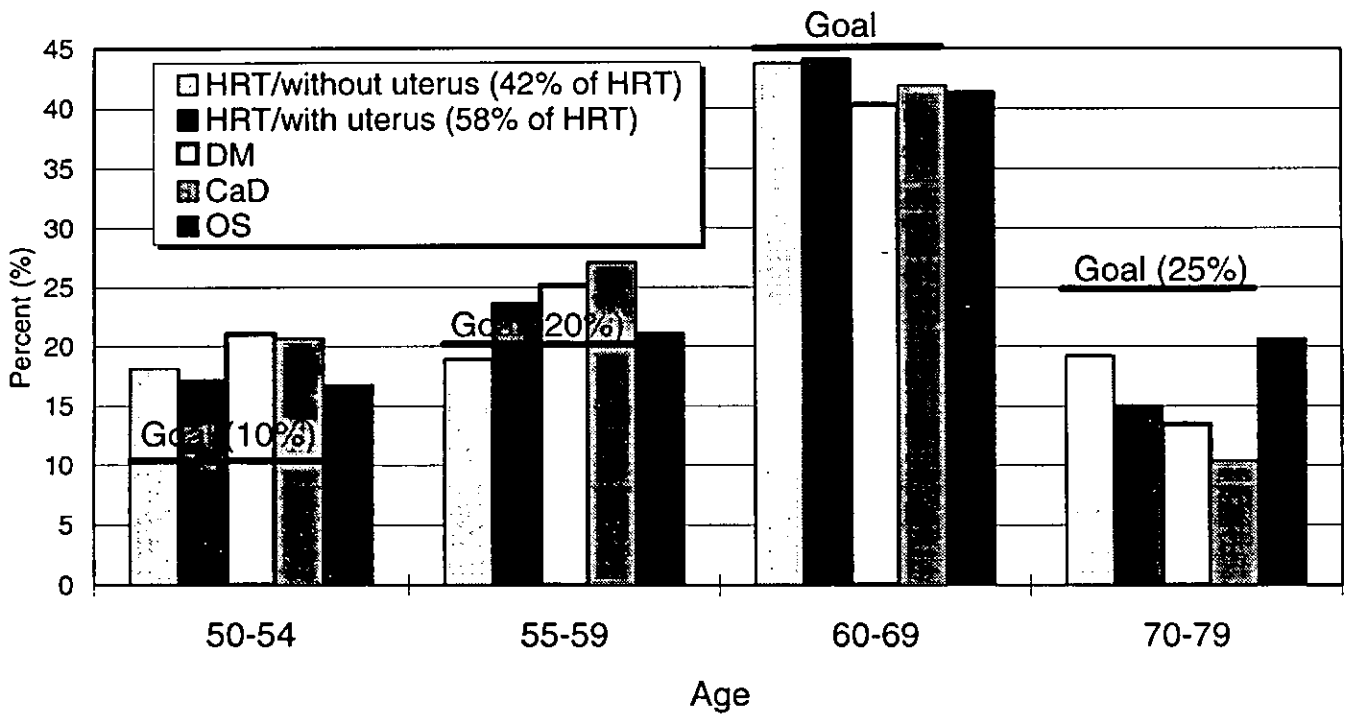


Figure 3.3
Distribution of Race and Ethnicity

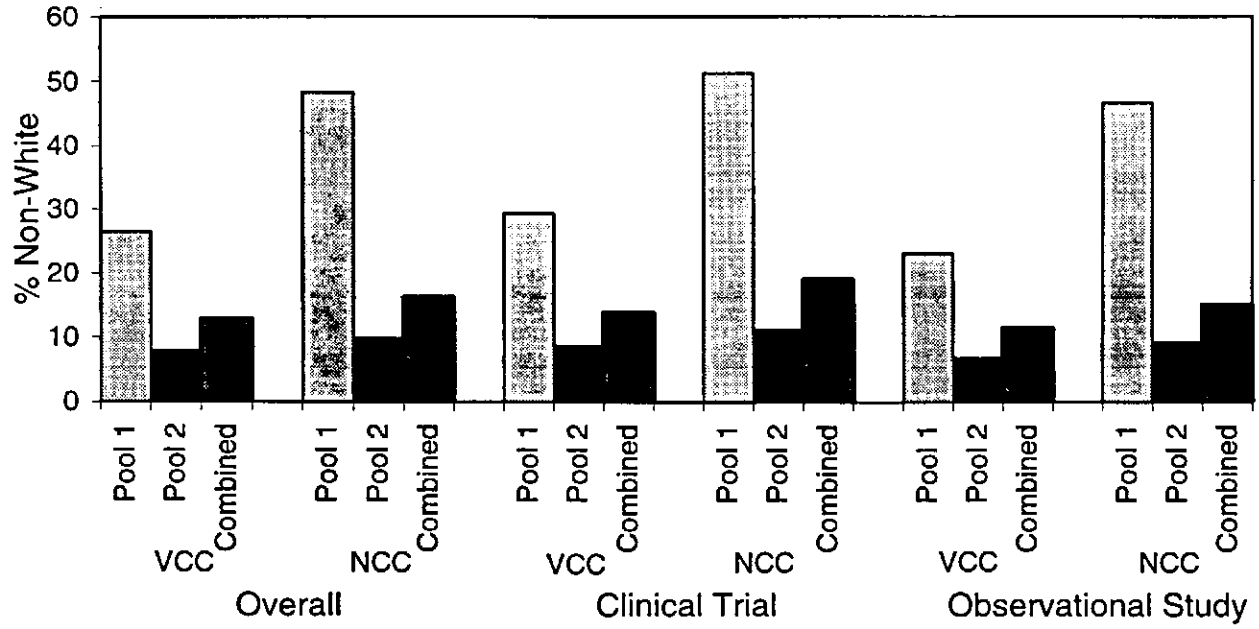


Table 3.1
Baseline Characteristics by Study Component

Demographics Data as of: 08/31/95

Short Verbiage	Question Response	Response Meaning	HRT w/o Uterus Count	HRT w/o Uterus Pct	HRT with Uterus Count	HRT with Uterus Pct	DM Count	DM Pct
Racial or ethnic group	1	American Indian or Alaskan Native	14	0.7	7	0.2	49	0.4
	2	Asian or Pacific Islander	19	0.9	30	1.0	92	0.8
	3	Black or African-American	310	15.0	199	6.7	1097	9.6
	4	Hispanic	83	4.0	110	3.7	282	2.5
	5	White	1624	78.6	2615	87.5	9851	85.8
	8	Other	11	0.5	23	0.8	85	0.7
		Value not entered	5	0.2	5	0.2	20	0.2
	Total		2066	100.0	2989	100.0	11476	100.0
Current marital status	1	Never married	58	2.8	119	4.0	499	4.3
	2	Divorced or separated	348	16.8	503	16.8	1673	14.6
	3	Widowed	428	20.7	503	16.8	1648	14.4
	4	Presently married	1198	58.0	1817	60.8	7449	64.9
	5	Marriage-like relationship	24	1.2	35	1.2	172	1.5
		Questionnaire not entered	2	0.1	3	0.1	2	0.0
		Value not entered	8	0.4	9	0.3	33	0.3
	Total		2066	100.0	2989	100.0	11476	100.0
Total family income	1	Less than $10,000	159	7.7	170	5.7	406	3.5
	2	$10,000 to $19,999	362	17.5	419	14.0	1268	11.0
	3	$20,000 to $34,999	588	28.5	800	26.8	2749	24.0
	4	$35,000 to $49,999	404	19.6	621	20.8	2452	21.4
	5	$50,000 to $74,999	279	13.5	485	16.2	2243	19.5
	6	$75,000 to $99,999	93	4.5	209	7.0	972	8.5
	7	$100,000 to $149,999	49	2.4	111	3.7	560	4.9
	8	$150,000 or more	19	0.9	49	1.6	238	2.1
	9	Don't know	57	2.8	50	1.7	238	2.1
		Questionnaire not entered	2	0.1	3	0.1	2	0.0
		Value not entered	54	2.6	72	2.4	348	3.0
	Total		2066	100.0	2989	100.0	11476	100.0

Table 3.1 (continued)

Demographics Data as of: 08/31/95 (continued)

Short Verbiage	Question Response	Response Meaning	HRT w/o Uterus Count	HRT w/o Uterus Pct	HRT with Uterus Count	HRT with Uterus Pct	DM Count	DM Pct
Highest grade in school	1	Didn't go to school	9	0.4	2	0.1	5	0.0
	2	Grade school (1-4 years)	20	1.0	26	0.9	28	0.2
	3	Grade school (5-8 years)	41	2.0	43	1.4	104	0.9
	4	Some high school (9-11 years)	130	6.3	119	4.0	339	3.0
	5	High school diploma or GED	456	22.1	586	19.6	2027	17.7
	6	Vocational or training school	272	13.2	322	10.8	1192	10.4
	7	Some college or Associate Degree	608	29.4	819	27.4	3357	29.3
	8	College graduate or Baccalaureate De	156	7.6	287	9.6	1232	10.7
	9	Some post-graduate or professional	172	8.3	337	11.3	1278	11.1
	10	Master's Degree	167	8.1	374	12.5	1650	14.4
	11	Doctoral Degree	19	0.9	61	2.0	225	2.0
		Questionnaire not entered	2	0.1	3	0.1	2	0.0
		Value not entered	14	0.7	10	0.3	37	0.3
	Total		2066	100.0	2989	100.0	11476	100.0
General Health History Data as of: 08/31/95								
Smoked 100 cigarettes	0	No	1068	51.7	1428	47.8	5788	50.4
	1	Yes	991	48.0	1535	51.4	5620	49.0
		Questionnaire not entered	2	0.1	8	0.3	20	0.2
		Value not entered	5	0.2	18	0.6	48	0.4
	Total		2066	100.0	2989	100.0	11476	100.0
12 alcoholic drinks ever	0	No	302	14.6	340	11.4	1186	10.3
	1	Yes	1754	84.9	2631	88.0	10239	89.2
		Questionnaire not entered	2	0.1	8	0.3	20	0.2
		Value not entered	8	0.4	10	0.3	31	0.3
	Total		2066	100.0	2989	100.0	11476	100.0

Table 3.1 (continued)

Breast Cancer Risk Factors Data as of: 08/31/95

Short Verbiage	Response Range	HRT w/o Uterus Count	HRT w/o Uterus Pct	HRT with Uterus Count	HRT with Uterus Pct	DM Count	DM Pct
Age at first period	0-9	39	1.9	37	1.2	156	1.4
	10	105	5.1	147	4.9	539	4.7
	11	283	13.7	425	14.2	1729	15.1
	12	535	25.9	758	25.4	3042	26.5
	13	585	28.3	860	28.8	3393	29.6
	14	276	13.4	427	14.3	1471	12.8
	15	123	6.0	182	6.1	645	5.6
	16	90	4.4	115	3.8	369	3.2
	17 or older	27	1.3	28	0.9	105	0.9
	Questionnaire not entered	0	0.0	2	0.1	4	0.0
	Value not entered	3	0.1	8	0.3	23	0.2
	Total	2066	100.0	2989	100.0	11476	100.0
How many live births	1	169	8.2	232	7.8	981	8.5
	2	473	22.9	699	23.4	2888	25.2
	3	471	22.8	754	25.2	2824	24.6
	4	352	17.0	461	15.4	1756	15.3
	5	214	10.4	249	8.3	831	7.2
	6	91	4.4	134	4.5	400	3.5
	7	45	2.2	64	2.1	202	1.8
	8 or more	65	3.1	69	2.3	210	1.8
	None	50	2.4	80	2.7	302	2.6
	Questionnaire not entered	0	0.0	2	0.1	4	0.0
	Value not entered	136	6.6	245	8.2	1078	9.4
	Total	2066	100.0	2989	100.0	11476	100.0
Age first full-term	0-20	438	21.2	393	13.1	1544	13.5
	20-24	849	41.1	1178	39.4	4687	40.8
	25-29	341	16.5	640	21.4	2423	21.1
	30-34	85	4.1	189	6.3	621	5.4
	35-39	14	0.7	46	1.5	157	1.4
	40-44	2	0.1	8	0.3	19	0.2
	45 or older	0	0.0	1	0.0	2	0.0
	Questionnaire not entered	0	0.0	2	0.1	4	0.0
	Value not entered	337	16.3	532	17.8	2019	17.6
	Total	2066	100.0	2989	100.0	11476	100.0

Table 3.1 (continued)

Breast Cancer Risk Factors Data as of: 08/31/95 (continued)

Short Verbiage	Question Response	Response Meaning	----HRT----- w/o Uterus Count	Pct	------HRT------ with Uterus Count	Pct	-----DM----- Count	Pct
Female relative breast cancer	0	No	757	36.6	1053	35.2	4065	35.4
	1	Yes	331	16.0	459	15.4	1935	16.9
	9	Don't know	12	0.6	16	0.5	99	0.9
		Questionnaire not entered	2	0.1	5	0.2	12	0.1
		Value not entered	964	46.7	1456	48.7	5365	46.7
	Total		2066	100.0	2989	100.0	11476	100.0
Breast Biopsy Ever		No	1742	84.3	2590	86.7	9537	83.1
		Yes	313	15.2	390	13.0	1908	16.6
		Value not entered	11	0.5	9	0.3	31	0.3
	Total		2066	100.0	2989	100.0	11476	100.0
One or both ovaries removed	0	No	842	40.8	2848	95.3	8041	70.1
	1	Yes, one was taken out	283	13.7	101	3.4	845	7.4
	2	Yes, both were taken out	753	36.4	8	0.3	2221	19.4
	3	Yes, unknown number taken out	68	3.3	1	0.0	96	0.8
	4	Yes, part of an ovary was taken out	47	2.3	16	0.5	120	1.0
	9	Don't know	63	3.0	4	0.1	110	1.0
		Questionnaire not entered	0	0.0	2	0.1	4	0.0
		Value not entered	10	0.5	9	0.3	39	0.3
	Total		2066	100.0	2989	100.0	11476	100.0
CHD Risk Factors Data as of: 08/31/95								
Angina	0	No	1932	93.5	2884	96.5	10955	95.5
	1	Yes	122	5.9	83	2.8	455	4.0
		Questionnaire not entered	2	0.1	2	0.1	7	0.1
		Value not entered	10	0.5	20	0.7	59	0.5
	Total		2066	100.0	2989	100.0	11476	100.0
Heart attack ever	0	No	2000	96.8	2960	99.0	11311	98.6
	1	Yes	66	3.2	29	1.0	165	1.4
	Total		2066	100.0	2989	100.0	11476	100.0
Current Antihypertensive Meds		No	1570	76.0	2487	83.2	8880	77.4
		Yes	496	24.0	502	16.8	2596	22.6
	Total		2066	100.0	2989	100.0	11476	100.0

Table 3.1 (continued)

CHD Risk Factors Data as of: 08/31/95 (continued)

Short Verbiage	Question Response	Response Meaning	----HRT----- w/o Uterus Count	Pct	------HRT------ with Uterus Count	Pct	-----DM----- Count	Pct
Current High Cholesterol Meds		No	1938	93.8	2845	95.2	10877	94.8
		Yes	128	6.2	144	4.8	599	5.2
	Total		2066	100.0	2989	100.0	11476	100.0
Family History of MI - Any Female		No	1295	62.7	1998	66.8	7639	66.6
		Yes	521	25.2	624	20.9	2525	22.0
		Don't know	45	2.2	74	2.5	232	2.0
		Value not entered	205	9.9	293	9.8	1080	9.4
	Total		2066	100.0	2989	100.0	11476	100.0
Family History of MI - Any Female <55		No	769	37.2	1045	35.0	4158	36.2
		Yes	101	4.9	119	4.0	478	4.2
		Don't know	75	3.6	111	3.7	365	3.2
		Value not entered	1121	54.3	1714	57.3	6475	56.4
	Total		2066	100.0	2989	100.0	11476	100.0
Family History of MI - Any Male		No	1074	52.0	1638	54.8	6251	54.5
		Yes	798	38.6	1114	37.3	4273	37.2
		Don't know	48	2.3	70	2.3	259	2.3
		Value not entered	146	7.1	167	5.6	693	6.0
	Total		2066	100.0	2989	100.0	11476	100.0
Family History of MI - Any Male <55		No	1532	74.2	2362	79.0	8914	77.7
		Yes	302	14.6	336	11.2	1426	12.4
		Don't know	86	4.2	124	4.1	442	3.9
		Value not entered	146	7.1	167	5.6	694	6.0
	Total		2066	100.0	2989	100.0	11476	100.0

Table 3.2
Physical Measures by Study Component

Measure	HRT	DM	Total
Weight (kg)	75.6 (0.2)	75.7 (0.1)	75.3 (0.1)
Height (cm)	161.8 (0.1)	162.5 (0.1)	162.3 (0.1)
BMI	28.9 (0.1)	28.8 (0.1)	28.7 (0.1)
Systolic BP	128.7 (0.3)	127.8 (0.2)	127.9 (0.2)
Diastolic BP	76.4 (0.1)	76.1 (0.1)	76.1 (0.1)

4. Follow-up and Retention

4.1 Overview

Routine follow-up contacts for the CT are designed to ascertain outcomes, assure safety, and assess and promote adherence to interventions. The follow-up schedule consists of annual clinic visits for all CT women, a semi-annual clinic visit for HRT women and a semi-annual contact (visit, telephone or mail contact at CC discretion) for DM women, and a telephone contact at six weeks post-randomization for HRT women. The Protocol defines a 4-week interval surrounding the anniversary of randomization, or surrounding the six month time point post-randomization as the designated contact window.

4.2 Adherence to Follow-up Procedures

Table 4.1 - Adherence to Follow-up Procedures summarizes adherence to the follow-up protocol by time since randomization, and study component. Women are considered to have been due for a contact if the corresponding 4-week contact window was completed by August 31, 1995, indicating that a contact should have occurred. Current data indicate that approximately 94% of the first semi-annual visits (SAV-1) required to date have been conducted, with 70% occurring within the 4-week window overall; in 94% of these visits all of the required data collection procedures have been completed.

For the first annual visit (AV1), 89% have been conducted, 67% within the four week window and 60% have completed all data collection activities. The corresponding statistics for the second semi-annual visit (SAV-2), while somewhat unstable based on the small numbers, are 79% conducted, 59% in window and 89% complete. For both SAV-1 and AV1, this represents a modest improvement in compliance with the procedures, attributable to more focus on follow-up at the VCCs and a slight relaxation in the definition of a visit occurrence.

There are small differences in follow-up rates between study components, HRT rates being slightly higher than DM. While small, these differences are likely to be persistent as women on HRT have to attend follow-up visits to stay on their hormones. This linkage between intervention and follow-up does not exist in DM so the perceived need to attend visits may be less in DM.

Clinical Center specific follow-up rates range from 83% to 99% for the SAV-1 and 52% to 99% for the AV1. Further discussion of monitoring and improving CC-specific performance may be found in *Section 8 - Clinical Center Performance Summary.*

Completeness of visits is lower than desirable, especially for AV1. Several factors contribute to this including lag time to key entry and assorted data problems and the difficulties in obtaining lab results from outside organizations.

Completeness of visits is greater for DM than HRT, undoubtedly because the number of procedures are fewer. HRT women are required to have annual mammograms and pelvic exams whereas DM women need only biennial mammography. As many of these activities

require requesting information from local providers, there may be a noticeable delay in completing the required activities.

Clinical Center specific completeness rates range from 84% to 98% for SAV-1 and 16% to 83% for AV1. The SAV-2 data are too sparse to break down by CC. This area requires increased attention and monitoring on the part of CCs, the CCC and the study committees.

4.3 Retention

Women may refuse to participate in continued intervention or follow-up activities. Women who withdraw from further intervention are strongly encouraged to participate in routine follow-up procedures to promote complete outcome ascertainment. Women who decline Protocol-defined safety related follow-up procedures are to be withdrawn from the intervention. Reports of women changing their participation status post-randomization and associated reasons are to be submitted on *Form 7 - Participation Status*.

Table 4.2 - Participation Status summarizes the current number of women who have asked to stop either their usual follow-up contacts or their intervention by study component and randomization assignment with an average follow-up time of nine months, approximately one half of one percent are not being followed according to the normal procedures, usually at the woman's request. Procedures for maintaining contact and for conducting limited surveillance of health and vital status are under review.

Currently 372 (7.4%) of the 5,055 women randomized to HRT have discontinued use of study hormones indefinitely. Removing the 331 women who were originally randomized to ERT and moved to PERT, of whom 22.7% stopped hormones, we would have an intervention drop-out rate of 6.3%. Estimating an average 9.0 months of follow-up for HRT and assuming an exponential drop-out rate for the first year, this would suggest the annual rate to be approximately 8.1%, as compared to a design assumption of 6%.

For DM, 1.8% of women randomized to the intervention have stopped the intervention activities. Assuming an average 9.2 months of follow-up and an exponential drop-out rate, we would project an annual rate of 2.4%.

Table 4.3 - Reasons for Stopping Interventions summarizes the frequency of reported reasons for stopping interventions by study component. The most commonly cited reasons for stopping HRT are: intervention related issues (54%) and health reasons (30%). Personal reasons (48%) were the most often stated among DM stopping intervention, followed by other (28%), intervention (21%) and health reasons (19%).

Table 4.1
Adherence to Follow-up Procedures

	Number due	Number Conducted	Number Conducted in Window	Number Fully Completed
6-week contact				
HRT	3469	2942 (85%)		
SAV-1	**8418**	**7908 (94%)**	**5882 (70%)**	**7431 (94%)**
HRT	2897	2763 (95%)	2328 (80%)	2264 (82%)
DM	6707	6278 (94%)	4494 (67%)	6087 (97%)
Intervention	2690	2543 (95%)	1821 (68%)	
Control	4017	3735 (93%)	2673 (67%)	
AV1	**4072**	**3614 (89%)**	**2731 (67%)**	**2168 (60%)**
HRT	1304	1203 (92%)	908 (70%)	418 (35%)
DM	3320	2921 (88%)	2202 (66%)	1937 (66%)
Intervention	1322	1188 (90%)	893 (68%)	
Control	1998	1733 (87%)	1309 (66%)	
SAV-2	**351**	**278 (79%)**	**202 (59%)**	**248 (89%)**
HRT	143	121 (85%)	99 (69%)	90 (74%)
DM	261	199 (76%)	142 (54%)	191 (96%)
Intervention	100	74 (74%)	57 (57%)	
Control	161	125 (78%)	85 (53%)	

Table 4.2
Participation Status

	N	Stopped Follow-up	Stopped Intervention
HRT[1]	**5055**	**29 (0.6%)**	**372 (7.4%)**
ERT → PERT	331	3 (0.9%)	75 (22.7%)
DM[2]	**11476**	**58 (0.5%)**	
Intervention	4600	18 (0.4%)	85 (1.8%)
Control	6876	40 (0.6%)	n.a.

[1] Average follow-up time for HRT participants is 9.0 months.

[2] Average follow-up time for DM participants is 9.2 months.

Table 4.3
Reasons for Stopping Interventions

Reasons[1]	HRT (N = 372)	DM (N = 85)
Personal	20 (5%)	41 (48%)
Travel	1 (0.3%)	3 (4%)
Study Procedures	5 (1%)	5 (6%)
Health	111 (30%)	16 (19%)
Intervention	201 (54%)	18 (21%)
Other	73 (20%)	24 (28%)
Not Given	22 (6%)	9 (11%)

[1] Multiple reasons may be reported for a woman

5. HRT Intervention Status

5.1 Adherence to Medication

Adherence to medications is assessed by medication rates and changes to study-prescribed hormones. Medication rates are determined by data collected at routine follow-up clinic visits using the actual or estimated number of tablets remaining in the returned bottles and the length of the interval between visits. For this report, women are considered to be adherent to HRT if they have taken 80% or more of their randomized medication for the given interval.

Protocol-defined changes to study medications occur because of hormone related symptoms, other adverse effects or hysterectomy. These changes can be to add progesterone, change to an open-label hormone, or change to another blinded study hormone (from PERT to ERT after a hysterectomy).

Table 5.1 - HRT Adherence Summary presents the proportion of women who were adherent to study hormones (excluding the 331 women with a uterus originally randomized to ERT) by time since randomization and study arm. Two approaches were used to handle women for whom pill counts or estimates were not available. The first column assumes that women without a pill count for this time point (10% at SAV-1 and 17% at AV1) are non-adherent (taking < 80% of pills), giving the most conservative estimate. The second column presents data limited to those women from whom we obtained a pill count or an estimated count (about 3% of participant gave estimates). Since we expect that those women who do not come to clinic or who forget to bring their bottles are likely to be less adherent than average, we believe the true value to lie somewhere between these estimates. This implies that the six month adherence rate is between 81% and 90%, and the annual rate is between 72% and 86%. The data for SAV-2 are too sparse yet to be reliable.

There is little variability between CCs when examining adherence using the best case scenario. The greater variability between clinics observed in the worst case scenario is associated with obtaining the adherence values, a function of loss to follow-up and incomplete or missing visits.

To better understand the HRT adherence patterns, *Table 5.2 - Risk Factors for HRT Adherence* presents these same adherence measures by age, ethnicity, hysterectomy status and performance of the 6-week call for both SAV-1 and AV1. Education and ethnicity have a strong effect on adherence as does the performance of the 6-week phone contact. Age and hysterectomy status were not strong predictors of adherence.

A number of women have had changes in their prescribed study medications. First, the 331 women with a uterus originally randomized to ERT have been transitioned to PERT (see *Section 5.6 - ERT to PERT Transition*). Other changes in medications include: two women changed from PERT to ERT following post randomization hysterectomies; 2 PERT women changed to ERT to manage other symptoms; and one woman changed from ERT to PERT after correcting the data error in the woman's hysterectomy status.

Finally, as noted in *Section 4.2 - Adherence to Follow-up Procedures*, 372 (7.4%) HRT women have discontinued study medications entirely.

5.2 Symptoms

Women may report symptoms potentially related to HRT at routine follow-up contacts or through non-routine contacts with the CC. The primary symptoms being monitored are bleeding and breast changes.

Bleeding among women with a uterus is a significant problem in the first year on study. *Table 5.3 - Reports of Bleeding* presents the number of reports of bleeding (among women with a uterus) by contact type. Twenty-five percent of these women reported bleeding at their six week contact, and at the first semi-annual contact, and 12% at the first annual contact. Though SAV-2 data are still scanty, the prevalence of bleeding at one year appears to be diminishing.

Table 5.4 - Other HRT Symptoms summarizes the breast changes at the 6 week, semi-annual and annual visits and at non-routine contacts. Note that a delay in implementing the data collection procedures for these symptoms reduces the available sample size compared to other displays.

5.3 Adverse Effects

Table 5.5 - Reports of Adverse Effects lists all reports submitted to the CCC. There have been six reports of adverse effects in the last 6 months: two new diagnoses of DVT, one case of cholecystitis; one pulmonary embolism, and four deaths.

5.4 Unblinding

Unblinding to the HRT randomization assignment is indicated for management of severe symptoms and for serious adverse effects. See WHI Manuals, *Vol. 2 - Procedures, Section 5.4 - Managing Symptoms, Section 5.5 - Major Health Problems* and *Section 5.6 - Unblinding* for details. As of August 31, 1995, 111 (2.2%) HRT participants' assignment had been unblinded. The primary reason for unblinding is persistent bleeding at 6 months post-randomization. In these instances, the protocol allows for the consulting gynecologist to be unblinded to better assess the need for an endometrial aspiration. The remaining cases represent unblinding for other symptoms, medical conditions, provider request and clinic error, 20 cases in total. A monthly review of unblinding occurrences has been initiated.

5.5 ERT to PERT Transition

By December 16, 1994, 331 non-hysterectomized women had been randomized to ERT. In January 1996, these women were personally contacted by the clinic and informed of the change in protocol. The CCC also sent information to all HRT participants regarding this change. Beginning in February and as soon thereafter as the local IRB approvals were in place, these women were transitioned to PERT. The transition required several steps including signing a new consent, having an endometrial aspiration if on ERT for eight or more months, taking MPA 10mg for 30 days and then changing to the PERT arm. All of these 331 women were unblinded but no other HRT participants were unblinded as a result. Clinics made every reasonable effort to keep all staff except the Clinic Practitioner blinded to these women's randomization assignments.

The initial response of these women to the change was positive and accepting. After the transition began, however, many women experienced symptoms, particularly bleeding. Though this was expected, many women have found it troublesome. To date 75 (23%) of these women have discontinued their hormones, 52 (69%) of whom cited intervention related issues, 12 (16%) claimed health reasons, and 2 (3%) mentioned WHI procedures as reasons for stopping.

Endometrial aspirations performed for these women (65 at AV1, 98 unscheduled) have yielded nine positive results: 5 with cystic hyperplasia, 2 with adenomatous hyperplasia and 2 having adenomatous hyperplasia with atypia.

Table 5.1
HRT Adherence Summary

	All Participants[1]		Participants with Pill Counts[1]	
	N	% Adherent[2]	N	% Adherent
SAV-1	2566	81.3	2321	89.9
AV1	1135	71.8	942	86.3

[1] Excludes 331 ERT-PERT participants and includes participants that stopped intervention/meds.

[2] If no collection then considered < 80% adherent.

Table 5.2
Risk Factors for HRT Adherence

	All HRT Participants[1]		Total Participants with Pill Counts[1]	
	N	% Adherent[2]	N	% Adherent
SAV-1	**2566**	**81.3**	**2321**	**89.9**
Age				
50-54	461	78.5	411	87.8
55-59	530	80.8	475	90.1
60-69	1154	83.3	1056	91.0
70-79	421	79.8	379	88.7
Ethnicity				
Non-white	352	71.0***	303	82.5***
White	2209	83.0	2015	91.0
Education				
0-8 Years	73	64.4***	57	82.5
Some H.S. or diploma	680	82.1	620	90.0
Any school after H.S.	1802	81.7	1634	90.1
Hysterectomy				
No	1347	82.0	1222	90.5
Yes	1219	80.5	1099	89.2
Had 6-week Call[3]				
No	195	68.2***	157	84.7*
Yes	1431	83.2	1318	90.4
AV1	**1135**	**71.8**	**942**	**86.3**
Age				
50-54	184	71.3	151	85.4
55-59	267	69.7	220	84.5
60-69	526	73.4	442	87.3
70-79	158	70.9	129	86.8
Ethnicity				
Non-white	132	62.9*	106	78.3*
White	998	72.9	834	87.3
Education				
0-8 Years	39	53.8*	29	72.4
Some H.S. or diploma	306	74.2	257	88.3
Any school after H.S.	784	71.9	655	86.1
Hysterectomy				
No	590	71.4	486	86.4
Yes	545	72.2	456	86.2
Had 6-week Call[3]				
No	28	42.9**	16	75.0
Yes	169	70.1	134	87.3

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[1] Excludes 331 ERT-PERT participants and includes participants that stopped intervention/meds.
[2] If no collection then considered < 80% adherent.
[3] Only includes participants randomized after 7/15/94.

Table 5.3
Reports of Bleeding

Data As Of: 08/31/95

	With Uterus	
6 Week HRT Phone Call		
Number with a *Form 10*[1]	1740	
Number with Bleeding	441	25.3%
Semi-Annual Visit 1		
Number Having Visit	1635	
Number with Bleeding	409	25.0%
Annual Visit 1		
Number Having Visit	808	
Number with Bleeding	100	12.4%
Semi-Annual Visit 2		
Number Having Visit	109	
Number with Bleeding	7	6.4%

[1] *Only includes participants randomized after 7/15/94.*

Table 5.4
Other HRT Symptoms

Data As Of: 08/31/95

	Without Uterus		With Uterus	
6 Week HRT Phone Call				
Number with a *Form 10*[1]	1495		2168	
Number with Breast Changes	152	10.2%	317	14.6%
Semi-Annual Visit 1				
Number with a *Form 10*	1093		1480	
Number with Breast Changes	105	9.6%	179	12.1%
Annual Visit 1				
Number with a *Form 10*	479		669	
Number with Breast Changes	43	9.0%	48	7.2%
Semi-Annual Visit 2				
Number with a *Form 10*	45		84	
Number with Breast Changes	2	4.4%	8	9.5%

[1] *Only includes participants randomized after 7/15/94.*

Table 5.5
Reports of Adverse Effects

WHI Number ID	Current Age	Adverse Reaction	Date of Onset
21-10-198P	71	DVT	6/18/94
28-10-619G	55	DVT	9/13/94
21-10-553Z	68	Pulmonary Embolism	3/13/95
30-11-750M	69	DVT	3/28/95
21-11-678X	52	DVT	5/2/95
30-11-215G	75	Cholecystitis	6/1/95
12-12-486	78	Death	9/25/95
24-10-446	72	Death	1/25/95
23-12-029	54	Death	9/25/95 (reported)
28-12-495	68	Death	6/7/95 (reported)

6. DM Modification Intervention Status

6.1 Timeliness of Intervention

Because the Dietary Modification intervention is delivered in a group format, the first major hurdle in conducting the DM Intervention is starting groups. Ideally, all women in the Intervention arm should start attending group sessions within 12 weeks of randomization. Waiting times of 20 weeks or more are a concern because of the lesser amount of intervention that can be delivered before the first Annual Visit. Once randomized, the CC nutritionists make monthly contacts (phone or mail) with DM Intervention participants to discuss group starting times. Women waiting four weeks receive a copy of *Your New Eating Style*, a brief overview of the intervention.

Table 6.1 - Timeliness of Intervention Group Formation describes the waiting time for women to begin their first intervention session by clinic group. Currently 3331 (72%) of the 4600 women randomized to DM Intervention have begun sessions. Of these 7% waited 20 weeks or more for their first session. Of the 1269 women waiting to begin sessions, 10% have waited 20 weeks or more.

Table 6.1
Timeliness of Intervention Group Formation

	VCC		NCC		Total
Randomized to Intervention	3888		712		4600
Intervention Started	3206 (82.5%)		125 (17.6%)		3331 (72.4%)
Waited ≥ 20 weeks	236 (7.4%)		2 (1.6%)		238 (7.1%)
Awaiting Intervention	682 (17.5%)		587 (82.4%)		1269 (27.6%)
Waiting ≥ 20 weeks	127 (18.6%)		0 (0.0%)		127 (10.0%)

6.2 Adherence to the Intervention Program

Adherence to the DM intervention is assessed by a variety of methods including attendance to group intervention sessions, completing make-up sessions, and by self-monitoring reports of fat, fruit, vegetable, and grain scores. Sessions 4, 8 and 12 are used as indicators of performance during year one of the intervention.

Table 6.2 - Intervention Program Adherence Summary describes the performance of DM Intervention women at these three sessions. Attendance is relatively high over the first 6 (weekly) sessions with 86% attending Session 4. When the sessions move to every other week beginning at Session 7, attendance declines (79% at Session 8 and 71% at Session 12). Experience from the Women's Health Trial suggests that attendance will decline when the time interval between sessions becomes longer. However, attendance was found to be

positively correlated with attaining fat intake goals, emphasizing the value of promoting attendances.

Completeness is defined as session attendance after taking into account make-up sessions. Make-up sessions may be completed by attending a different group or by individual session with a group nutritionist. The effect of make-up compared to regular group attendance on attaining intervention goals is unknown. Make-up sessions do increase staff workload and clinics are encouraged to minimize the need for make-up sessions. Completeness is above 90% for Sessions 1 through 14 and greater than 96% for the weekly sessions (1 - 6).

Self monitored fat gram scores are collected and recorded at each session beginning with Session 3 so that participants and nutritionists can track progress toward the goal. The CCC monitors fat scores collected at Sessions 4, 8, 12, and 16, with the expectation that participants should have attained their fat gram goals by Session 8. Nutritionists provide additional assistance, at a minimum after Sessions 8, 12, and 16 to women exceeding their fat gram goals by 25%. This self-monitoring was also found to be correlated positively with attaining fat intake goals so it is important for participants to maintain self-monitoring.

Self monitoring scores were obtained from 94% of participants at Session 4, 89% at Session 8 and 85% at Session 12. Because missing values are potential indicators of poorer adherence, the complete collection of these data is a priority. Among those women with scores available, the average reported fat score was lower than the average goal beginning at Session 4 and continuing through Session 18. At Session 12, 78% of women were less than their goal and 91% were within 5 grams of achieving their goal.

Self-monitored fruit/vegetable and grain scores are collected and recorded at each session beginning at Session 8 so that participants and nutritionists can track progress toward the goal. The CCC monitors fruit/vegetable scores at Sessions 8, 12, and 16, with the expectation that participants should have attained their fruit/vegetable goal of 5 servings per day by Session 12. The goal for grains is six or more servings per day. Over 85% of women provided fruit/vegetable and grain scores at Session 12. The average scores were approximately 5.5 servings per day of fruit and vegetable and 5.1 servings per day of grain.

6.3 Comparison of Dietary Intake

Dietary intake in DM is assessed at baseline and post-randomization in both the Intervention and Control arms with three instruments: the FFQ, the 4DFR, and the 24 Hour Recall (24 HR). The WHI dietary assessment instruments do not measure supplement intake. (Current supplement information is obtained at selected time points in conjunction with current medications.) All women in the DM complete an FFQ during screening (baseline) and at their first annual clinic visit. All other assessment both at other times and using other instruments are administered on subsamples of participants.

Table 6.3 - Nutrient Intake Monitoring displays baseline and year one data by treatment arm for percent energy from fat, total energy, total fat, and saturated fat for DM studywide. *Table 6.4 - Nutrient Intake Monitoring* among Minority Women provides a parallel summary for minorities (all races and ethnicities combined).

Data are reported two ways for the FFQ: (1) all baseline FFQs (Baseline) and (2) an FFQ annual visit cohort (AV Cohort) including FFQs from the DM participants who have completed an FFQ at the first annual visit and at baseline. Within the FFQ AV Cohort, data are reported at baseline, year one, and baseline subtracted from year one (Year 1 - Baseline). Hypothesis testing between treatment arms involving year one data from the FFQ was conducted using the AV Cohort. Non-normally distributed data (total energy, total fat and saturated fat, except Year 1 - Baseline) were transformed logarithmically before testing for treatment differences by t-test. Arithmetic means and standard deviations are presented for all nutrients. There are currently only 48 4DFRs (19 Intervention and 29 Control) for Year 1, thus these nutrient intake data are not presented. The reader is advised to interpret the 24 hour recall data cautiously as the sample size is small.

We define the intervention effect as [(Intervention Year 1-Baseline) compared to (Control Year 1-Baseline)]. The average year one intervention effects show statistically significant reductions in percent energy from fat: 11.3%, and 8.6% reductions of energy from fat for all and for minority participants, respectively (*Tables 6.3, 6.4*). However, percent energy from fat at Year 1, measured by the FFQ, is 23.7%, which is higher than the DM Intervention goal of 20% energy from fat. The 24HR data are collected two months prior to the annual visit and thus reflect intervention effects of the DM. Percent energy from fat, studywide, in the Intervention group (20.9%) is significantly lower than in the Control group (32.8%) as measured in the 24HR (*Table 6.3*). The difference between treatment arms is lower than desirable, owing in part to the lower reported fat intake in the Controls and potentially to the Intervention group not achieving the design goals. Note that the baseline FFQ percentage of calories from fat averages are inflated, probably by about 3-4%, due to the use of the FFQ as a screening tool.

Thirty-four percent of DM Intervention women, studywide, had less than or equal to 20% energy from fat at Year 1 as measured by the FFQ (*Table 6.3*), yet seventy-eight percent of DM Intervention women, studywide, met their fat gram goal, as assessed by self-monitoring (*Table 6.2*). We attribute this discrepancy to an apparent underestimation of fat intake by the self-monitoring process. The underestimation is likely due to a variety of factors, such as limitations of the self-monitoring instruments (by not having all-inclusive lists of foods) and recording bias. This apparent underestimation of fat intake by self-monitoring has provided the basis for a recent decision to change the fat gram goal algorithm used for self-monitoring. The DM Intervention goal remains 20% energy from fat but the self-monitoring tool goals are adjusted downward to approximately 15% of estimated post dietary change energy to account for this bias (most individual goals are now in the range 24-26 grams of fat daily).

The FFQ baseline mean energy and fat intake values appear higher than those for women 50-79 years reported by the Third National Health and Nutrition Examination Survey, Phase 1, 1988-1991 (NHANES III, Phase 1). This discrepancy is likely attributable to the use of the FFQ as a screening tool which may shift the mean fat intake upward by three to four percent. Actual baseline average percentage of calories from fat is likely about 35%, as is suggested by baseline 4DFR's and Year 1 FFQ's.

Table 6.5 - Body Weight displays baseline and year one body weight data per treatment arm for DM studywide, DM non-white, and DM white participants.

Modest weight loss would be consistent with adhering to a low-fat dietary pattern as the average intervention energy intake usually does not reach the pre-intervention level. Body weight, on average studywide, decreased 2.4 kg in the Intervention group and increased 0.1 kg in the Control group one year after randomization. The difference between arms is statistically significant ($p = < 0.01$) for all women and for minority women.

At the request of the DSMB, we have included estimates of the upper and lower tails of the frequency distribution for reported intake of selected nutrients % energy from fat; total energy; total fat; saturated fat; and calcium from dietary and total sources. This display was intended to assist in evaluating participant safety, particularly the effect of the dietary intervention on nutrient intakes compared to the control group.

Total energy intake appears to be similar in the intervention and control groups for the lower 5th and 10th percentiles, though both are lower than is nutritionally optimal for weight-maintaining women in the WHI age category. Percent total fat intake appears to be adequate for women in the DM Intervention even at the lower end of the frequency distribution (based on the 1993 FAO recommendations of a minimum of 15% energy from fat for adults). Assuming that polyunsaturated fat accounts for at least one-third of the total fat intake, we can extrapolate that essential fatty acid consumption is probably adequate.

Calcium intake, from both dietary and supplement sources, does not appear to be adversely impacted by the DM Intervention. Women at the lower ends of the frequency distribution in either the Control or Intervention groups are not meeting the RDA for calcium. (Calcium intake from antacids is assumed to be one dosage per day.)

Table 6.2
Intervention Program Adherence Summary

	Intervention Session		
	4	**8**	**12**
Attendance	86%	79%	71%
Completeness	97%	94%	92%
Self-Monitoring			
Fat gram			
Score obtained	94%	89%	85%
Average score	31.6	28.4	27.3
Average goal	32.3	32.2	32.0
Fruit/Vegetable			
Score obtained	n.a	87%	85%
Average score	n.a	5.4	5.5
Grain			
Score obtained	n.a	87%	85%
Average score	n.a	4.8	5.1

Table 6.3
Nutrient Intake Monitoring

	Intervention			Control			Comparison of Treatment Arms
	N	Mean	SD	N	Mean	SD	p-values
% Energy from Fat							
FFQ							
Baseline	4600	38.8	4.9	6876	39.0	5.0	0.07
AV Cohort: Baseline	1142	38.9	4.9	1685	38.9	4.9	0.64
Year 1*	1142	23.7	7.3	1685	35.1	7.2	0.00
Year 1 - Baseline	1142	-15.1	7.7	1685	-3.8	6.7	0.00
4DFR Baseline	186	34.0	6.1	294	33.0	6.3	0.67
24 Hr Recall	29	20.9	8.9	46	32.8	8.0	0.00
Total Energy (kcal)							
FFQ							
Baseline	4600	1821.4	746.6	6876	1807.8	709.4	0.60
AV Cohort: Baseline	1142	1827.2	793.6	1685	1818.0	711.3	0.86
Year 1	1142	1505.3	521.6	1685	1576.9	621.5	0.04
Year 1 - Baseline	1142	-321.9	708.4	1685	-241.1	626.2	0.00
4DFR Baseline	186	1755.9	433.8	294	1715.4	434.3	0.29
24 Hr Recall	29	1606.6	348.5	46	1696.2	492.7	0.60
Total Fat (g)							
FFQ							
Baseline	4600	79.4	37.1	6876	79.0	35.3	0.97
AV Cohort: Baseline	1142	79.7	40.1	1685	79.3	35.1	0.76
Year 1	1142	39.7	19.6	1685	62.5	30.1	0.00
Year 1 - Baseline	1142	-40.0	37.3	1685	-16.8	32.4	0.00
4DFR Baseline	186	67.0	23.0	294	64.0	23.5	0.07
24 Hr Recall	29	38.6	21.1	46	62.9	25.1	0.00
Saturated Fat (g)							
FFQ							
Baseline	4600	28.0	14.2	6876	27.8	13.4	0.63
AV Cohort: Baseline	1142	28.2	15.7	1685	27.8	13.2	0.97
Year 1	1142	13.9	7.6	1685	22.1	11.6	0.00
Year 1 - Baseline	1142	-14.3	14.5	1685	-5.7	12.1	0.00
4DFR Baseline	186	22.3	8.6	294	21.3	8.7	0.10
24 Hr Recall	29	12.6	8.1	46	20.7	9.5	0.00

* 387 intervention women had < = 20% energy from fat at year 1.

Table 6.4
Nutrient Intake Monitoring in Minority Women

	Intervention			Control			Comparison of Treatment Arms
	N	Mean	SD	N	Mean	SD	p-values
% Energy from Fat							
FFQ							
Baseline	662	39.7	5.3	963	39.6	5.1	0.64
AV Cohort: Baseline	110	39.9	5.7	156	39.4	5.0	0.41
Year 1*	110	26.8	8.1	156	34.9	7.7	0.00
Year 1 - Baseline	110	-13.1	8.3	156	-4.5	7.4	0.00
4DFR Baseline	16	35.8	6.6	43	35.0	5.2	0.62
24 Hr Recall	2	28.1	9.3	4	32.5	11.1	
Total Energy (kcal)							
FFQ							
Baseline	662	1770.9	844.7	963	1755.6	838.6	0.79
AV Cohort: Baseline	110	1842.7	971.1	156	1753.3	960.8	0.34
Year 1	110	1440.6	537.4	156	1333.7	622.3	0.04
Year 1 - Baseline	110	-402.1	830.9	156	-419.6	905.9	0.87
4DFR Baseline	16	1618.3	455.0	43	1628.4	365.5	0.80
24 Hr Recall	2	1236.6	140.1	4	1498.4	124.4	
Total Fat (g)							
Baseline	662	78.9	41.5	963	78.1	41.7	0.73
AV Cohort: Baseline	110	82.0	46.2	156	78.0	48.4	0.28
Year 1	110	43.2	21.4	156	52.7	30.6	0.01
Year 1 - Baseline	110	-38.9	43.7	156	-25.3	47.6	0.02
4DFR Baseline	16	64.2	21.0	43	64.1	19.5	0.99
24 Hr Recall	2	37.5	9.0	4	53.5	16.9	
Saturated Fat (g)							
FFQ							
Baseline	662	26.6	14.9	963	26.2	15.0	0.52
AV Cohort: Baseline	110	27.8	17.6	156	26.0	17.4	0.25
Year 1	110	14.7	7.8	156	17.7	11.1	0.03
Year 1 - Baseline	110	-13.1	16.4	156	-8.3	16.9	0.02
4DFR Baseline	16	19.1	7.0	43	20.1	7.2	0.64
24 Hr Recall	2	12.5	2.4	4	17.6	5.7	

* 21 non-white intervention women had < = 20% calories from fat at year 1.

Table 6.5
Body Weight

	Intervention			Control			Comparison of Treatment Arms
	N	Mean	SD	N	Mean	SD	p-values
Body Weight (kg)							
All Participants							
Baseline	4600	75.9	15.2	6876	75.6	14.9	0.27
AV Cohort: Baseline	1152	75.3	14.9	1701	74.7	14.2	0.25
Year 1	1152	72.9	16.5	1701	74.7	15.8	0.00
Year 1 - Baseline	1152	-2.4	8.3	1701	0.1	7.8	0.00
Body Weight (kg)							
Minority Participants							
Baseline	662	80.8	17.2	963	79.7	17.3	0.18
AV Cohort: Baseline	114	80.6	16.6	163	77.1	17.6	0.10
Year 1	114	77.6	17.2	163	76.7	18.2	0.65
Year 1 - Baseline	114	-2.9	5.3	163	-0.4	7.9	0.00

Table 6.6
Selected Percentiles for Key Nutrients Based on FFQ Data from AV1

Intervention	5%	10%	50%	90%	95%
% Energy from Fat	13.7	15.2	22.7	34.0	37.6
Total Energy (kcal)	751.4	902.0	1453.5	2123.0	2389.1
Total Fat (g)	16.6	19.5	36.3	63.2	76.1
Saturated Fat (g)	5.3	6.4	12.4	22.8	27.3
Calcium FFQ (mg)	255.8	343.0	709.7	1389.0	1643.2
Total Calcium (mg)	277.5	361.9	826.6	1862.2	2251.3
Control					
% Energy from Fat	22.9	26.0	35.3	44.0	46.6
Total Energy (kcal)	711.0	868.3	1496.6	2382.9	2703.2
Total Fat (g)	23.3	29.3	57.6	102.1	116.6
Saturated Fat (g)	7.7	9.7	20.3	36.9	43.7
Calcium FFQ (mg)	242.4	312.9	638.6	1233.0	1451.4
Total Calcium (mg)	257.7	332.4	735.2	1587.0	1927.8

7. Outcomes

7.1 Overview

The identification of potential WHI outcomes for CT participants begins with the self-administered *Form 33 - Medical History Update*, which is to be completed every six months. The CCs then follow-up on these self-reported outcomes by obtaining medical records and submitting them for review by a local physician adjudicator. A portion of the locally adjudicated outcomes are then reviewed centrally in an attempt to standardize the definition of WHI outcomes studywide.

Due to the time involved in obtaining medical records and reviewing those records for WHI outcomes, there will tend to be a substantial delay between the ascertainment of a potential WHI outcome on a *Form 33* and the final verification of that outcome. For this reason, monitoring reports will include counts of self-reported outcomes which are still pending verification.

When reviewing the results reported for the unverified self-reported outcomes, it is important to keep in mind the limitations of such data. In particular, although the participants are asked to report only those potential outcomes occurring since their last medical history update (*Form 33*), it is apparent that the subtleties behind such a request are missed by some women. These errors will be identified in the outcome verification process, however the results presented in this report will not yet have been corrected.

7.2 Self-Reported Outcomes

As of August 31, 1995, one or more *Form 33s* have been completed by 8,279 participants. The average number of *Form 33s* per participant is 1.57 (range 1 to 3 forms). As the *Form 33s* are to be administered semiannually, this corresponds to an average length of follow up of approximately 8.8 months (range approximately 6 to 18 months).

Table 7.1 presents the proportion of patients reporting potential WHI outcomes by CT participation (HRT with uterus, HRT without uterus, and DM). Overall, approximately 11.8% of participants report at least one hospitalization since randomization, with similar distributions in both HRT strata and in DM. The incidences of specific cardiovascular, cancer, or fracture outcomes are also displayed in *Table 7.1*, and, again, results for the HRT strata and the DM are similar.

7.3 Preliminary Reports of Deaths

According to the WHI protocol, deaths of participants while on study are to be reported to the CCC within 48 hours. These deaths are then investigated and locally adjudicated by a process similar to that for *Form 33* data.

Between the beginning of the clinical trials and October 27, 1995, the CCC has received reports of 15 deaths for CT participants: Four patients enrolled in the HRT have died, and twelve patients enrolled in DM have died. One of these deaths represents a patient enrolled in both HRT and DM.

7.4 Verified WHI Outcomes

At this early stage of the trial, no verified outcomes are available for reporting.

Table 7.1
Self-Reported Outcomes for Clinical Trials

	Hormone Replacement		Dietary
	No Uterus	Uterus	
Number of participants with *Form 33**	1197	1632	6591
Mean follow-up (months)**	8.8	8.5	8.8
Hospitalized	154 (12.9%)	186 (11.4%)	754 (11.4%)
Angina	10 (0.8%)	0 (0.0%)	15 (0.2%)
Heart Attack	7 (0.6%)	2 (0.1%)	5 (0.1%)
Heart Failure	2 (0.2%)	1 (0.1%)	2 (0.0%)
CABG or PTCA	6 (0.5%)	2 (0.1%)	7 (0.1%)
Carotid Endar	0 (0.0%)	1 (0.1%)	3 (0.0%)
PVD	0 (0.0%)	1 (0.1%)	1 (0.0%)
DVT	1 (0.1%)	5 (0.3%)	6 (0.1%)
Pulm Embol	0 (0.0%)	3 (0.2%)	3 (0.0%)
Other CV hosp	12 (1.0%)	3 (0.2%)	40 (0.6%)
Stroke	7 (0.6%)	7 (0.4%)	30 (0.5%)
Cancer	19 (1.6%)	21 (1.3%)	111 (1.7%)
Breast	1 (0.1%)	5 (0.3%)	13 (0.2%)
Ovary	0 (0.0%)	0 (0.0%)	3 (0.0%)
Endometrial	0 (0.0%)	0 (0.0%)	1 (0.0%)
Colorectal	1 (0.1%)	4 (0.2%)	4 (0.1%)
Other (non-skin)	4 (0.3%)	6 (0.4%)	29 (0.4%)
Fractures	29 (2.4%)	39 (2.4%)	158 (2.4%)
Hip	1 (0.1%)	0 (0.0%)	3 (0.0%)
Hysterectomy	1 (0.1%)	5 (0.3%)	20 (0.3%)
Diabetes (treated)	26 (2.2%)	19 (1.2%)	83 (1.3%)

* Number of participants with at least one *Form 33* having valid data regarding hospitalizations. Due to variation in missing or erroneous data by question on *Form 33*, the denominators for specific conditions will vary slightly.

** Mean follow-up is computed as the mean number of *Form 33s* per patient times 6 months.

8. Clinical Center Performance Monitoring

8.1 Performance Monitoring Plan

In June 1995, the CCC implemented a four-step plan for monitoring and assisting CC performance. The purpose of the four steps is to identify clinic-specific performance issues in a timely fashion, to reinforce good performance, and to provide assistance or institute corrective action if performance is inadequate. As part of this four-step plan, the functions of the Regional Resource Center (RRC) at Bowman Gray School of Medicine were changed to include activities related to this new plan. The RRC was also renamed the Clinical Facilitation Center (CFC) to reflect this change in activities. The four monitoring levels are described below.

Progress of the CC monitoring and follow-up is reported to the Steering Committee. A summary of Level 1 and Level 2 activities is reported by the CCC on a monthly basis, while Level 3 and Level 4 activities will be reported by the Clinical Facilitation Center on a quarterly basis.

Level 1: Routine Performance Monitoring and Follow-up

CCC quality assurance staff and lead staff liaisons regularly contact the clinic lead staff, review database reports, and perform standard QA visits to all clinics. They monitor clinic-specific and study-wide performance in key areas to provide timely and routine feedback on performance to the clinics in question; and to provide assistance (e.g., advice, training) where performance needs improvement.

Level 2: Performance Monitoring Committee

The Performance Monitoring Committee (PMC), formed in July 1995, reviews and notes persistent concerns in clinic performance The Committee membership includes two members from the CFC, two members from the Project Office, and two members from the CCC. The PMC, meeting via regular conference calls, determines the assistance or other action that may be needed at selected clinics in the upcoming month. The PMC also identifies the person(s) who will, if asked, carry out such activities and identifies any study-wide issues to be brought to the attention of the Steering Committee

Level 3: Follow Up on Persistent Issues

The CFC is responsible for seeing that the recommended activities identified by the PMC are carried out in a timely fashion. The CFC staff conducts these interactions where appropriate or requests assistance of another person or group with specialized expertise in the area of concern. A Level 3 site visit may be conducted with one to three members from the CFC, Project Office and/or CCC, but without selected PIs or lead staff from the other clinics.

Level 4: Performance Enhancement Site Visit.

If the interactions with the PMC do not yield timely results, or if there are sufficiently serious clinic issues, a Level 4 performance enhancement site visit is conducted. In addition to CFC

staff, the site visit team will typically include investigators and staff from other WHI clinics and representative from the Project Office and the CCC. The composition of the site visit team depends, in great part, on the specific problem areas to be addressed. The CFC takes the lead in coordinating and arranging these visits, prepares a written report summarizing the site visit team's finding (for review by the site visit team), submits the report to the chair of the PMC, and monitors the progress toward achieving site visit recommendations. A copy of the final report is sent to the clinic, Project Office, and CCC.

8.2 PMC Summary Report

A PMC Summary Report was developed to assist the PMC in monitoring the clinic performance. The report consists of a CC profile table and data summary tables. *Table 8.1 - Clinical Center Profile* gives information about unique clinic set-up and functions that may influence clinic performance. Included are indicators of enhanced recruitment, minority recruitment status, use of satellite sites, participation in multiple studies, and designation as a bone density site. It also shows the number of times the clinic has had turnover of lead staff and involvement in ancillary studies.

The data summary tables include data on the following clinic activities: recruitment, recruitment of minorities for Pool 1 clinics, follow-up, retention, HRT intervention, DM intervention, central laboratory, and data management. Within each table, the performance of each clinic is detailed for key activities related to the listed category. For example, the summary recruitment table shows the cumulative percent randomizations/enrollments into each study component and the percent of goal for the 70 - 79 age group. Within each table, the final column shows a summary percentage for each clinic for the activities presented in the table. Footnotes on each table indicate from which routine database reports the data come. Clinic performance is further summarized in one summary table listing the summary percentages of each of the previous tables, thereby presenting an overview of clinic performance in one table. The PMC report, showing cumulative data through June 30, 1995 and through August 30, 1995, is shown in *Table 8.2*.

The PMC report will be updated every quarter and sent to the PMC. A version of the PMC report without the clinic rankings will be sent to each clinic PI. The PMC recommended several changes, such as showing activities within the last quarter, so improvements or problems within the last quarter can be more easily monitored. This change will be made for the next PMC report. Other planned additions to the report include a summary of the CaD component activities, outcomes activities, and possibly a summary of the QA visits conducted by the CCC staff.

8.3 PMC Committee Activity

The PMC began meeting via conference call on August 7 and 15. Current membership includes Anne McTiernan, Co-Project Director of the CCC and chair of the PMC, Garnet Anderson, Co-Project Director of the CCC, Curt Furburg, PI of the CFC, Sally Shumaker, Co-PI of the CFC, Jacques Rossouw, WHI Project Officer, and Linda Pottern, WHI Project Office. The Committee has scheduled two calls per month through the end of the year to

expedite review of all 40 clinics. The frequency of these calls is expected to decrease to once a month beginning in January.

Before each call, narrative summaries of performance for each clinic to be discussed are circulated to all PMC members. The summaries include information from routine Level 1 monitoring activities and are reviewed and updated by CCC lead staff liaisons as appropriate. During the call, action items from the previous call are reviewed, the clinic summaries are reviewed, and new action items are identified. After discussion on the PMC call, a letter summarizing the PMC discussion is sent to the clinic PI. As of August 31, 1995, three Level 4 and one Level 3 site visits had been planned.

Table 8.1
Clinical Center Profile

	Enhanced Recruitment	Minority	Satellite	Multiple Studies	Bone Density	Lead Staff Turnover: PI	Clinic Manager	Recruitment Coordinator	Lead Practitioner	Lead Nutritionist	Data Coordinator	Ancillary Studies: Active: Coordinating	Active: Participating in	Proposed[1]: Coordinating	Proposed[1]: Participating in
VCCs															
Atlanta		Y		Y					1						1
Birmingham	125	Y		Y	Y					1		2		1	4
Bowman			Y				2	2	2						
Brigham	150									1	1			3	1
Buffalo								1		1				1	2
Chicago			Y	Y				1						1	1
Iowa	*		Y	Y							1			1	1
LaJolla	150	Y	Y	Y			1	3	1	1		2		2	4
Memphis	125		Y	Y							1				1
Minneapolis	125			Y										1	1
Newark				Y			2							1	
Pawtucket	175		Y						1						
Pittsburgh				Y	Y				1			1		1	
Seattle				Y				1	1		1	1			
Tucson	*	Y	Y	Y	Y	1	1	1	2	1	1	1			
UCDavis				Y			2	2	1						
NCCs															
Chapel Hill							1	1			1				
Chi-Rush		Y	Y	Y							1				1
Cincinnati								1							
Columbus				Y				1		1					
Detroit		Y							1					1	
Gainesville			Y	Y/N											
GWU-DC				Y											
Honolulu		Y		Y			1							1	1
Houston								1							
Irvine								1							1
LA				Y			1				1				
Madison									1						
Medlantic		Y		Y						1					
Miami		Y		Y				1		1					1
Milwaukee											1				
Nevada				Y											
NY City														2	
Oakland				Y											
Portland				Y											
San Antonio		Y		Y				1							
Stanford								1			1				
Stony Brook															
Torrance				Y				1	1					1	
Worcester				Y						1					

[1] Six pending ancillary studies propose the involvement of several unspecified CCs.

Table 8.2
Clinical Center Performance Summary

Summary - VCC

	Recruitment		Followup		Retention		HRT Intervention		DM Intervention		CaD Intervention		Outcomes		Central Lab		Data		Overall		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	73	67	90	87	–	96	–	84	88	86	–	–	–	–	92	94	89	90	86	86	6
Birmingham	79	82	91	92	–	97	–	90	87	83	–	–	–	–	96	95	72	74	85	87	4
Bowman	56	42	79	72	–	96	–	85	85	80	–	–	–	–	95	93	89	89	81	80	15
Brigham	66	54	92	89	–	98	–	92	89	87	–	–	–	–	93	93	71	69	82	83	9
Buffalo	88	88	83	83	–	96	–	84	86	78	–	–	–	–	90	94	94	94	88	88	3
Chicago	68	60	61	70	–	98	–	92	89	86	–	–	–	–	88	92	82	82	78	83	10
Iowa	92	97	98	90	–	98	–	92	89	89	–	–	–	–	93	97	93	93	93	94	1
LaJolla	70	66	72	65	–	93	–	87	80	84	–	–	–	–	92	94	88	88	80	82	12
Memphis	75	79	89	76	–	97	–	92	86	85	–	–	–	–	93	90	68	65	82	83	8
Minneapolis	65	72	92	90	–	97	–	93	92	90	–	–	–	–	95	97	94	93	88	90	2
Newark	52	59	65	49	–	100	–	88	77	83	–	–	–	–	86	91	86	83	73	79	16
Pawtucket	53	50	49	64	–	95	–	90	91	89	–	–	–	–	93	95	83	84	74	81	14
Pittsburgh	77	74	72	76	–	97	–	91	87	90	–	–	–	–	90	92	87	87	83	87	5
Seattle	72	70	73	52	–	97	–	95	86	87	–	–	–	–	89	93	95	92	83	84	7
Tucson	80	77	71	63	–	97	–	78	78	77	–	–	–	–	87	91	91	91	81	82	13
UCDavis	81	70	82	76	–	99	–	89	80	81	–	–	–	–	90	90	75	73	81	82	11

Note: Summary data is taken from the summary columns of the following reports.

Table 8.2 (continued)

Summary - NCC

	Recruitment		Followup		Retention		HRT Intervention		DM Intervention		CaD Intervention		Outcomes		Central Labs		Data		Overall		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Chapel Hill	32	27	–	–	–	–	–	–	–	–	–	–	–	–	81	94	–	94	57	72	11
Chi-Rush	7	8	–	–	–	–	–	–	–	–	–	–	–	–	61	77	–	83	34	56	24
Cincinnati	59	39	–	–	–	–	–	–	–	–	–	–	–	–	71	90	–	86	65	72	12
Columbus	11	13	–	–	–	–	–	–	–	–	–	–	–	–	96	96	–	77	54	62	20
Detroit	5	17	–	–	–	–	–	–	–	–	–	–	–	–	81	87	–	66	43	57	23
Gainesville	135	89	–	–	–	–	–	–	–	–	–	–	–	–	97	98	–	96	116	94	1
GWU-DC	108	65	–	–	–	–	–	–	–	–	–	–	–	–	98	99	–	94	103	86	2
Honolulu	44	24	–	–	–	–	–	–	–	–	–	–	–	–	97	98	–	49	71	57	22
Houston	76	52	–	–	–	–	–	–	–	–	–	–	–	–	94	96	–	68	85	72	10
Irvine	14	20	–	–	–	–	–	–	–	–	–	–	–	–	96	94	–	85	55	66	17
LA	24	24	–	–	–	–	–	–	–	–	–	–	–	–	100	98	–	69	62	64	19
Madison	40	37	–	–	–	–	–	–	–	–	–	–	–	–	100	99	–	100	70	79	4
Medlantic	72	50	–	–	–	–	–	–	–	–	–	–	–	–	81	94	–	85	76	76	6
Miami	18	18	–	–	–	–	–	–	–	–	–	–	–	–	99	98	–	94	58	70	14
Milwaukee	44	44	–	–	–	–	–	–	–	–	–	–	–	–	93	94	–	97	68	78	5
Nevada	51	46	–	–	–	–	–	–	–	–	–	–	–	–	97	97	–	99	74	80	3
NY City	44	40	–	–	–	–	–	–	–	–	–	–	–	–	88	88	–	84	66	71	13
Oakland	37	34	–	–	–	–	–	–	–	–	–	–	–	–	96	95	–	79	67	69	16
Portland	34	29	–	–	–	–	–	–	–	–	–	–	–	–	97	96	–	47	66	57	21
San Antonio	71	44	–	–	–	–	–	–	–	–	–	–	–	–	95	86	–	93	83	74	7
Stanford	5	14	–	–	–	–	–	–	–	–	–	–	–	–	96	88	–	89	51	64	18
Stony Brook	20	26	–	–	–	–	–	–	–	–	–	–	–	–	92	95	–	97	56	73	9
Torrance	30	27	–	–	–	–	–	–	–	–	–	–	–	–	97	97	–	96	64	73	8
Worcester	28	22	–	–	–	–	–	–	–	–	–	–	–	–	92	94	–	94	60	70	15

Note: Summary data is taken from the summary columns of the following reports.

Table 8.2 (continued)

Recruitment - VCC

	HRT[1] % goal		DM[1] % goal		Ca/D[2] % goal		OS[3] % goal		Age - HRT[4] % goal, 70 - 79		Age - DM[4] % goal, 70 - 79		Overall weighted average*		
	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	Rank
Atlanta	79	74	101	96	–	57	97	97	30	29	38	36	73	67	10
Birmingham	99	90	95	89	–	113	91	88	42	39	34	32	79	82	3
Bowman	66	65	68	67	–	0	64	59	38	34	28	27	56	42	16
Brigham	61	59	90	87	–	27	39	34	46	43	60	57	66	54	14
Buffalo	77	75	104	101	–	100	137	134	75	71	63	58	88	88	2
Chicago	48	49	90	90	–	35	52	48	58	58	80	84	68	60	12
Iowa	137	129	94	89	–	131	65	64	63	58	38	35	92	97	1
LaJolla	70	67	71	69	–	62	72	63	70	68	66	67	70	66	11
Memphis	92	87	88	86	–	97	57	60	61	59	36	41	75	79	4
Minneapolis	60	61	99	98	–	97	91	89	23	22	36	32	65	72	7
Newark	59	59	74	78	–	61	34	82	29	31	27	32	52	59	13
Pawtucket	65	58	64	61	–	51	62	57	34	31	24	24	53	50	15
Pittsburgh	70	70	85	85	–	62	226	219	40	41	40	41	77	74	6
Seattle	62	61	97	95	–	66	70	59	49	52	67	70	72	70	8
Tucson	60	58	89	92	–	72	137	143	74	70	77	73	80	77	5
UCDavis	60	62	100	101	–	36	119	105	55	57	89	84	81	70	9
*weights:	1		1		1		0.25		0.5		0.5				

[1] From WHIP1109. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP0770.
[2] From WHIP1125. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP1139.
[3] From WHIP1126. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP1139.
[4] Derived from WHIP0578. Available at CC as WHIP0775.

Table 8.2 (continued)

Recruitment - NCC

	HRT[1] % goal		DM[1] % goal		Ca/D[2] % goal		OS[3] % goal		Age - HRT[4] % goal, 70 - 79		Age - DM[4] % goal, 70 - 79		Overall weighted average*		
	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	cum., Jun 95	cum., Aug 95	Rank
Chapel Hill	30	23	37	56	–	–	69	66	43	22	0	15	32	27	14
Chi-Rush	8	11	6	15	–	–	13	13	0	0	12	6	7	8	24
Cincinnati	43	39	80	73	–	–	96	84	43	32	43	28	59	39	9
Columbus	0	0	28	43	–	–	0	25	0	0	19	12	11	13	23
Detroit	3	31	11	31	–	–	10	12	0	11	0	0	5	17	21
Gainesville	165	153	125	109	–	–	222	170	97	86	93	59	135	89	1
GWU-DC	73	73	155	108	–	–	246	183	86	76	37	25	108	65	2
Honolulu	22	23	48	33	–	–	158	96	43	32	25	15	44	24	16
Houston	97	99	105	87	–	–	94	82	11	11	31	22	76	52	3
Irvine	11	16	14	32	–	–	61	70	11	22	0	12	14	20	19
LA	19	27	37	41	–	–	30	50	11	22	19	19	24	24	17
Madison	38	47	37	56	–	–	132	114	32	38	12	15	40	37	10
Medlantic	73	70	85	84	–	–	98	75	65	49	37	28	72	50	4
Miami	16	26	23	30	–	–	30	39	11	16	12	6	18	18	20
Milwaukee	35	55	82	87	–	–	73	55	0	22	12	37	44	44	6
Nevada	38	45	59	70	–	–	165	143	22	43	37	43	51	46	5
NY City	38	49	50	65	–	–	114	111	22	32	31	25	44	40	8
Oakland	22	31	45	53	–	–	135	165	22	16	19	25	37	34	11
Portland	24	28	56	63	–	–	20	16	22	22	31	31	34	29	12
San Antonio	89	78	90	65	–	–	53	55	32	32	43	25	71	44	7
Stanford	0	9	3	29	–	–	56	74	0	5	0	3	5	14	22
Stony Brook	16	28	34	53	–	–	53	77	0	5	0	12	20	26	15
Torrance	19	28	34	42	–	–	97	89	22	16	19	28	30	27	13
Worcester	0	16	56	46	–	–	101	84	0	11	19	12	28	22	18
*weights:	1		1		1		0.25		0.5		0.5				

[1] From WHIP1109. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP0770.
[2] From WHIP1125. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP1139.
[3] From WHIP1126. Distributed in CC Monthly Activity Reports. Can be run at CC as WHIP1139.
[4] Derived from WHIP0578. Available at CC as WHIP0775.

Table 8.2 (continued)

Minority Randomization/Enrollment at Pool 1 Clinics

	% Non-white HRT/DM/OS[1]		
VCCs	cum., Jun 95	cum., Aug 95	Rank
Atlanta	29	31	6
Birmingham	30	33	5
LaJolla	23	25	8
Tucson	14	15	10
NCCs			
Chi-Rush	60	59	3
Detroit	48	38	4
Honolulu	73	73	1
Medlantic	60	60	2
Miami	36	30	7
San Antonio	16	19	9

[1] Derived from WHIP0960. Distributed in Monthly Activity Reports. Can be run at CC as WHIP777.

Table 8.2 (continued)

Follow-up - VCC

	6 Week[1]		Semi-Annual 1						Annual Visit 1						Semi-Annual 2						Overall*		
	Conducted		Conducted[2]		+/- 2 wks[2]		Complete[3]		Conducted[2]		+/- 2 wks[2]		Complete[3]		Conducted[3]		+/- 2 wks[3]		Complete[3]				
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	–	94	91	91	76	75	–	95	99	97	93	92	–	68	–	n/a	–	n/a	–	n/a	90	87	5
Birmingham	–	93	98	99	85	86	–	97	96	98	84	84	–	69	–	100	–	95	–	95	91	92	1
Bowman	–	79	90	90	63	63	–	91	89	87	74	71	–	67	–	56	–	38	–	78	79	72	10
Brigham	–	91	98	98	79	79	–	97	99	99	91	91	–	83	–	96	–	63	–	91	92	89	4
Buffalo	–	96	93	94	57	62	–	94	96	96	85	83	–	67	–	81	–	68	–	93	83	83	6
Chicago	–	92	93	93	45	46	–	94	75	78	29	30	–	65	–	67	–	33	–	100	61	70	11
Iowa	–	99	100	100	95	95	–	96	99	98	99	95	–	74	–	83	–	83	–	80	98	90	3
LaJolla	–	83	82	84	59	61	–	88	86	92	61	63	–	7	–	67	–	17	–	88	72	65	12
Memphis	–	68	92	92	78	78	–	91	96	96	88	85	–	32	–	61	–	61	–	94	89	76	9
Minneapolis	–	99	98	99	78	80	–	97	100	99	93	92	–	83	–	84	–	77	–	95	92	90	2
Newark	–	80	80	87	41	45	–	95	81	85	60	62	–	38	–	0	–	0	–	0	65	49	16
Pawtucket	–	90	87	87	59	58	–	93	36	52	13	10	–	48	–	73	–	40	–	91	49	64	13
Pittsburgh	–	90	94	99	59	67	–	96	94	97	40	39	–	57	–	96	–	30	–	92	72	76	8
Seattle	–	81	96	95	58	57	–	97	77	87	61	51	–	56	–	0	–	0	–	0	73	52	15
Tucson	–	31	94	94	55	57	–	94	84	84	50	50	–	53	–	59	–	59	–	50	71	63	14
UCDavis	–	97	89	92	77	78	–	86	88	88	76	77	–	45	–	61	–	58	–	83	82	76	7

NOTES: Conducted = % of visits due for which at least one task has been key-entered.
+/- 2 weeks = % of visits due that have been conducted within 2 weeks of the target date.
Complete = % of visits conducted for which all expected tasks have been key-entered. Specifically,

Semi-Annual Contact 1:
HRT: tasks 10, 33, 950, 951
DM: task 33

Annual Visit 1:
HRT: tasks 10, 33, 38, 44, 45, 80, 81, 84, 85, 100, 950, 951
DM: task 33, 38, 44, 45, 60, 80, 84, 100
CaD: tasks 15, 33, 38, 44, 45, 80, 81, 84, 100, 950

Semi-Annual Contact 2:
HRT: tasks 10, 33, 950, 951
DM: task 33
CaD: tasks 33, 950, 951

[1] From WHIP1131. Can be run at CC as WHIP0781 or WHIP0786.
[2] From WHIP0769. Distributed in CC Monthly Activity Reports.
[3] From WHIP1140, a new report not yet distributed to CCs.
* Equal weights assigned to each follow-up activity.

Table 8.2 (continued)

Retention - VCC

	HRT[1]				DM[2]				CaD				OS				
	% Continuing Intervention		% Continuing Followup		% Continuing Intervention		% Continuing Followup		% Continuing Intervention		% Continuing Followup		% Continuing Followup		Overall*		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	–	90	–	100	–	96	–	100	–	–	–	–	–	–	–	96	12
Birmingham	–	91	–	100	–	98	–	99	–	–	–	–	–	–	–	97	10
Bowman	–	89	–	98	–	100	–	99	–	–	–	–	–	–	–	96	14
Brigham	–	91	–	100	–	100	–	100	–	–	–	–	–	–	–	98	5
Buffalo	–	88	–	100	–	98	–	99	–	–	–	–	–	–	–	96	13
Chicago	–	91	–	99	–	100	–	100	–	–	–	–	–	–	–	98	4
Iowa	–	94	–	100	–	100	–	100	–	–	–	–	–	–	–	98	3
LaJolla	–	90	–	97	–	90	–	96	–	–	–	–	–	–	–	93	16
Memphis	–	95	–	99	–	96	–	99	–	–	–	–	–	–	–	97	8
Minneapolis	–	92	–	100	–	98	–	100	–	–	–	–	–	–	–	97	6
Newark	–	99	–	100	–	100	–	100	–	–	–	–	–	–	–	100	1
Pawtucket	–	84	–	100	–	97	–	100	–	–	–	–	–	–	–	95	15
Pittsburgh	–	89	–	99	–	100	–	100	–	–	–	–	–	–	–	97	11
Seattle	–	93	–	99	–	98	–	100	–	–	–	–	–	–	–	97	7
Tucson	–	93	–	100	–	96	–	99	–	–	–	–	–	–	–	97	9
UCDavis	–	96	–	100	–	99	–	100	–	–	–	–	–	–	–	99	2

Notes: Continuing Intervention = % of randomized participants (intervention participants for DM) with follow-up status 1 - 4 on Form 7.
Continuing Follow-up = % of randomized participants with "active intervention" status.

[1] From report WHIP0745, a new report not yet distributed to CCs.
[2] From report WHIP0748, a new report not yet distributed to CCs.
* Equal weight is attached to each program component.

Table 8.2 (continued)

HRT Intervention - VCC

	% Women ≥ 80% Adherent[1] at Annual Visit		% Women with Pill Count at Annual Visit[2]		% Blinding[3]		Overall weighted ave*		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	–	79	–	83	–	97	–	84	14
Birmingham	–	87	–	90	–	98	–	90	8
Bowman	–	86	–	79	–	99	–	85	13
Brigham	–	91	–	91	–	98	–	92	6
Buffalo	–	79	–	83	–	95	–	84	15
Chicago	–	85	–	97	–	98	–	92	3
Iowa	–	90	–	91	–	98	–	92	5
LaJolla	–	80	–	88	–	99	–	87	12
Memphis	–	88	–	94	–	99	–	92	4
Minneapolis	–	88	–	98	–	94	–	93	2
Newark	–	81	–	91	–	97	–	88	11
Pawtucket	–	88	–	88	–	95	–	90	9
Pittsburgh	–	84	–	94	–	99	–	91	7
Seattle	–	94	–	92	–	100	–	95	1
Tucson	–	72	–	74	–	100	–	78	16
UCDavis	–	92	–	83	–	93	–	89	10
*Weighted average with weights									
Weights	1		1		0.5				

[1] Adherent as measured by pill count or estimate at annual visit 1, excluding ERT→PERT participants. From data analysis, not yet routinely distributed to CCs.

[2] % of Annual Visit 1s conducted that include study pill collections. From WHIP1141, a new report not yet distributed to CCs.

[3] % Blinding = % of ppts for whom no unblinding occured. From DSMB report not routinely distributed to CCs.

Table 8.2 (continued)

DM Intervention - VCC

	Timeliness of group formation[1]		Adherence (Session 12) Performance % Attendance[2]		Performance % Complete[3]		Fat Gram % Collected[4]		Fat Gram % < goal[5]		Fat Gram % < goal +5 g[6]		Fruit/Veg % Collected[4]		Grain % Collected[4]		Summary weighted ave*		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	94	94	71	72	94	92	92	87	–	78	–	90	92	87	92	87	88	86	8
Birmingham	86	84	78	70	97	89	87	81	–	79	–	93	84	80	84	80	87	83	12
Bowman	93	91	71	72	95	86	81	76	–	68	–	88	81	76	81	76	85	80	14
Brigham	94	94	73	72	93	91	95	92	–	80	–	90	95	92	95	92	89	87	5
Buffalo	89	87	83	77	90	93	84	78	–	56	–	80	84	78	84	78	86	78	15
Chicago	92	92	75	76	90	90	96	96	–	68	–	89	96	96	96	96	89	86	7
Iowa	85	82	73	70	99	98	96	94	–	92	–	98	96	94	96	94	89	89	3
LaJolla	81	80	73	74	92	93	77	78	–	85	–	94	77	78	77	78	80	84	10
Memphis	98	98	71	69	91	89	85	85	–	80	–	90	85	85	85	85	86	85	9
Minneapolis	96	96	78	77	97	95	95	92	–	83	–	96	95	92	95	92	92	90	1
Newark	92	93	48	54	90	94	79	88	–	75	–	90	79	88	79	88	77	83	11
Pawtucket	94	93	75	75	98	98	94	94	–	76	–	96	94	94	94	94	91	89	4
Pittsburgh	96	95	76	78	91	95	87	91	–	85	–	93	87	91	87	91	87	90	2
Seattle	94	93	76	77	96	95	80	81	–	84	–	93	77	78	77	78	86	87	6
Tucson	84	82	61	57	89	86	79	72	–	76	–	89	79	72	79	72	78	77	16
UCDavis	93	94	60	61	92	91	77	79	–	73	–	87	77	79	77	79	80	81	13
*weights:	1		1		1		1		1		1		0.25		0.25				

[1] Timeliness of group formation = % women randomized to DM intervention who started intervention within 20 weeks or randomization or have been waiting less than 20 weeks but have not yet started intervention. Derived from WHIP1110 and WHIP1118, which are distributed with CC Monthly Activity Reports.

[2] % Attendance = women who attended session 12 / women for whom session data have been key-entered. Derived from WHIP0588. Available to CCs through WHIP0427.

[3] Completeness = % women attending group sessions or completing make-up activities. From WHIP1114. Available to CCs as WHIP0421.

[4] % collected = women who turned in scores for session 12 / women for whom session data have been key-entered. Derived from WHIP0588. Available to CCs through WHIP0423.

[5] % of women with fat scores equal to or less than their fat gram goals. From data analysis not yet routinely distributed to CCs.

[6] % of women with fat scores equal to or less than their fat gram goals + five grams. From data analysis not yet routinely distributed to CCs.

Table 8.2 (continued)

Central Laboratory - VCC

	ECGs				Blood				4DFRs		Summary average		
	Tracking % Matching[1]		Grade % grades 1 - 3[2]		Tracking % Matching[3]		% Complete[4]		% Error-Free[5]				
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Atlanta	97	98	91	91	99	100	87	88	83	92	92	94	7
Birmingham	99	100	93	92	100	100	96	95	91	89	96	95	3
Bowman	96	98	90	90	97	98	92	93	100	89	95	93	8
Brigham	98	100	93	93	100	100	94	93	80	80	93	93	9
Buffalo	93	98	94	94	100	100	97	97	67	81	90	94	5
Chicago	97	99	92	93	98	98	99	99	56	72	88	92	11
Iowa	99	100	93	93	99	99	98	98	75	96	93	97	1
LaJolla	91	95	90	90	100	100	97	97	82	88	92	94	6
Memphis	96	98	89	89	99	99	90	89	90	75	93	90	16
Minneapolis	100	100	100	100	100	100	100	100	77	83	95	97	2
Newark	94	96	92	93	100	100	95	95	50	73	86	91	13
Pawtucket	98	99	90	91	99	99	99	99	80	88	93	95	4
Pittsburgh	99	99	90	90	99	99	99	98	64	73	90	92	12
Seattle	96	99	88	88	99	99	93	93	71	86	89	93	10
Tucson	94	97	88	88	98	99	93	93	60	77	87	91	14
UCDavis	95	96	95	95	100	100	99	99	60	60	90	90	15

[1] Matching rates based on ECGs reported by EPICARE. From WHIP1022. Distributed in CC Monthly QA Reports.
[2] % ECGs of acceptable quality (grades 1 - 3). Derived from WHIP1023. Distributed in CC Monthly QA Reports.
[3] Matching rates for blood samples based on samples received at Ogden. From WHIP1042. Distributed in CC Monthly QA Reports.
[4] % Complete blood aliquots, based on aliquots required for visit type. From WHIP1044. Distributed in CC Monthly QA Reports.
[5] % Error free archived 4DFRs, cumulative from January 1, 1995. Derived from WHIP0935. Distributed to CCs quarterly.

Table 8.2 (continued)

Central Laboratory - NCC

	ECGs				Blood				4DFRs		Summary		
	Tracking % Matching[1]		Grade % grades 1 - 3[2]		Tracking % Matching[3]		% Complete[4]		% Error-Free[5]		average		
	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	cum., June 95	cum., Aug 95	Rank
Chapel Hill	46	94	90	96	99	99	89	89			81	94	14
Chi-Rush	0	29		90	85	92	96	96			61	77	24
Cincinnati	4	83	100	97	99	99	82	82			71	90	19
Columbus	100	100	100	100	100	100	83	83			96	96	11
Detroit		100		88	100	99	63	63			81	87	22
Gainesville	100	100	94	95	100	100	96	99			97	98	4
GWU-DC	99	100	95	94	100	100	99	99		100	98	99	2
Honolulu	100	100	91	93	99	100	100	100			97	98	6
Houston	93	97	95	95	97	99	90	90		100	94	96	9
Irvine	100	100	100	92	99	99	86	86			96	94	15
LA	100	100	100	96	100	98	100	99			100	98	5
Madison	100	97	100	100	100	100	98	98			100	99	1
Medlantic	53	99	74	81	99	99	97	97			81	94	17
Miami	100	100	100	100	100	99	95	95			99	98	3
Milwaukee	100	100	77	81	100	100	94	94			93	94	16
Nevada	100	97	91	90	99	100	97	97		100	97	97	8
NY City	94	98	64	62	99	100	93	93			88	88	21
Oakland	97	100	97	90	100	100	90	90			96	95	13
Portland	93	94	100	97	100	99	95	95			97	96	10
San Antonio	99	99	94	93	100	100	88	88		50	95	86	23
Stanford		73		88	99	100	94	94			96	88	20
Stony Brook	90	100	89	88	98	100	93	93			92	95	12
Torrance	100	100	91	90	100	100	98	98			97	97	7
Worcester	82	92	91	89	100	99	94	94			92	94	18

[1] Matching rates based on ECGs reported by EPICARE. From WHIP1022. Distributed in CC Monthly QA Reports.
[2] % ECGs of acceptable quality (grades 1 - 3). Derived from WHIP1023. Distributed in CC Monthly QA Reports.
[3] Matching rates for blood samples based on samples received at Ogden. From WHIP1042. Distributed in CC Monthly QA Reports.
[4] % Complete blood aliquots, based on aliquots required for visit type. From WHIP1044. Distributed in CC Monthly QA Reports.
[5] % Error free archived 4DFRs, cumulative from January 1, 1995. Derived from WHIP0935. Distributed to CCs quarterly.

Table 8.2 (continued)

Data Management - VCC

	Timeliness of key-entry[1]		
	cum., June 95	cum., Aug 95	Rank
Atlanta	89	90	6
Birmingham	72	74	13
Bowman	89	89	7
Brigham	71	69	15
Buffalo	94	94	1
Chicago	82	82	12
Iowa	93	93	3
LaJolla	88	88	8
Memphis	68	65	16
Minneapolis	94	93	2
Newark	86	83	11
Pawtucket	83	84	10
Pittsburgh	87	87	9
Seattle	95	92	4
Tucson	91	91	5
UCDavis	75	73	14

[1] Timeliness = % data entered within two weeks. From WHIP1112. Distributed with CC Quality Assurance Reports. Can be run by CC as WHIP0774.

Table 8.2 (continued)

Data Management - NCC

	Timeliness of key-entry[1]		
	cum., June 95	cum., Aug 95	Rank
Chapel Hill	–	94	7
Chi-Rush	–	83	17
Cincinnati	–	86	13
Columbus	–	77	19
Detroit	–	66	22
Gainesville	–	96	6
GWU-DC	–	94	10
Honolulu	–	49	23
Houston	–	68	21
Irvine	–	85	15
LA	–	69	20
Madison	–	100	1
Medlantic	–	85	14
Miami	–	94	9
Milwaukee	–	97	4
Nevada	–	99	2
NY City	–	84	16
Oakland	–	79	18
Portland	–	47	24
San Antonio	–	93	11
Stanford	–	89	12
Stony Brook	–	97	3
Torrance	–	96	5
Worcester	–	94	8

[1] Timeliness = % data entered within two weeks. From WHIP1112. Distributed with CC Quality Assurance Reports. Can be run by CC as WHIP0774.

9. Timeline

WHI Manuals, *Vol. 1 - Study Protocol and Polices, Protocol Section 11 - Timetable* defines the study timeline, reflecting the progress and expectations as of August, 1994. The official startup of all activities has be implemented on schedule with the exception of OS and CaD recruitment. The delay in OS for Office of Management and Budget approval created problems for VCCs in managing CT ineligible women and in planning VCC operations to achieve full OS recruitment within the recruitment timeline. To address this issue, in August 1994, the NIH Project Office agreed to extend VCC recruitment period for OS for one year.

The delay in CaD start-up was a result of difficulties in obtaining the supplements from the manufacturer. This results in a small loss in the expected person-years of observation as about 2,800 women were randomized more than 1 year before CaD was officially open and thus they missed the scheduled randomization at the first year follow-up visit. Since these women will be offered CaD participation at the second annual visit so the total loss in person years is small.

The startup of the NCCs has been similar to the VCC experience. Though the NCCs appeared to get off the mark more quickly than VCCs their recruitment curve is now quite similar to the VCC's. NCCs are being strongly encouraged to be as aggressive as possible in meeting their goals and in making up any existing deficits.

To meet the shortfall in recruitment created by the funding of 40 CCs rather than 45, 6 VCCs have been funded for increased recruitment (see *Section 2.2*). This additional recruitment will extend these VCCs' recruitment efforts through the NCC recruitment period (January 1998), if necessary. This accounts for the equivalent of 2.5 additional CCs. Two other VCCs are negotiating for selected enhanced recruitment. The NIH has also issued a request for proposals for enhanced recruitment in NCCs (Letter of intent due November 13, 1995). Approximately 2.5 full clinic equivalents are needed to make up the shortfall. Others will need to commit to further recruitment if the overall goals are to be met.

During the next six months, VCCs will be preparing for the end of their CT recruitment (August 31, 1995), with the anticipation that many will attempt to extend their recruitment to meet their goals. DM Intervention activities will be nearing their peak with many women in the active DM Intervention phase and a substantial number will be involved in maintenance. Similarly for HRT, VCCs will be managing a large number of women in their first or second year of hormone use and maintaining adherence during this time will be critical. For CaD, VCCs will obtain a good indication of women's willingness to be randomized and their adherence to this protocol. Follow-up activities will be increasingly emphasized and VCCs will be expected to be adjudicating outcomes in this period.

During this same period, NCCs will be asked to meet their screening and enrollment goals for HRT, DM and OS begin to make up any deficits accrued so far and initiate follow-up on those already randomized.

The CCC will be refining follow-up procedures for CT, specifically defining follow-up goals and minimum requirements, and the procedures for outcomes documentation and adjudication. The CCC will also be starting the centralized follow-up of OS women and the

analysis of stored blood specimens. Additional efforts on quality assurance, adherence and retention, trial monitoring and reporting are also underway.

10. Design and Power

CT power calculations were based on assumptions involving the accrual rate, baseline characteristics, adherence to intervention (drop-outs) and control (drop-ins or drift), loss to follow-up, and incidence rates in the control groups, as well as the hypothesized intervention effects. See *Appendix 2-A3* of the WHI protocol (WHI Manuals, *Vol. 1 - Study Protocol and Policies, Section 1-A3 - Statistical Power for WHI Clinical Trial and Observational Trial*) for more details.

The change in the HRT protocol had a noticeable effect on power. Under the previous design, women with and without a uterus could be randomized to ERT, thereby allowing the simultaneous use of the two placebo groups for the ERT vs. placebo comparison. This efficient use of the placebo group allowed us to weigh the allocation scheme for women with a uterus to assure adequate power of the PERT vs. placebo comparison. Under the revised design, however, the power for each active to placebo group comparison relies solely on the data within the relevant hysterectomy stratum. To assure adequate power for both of these comparisons, we increased the HRT sample size by 2,500 and set the target hysterectomy rate at 45%.

Table 10.1 - Design Assumptions and Current Estimates summarizes the design parameters under the current protocol and the related observable quantities. As noted in earlier sections, the data are not adequate yet to provide useful estimates of factors related to follow-up.

The lag in accrual and the under-recruitment of women aged 70-79 has been presented and discussed among WHI Investigators. It seems likely that the original VCC goals cannot be met without a substantial extension of their recruitment period. Even if monthly goals were met, VCCs would need approximately 10 months to catch up. A more reasonable estimate may be over 14 months if they can sustain accrual rates at 70% of goal. NCC experience to date is limited but does not depart strongly from the VCC trends. Current priorities are to address first the lag in recruitment on a clinic-by-clinic basis and then to work on subgroup goals. The recently implemented plan for monitoring and limiting the recruitment by age group represents an additional attempt to assure compliance to design assumptions.

Table 10.1
Design Assumptions and Current Estimates

	Parameter	Design Value	Current Estimate for HRT	DM
Accrual Rate	Average follow-up	8.92 yrs.	8.66[1]	8.78[1]
Baseline Characteristics	% randomized as			
Age	50-54	10%	17%	20%
	55-59	20%	21%	25%
	60-69	45%	45%	41%
	70-79	25%	17%	14%
Hysterectomy Status	Intact Uterus	55%	59%	
	Hysterectomized	45%	41%	
Loss to Follow-up/ Competing Risk	Event rate (%/year) CHD	2%	no data available	
	All others	3%		
Outcomes	Incidence Rates among Control Group			
Breast Cancer	(%/year)	0.355%[2]	no data available	
Colon Cancer		0.160%[2]		
CHD		0.294%[2]		
Hip Fractures		0.258%[2]		

[1] Assumes monthly goals will be met in all remaining months and that all current deficits will be filled by February 1997 for DM and May 1994 for HRT

[2] These values represent the expected incidence among control women during the early years of the study. Aging effects and secular trends are incorporated in the design, as appropriate.

Table 10.1. (continued)
Design Assumption and Current Estimates

Adherence	Parameter	Design Value		Current Estimate for	
DM Intervention	% cal from fat	Intervention	Control	Intervention	Control
	Baseline	38	38	35.0[3]	35.0[3]
	Year 01	21.7	37.8	22.3	33.9[4]
	Year 02	22.6	37.2		
	Year 10	26	34		
HRT	% changing arms				
	Year 1	6%		8.1%	
	Years 2-10	3%/year		No data available.	

[3] Based on 480 *Four Day Food Records* (186 Intervention, 294 Control) and 1685 Year 1 Control group FFQ's (see *Table 6.3*).

[4] Preliminary data based on 75 *24 Hour Recalls* obtained near end of first year (29 Intervention, 46 Control) and 1142 Intervention and 1685 Control FFQ's at Year 1 (see *Table 6.3*). Year 1 *Four Day Food Record* data not yet available.

11. Study Activities

A number of WHI-related scientific endeavors have been initiated by study investigators. Publications in scholarly journals are approved through the Presentations and Publications Advisory Committee and the Project Office. Ancillary studies are approved by the Design and Analysis Advisory Committee and the Project Office. Those initiatives that could potentially threaten the integrity of the Clinical Trial results before the completion of the study are to be referred to the DSMB for review. A full statement of the relevant policies may be found in the *WHI Manuals, Vol. 1 - Study Protocol and Policies, Section 3 - Study Policies.*

Table 11.1 - Publications presents current and planned publications that have been approved by the Publications and Presentations Committee.

Table 11.2 - Ancillary Studies lists all ancillary study proposals received by the Design and Analysis Committee along with some key features of the studies and their current status.

Table 11.1
Publications

1. Rossouw, Finnegan, Pottern, McGowan, Clifford. The evolution of the Women's Health Initiative: Perspectives from the NIH. Published in the American Medical Women's Association 1995; 50:50-55.

2. McTiernan, Franzi, Johnson, Manson, Nevitt, Rossouw, Taylor, Carleton. Informed consent in the Women's Health Initiative Clinical Trial and Observational Study. Accepted for publication by the Journal of Women's Health. Anticipated date of publication is October 1995.

3. Tinker, Burrows, Henry, Patterson, Van Horn, Rupp. Book chapter entitled "The Women's Health Initiative: Overview of the nutrition components"...for book titled "Nutrition and Women's Health." Book chapter accepted by publisher; anticipated publish date, October 1995.

4. Anderson, Davis, Koch. A comprehensive data management system for multicenter studies. Paper accepted by Controlled Clinical Trials, pending revisions.

5. Patterson, Caggiula, Coates, Kristal, Ritenbaugh, Snetselaar, Stern, Tylavsky, Van Horn. Low-fat diet practices of older women: Prevalence and implications for dietary assessment. Submitted to Journal of the American Dietetic Association.

6. Freedman, Anderson, Kipnis, Prentice, Wang, Rossouw, Wittes, Demets. An approach to monitoring the results of long-term disease prevention trials: Examples from the Women's Health Initiative. Final draft approved by P & P Committee. Awaiting approval of NIH; with submission to Controlled Clinical Trials in the next 2-4 weeks.

7. Matthews, Shumaker, Hunt, Bowen, Klesges, Kaplan, Ritenbaugh, Langer, Weiss. American Psychologist journal paper on Women's Health Initiative. Second draft in preparation.

8. Johnson, McTiernan, Bachman, Beresford, Dunne, Grady, Judd, Hunninghake, Manson. Combined hormone replacement therapy and occurrence of disease in post-menopausal women. First draft written.

9. WHI Study Groups. Design of the Women's Health Initiative Clinical Trial and Observational Study Draft manuscript. (Writing group: Prentice, Rossouw, Furberg, Johnson, Henderson, Cummings, Manson, Freedman, Oberman, Kuller.) WHI design manuscript. Draft in preparation.

Table 11.2
Ancillary Studies

Study ID#	Title (abbrev.)	Study's Principal Investigator(s)	WHI Investigator	Endpoint	D&A Approval	Status	Active?	ID#s of Other Participating Clinics	Study Population	Sample Size	Speci-mens?
AS1	ADAPT	John Crouse	Greg Burke	Athero.	Approval	not funded, no resubmission	NA	NA	DM	4,000	NA
AS2	PLCO-OS	Joel Weissfeld	Lew Kuller	Ca. Scrg.	Not an Ancillary Study	not active	NA	NA	OS	2,200	NA
AS3	PLCO-Partners	Joel Weissfeld	Lew Kuller		Concept Approval	not funded, no resubmission	NA	NA	WHI Partners	NA	NA
AS4	Prostate Cancer-Partners	Al Oberman James Shikany	Al Oberman	Prostate Ca.	Concept Approval	pending submission	no	ALL	DM Partners	10,922	NA
AS5	Fat Distaste	Pamela Green	Deb Bowen	Fat Distaste	Approval	funded	yes	Seattle only	DM	160	NA
AS6	Arthritis	Susan Hughes	Phil Greenland	Mus. Dis. Prev.	Approval	not funded, no resubmission	NA	NA	OS	1,200	NA
AS7	Ankle/Arm BPI	Lewis Kuller	Lew Kuller	AAI	Approval	under review	no	12, 14, 16, 22, 24, 25, 45	HRT	6,500	NA
AS8	Partner's Health Study	Robert Langer	Robert Langer	CVD	Approval	not funded,	yes	LaJolla only	WHI Partners	1,500	NA
AS9	Oral Bone Loss	Cora E. Lewis	Al Oberman	Oral Bone Loss	Approval	funded	yes	Birmingham only	OS	1,000	NA
AS10	Urine Metabolites	Elaine Meilahn	Lew Kuller	UA Metab/Br. Ca.	Approval	not funded, no resubmission	NA	NA	DM	80,000	NA
AS11	Sleep and Mood Predictors	Daniel Kripke	Robert Langer	Sleep/Mood	Approval	funded	yes	LaJolla only	OS	600	urine
AS12	Empowerment	Charles Mouton	Norm Lasser	Nut. Emp.	Disapproved	not active	NA	NA	DM only	360	NA

Table 11.2 (continued)

Study ID#	Title (abbrev.)	Study's Principal Investigator(s)	WHI Investigator	Endpoint	D&A Approval	Status	Active?	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?
AS13	Spinal Stenosis	Lewis Kuller	Lew Kuller	Spinal Stenosis	Approval	funded	yes	Pittsburgh only	CT	150	NA
AS14	HDL Metabolism	Scott Going,	Tom Moon	HDL Metab.	Approval	funded	yes	Tucson only	OS	200	NA
AS15	Osteopenia	Jean Wactawski-Wende	Maurizio Trevisan	Osteo/Perio	Approval	under review	no	Buffalo only	OS	1,948	NA
AS16	LEAD & BPI	Mary McDermott	Phil Greenland	LEAD	Approval	not funded, no resubmission	NA	NA	OS, 65+	5,500	NA
AS17	Domestic Violence	Charles Mouton	Norm Lasser	Dom. Viol.	Approval	not funded, will resubmit	no	Newark only	OS	1,000	NA
AS18	Fat Aversion	Jim Grizzle	Deb Bowen	Fat Aversion	Approval	under review	no	12, 19, 64	WHT women	120	NA
AS19	Coagulation Proteins	Anthony Orencia	Phil Greenland	Coag.	Conditional Approval	pending submission	no	21, 22, 60	OS	782	1.2 ml
AS20	EBCT-1 (Coronary Screening)	Robert Detrano	Rowan Chlebowski	CT Scans	Approval	under review	no	63	OS	2,666	NA
AS21	EBCT-2 (Effect of DM, HRT, CaD)	Robert Detrano	Rowan Chlebowski	Athero.	Approval	not funded, no resubmission	NA	NA	CT	2,666	NA
AS22	Vascular Compliance	Jennifer Robinson	Harbor UCLA Richard Grimm	Vas. Compl.	Conditional Approval	under review	no	Minneapolis only	CT	500	NA
AS23	NSAIDS	Randall Harris	Rebecca Jackson	Br. Ca. & Co. Ca.	To P&P; Not an Ancillary Study	not active	NA	NA	OS	100,000	NA
AS24	Skeletal Health	Diane Schneider	Robert Langer	Skeletal Health	Approval	under review	no	LaJolla only	OS	168	NA
AS25	Ankle-Arm BPI	Kamal Masaki	David Curb	AAI	Approval	under review	no	Hawaii only	OS	2,700	NA

Table 11.2 (continued)

Study ID#	Title (abbrev.)	Study's Principal Investigator(s)	WHI Investigator	Endpoint	D&A Approval	Status	Active?	ID#s of Other Participating Clinics	Study Population	Sample Size	Speci-mens?
AS26	Knee-Hip OA	James Cerhan	Robert Wallace	OA	Conditional Approval	under review	no	ALL	HRT	11,374	NA
AS27	Vitamin D, Calcium, & Breast Cancer	Barbara Hulka	David Sheps	Br. Ca.	Approval	under review	no	ALL	CaD/OS	2,600	2 ml
AS28	Aging	S. Wassertheil-Smoller		Aging	Concept Approval	pending submission	no	NYC only	NYC OS ppts.	NA	1.5 ml
AS29	Oxidation Status	Michael Gaziano JoAnn Manson	JoAnn Manson	Oxidation	Conditional Approval	under review	no	Boston only	HRT	300	NA
AS30	Lung Cancer	Geoffrey Kabat	S. Wassertheil-Smoller	Lung Ca.	Approval	pending submission	no	ALL	OS	67,000	2.5 ml
AS31	Eye Care Use	Kleinstein	Al Oberman	Eye Care Use	Approval	under review	no	Birmingham only	OS	300	NA
AS32	Recruitment Tech.	Edwards	Robert Langer	Recruit.	Approval	under review	no	LaJolla only	NA	400	NA
AS33	HRT and Body Fat	Charlotte Mayo	Al Oberman	Body Fat	Approval	funded	yes	Birmingham only	OS	690	NA
AS34	Bone Morphology	Dorothy Nelson	Susan Hendrix	Bone Morph.	Approval	under review	no	Detroit only	CT	400	NA
AS35	Risk Factors for Fatigue	Arthur Hartz	Jane Kotchen	Fatigue	not approved, invited to resubmit for 11/18	under review	no	21	NA	3,000	NA
AS36	HRT and Mammographic Density	Barbara Hulka	David Sheps	Mamm. Density	Approval	under review	no	ALL	HRT	NA	NA
AS37	Lipid Markers	JoAnn Manson		Athero.	decision postponed to 9/18	NA	no	12, 15, 22	NA	NA	NA

Table 11.2 (continued)

Study ID#	Title (abbrev.)	Study's Principal Investigator(s)	WHI Investigator	Endpoint	D&A Approval	Status	Active?	ID#s of Other Participating Clinics	Study Population	Sample Size	Speci-mens?
AS38	Hemostatis	Paul Ridker	JoAnn Manson	Coronary Dis.	decision postponed to 9/18	NA	no	12, 15, 22	NA	NA	NA
AS39	HRT and Dementia	Sally Shumaker	Curt Furberg	Dementia	Approval	under review	no	ALL	HRT women	4,800	NA
AS40	Mammography Behavior	S. Wassertheil-Smoller	S. Wassertheil-Smoller	Mamm.	pending discussion	pending submission	no	NYC only	NYC ppts.	All	NA
AS41	Metab. Lipoproteins	Joel Morrisett	John Foreyt	CVD	not approved	pending submission	NA	Houston only	Houston ppts.	24	blood
AS42	Antioxidants	Dana Seeley	Michael Nevitt	Osteo.	pending discussion	pending submission	no	12, 28, 29	9000 BD	360	serum
AS43	Bone Mass	William Goodman	Howard Judd	Osteo.	not approved	pending submission	NA	UCLA only	Los Angeles CT	362	blood, urine