



New Morning Sickness Drug Diclegis Has Troubled History

May 20, 2013 By [Ted Oshman](https://www.oshmanlaw.com/news-center/author/ted-oshman/) (<https://www.oshmanlaw.com/news-center/author/ted-oshman/>)

The morning sickness drug Diclegis may have only been approved



(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm347087.htm>) by the Food and Drug Administration recently, but [Betty Mekdeci](#) (</news-center/driven-to-action/>) has known it well for nearly 40 years.

Diclegis is a combination of pyridoxine (vitamin B6) and doxylamine being offered by Canada's Duchesnay Inc. This drug combination was once sold under the name Bendectin before its manufacturer pulled it from the market in 1983.

Bendectin is what Mekdeci believes caused her son David to be born with a heart defect and a deformed left arm in 1975. She wasn't the only mother who gave birth to a child with a serious birth defect (</pharmaceutical-litigation/birth-defect-drugs/>) after taking Bendectin. Far from it.

After the birth of their son, Mekdeci and her husband Mike began an uphill battle against a giant pharmaceutical company to illustrate the dangers of the drug and get it off the market.

'It Was Like a Bad TV Movie'

The Mekdecis didn't know where to start looking for answers on behalf of their infant son. They sent a number of letters to the FDA, finally getting a response when they sent along a photo of David in a cowboy suit. Someone at the FDA hinted that they might be on to something.

So they filed requests under the Freedom of Information Act seeking government documents on Bendectin. But the cost for the government to copy the documents was more than the couple – she a freelance writer, he a teacher, both raising a growing family – could afford. They had hit a wall.

“It was like a bad TV movie,” Betty Mekdeci said.

But they found allies in an unlikely place: the same government agency that approved Bendectin. Mekdeci said “five or six” people at the FDA would point her in the right direction in her search. Some generous soul made microfiche copies of the slew of documents and studies the Mekdecis couldn’t afford and sent them over.

Without this help, Mekdeci said she never would have made it as far as she did. It also reinforced her belief that what she was seeking was very real.

“It was like a riddle. I would not have had the confidence that I knew what I was doing without help,” Mekdeci recalled. “How could I take on Bendectin if I didn’t have people telling me what to do and how to do it?”

Taking on a Giant

Fast forward to 1980. With a team of attorneys at their side, the Mekdeci’s case against manufacturer Merrell Dow eventually found its way to a courtroom. The Mekdeci’s case rested largely on animal studies of Bendectin. The jury awarded the case to the Mekdecis, but their verdict gave the family only \$20,000 to cover past and future medical expenses.

“I was fine with that. We won,” Mekdeci said.

But it didn’t last. A judge tossed the verdict and ordered a new trial. This time, the jury sided with Merrell Dow. The Mekdecis appealed to the 11th Circuit Court of Appeals.

In their 1983 decision, circuit court justices detailed the “extraordinary tale” of the Mekdeci’s litigation and its history, including the Mekdecis’ struggles with their own attorneys. The justices wrote that the evidence revealed “disturbing questions” regarding the ethics of the couple’s attorneys and suggested they did not fulfill their obligations to the Mekdecis.

While the Mekdecis had entered uncharted territory when their case began, by the time of the second trial, Bendectin was subject to a growing number of lawsuits that were potentially more profitable than the Mekdecis’ case. The appellate decision suggests the attorneys “abandoned” the Mekdecis to pursue more profitable Bendectin cases, and even touted the first Mekdeci trial as a selling point to get more cases.

The court ruled, however, that this was not sufficient to overturn the verdict.

Many cases against the company were handled by the high-profile attorney Melvin Belli, who initially took the Mekdeci’s case and was involved behind the scenes throughout the litigation. One of the Bendectin cases, Daubert v. Merrell Dow Pharmaceuticals (https://en.wikipedia.org/wiki/Daubert_v._Merrell_Dow_Pharmaceuticals,_Inc.), went all the way to the U.S. Supreme Court and became a landmark decision in the legal community for its effect of the admissibility of expert testimony.

In the midst of this bad publicity, Merrell Dow took Bendectin off the market in 1983, citing financial — not safety — concerns. The *New York Times* reported (<http://www.nytimes.com/1983/06/19/weekinreview/shadow-of-doubt-wipes-out-bendectin.html>) that some 300 lawsuits were pending against the company at the time.

A Question of Money, Not Safety

Even after pulling Bendectin, Merrell Dow maintained that the drug was safe. The company said the lawsuits raised the company's insurance premiums to the point that Bendectin was less profitable than desired. The decision to take it off the market came because the company wasn't making enough money.

Even when the dangers had been made public and Bendectin was on the verge of being pulled from the market, 1 in 10 pregnant women were taking the drug, the *Times* reported. Bendectin was the only drug approved for the treatment of morning sickness at the time, and, in the years that followed, no drug came along to take its place.

For this reason, Diclegis will likely be a hit on the pharmaceutical market.

The Good Fight

Betty Mekdeci's fight didn't end in 1983. During the Bendectin battle, the Mekdecis formed Birth Defect Research for Children (<http://birthdefects.org/>) to serve as a resource for parents whose children face birth defects. The organization is as active as ever today and currently maintains a thorough registry of birth defects (<http://birthdefects.org/national-birth-defect-registry/>) in an attempt to spot patterns in their occurrence.

In a 1982 letter to then Surgeon General C. Everett Koop, Mekdeci wrote: "We feel that if our group can prevent the birth of a single defective baby, we have performed a valuable service to our country and its families."

For more on the organization, see this The Oshman Firm blog post (</news-center/driven-to-action/>).

ENDING THE SALE OF DANGEROUS DRUGS

Mekdeci never received a dollar of compensation from Merrell Dow for David's birth defect, but she's OK with that. For her, it was more about the goal in the end: getting Bendectin off the market.

Ultimately, she said, the pharmaceutical business is just that – a business. She doesn't put it past companies to market ineffective or dangerous drugs if they can make a dime from it. Even Bendectin, she said, didn't do a great job of curbing her morning sickness.

"It's not a life-saving drug. Its not even a particularly effective drug," she said. "The only thing it has going for it is it's a big moneymaker."

The FDA says Diclegis is safe, and they have many doctors on their side. The link between pyridoxine/doxylamine and birth defects is not as well documented as that of selective serotonin reuptake inhibitor anti-depressants (</pharmaceutical-litigation/zoloft/>). When Bendectin was pulled, the *Times* called the research on Bendectin "inconclusive and contradictory."

But Mekdeci is convinced. For her, her son David is proof of the drug's potential for harm.

She worries mothers-to-be will start taking Diclegis without knowledge of its history. Mekdeci — who has almost four decades of experience with birth defects under her belt — offered a warning.

"If I had known what I knew today, you think I just wouldn't have been sick for nine months?" she said. "That's a lot better than being sick at heart for 38 years knowing what your son's been through and will go through."

Sales of Diclegis will begin in June. Will history repeat itself? Will litigation from devastated parents follow?



About Ted Oshman (<https://www.oshmanlaw.com/news-center/author/ted-oshman/>)

Ted Oshman has been with The Oshman Firm since 1988 serving clients for over 25 years. Learn more about Ted's background and featured practice areas [here](http://oshmanlaw.com/about-the-firm/ted-oshman/). (<http://oshmanlaw.com/about-the-firm/ted-oshman/>)

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4 RESPONSES TO "NEW MORNING SICKNESS DRUG DICLEGIS HAS TROUBLED HISTORY"



Jo-Ann negron

June 19, 2013 (<https://www.oshmanlaw.com/news-center/diclegis-troubled-history/#comment-16>)

As someone who was affected by Bendectin, I have a birth defect my mother took Bendectin when she was pregnant with me in 1978. I pray that this drug will not cause birth defects, and that history does not repeat itself. It would be heart breaking if that were to happen again.

[Reply](#)



Anne M

July 5, 2013 (<https://www.oshmanlaw.com/news-center/diclegis-troubled-history/#comment-17>)

I took Bendectin during my pregnancy in 1973... my son has learning disabilities and cannot keep a job — he cannot fill out job applications, he is unsuccessful with testing, especially Math which keeps him out of many jobs. It's been a lifetime of special schools, special classes and lots of related issues... he is unable to support himself so he gets 1/2 of MY income every month! He is 39.

[Reply](#)



Anna

July 9, 2013 (<https://www.oshmanlaw.com/news-center/diclegis-troubled-history/#comment-18>)

The actual history of this drug includes that Canadian women have been taking it for decades, it's been extensively studied, and the science is very clear it does not cause defects. This article is fear mongering.

[Reply](#).



Shawn

January 18, 2016 (<https://www.oshmanlaw.com/news-center/diclegis-troubled-history/#comment-1209>).

Anna, have you reviewed the animal studies with Bendectin both the three ingredient drug and the later two ingredient drug? Until you do, please dont speak so foolishly.

[Reply](#).

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the Court describes the constitutional infirmity in those cases as follows: "[T]he government had seized or otherwise restrained materials suspected of being obscene without a prior judicial determination that they were in fact so." *Ante*, at 2771-2772. But the same constitutional defect is present in the case before us today, and the Court fails to explain why it is not fatal to the forfeiture punishment here under review. Thus, while in the past we invalidated seizures which resulted in a temporary removal of presumptively protected materials from circulation, today the Court approves of Government measures having the same permanent effect. In my view, the forfeiture of expressive material here that had not been adjudged to be obscene, or otherwise without the protection of the First Amendment, was unconstitutional.

* * *

Given the Court's principal holding, I can interpose no objection to remanding the case for further consideration under the Eighth Amendment. But it is unnecessary to reach the Eighth Amendment question. The Court's failure to reverse this flagrant violation of the right of free speech and expression is a deplorable abandonment of fundamental First Amendment principles. I dissent from the judgment and from the opinion of the Court.



509 U.S. 579, 125 L.Ed.2d 469

¹⁵⁷⁹ William DAUBERT, et ux.,
etc., et al., Petitioners,

v.

MERRELL DOW PHARMACEUTICALS,
INC.

No. 92-102.

Argued March 30, 1993

Decided June 28, 1993.

Infants and their guardians ad litem
sued pharmaceutical company to recover for

limb reduction birth defects allegedly sustained as result of mothers' ingestion of anti-nausea drug Bendectin. The United States District Court for the Southern District of California, 727 F.Supp. 570, granted company's motion for summary judgment, and plaintiffs appealed. The Court of Appeals, 951 F.2d 1128, affirmed. Plaintiffs filed petition for writ of certiorari, which was granted. The Supreme Court, Justice Blackmun, held that: (1) "general acceptance" is not necessary precondition to admissibility of scientific evidence under Federal Rules of Evidence, and (2) Rules assign to trial judge the task of ensuring that expert's testimony both rests on reliable foundation and is relevant to task at hand.

Vacated and remanded.

Chief Justice Rehnquist filed opinion concurring in part and dissenting in part in which Justice Stevens joined.

1. Evidence ⇨150

Federal Rules of Evidence superseded *Frye* "general acceptance" test for admissibility of scientific evidence. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

2. Federal Civil Procedure ⇨21

Supreme Court interprets legislatively enacted Federal Rules of Evidence as it would any statute.

3. Evidence ⇨99

Basic standard of relevance under Federal Rules of Evidence is liberal one. Fed. Rules Evid. Rules 401, 402, 28 U.S.C.A.

4. Evidence ⇨150

Rigid "general acceptance" requirement for admission of scientific evidence would be at odds with "liberal thrust" of Federal Rules of Evidence and their general approach of relaxing traditional barriers to "opinion" testimony. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

5. Evidence $\Rightarrow$ 150

Trial judge is not disabled under Federal Rules of Evidence from screening purportedly scientific evidence. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

6. Evidence $\Rightarrow$ 150

Under Federal Rules of Evidence, trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

7. Evidence $\Rightarrow$ 150

"Scientific," within meaning of Federal Rule of Evidence stating that if "scientific," technical, or other specialized knowledge will assist trier of fact to understand evidence or to determine fact in issue an expert may testify thereto, implies grounding in methods and procedures of science. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

8. Evidence $\Rightarrow$ 508

"Knowledge," within meaning of Federal Rule of Evidence stating that if scientific, technical, or other specialized "knowledge" will assist trier of fact to understand evidence or to determine fact in issue an expert may testify thereto, connotes more than subjective belief or unsupported speculation. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

9. Evidence $\Rightarrow$ 508

Subject of scientific knowledge need not be "known" to certainty to permit expert testimony, since, arguably, there are not certainties in science. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

10. Evidence $\Rightarrow$ 508

Inference or assertion must be derived by scientific method to qualify as "scientific knowledge," within meaning of Federal Rule of Evidence stating that if scientific, technical, or other specialized knowledge will assist trier of fact to understand evidence or to

determine fact in issue an expert may testify thereto. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

11. Evidence $\Rightarrow$ 555.1

For scientific testimony to be admitted, proposed testimony must be supported by appropriate validation, in other words, "good grounds" based on what is known. Fed. Rules Evid. Rule 702, 28 U.S.C.A.

12. Evidence $\Rightarrow$ 508

Requirement under Federal Rule of Evidence that expert's testimony pertain to "scientific knowledge" establishes standard of evidentiary reliability. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

13. Evidence $\Rightarrow$ 150

In case involving scientific evidence, evidentiary reliability will be based upon scientific reliability. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

14. Evidence $\Rightarrow$ 150

Condition for admission of scientific evidence or testimony under Federal Rule of Evidence, that evidence or testimony assist trier of fact to understand evidence or to determine fact in issue, goes primarily to relevance. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

15. Evidence $\Rightarrow$ 150

In determining admissibility of scientific evidence or testimony, scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

16. Evidence $\Rightarrow$ 150

"Helpfulness" standard under Federal Rule of Evidence for admissibility of scientific evidence or testimony requires valid scientific connection to pertinent inquiry as precondition to admissibility. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

17. Evidence ⇐505

Unlike ordinary witness, expert is permitted wide latitude to offer opinions, including those that are not based on first-hand knowledge or observation. Fed.Rules Evid. Rules 701–703, 28 U.S.C.A.

18. Evidence ⇐508

Presumably, relaxation under Federal Rules of Evidence of usual requirement of first-hand knowledge when there is testimony by expert is premised on assumption that expert's opinion will have reliable basis in knowledge and experience of his discipline. Fed.Rules Evid.Rules 701–703, 28 U.S.C.A.

19. Evidence ⇐508

Faced with proffer of expert scientific testimony, trial judge must determine at outset whether expert is proposing to testify to (1) scientific knowledge that (2) will assist trier of fact to understand or determine fact in issue; preliminary assessment must be made of whether reasoning or methodology underlying testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to facts in issue. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

20. Evidence ⇐546

Preliminary questions concerning qualification of person to be witness, existence of privilege, or admissibility of evidence should be established by preponderance of proof. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

21. Evidence ⇐150

Requirements for admissibility of scientific testimony or opinion under Federal Rule of Evidence do not apply specially or exclusively to unconventional evidence. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

22. Evidence ⇐9

Scientific theories that are so firmly established as to have obtained status of scientific law, such as laws of thermodynamics, properly are subject to judicial notice. Fed. Rules Evid.Rule 201, 28 U.S.C.A.

23. Evidence ⇐555.1

Definitive checklist or test does not exist in making preliminary assessment of whether reasoning or methodology underlying expert testimony is scientifically valid and whether that reasoning or methodology properly can be applied to facts in issue. Fed.Rules Evid. Rule 104(a), 28 U.S.C.A.

24. Evidence ⇐508

Ordinarily, key question to be answered in determining whether theory or technique is scientific knowledge that will assist trier of fact, and, thus, whether expert testimony is admissible, will be whether theory or technique can be, and has been, tested. Fed. Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

25. Evidence ⇐508

In determining whether theory or technique is scientific knowledge that will assist trier of fact, and, thus, whether expert testimony is admissible, is whether theory or technique has been subjected to peer review and publication. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

26. Evidence ⇐508

Publication of theory or technique, which is but one element of peer review, is not sine qua non of admissibility of expert testimony; publication does not necessarily correlate with reliability, and, in some instances, well-grounded but innovative theories will not have been published. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

27. Evidence ⇐508

Fact of publication of theory or technique, or lack thereof, in peer-review journal will be relevant, though not dispositive, consideration in assessing scientific validity of particular technique or methodology on which expert opinion is premised; submission to scrutiny of scientific community is component of “good science,” in part because it increases likelihood that substantive flaws in methodology will be detected. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

28. Evidence ⇨508

In determining admissibility of expert opinion regarding particular scientific technique, court ordinarily should consider known or potential rate of error, and existence and maintenance of standards controlling technique's operation. Fed.Rules Evid. Rules 104(a), 702, 28 U.S.C.A.

29. Evidence ⇨508

"General acceptance" of scientific theory or technique can have bearing in determining admissibility of expert testimony. Fed.Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

30. Evidence ⇨150

Widespread acceptance of scientific theory or technique can be important factor in ruling particular evidence admissible, and known technique that has been able to draw only minimal support within community may properly be viewed with skepticism. Fed. Rules Evid.Rules 104(a), 702, 28 U.S.C.A.

31. Evidence ⇨150

Inquiry envisioned by Federal Rule of Evidence pertaining to admission of scientific testimony and evidence is flexible one. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

32. Evidence ⇨150

Overarching subject of Federal Rule of Evidence on admission of scientific testimony and evidence is scientific validity, and, thus, evidentiary relevance and reliability, of principles that underlie proposed submission. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

33. Evidence ⇨150

Focus of Federal Rule of Evidence on admission of scientific testimony and evidence must be solely on principles and methodology, not on conclusions that they generate. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

* The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader.

34. Evidence ⇨546

Judge assessing proffer of expert's scientific testimony under Federal Rule of Evidence on testimony by experts should also be mindful of other applicable rules, including rule on expert opinions based on otherwise inadmissible hearsay, rule allowing court to procure assistance of expert of its own choosing, and rule permitting exclusion of relevant evidence if its probative value is substantially outweighed by danger of unfair prejudice, confusion of issues, or misleading jury. Fed. Rules Evid.Rules 403, 702, 703, 706, 28 U.S.C.A.

35. Federal Civil Procedure ⇨2146, 2546

In event that trial court concludes that scintilla of scientific evidence presented supporting a position is insufficient to allow reasonable juror to conclude that position more likely than not is true, court remains free to direct verdict, and likewise to grant summary judgment. Fed.Rules Civ.Proc.Rules 50(a), 56, 28 U.S.C.A.; Fed.Rules Evid.Rule 702, 28 U.S.C.A.

36. Federal Civil Procedure ⇨21

Federal Rules of Evidence are designed not for exhaustive search for cosmic understanding but for particularized resolution of legal disputes.

*Syllabus **

Petitioners, two minor children and their parents, alleged in their suit against respondent that the children's serious birth defects had been caused by the mothers' prenatal ingestion of Bendectin, a prescription drug marketed by respondent. The District Court granted respondent summary judgment based on a well-credentialed expert's affidavit concluding, upon reviewing the extensive published scientific literature on the subject, that maternal use of Bendectin has not been shown to be a risk factor for human birth defects. Although petitioners had responded with the testimony of eight other well-credentialed experts, who based their conclusion

See *United States v. Detroit Lumber Co.*, 200 U.S. 321, 337, 26 S.Ct. 282, 287, 50 L.Ed. 499.

that Bendectin can cause birth defects on animal studies, chemical structure analyses, and the unpublished “reanalysis” of previously published human statistical studies, the court determined that this evidence did not meet the applicable “general acceptance” standard for the admission of expert testimony. The Court of Appeals agreed and affirmed, citing *Frye v. United States*, 54 App. D.C. 46, 47, 293 F. 1013, 1014, for the rule that expert opinion based on a scientific technique is inadmissible unless the technique is “generally accepted” as reliable in the relevant scientific community.

Held: The Federal Rules of Evidence, not *Frye*, provide the standard for admitting expert scientific testimony in a federal trial. Pp. 2792–2799.

(a) *Frye*’s “general acceptance” test was superseded by the Rules’ adoption. The Rules occupy the field, *United States v. Abel*, 469 U.S. 45, 49, 105 S.Ct. 465, 467, 83 L.Ed.2d 450, and, although the common law of evidence may serve as an aid to their application, *id.*, at 51–52, 105 S.Ct., at 468–469, respondent’s assertion that they somehow assimilated *Frye* is unconvincing. Nothing in the Rules as a whole or in the text and drafting history of Rule 702, which specifically governs expert testimony, gives any indication that “general acceptance” is a necessary precondition to the admissibility of scientific evidence. Moreover, such a rigid standard would be at odds with the Rules’ liberal thrust and their general approach of relaxing the traditional barriers to “opinion” testimony. Pp. 2792–2794.

(b) The Rules—especially Rule 702—place appropriate limits on the admissibility of purportedly scientific evidence by assigning to the trial judge the task of ensuring that an expert’s testimony both rests on a reliable foundation and is relevant to the task at hand. The reliability standard is established by Rule 702’s requirement that an expert’s testimony pertain to “scientific . . . knowledge,” since the adjective “scientific”

implies a grounding in science’s methods and procedures, while the word “knowledge” connotes a body of known facts or of ideas inferred from such facts or accepted as true on good grounds. The Rule’s requirement that the testimony “assist the trier of fact to understand the evidence or to determine a fact in issue” goes primarily to relevance by demanding a valid scientific connection to the pertinent inquiry as a precondition to admissibility. Pp. 2794–2796.

(c) Faced with a proffer of expert scientific testimony under Rule 702, the trial judge, pursuant to Rule 104(a), must make a preliminary assessment of whether the testimony’s underlying reasoning or methodology is scientifically valid and properly can be applied to the facts at issue. Many considerations will bear on the inquiry, including whether the theory or technique in question can be (and has been) tested, whether it has been subjected to peer review and publication, its known or potential error rate and the existence and maintenance of standards controlling its operation, and whether it has attracted widespread acceptance within a relevant scientific community. The inquiry is a flexible one, and its focus must be solely on principles and methodology, not on the conclusions that they generate. Throughout, the judge should also be mindful of other applicable Rules. Pp. 2796–2798.

(d) Cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof, rather than wholesale exclusion under an uncompromising “general acceptance” standard, is the appropriate means by which evidence based on valid principles may be challenged. That even limited screening by the trial judge, on occasion, will prevent the jury from hearing of authentic scientific breakthroughs is simply a consequence of the fact that the Rules are not designed to seek cosmic understanding but, rather, to resolve legal disputes. Pp. 2798–2799.

951 F.2d 1128 (CA9 1991), vacated and remanded.

BLACKMUN, J., delivered the opinion for a unanimous Court with respect to Parts I and II-A, and the opinion of the Court with respect to Parts II-B, II-C, III, and IV, in which WHITE, O'CONNOR, SCALIA, KENNEDY, SOUTER, and THOMAS, JJ., joined. REHNQUIST, C.J., filed an opinion concurring in part and dissenting in part, in which STEVENS, J., joined, *post*, p. 2799.

¹Michael H. Gottesman, Washington, DC, for petitioners.

Charles Fried, Cambridge, MA, for respondent.

²Justice BLACKMUN delivered the opinion of the Court.

In this case we are called upon to determine the standard for admitting expert scientific testimony in a federal trial.

I

Petitioners Jason Daubert and Eric Schuller are minor children born with serious birth defects. They and their parents sued respondent in California state court, alleging that the birth defects had been caused by the mothers' ingestion of Bendectin, a prescription antinausea drug marketed by respondent. Respondent removed the suits to federal court on diversity grounds.

After extensive discovery, respondent moved for summary judgment, contending that Bendectin does not cause birth defects

in humans and that petitioners would be unable to come forward with any admissible evidence that it does. In support of its motion, respondent submitted an affidavit of Steven H. Lamm, physician and epidemiologist, who is a well-credentialed expert on the risks from exposure to various chemical substances.¹ Doctor Lamm stated that he had reviewed all the literature on Bendectin and human birth defects—more than 30 published studies involving over 130,000 patients. No study had found Bendectin to be a human teratogen (*i.e.*, a substance capable of causing malformations in fetuses). On the basis of this review, Doctor Lamm concluded that maternal use of Bendectin during the first trimester of pregnancy has not been shown to be a risk factor for human birth defects.

³Petitioners did not (and do not) contest this characterization of the published record regarding Bendectin. Instead, they responded to respondent's motion with the testimony of eight experts of their own, each of whom also possessed impressive credentials.² These experts had concluded that Bendectin can cause birth defects. Their conclusions were based upon "in vitro" (test tube) and "in vivo" (live) animal studies that found a link between Bendectin and malformations; pharmacological studies of the chemical structure of Bendectin that purported to show similarities between the structure of the drug and that of other substances known to cause birth defects; and the "reanalysis" of previously

1. Doctor Lamm received his master's and doctor of medicine degrees from the University of Southern California. He has served as a consultant in birth-defect epidemiology for the National Center for Health Statistics and has published numerous articles on the magnitude of risk from exposure to various chemical and biological substances. App. 34-44.
2. For example, Shanna Helen Swan, who received a master's degree in biostatistics from Columbia University and a doctorate in statistics from the University of California at Berkeley, is chief of the section of the California Department of Health and Services that determines causes of birth defects and has served as a consultant to

the World Health Organization, the Food and Drug Administration, and the National Institutes of Health. *Id.*, at 113-114, 131-132. Stuart A. Newman, who received his bachelor's degree in chemistry from Columbia University and his master's and doctorate in chemistry from the University of Chicago, is a professor at New York Medical College and has spent over a decade studying the effect of chemicals on limb development. *Id.*, at 54-56. The credentials of the others are similarly impressive. See *Id.*, at 61-66, 73-80, 148-153, 187-192, and Attachments 12, 20, 21, 26, 31, and 32 to Petitioners' Opposition to Summary Judgment in No. 84-2013-G(1) (SD Cal.).

published epidemiological (human statistical) studies.

The District Court granted respondent's motion for summary judgment. The court stated that scientific evidence is admissible only if the principle upon which it is based is "sufficiently established to have general acceptance in the field to which it belongs." 727 F.Supp. 570, 572 (S.D.Cal. 1989), quoting *United States v. Kilgus*, 571 F.2d 508, 510 (CA9 1978). The court concluded that petitioners' evidence did not meet this standard. Given the vast body of epidemiological data concerning Bendectin, the court held, expert opinion which is not based on epidemiological evidence ¹⁵⁸⁴is not admissible to establish causation. 727 F.Supp., at 575. Thus, the animal-cell studies, live-animal studies, and chemical-structure analyses on which petitioners had relied could not raise by themselves a reasonably disputable jury issue regarding causation. *Ibid.* Petitioners' epidemiological analyses, based as they were on recalculations of data in previously published studies that had found no causal link between the drug and birth defects, were ruled to be inadmissible because they had not been published or subjected to peer review. *Ibid.*

The United States Court of Appeals for the Ninth Circuit affirmed. 951 F.2d 1128 (1991). Citing *Frye v. United States*, 54 App.D.C. 46, 47, 293 F. 1013, 1014 (1923), the court stated that expert opinion based on a scientific technique is inadmissible unless the technique is "generally accepted" as reliable in the relevant scientific community. 951 F.2d, at 1129-1130. The court declared that expert opinion based on a methodology that diverges "significantly from the procedures accepted by recognized authorities in the field ... cannot be shown to be 'generally accepted as a reliable technique.'" *Id.*, at 1130, quoting *United States v. Solomon*, 753 F.2d 1522, 1526 (CA9 1985).

The court emphasized that other Courts of Appeals considering the risks of Bendectin had refused to admit reanalyses of epi-

demiological studies that had been neither published nor subjected to peer review. 951 F.2d, at 1130-1131. Those courts had found unpublished reanalyses "particularly problematic in light of the massive weight of the original published studies supporting [respondent's] position, all of which had undergone full scrutiny from the scientific community." *Id.*, at 1130. Contending that reanalysis is generally accepted by the scientific community only when it is subjected to verification and scrutiny by others in the field, the Court of Appeals rejected petitioners' reanalyses as "unpublished, not subjected to the normal peer review process and generated solely for use in litigation." *Id.*, at 1131. The ¹⁵⁸⁵court concluded that petitioners' evidence provided an insufficient foundation to allow admission of expert testimony that Bendectin caused their injuries and, accordingly, that petitioners could not satisfy their burden of proving causation at trial.

We granted certiorari, 506 U.S. 914, 113 S.Ct. 320, 121 L.Ed.2d 240 (1992), in light of sharp divisions among the courts regarding the proper standard for the admission of expert testimony. Compare, e.g., *United States v. Shorter*, 257 U.S.App.D.C. 358, 363-364, 809 F.2d 54, 59-60 (applying the "general acceptance" standard), cert. denied, 484 U.S. 817, 108 S.Ct. 71, 98 L.Ed.2d 35 (1987), with *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*, 911 F.2d 941, 955 (CA3 1990) (rejecting the "general acceptance" standard).

II

A

In the 70 years since its formulation in the *Frye* case, the "general acceptance" test has been the dominant standard for determining the admissibility of novel scientific evidence at trial. See E. Green & C. Nesson, Problems, Cases, and Materials on Evidence 649 (1983). Although under increasing attack of late, the rule continues to be followed by a

majority of courts, including the Ninth Circuit.³

The *Frye* test has its origin in a short and citation-free 1923 decision concerning the admissibility of evidence derived from a systolic blood pressure deception test, a crude precursor to the polygraph machine. In what has become a famous (perhaps infamous) passage, the then Court of Appeals for the District of Columbia described the device and its operation and declared:

"Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages¹⁵⁸⁶ is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized, and while courts will go a long way in admitting expert testimony deduced from a well-recognized scientific principle or discovery, *the thing from which the deduction is made must be sufficiently established to have gained general acceptance in the particular field in which it belongs.*" 54 App.D.C., at 47, 293 F., at 1014 (emphasis added).

3. For a catalog of the many cases on either side of this controversy, see P. Giannelli & E. Imwinkelried, *Scientific Evidence* § 1-5, pp. 10-14 (1986 and Supp.1991).

4. See, e.g., Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 Nw.U.L.Rev. 643 (1992) (hereinafter Green); Becker & Orenstein, *The Federal Rules of Evidence After Sixteen Years—the Effect of "Plain Meaning" Jurisprudence, the Need for an Advisory Committee on the Rules of Evidence, and Suggestions for Selective Revision of the Rules*, 60 Geo.Wash.L.Rev. 857, 876-885 (1992); Hanson, *James Alphonzo Frye is Sixty-Five Years Old; Should He Retire?*, 16 West.St. U.L.Rev. 357 (1989); Black, *A Unified Theory of Scientific Evidence*, 56 Ford.L.Rev. 595 (1988); Imwinkelried, *The "Bases" of Expert Testimony: The Syllogistic Structure of Scientific Testimony*, 67 N.C.L.Rev. 1 (1988); *Proposals for a Model Rule on the Admissibility of Scientific Evidence*, 26 Jurimetrics J. 235 (1986); Giannelli, *The Admissibility of Novel Scientific Evidence: Frye v. United States, a Half-Century Later*, 80 Colum.L.Rev. 1197 (1980); *The Supreme Court*, 1986 Term, 101 Harv.L.Rev. 7, 119, 125-127 (1987).

Because the deception test had "not yet gained such standing and scientific recognition among physiological and psychological authorities as would justify the courts in admitting expert testimony deduced from the discovery, development, and experiments thus far made," evidence of its results was ruled inadmissible. *Ibid.*

[1] The merits of the *Frye* test have been much debated, and scholarship on its proper scope and application is legion.⁴ ¹⁵⁸⁷Petitioners' primary attack, however, is not on the content but on the continuing authority of the rule. They contend that the *Frye* test was superseded by the adoption of the Federal Rules of Evidence.⁵ We agree.

[2, 3] We interpret the legislatively enacted Federal Rules of Evidence as we would any statute. *Beech Aircraft Corp. v. Rainey*, 488 U.S. 153, 163, 109 S.Ct. 439, 446, 102 L.Ed.2d 445 (1988). Rule 402 provides the baseline:

"All relevant evidence is admissible, except as otherwise provided by the Constitution of the United States, by Act of Congress,

Indeed, the debates over *Frye* are such a well-established part of the academic landscape that a distinct term—"Frye-ologist"—has been advanced to describe those who take part. See Behringer, *Introduction, Proposals for a Model Rule on the Admissibility of Scientific Evidence*, 26 Jurimetrics J. 237, 239 (1986), quoting Lacey, *Scientific Evidence*, 24 Jurimetrics J. 254, 264 (1984).

5. Like the question of *Frye*'s merit, the dispute over its survival has divided courts and commentators. Compare, e.g., *United States v. Williams*, 583 F.2d 1194 (CA2 1978) (*Frye* is superseded by the Rules of Evidence), cert. denied, 439 U.S. 1117, 99 S.Ct. 1025, 59 L.Ed.2d 77 (1979) with *Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1111, 1115-1116 (CA5 1991) (en banc) (*Frye* and the Rules coexist), cert. denied, 503 U.S. 912, 112 S.Ct. 1280, 117 L.Ed.2d 506 (1992), 3 J. Weinstein & M. Berger, *Weinstein's Evidence* ¶ 702[03], pp. 702-36 to 702-37 (1988) (hereinafter Weinstein & Berger) (*Frye* is dead), and M. Graham, *Handbook of Federal Evidence* § 703.2 (3d ed. 1991) (*Frye* lives). See generally P. Giannelli & E. Imwinkelried, *Scientific Evidence* § 1-5, at 28-29 (citing authorities).

by these rules, or by other rules prescribed by the Supreme Court pursuant to statutory authority. Evidence which is not relevant is not admissible."

"Relevant evidence" is defined as that which has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Rule 401. The Rule's basic standard of relevance thus is a liberal one.

Frye, of course, predated the Rules by half a century. In *United States v. Abel*, 469 U.S. 45, 105 S.Ct. 465, 83 L.Ed.2d 450 (1984), we considered the pertinence of background common law in interpreting the Rules of Evidence. We noted that the Rules occupy the field, *id.*, at 49, 105 S.Ct., at 467, but, quoting Professor Cleary, the Reporter, ¹⁵⁸⁸explained that the common law nevertheless could serve as an aid to their application:

"In principle, under the Federal Rules no common law of evidence remains. 'All relevant evidence is admissible, except as otherwise provided....' In reality, of course, the body of common law knowledge continues to exist, though in the somewhat altered form of a source of guidance in the exercise of delegated powers.'" *Id.*, at 51-52, 105 S.Ct., at 469.

We found the common-law precept at issue in the *Abel* case entirely consistent with Rule 402's general requirement of admissibility, and considered it unlikely that the drafters had intended to change the rule. *Id.*, at 50-51, 105 S.Ct., at 468-469. In *Bourjaily v. United States*, 483 U.S. 171, 107 S.Ct. 2775, 97 L.Ed.2d 144 (1987), on the other hand, the Court was unable to find a particular common-law doctrine in the Rules, and so held it superseded.

6. Because we hold that *Frye* has been superseded and base the discussion that follows on the content of the congressionally enacted Federal Rules of Evidence, we do not address petitioners' argument that application of the *Frye* rule in this

[4] Here there is a specific Rule that speaks to the contested issue. Rule 702, governing expert testimony, provides:

"If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise."

Nothing in the text of this Rule establishes "general acceptance" as an absolute prerequisite to admissibility. Nor does respondent present any clear indication that Rule 702 or the Rules as a whole were intended to incorporate a "general acceptance" standard. The drafting history makes no mention of *Frye*, and a rigid "general acceptance" requirement would be at odds with the "liberal thrust" of the Federal Rules and their "general approach of relaxing the traditional barriers to 'opinion' testimony." *Beech Aircraft Corp. v. Rainey*, 488 U.S., at 169, 109 S.Ct., at 450 (citing Rules 701 to 705). See also Weinstein, Rule 702 of the Federal Rules of Evidence is ¹⁵⁸⁹Sound; It Should Not Be Amended, 138 F.R.D. 631 (1991) ("The Rules were designed to depend primarily upon lawyer-adversaries and sensible triers of fact to evaluate conflicts"). Given the Rules' permissive backdrop and their inclusion of a specific rule on expert testimony that does not mention "general acceptance," the assertion that the Rules somehow assimilated *Frye* is unconvincing. *Frye* made "general acceptance" the exclusive test for admitting expert scientific testimony. That austere standard, absent from, and incompatible with, the Federal Rules of Evidence, should not be applied in federal trials.⁶

B

[5, 6] That the *Frye* test was displaced by the Rules of Evidence does not mean,

diversity case, as the application of a judge-made rule affecting substantive rights, would violate the doctrine of *Erie R. Co. v. Tompkins*, 304 U.S. 64, 58 S.Ct. 817, 82 L.Ed. 1188 (1938).

however, that the Rules themselves place no limits on the admissibility of purportedly scientific evidence.⁷ Nor is the trial judge disabled from screening such evidence. To the contrary, under the Rules the trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable.

[7–13] The primary locus of this obligation is Rule 702, which clearly contemplates some degree of regulation of the subjects and theories about which an expert may testify. “If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue” an expert “may testify thereto.” (Emphasis added.) The subject of an expert’s testimony must ⁵⁹⁰be “scientific . . . knowledge.”⁸ The adjective “scientific” implies a grounding in the methods and procedures of science. Similarly, the word “knowledge” connotes more than subjective belief or unsupported speculation. The term “applies to any body of known facts or to any body of ideas inferred from such facts or accepted as truths on good grounds.” Webster’s Third New International Dictionary 1252 (1986). Of course, it would be unreasonable to conclude that the subject of scientific testimony must be “known” to a certainty; arguably, there are no certainties in science. See, e.g., Brief for Nicolaas Bloembergen et al. as *Amici Curiae*

9 (“Indeed, scientists do not assert that they know what is immutably ‘true’—they are committed to searching for new, temporary, theories to explain, as best they can, phenomena”); Brief for American Association for the Advancement of Science et al. as *Amici Curiae* 7–8 (“Science is not an encyclopedic body of knowledge about the universe. Instead, it represents a *process* for proposing and refining theoretical explanations about the world that are subject to further testing and refinement” (emphasis in original)). But, in order to qualify as “scientific knowledge,” an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation—i.e., “good grounds,” based on what is known. In short, the requirement that an expert’s testimony pertain to “scientific knowledge” establishes a standard of evidentiary reliability.⁹

[14–16] ⁵⁹¹Rule 702 further requires that the evidence or testimony “assist the trier of fact to understand the evidence or to determine a fact in issue.” This condition goes primarily to relevance. “Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful.” 3 Weinstein & Berger ¶702[02], p. 702–18. See also *United States v. Downing*, 753 F.2d 1224, 1242 (CA3 1985) (“An additional consid-

7. THE CHIEF JUSTICE “do[es] not doubt that Rule 702 confides to the judge some gatekeeping responsibility,” *post*, at 2800, but would neither say how it does so nor explain what that role entails. We believe the better course is to note the nature and source of the duty.

8. Rule 702 also applies to “technical, or other specialized knowledge.” Our discussion is limited to the scientific context because that is the nature of the expertise offered here.

9. We note that scientists typically distinguish between “validity” (does the principle support what it purports to show?) and “reliability” (does application of the principle produce consistent results?). See Black, 56 Ford.L.Rev., at 599. Although “the difference between accuracy, validity, and reliability may be such that each is distinct from the other by no more than a hen’s

kick,” Starrs, *Frye v. United States Restructured and Revitalized: A Proposal to Amend Federal Evidence Rule 702*, 26 Jurimetrics J. 249, 256 (1986), our reference here is to *evidentiary* reliability—that is, trustworthiness. Cf., e.g., Advisory Committee’s Notes on Fed. Rule Evid. 602, 28 U.S.C.App., p. 755 (“[T]he rule requiring that a witness who testifies to a fact which can be perceived by the senses must have had an opportunity to observe, and must have actually observed the fact” is a ‘most pervasive manifestation’ of the common law insistence upon ‘the most reliable sources of information’” (citation omitted)); Advisory Committee’s Notes on Art. VIII of Rules of Evidence, 28 U.S.C.App., p. 770 (hearsay exceptions will be recognized only “under circumstances supposed to furnish guarantees of trustworthiness”). In a case involving scientific evidence, *evidentiary reliability* will be based upon *scientific validity*.

eration under Rule 702—and another aspect of relevancy—is whether expert testimony proffered in the case is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute”). The consideration has been aptly described by Judge Becker as one of “fit.” *Ibid.* “Fit” is not always obvious, and scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes. See Starrs, *Frye v. United States* Restructured and Revitalized: A Proposal to Amend Federal Evidence Rule 702, 26 *Jurimetrics J.* 249, 258 (1986). The study of the phases of the moon, for example, may provide valid scientific “knowledge” about whether a certain night was dark, and if darkness is a fact in issue, the knowledge will assist the trier of fact. However (absent creditable grounds supporting such a link), evidence that the moon was full on a certain night will not assist the trier of fact in determining whether an individual was unusually likely to have behaved irrationally on that night. Rule 702’s “helpfulness” ¹⁰ standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility.

[17, 18] That these requirements are embodied in Rule 702 is not surprising. Unlike an ordinary witness, see Rule 701, an expert is permitted wide latitude to offer opinions, including those that are not based on firsthand knowledge or observation. See Rules 702 and 703. Presumably, this relaxation of the usual requirement of firsthand knowledge—a rule which represents “a ‘most pervasive manifestation’ of the common law in-

sistence upon ‘the most reliable sources of information,’” Advisory Committee’s Notes on Fed. Rule Evid. 602, 28 U.S.C.App., p. 755 (citation omitted)—is premised on an assumption that the expert’s opinion will have a reliable basis in the knowledge and experience of his discipline.

C

[19–23] Faced with a proffer of expert scientific testimony, then, the trial judge must determine at the outset, pursuant to Rule 104(a),¹⁰ whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue.¹¹ This entails a preliminary assessment of whether the reasoning or methodology⁵⁹³ underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue. We are confident that federal judges possess the capacity to undertake this review. Many factors will bear on the inquiry, and we do not presume to set out a definitive checklist or test. But some general observations are appropriate.

[24] Ordinarily, a key question to be answered in determining whether a theory or technique is scientific knowledge that will assist the trier of fact will be whether it can be (and has been) tested. “Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry.” Green 645. See also C. Hempel, *Philosophy of Natural Science* 49 (1966)

10. Rule 104(a) provides:

“Preliminary questions concerning the qualification of a person to be a witness, the existence of a privilege, or the admissibility of evidence shall be determined by the court, subject to the provisions of subdivision (b) [pertaining to conditional admissions]. In making its determination it is not bound by the rules of evidence except those with respect to privileges.” These matters should be established by a preponderance of proof. See *Bourjaily v. United States*, 483 U.S. 171, 175–176, 107 S.Ct. 2775, 2778–2779, 97 L.Ed.2d 144 (1987).

11. Although the *Frye* decision itself focused exclusively on “novel” scientific techniques, we do not read the requirements of Rule 702 to apply specially or exclusively to unconventional evidence. Of course, well-established propositions are less likely to be challenged than those that are novel, and they are more handily defended. Indeed, theories that are so firmly established as to have attained the status of scientific law, such as the laws of thermodynamics, properly are subject to judicial notice under Federal Rule of Evidence 201.

("[T]he statements constituting a scientific explanation must be capable of empirical test"); K. Popper, *Conjectures and Refutations: The Growth of Scientific Knowledge* 37 (5th ed. 1989) ("[T]he criterion of the scientific status of a theory is its falsifiability, or refutability, or testability") (emphasis deleted).

[25–27] Another pertinent consideration is whether the theory or technique has been subjected to peer review and publication. Publication (which is but one element of peer review) is not a *sine qua non* of admissibility; it does not necessarily correlate with reliability, see S. Jasanoff, *The Fifth Branch: Science Advisors as Policymakers* 61–76 (1990), and in some instances well-grounded but innovative theories will not have been published, see Horrobin, *The Philosophical Basis of Peer Review and the Suppression of Innovation*, 263 *JAMA* 1438 (1990). Some propositions, moreover, are too particular, too new, or of too limited interest to be published. But submission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will be detected. See J. Ziman, *Reliable Knowledge: An Exploration* 159⁴ of the Grounds for Belief in Science 130–133 (1978); Relman & Angell, *How Good Is Peer Review?*, 321 *New Eng. J. Med.* 827 (1989). The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

[28] Additionally, in the case of a particular scientific technique, the court ordinarily should consider the known or potential rate

of error, see, e.g., *United States v. Smith*, 869 F.2d 348, 353–354 (CA7 1989) (surveying studies of the error rate of spectrographic voice identification technique), and the existence and maintenance of standards controlling the technique's operation, see *United States v. Williams*, 583 F.2d 1194, 1198 (CA2 1978) (noting professional organization's standard governing spectrographic analysis), cert. denied, 439 U.S. 1117, 99 S.Ct. 1025, 59 L.Ed.2d 77 (1979).

[29, 30] Finally, "general acceptance" can yet have a bearing on the inquiry. A "reliability assessment does not require, although it does permit, explicit identification of a relevant scientific community and an express determination of a particular degree of acceptance within that community." *United States v. Downing*, 753 F.2d, at 1238. See also 3 Weinstein & Berger ¶ 702[03], pp. 702–41 to 702–42. Widespread acceptance can be an important factor in ruling particular evidence admissible, and "a known technique which has been able to attract only minimal support within the community," *Downing*, 753 F.2d, at 1238, may properly be viewed with skepticism.

[31–33] The inquiry envisioned by Rule 702 is, we emphasize, a flexible one.¹² Its overarching subject is the scientific validity⁵⁹⁵—and thus the evidentiary relevance and reliability—of the principles that underlie a proposed submission. The focus, of course, must be solely on principles and methodology, not on the conclusions that they generate.

[34] Throughout, a judge assessing a proffer of expert scientific testimony under Rule 702 should also be mindful of other applicable rules. Rule 703 provides that expert opinions based on otherwise inadmissi-

12. A number of authorities have presented variations on the reliability approach, each with its own slightly different set of factors. See, e.g., *Downing*, 753 F.2d, at 1238–1239 (on which our discussion draws in part); 3 Weinstein & Berger ¶ 702[03], pp. 702–41 to 702–42 (on which the *Downing* court in turn partially relied); McCormick, *Scientific Evidence: Defining a New Approach to Admissibility*, 67 *Iowa L.Rev.* 879,

911–912 (1982); and Symposium on Science and the Rules of Evidence, 99 *F.R.D.* 187, 231 (1983) (statement by Margaret Berger). To the extent that they focus on the reliability of evidence as ensured by the scientific validity of its underlying principles, all these versions may well have merit, although we express no opinion regarding any of their particular details.

ble hearsay are to be admitted only if the facts or data are "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject." Rule 706 allows the court at its discretion to procure the assistance of an expert of its own choosing. Finally, Rule 403 permits the exclusion of relevant evidence "if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury..." Judge Weinstein has explained: "Expert evidence can be both powerful and quite misleading because of the difficulty in evaluating it. Because of this risk, the judge in weighing possible prejudice against probative force under Rule 403 of the present rules exercises more control over experts than over lay witnesses." Weinstein, 138 F.R.D., at 632.

III

[35] We conclude by briefly addressing what appear to be two underlying concerns of the parties and *amici* in this case. Respondent expresses apprehension that abandonment of "general acceptance" as the exclusive requirement for admission will result in a "free-for-all" in which befuddled juries are confounded by absurd and irrational pseudoscientific assertions.⁵⁹⁶ In this regard respondent seems to us to be overly pessimistic about the capabilities of the jury and of the adversary system generally. Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence. See *Rock v. Arkansas*, 483 U.S. 44, 61, 107 S.Ct. 2704, 2714, 97 L.Ed.2d 37 (1987). Additionally, in the event the trial court concludes that the scintilla of evidence presented supporting a position is insufficient to allow a reasonable juror to conclude that the position more likely than not is true, the court remains free to direct a judgment, Fed.Rule Civ.Proc. 50(a), and likewise to grant summary judgment, Fed.Rule Civ.Proc. 56. Cf., e.g., *Turpin v. Merrell Dow Pharmaceuticals, Inc.*, 959 F.2d 1349 (CA6)

(holding that scientific evidence that provided foundation for expert testimony, viewed in the light most favorable to plaintiffs, was not sufficient to allow a jury to find it more probable than not that defendant caused plaintiff's injury), cert. denied, 506 U.S. 826, 113 S.Ct. 84, 121 L.Ed.2d 47 (1992); *Brock v. Merrell Dow Pharmaceuticals, Inc.*, 874 F.2d 307 (CA5 1989) (reversing judgment entered on jury verdict for plaintiffs because evidence regarding causation was insufficient), modified, 884 F.2d 166 (CA5 1989), cert. denied, 494 U.S. 1046, 110 S.Ct. 1511, 108 L.Ed.2d 646 (1990); Green 680-681. These conventional devices, rather than wholesale exclusion under an uncompromising "general acceptance" test, are the appropriate safeguards where the basis of scientific testimony meets the standards of Rule 702.

[36] Petitioners and, to a greater extent, their *amici* exhibit a different concern. They suggest that recognition of a screening role for the judge that allows for the exclusion of "invalid" evidence will sanction a stifling and repressive scientific orthodoxy and will be inimical to the search for truth. See, e.g., Brief for Ronald Bayer et al. as *Amici Curiae*. It is true that open debate is an essential part of both legal and scientific analyses. Yet there are important differences between the quest for truth in the courtroom and the quest⁵⁹⁷ for truth in the laboratory. Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly. The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance. Conjectures that are probably wrong are of little use, however, in the project of reaching a quick, final, and binding legal judgment—often of great consequence—about a particular set of events in the past. We recognize that, in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of au-

thentic insights and innovations. That, nevertheless, is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.¹³

IV

To summarize: "General acceptance" is not a necessary precondition to the admissibility of scientific evidence under the Federal Rules of Evidence, but the Rules of Evidence—especially Rule 702—do assign to the trial judge the task of ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand. Pertinent evidence based on scientifically valid principles will satisfy those demands.

The inquiries of the District Court and the Court of Appeals focused almost exclusively on "general acceptance," as gauged by publication and the decisions of other courts. Accordingly,⁵⁹⁸ the judgment of the Court of Appeals is vacated, and the case is remanded for further proceedings consistent with this opinion.

It is so ordered.

Chief Justice REHNQUIST, with whom Justice STEVENS joins, concurring in part and dissenting in part.

The petition for certiorari in this case presents two questions: first, whether the rule of *Frye v. United States*, 54 App.D.C. 46, 293 F. 1013 (1923), remains good law after the enactment of the Federal Rules of Evidence; and second, if *Frye* remains valid, whether it requires expert scientific testimony to have been subjected to a peer review process in order to be admissible. The Court concludes, correctly in my view, that the *Frye* rule did not survive the enactment of the Federal Rules of Evidence, and I

therefore join Parts I and II-A of its opinion. The second question presented in the petition for certiorari necessarily is mooted by this holding, but the Court nonetheless proceeds to construe Rules 702 and 703 very much in the abstract, and then offers some "general observations." *Ante*, at 2796.

"General observations" by this Court customarily carry great weight with lower federal courts, but the ones offered here suffer from the flaw common to most such observations—they are not applied to deciding whether particular testimony was or was not admissible, and therefore they tend to be not only general, but vague and abstract. This is particularly unfortunate in a case such as this, where the ultimate legal question depends on an appreciation of one or more bodies of knowledge not judicially noticeable, and subject to different interpretations in the briefs of the parties and their *amici*. Twenty-two *amicus* briefs have been filed in the case, and indeed the Court's opinion contains no fewer than 37 citations to *amicus* briefs and other secondary sources.

⁵⁹⁹The various briefs filed in this case are markedly different from typical briefs, in that large parts of them do not deal with decided cases or statutory language—the sort of material we customarily interpret. Instead, they deal with definitions of scientific knowledge, scientific method, scientific validity, and peer review—in short, matters far afield from the expertise of judges. This is not to say that such materials are not useful or even necessary in deciding how Rule 703 should be applied; but it is to say that the unusual subject matter should cause us to proceed with great caution in deciding more than we have to, because our reach can so easily exceed our grasp.

But even if it were desirable to make "general observations" not necessary to de-

13. This is not to say that judicial interpretation, as opposed to adjudicative factfinding, does not share basic characteristics of the scientific endeavor: "The work of a judge is in one sense enduring and in another ephemeral.... In the

endless process of testing and retesting, there is a constant rejection of the dross and a constant retention of whatever is pure and sound and fine." B. Cardozo, *The Nature of the Judicial Process* 178, 179 (1921).

cide the questions presented, I cannot subscribe to some of the observations made by the Court. In Part II-B, the Court concludes that reliability and relevancy are the touchstones of the admissibility of expert testimony. *Ante*, at 2795-2796. Federal Rule of Evidence 402 provides, as the Court points out, that "[e]vidence which is not relevant is not admissible." But there is no similar reference in the Rule to "reliability." The Court constructs its argument by parsing the language "[i]f scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, . . . an expert . . . may testify thereto . . ." Fed. Rule Evid. 702. It stresses that the subject of the expert's testimony must be "scientific . . . knowledge," and points out that "scientific" "implies a grounding in the methods and procedures of science" and that the word "knowledge" "connotes more than subjective belief or unsupported speculation." *Ante*, at 2795. From this it concludes that "scientific knowledge" must be "derived by the scientific method." *Ibid*. Proposed testimony, we are told, must be supported by "appropriate validation." *Ibid*. Indeed, in footnote 9, the Court decides that "[i]n a case involving scientific evidence, *evidentiary*⁶⁰⁰ *reliability* will be based upon *scientific validity*." *Ante*, at 2795, n. 9 (emphasis in original).

Questions arise simply from reading this part of the Court's opinion, and countless more questions will surely arise when hundreds of district judges try to apply its teaching to particular offers of expert testimony. Does all of this *dicta* apply to an expert seeking to testify on the basis of "technical or other specialized knowledge"—the other types of expert knowledge to which Rule 702 applies—or are the "general observations" limited only to "scientific knowledge"? What is the difference between scientific knowledge and technical knowledge; does Rule 702 actually contemplate that the phrase "scientific, technical, or other specialized knowledge" be broken down into numer-

ous subspecies of expertise, or did its authors simply pick general descriptive language covering the sort of expert testimony which courts have customarily received? The Court speaks of its confidence that federal judges can make a "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Ante*, at 2796. The Court then states that a "key question" to be answered in deciding whether something is "scientific knowledge" "will be whether it can be (and has been) tested." *Ibid*. Following this sentence are three quotations from treatises, which not only speak of empirical testing, but one of which states that the "‘criterion of the scientific status of a theory is its falsifiability, or refutability, or testability,’" *Ante*, at 2797.

I defer to no one in my confidence in federal judges; but I am at a loss to know what is meant when it is said that the scientific status of a theory depends on its "falsifiability," and I suspect some of them will be, too.

I do not doubt that Rule 702 confides to the judge some gatekeeping responsibility in deciding questions of the admissibility of proffered expert testimony. But I do not think ⁶⁰¹it imposes on them either the obligation or the authority to become amateur scientists in order to perform that role. I think the Court would be far better advised in this case to decide only the questions presented, and to leave the further development of this important area of the law to future cases.



FDA Approves Duchesnay USA's Diclegis® for Treatment of Nausea and Vomiting of Pregnancy (NVP)

Diclegis becomes only FDA-approved treatment for "morning sickness" in decades



NEWS PROVIDED BY

Duchesnay USA →

Apr 08, 2013, 08:51 ET

ROSEMONT, Pa., April 8, 2013 /PRNewswire/ -- Duchesnay USA today announced that the Food and Drug Administration (FDA) has granted approval for Diclegis® (doxylamine succinate 10mg, pyridoxine hydrochloride 10mg) delayed-release tablets for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management.ⁱ It is the only FDA-approved treatment for NVP, more commonly known as morning sickness, in more than 30 years.

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The FDA granted Diclegis Pregnancy Category A status which means the results of controlled studies have not shown an increased risk to an unborn baby during pregnancy.^{i,ii} The two active ingredients in Diclegis that reduce nausea and vomiting in pregnancy – doxylamine succinate and pyridoxine hydrochloride, or vitamin B₆, – have been recommended as a first-line pharmacotherapy by the American Congress of Obstetricians and Gynecologists (ACOG) guidelines for the last nine years.ⁱⁱⁱ

"The FDA approval of Diclegis provides an important new treatment to the millions of women suffering from nausea and vomiting of pregnancy, and fills a 30 year void in the treatment of NVP," said **Gilbert Godin, Chief Executive Officer, Duchesnay USA**. "Duchesnay USA is honored to bring the only FDA-approved treatment to help control symptoms of morning sickness to market. Duchesnay has been dedicated to the health of pregnant women and their unborn children for years and is taking every step to make Diclegis available for women suffering from NVP."

NVP is a medical condition that affects 70 to 85 percent of pregnant women with symptoms ranging from nausea to severe vomiting and retching that can last throughout the day.^{iii,iv} Some pregnant women may experience symptoms throughout their pregnancy.^{iv}

"Millions of pregnant women suffering every year from nausea and vomiting of pregnancy now have a safe and effective FDA-approved treatment. Until now, women have been without an FDA-approved prescription option to help treat NVP symptoms, also known as morning sickness," said **Dr. Shannon Clark, Associate Professor, Division of Maternal and Fetal Medicine, University of Texas Medical Branch – Galveston**. "Diclegis provides a safe and effective option for pregnant women. Its active ingredients are the most studied for this purpose."

Diclegis is expected to be widely available in the US by the end of May 2013.

Efficacy and Safety Profile of Diclegis in Patients with Nausea and Vomiting of Pregnancy

Diclegis has proven to be a safe and effective treatment option for nausea and vomiting of Pregnancy (NVP).

The New Drug Application submission with the FDA was based on a 15-day double-blind, randomized, multi-center placebo-controlled trial studying pregnant women 18 years of age or older, 7 to 14 weeks gestation, with NVP. Use of Diclegis resulted in significantly larger improvement in symptoms of NVP compared with placebo, based on the PUQE score. This study concluded that Diclegis delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating NVP.ⁱ

Diclegis Dosage and Administration



Diclegis (doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg) delayed-release tablets is the only FDA-approved prescription treatment for nausea and vomiting of pregnancy in women who do not respond to conservative management.ⁱ

Initially, a patient takes two Diclegis delayed-release tablets orally at bedtime (Day 1). If symptoms persist into the afternoon of Day 2, the patient takes the usual dose of two tablets at bedtime that night and then adds one tablet the following morning on Day 3. If symptoms still persist on Day 4, the patient takes one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime. The maximum recommended dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime) daily. Diclegis is taken as a daily prescription and not on an as needed basis to help control symptoms throughout the day.ⁱ

Important Safety Information for Diclegis

Indication

Diclegis[®] is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

Do not take Diclegis if you are allergic to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride, or any of the ingredients in Diclegis. You should also not take Diclegis in combination with medicines called monoamine oxidase (MAO) inhibitors, as these medicines can intensify and prolong the adverse CNS effects of Diclegis. Use of MAOs may also prolong and intensify the anticholinergic (drying) effects of antihistamines.

The most common side effect of Diclegis is drowsiness. You should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Diclegis until cleared to do so by your healthcare provider.

Do not take Diclegis with alcohol or sedating medicines, including other antihistamines (present in some cough and cold medications), opiates, or sleep aids, because severe drowsiness can happen or become worse, causing falls or accidents.

Diclegis should be used with caution in women who have: (1) asthma, (2) increased pressure in the eye, (3) an eye problem called narrow angle glaucoma, (4) a stomach problem called stenosing peptic ulcer, (5) pyloroduodenal obstruction, or (6) a bladder problem called bladder-neck obstruction.

Fatalities have been reported from doxylamine overdose in children. Children appear to be at a high risk for cardiorespiratory arrest. However, the safety and effectiveness of Diclegis in children younger than 18 years have not been established.

Diclegis is a delayed-release formulation; therefore, signs and symptoms of intoxication may not be apparent immediately. Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, and tachycardia. If you suspect an overdose or seek additional overdose information, you can contact a poison control center at 1-800-222-1222.

The FDA granted Diclegis Pregnancy Category A status, which means that the results of controlled studies have not shown risk to an unborn baby during pregnancy.

Women should not breast-feed while using Diclegis because the antihistamine component (doxylamine succinate) in Diclegis can pass into breast milk. Excitement, irritability, and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of Diclegis resulting in worsening of their apnea or respiratory conditions.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information.

For full prescribing information, please visit www.Diclegis.com.

About Nausea and Vomiting of Pregnancy (NVP)

Nausea and vomiting of pregnancy (NVP), or morning sickness, affects 70 to 85 percent of pregnant women, with symptoms that range from nausea to severe vomiting and retching.^{iii,iv} For most pregnant women, symptoms generally cease at approximately 16 to 20 weeks.^{iv} However, some women can experience symptoms throughout their pregnancy.^{iv}

About Duchesnay USA

Duchesnay USA is a unique healthcare company devoted to safeguarding the health and well-being of expectant mothers and their unborn babies. Its affiliate company, Duchesnay Inc. was founded in 1970 in Canada. The family-owned company realigned its business in 1992 to focus specifically on pregnant women after a family member experienced a very difficult pregnancy. Duchesnay USA was established in Rosemont, Pennsylvania in 2011 to pursue that same mission. Realizing a lack of sufficient information on medications for use in pregnancy, Duchesnay USA strives to ensure that expectant women who require pharmacological treatments have access to proper medical advice and therapies that are safe for them and their unborn babies. Duchesnay USA's mission is to develop pharmacological solutions to reduce the symptoms of nausea and vomiting during pregnancy (NVP). For more information on Duchesnay USA, please visit www.DuchesnayUSA.com.

ⁱ Diclegis Product Label

ⁱⁱ Department of Health and Human Services, Food and Drug Administration. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Federal Register. 2008; 73 (104):30831-68.

ⁱⁱⁱ American College of Obstetricians and Gynecologists. Nausea and vomiting of pregnancy. ACOG Practice Bulletin. 2004;52.

^{iv} Clark S, Costantine M, Hankins GDV. Review of NVP and HG and early pharmacotherapeutic Intervention. Obstetrics and Gynecology International Volume. 2012.

^v Duchesnay Inc. – data on file

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FDA Update on the Safety of Silicone Gel-Filled Breast Implants

June 2011

**Center for Devices and Radiological Health
U.S. Food and Drug Administration**



FDA Update on the Safety of Silicone Gel-Filled Breast Implants

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I. Introduction

Breast implants are medical devices that are used to augment breast size or to reconstruct the breast following mastectomy or to correct a congenital abnormality. Breast implants consist of a silicone outer shell and a filler (most commonly silicone gel or saline). Approximately 5 to 10 million women worldwide have breast implants.

According to the [American Society of Plastic Surgeons National Clearinghouse of Plastic Surgery Procedural Statistics](#), there were 296,203 breast augmentation procedures and 93,083 breast reconstruction procedures performed in the United States in 2010. Approximately half the procedures used saline-filled implants and half used silicone gel-filled implants. Figure 1 shows a photograph of a woman holding a breast implant.



Figure 1. Photograph of a woman holding a breast implant.

II. Purpose

The FDA approved two silicone gel-filled breast implants in November 2006. This report provides an update on the clinical information about these products. The report includes:

- Preliminary data from the post-approval studies that the FDA required manufacturers to conduct as conditions of approval;
- A summary and analysis of adverse events reported to FDA since approval; and
- A review and analysis of recent clinical publications about the safety and effectiveness of silicone gel-filled breast implants.

This document is not intended to provide a comprehensive clinical update about the safety of saline-filled breast implants. Updated labeling and other information about saline-filled breast implants can be found on the FDA website at www.fda.gov/breastimplants.

III. Overview

History of the Regulation of Silicone Gel-Filled Breast Implants

Silicone gel-filled breast implants were introduced to the U.S. in 1962. When the U.S. Congress passed the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, breast implants were considered moderate risk (Class II) devices and required to comply with general controls and performance standards. The FDA reviewed new breast implants through the 510(k) premarket notification process as it did other Class II products.

In the early 1980s, concerns arose about the safety of breast implants, in particular silicone gel-filled breast implants. FDA's new surveillance systems identified frequent local complications and adverse outcomes, and other published case reports described cancer and connective tissue disease in some women with breast implants. In response, the FDA reclassified breast implant into Class III, higher-risk products needing premarket approval (PMA), and called for manufacturers to provide data demonstrating the devices were safe and effective.

In 1992, the FDA determined that the manufacturers had not adequately addressed public concerns about certain complications, such as implant rupture and silicone leakage. Following the advice of an outside expert advisory panel, the FDA removed all silicone gel-filled breast implants from the market and required manufacturers to submit premarket approval applications that contained data on safety and effectiveness.

In order to meet a public health need, the FDA allowed manufacturers to provide silicone gel-filled implants for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Manufacturers enrolled women who received silicone gel-filled breast implants for these purposes in *Adjunct Studies* so that data could be collected about device performance and safety.

The FDA also called for more data on saline-filled breast implants, although it allowed them to remain on the market. During the next 14 years, with silicone gel-filled implants largely unavailable, many women opted for saline-filled breast implants.

In 1999, the Institute of Medicine (IOM) released a comprehensive report of the published literature and ongoing studies on breast implants, entitled *Safety of Silicone Breast Implants*.¹ The report made a clear distinction between local complications and systemic health concerns. It concluded that local complications were "the primary safety issue with silicone breast implants." These local complications, which included rupture, pain, capsular contracture, disfigurement, and serious infection, lead to medical interventions and repeat surgeries. Importantly, the IOM report concluded that there was no evidence that silicone breast implants caused systemic health effects such as cancer or autoimmune disease.

The FDA Breast Implant website, www.fda.gov/breastimplants contains a detailed [Regulatory History of Breast Implants in the U.S.](#)

U.S. Approved Silicone Gel-Filled Breast Implants

In November 2006, the FDA approved Allergan's* Natrelle Silicone Gel-Filled Breast Implants and Mentor's MemoryGel Silicone Gel-Filled Breast Implants. The FDA based its approvals on the manufacturers' clinical studies, called *Core Studies*, which followed hundreds of women with silicone gel-filled breast implants for 3 (Mentor) or 4 (Allergan) years. Despite frequent local complications and adverse outcomes, the FDA determined that the benefits and risks of breast implants were sufficiently well understood for women to make informed decisions about their use.

Data from each study are available in their respective [PMA Summaries of Safety and Effectiveness](#). The FDA approved both devices for breast reconstruction for women of any age and breast augmentation for women at least age 22.

Postmarket Surveillance

When the FDA approved silicone gel-filled breast implants in the U.S. in 2006, it recognized that there were limited data on rare events and long-term outcomes. In order to better understand the long-term performance of these devices and to monitor for previously unrecognized adverse events, the FDA required the manufacturers to conduct post-approval studies, analyzed silicone gel-filled breast implant Medical Device Reports (MDR) submitted to FDA, performed periodic literature reviews, and evaluated correspondence from researchers, health care providers, patients, and concerned citizens.

Conditions of Approval

As conditions of approval, the FDA required each manufacturer of silicone gel-filled breast implants to conduct six post-approval studies to characterize the long-term performance and safety of the devices. The FDA believes that data from these long-term, post-approval studies will provide important information for women, their families and friends, and health care providers, and may lead to improvements in implant design and labeling.

Due to the length of the studies required by the FDA, they have not all been completed. Rather than waiting for all studies to be completed, FDA believes it is important to share currently available information so that women may make informed decisions about their health care.

The required post-approval studies for silicone gel-filled breast implants are as follows:

* Allergan was formally known as Inamed, which was formerly McGhan.

(1) *Core Post-Approval Studies (Core Studies)* – To assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications. These studies were designed to follow women for 10 years after initial implantation.

(2) *Large Post-Approval Studies (Large Studies)* – To assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients and following them for 10-years.

(3) *Device Failure Studies (Failure Studies)* – To further characterize the modes and causes of failure of explanted devices over a 10-year period.

(4) *Focus Group Studies* – To improve the format and content of the patient labeling.

(5) *Annual Physician Informed Decision Survey (Informed Decision Study)* – To monitor the process of how patient labeling is distributed to women considering silicone gel-filled breast implants.

(6) *Adjunct Studies* – To provide performance and safety information about silicone gel-filled breast implants provided to U.S. women from 1992-2006, prior to approval, when implants could only be used for reconstruction and replacement of existing implants.

IV. Detailed Summary of Post-Approval Studies for Silicone Gel-Filled Breast Implants

Key Points from Post-Approval Studies

- The FDA required each company to design and conduct six post-approval studies as conditions of approval.
- Key local complications and adverse outcomes observed include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection.
- The local complications observed in the silicone gel-filled breast implant post-approval studies are consistent with complications noted at the time of approval.
- The longer a woman has silicone gel-filled breast implants, the more likely she is to experience local complications or adverse outcomes. As many as 1 in 5 primary augmentation patients and 1 in 2 primary reconstruction patients require implant removal within 10 years of implantation.
- Limitations in the post-approval studies to date preclude the detection of very rare rates of complications. However, post-approval studies to date do not show evidence that silicone gel-filled breast implants cause connective tissue disease or reproductive problems.
- Differences in study design, clinical endpoints and definitions, and patient populations preclude direct comparisons of the post-approval study results for the two approved silicone gel-filled breast implants.
- Patient follow-up rates are lower than anticipated, limiting the ability to draw definitive conclusions and to detect rare complications.
- This represents an interim analysis of currently available data. Data collection is on-going.

NOTE: This section contains detailed results from the post-approval studies of silicone gel-filled breast implants based on reports that the FDA received and validated as of May 31, 2011. Each manufacturer developed its own scientifically sound study design and statistical analyses. As a result, there are important differences between the two studies, including variations in number of study participants, patient enrollment criteria, clinical endpoints and definitions. These differences preclude direct comparisons of the two approved silicone gel-filled breast implants. In some cases, low patient follow-up rates may limit interpretation of the data.

As conditions of approval, the FDA required Allergan and Mentor to conduct six post-approval studies, including: (1) *Core Studies*, (2) *Large Studies*, (3) *Device Failure Studies*, (4) *Focus Group Studies*, (5) *Annual Physician Informed Decision Studies*, and (6) *Adjunct Studies*.

For the *Large Study*, the FDA required each manufacturer to report interim study results twice each year for the first 2 years and annually thereafter. In addition, manufacturers provide quarterly updates on *Large Study* enrollment and follow-up. For all other studies, the manufacturers must submit annual reports to the FDA until study completion.

Both manufacturers have completed their *Focus Group Studies*. The other post-approval studies are ongoing. Both manufacturers have closed enrollment for their *Core Studies* and *Large Studies*. Follow-up in those studies continues but has been below target rates. [Table 1](#) shows the enrollment and current follow-up status of each post-approval study.

Participants in the *Core Studies* and the *Large Studies* were enrolled in one of the following study cohorts:

- **Primary Augmentation** – women who received breast implants to increase the size of their breasts.
- **Primary Reconstruction** – women who received breast implants to replace breast tissue that was removed due to disease or trauma or that failed to develop properly.
- **Revision Augmentation** – women who received breast implants to correct or improve the results of primary breast augmentation surgeries.
- **Revision Reconstruction** – women who received breast implants to correct or improve the results of primary breast reconstruction surgeries.

Core Post-Approval Studies (*Core Studies*)

Purpose:

The purpose of the *Core Studies* was to gather data on longer-term safety and effectiveness of silicone gel-filled breast implants among participants enrolled in the studies conducted prior to approval, and to evaluate the effectiveness of magnetic resonance imaging (MRI) screening in detecting implant rupture.

Study Design:

The *Core Studies* followed participants enrolled in pre-approval studies of silicone gel-filled breast implants, and conducted clinical assessments of patients at six months, 1 year and annually thereafter for a total of 10 years.

Each study assigned participants to either an MRI group or a non-MRI group. Participants in the MRI group received MRIs on a specific schedule to screen for rupture. The timing of the MRI assessments and the methods of assigning participants to the MRI group differ by manufacturer. In addition, all participants (MRI group and non MRI group) received MRIs any time there were symptoms of a rupture.

The Allergan *Core Study* enrolled 715 patients and the Mentor *Core Study* enrolled 1,008 patients. [Table 2](#) presents enrollment numbers for the *Core Studies* by indication, manufacturer, and MRI study group status.

Based on the 2010 annual reports, the preliminary follow-up rates at 10 years post-implant are 66 percent for Allergan, and at 8 years post-implant are 58 percent for Mentor ([Table 1](#)). Longer

term follow-up is available for the Allergan *Core Study* participants because the study began enrolling patients approximately 20 months before the Mentor *Core Study*.

Each study had some patients who were not available for follow-up because they had died or discontinued participation.

Final results should be available in 2012, after all patients have been followed for at least 10 years.

Results:

Local Complications and Adverse Outcomes

The most frequently observed complications and adverse outcomes in each *Core Study* include capsular contracture, reoperation, removal of the implant, and implant rupture. Other common complications cited in the Allergan study included asymmetry, scarring, and breast pain. Other common complications cited in the Mentor study included changes in nipple and breast sensation. Cumulative incidence rates of complications are displayed in [Table 3](#) (Allergan) and [Table 4](#) (Mentor).

Several observations can be made based on the available data. First, not surprisingly, the cumulative incidence rate of each complication increases over time.

Second, complication rates vary greatly depending on the type of surgery performed (primary vs. revision, augmentation vs. reconstruction). For many of the complications and adverse outcomes, rates are higher for patients undergoing revision augmentation and primary reconstruction than for primary augmentation. For example, the incidence of breast implant removal by 10 years post-implant for patients receiving Allergan silicone gel-filled breast implants is 32.4 percent for revision augmentation patients and 53.8 percent for primary reconstruction patients compared to 20.8 percent for primary augmentation patients. Similarly, for Mentor patients at 8 years post-implant, the incidence of breast implant removal is 21.1 percent for revision augmentation patients and 23.3 percent for primary reconstruction patients compared to 7.3 percent for primary augmentation. Detailed cumulative incidence rates of capsular contracture, reoperation, and implant removal are displayed in [Table 5](#) and [Table 6](#).

Third, the longer women had breast implants, the more likely they were to have them removed. In the *Core Studies*, Allergan reported a total of 293 implant removals over 10 years of follow-up, and Mentor reported a total of 195 implant removals over 8 years of follow-up. The most frequent reasons for implant removal for each study were capsular contracture, rupture, malposition, and wrinkling or ripping. [Table 7](#) and [Table 8](#) present data on the reasons for implant removal.

Finally, the most frequently reported reason for reoperation varied with type of surgery. A reoperation is defined as any additional surgical procedure performed on the breast and/or implant after initial breast implantation and includes minor surgical procedures such as breast biopsies.

In the *Core Studies*, Allergan reported 434 reoperations on 285 patients over 10 years, and

Mentor reported 385 reoperations on 276 patients over 8 years post-implant. The majority of silicone gel-filled breast implant patients in the *Core Studies* did not require reoperation.

For both manufacturers, capsular contracture and breast asymmetry were the most common reasons for reoperation in the primary augmentation and primary reconstruction groups, respectively. Other significant reasons for reoperation included the need for biopsy, breast cancer mass, implant malposition, breast sagging (ptosis), implant rupture, hematoma or seroma, scarring, and patient request for style or size change. [Table 9](#) and [Table 10](#) show details of the reasons for reoperations for each manufacturer.

Rupture Rates

In each *Core Study*, rupture rates varied by device and indication. The cumulative incidence of rupture rates among Allergan implants in the MRI group at 10 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	10.1 percent (7.4 to 13.7)
Revision augmentation	6.3 percent (2.8 to 13.7)
Primary reconstruction	27.2 percent (17.3 to 41.3)
Revision reconstruction	6.7 percent (0.2 to 31.9)

The cumulative incidence of rupture rates among Mentor implants at 8 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	13.6 percent (7.6 to 23.6)
Revision augmentation	15.5 percent (6.5 to 34.6)
Primary reconstruction	14.0 percent (7.6 to 25)
Revision reconstruction	21.3 percent (7.3 to 53.3)

In the Allergan *Core Study*, the majority of ruptures were accompanied by symptoms; depending on the cohort, up to 35 percent of ruptures may be silent.

Connective Tissue Diseases (CTD)

Among the Allergan *Core Study* participants, over 10 years of follow-up, there have been nine diagnoses of CTD. These include four cases of rheumatoid arthritis, three cases of fibromyalgia, one case of Raynaud's Syndrome, and one case of undifferentiated CTD.

Among the Mentor *Core Study* participants, over the 8- year period of follow-up, there have been 28 confirmed diagnoses of connective tissue, autoimmune, or rheumatic disease in 21 patients. These include seven reports of fibromyalgia, six cases of rheumatoid or inflammatory arthritis, three cases of chronic fatigue syndrome, three cases of thyroid-related disease, one case of systemic lupus erythematosus, and eight other miscellaneous and unspecified CTD cases.

Reproduction and Lactation Problems

In the *Core Study*, Allergan reported 45 post-implant reproduction problems in 44 patients over 10 years; most of the problems were spontaneous abortions, miscarriages or infertility. Most of the problems occurred in the primary augmentation and revision augmentation groups. In Allergan's primary reconstruction group, there was one report of a planned abortion to treat a medical problem and one report of no menses. There were no reports of post-implant reproduction problems among women who received the implants for revision reconstruction.

In Allergan's primary and revision augmentation groups, there were 30 post-implant problems with lactation reported in 24 patients, predominantly inadequate milk production. No post-implant lactation problems were reported among women who received the implants for reconstruction or revision reconstruction.

In the *Core Study*, Mentor reported 153 patients with pregnancies over 8 years. Twenty-three of these patients reported miscarriages, and one patient reported a stillborn delivery. Seventy patients reported attempting to breastfeed and of these, 13 reported lactation difficulties and nine reported an inadequate milk supply.

Breast Cancer

In the Allergan *Core Study*, 602 patients received silicone gel-filled breast implants for primary or revision augmentation. Of these, five were diagnosed with breast cancer through 10 years of post-implant follow-up.

In the Mentor *Core Study*, there were four new diagnoses of breast cancer among the 697 primary and revision augmentation patients through 8 years of follow-up.

Discussion:

The long-term follow-up of participants in the *Core Studies* demonstrates that a significant percentage of women who receive silicone gel-filled breast implants experience complications and adverse outcomes.

The most frequently observed complications and adverse outcomes include capsular contracture, reoperation, removal of the implant, and implant rupture. The cumulative incidence of these complications increases over time – the longer a woman has breast implants, the more likely she is to experience a complication.

These studies did not demonstrate an association of silicone gel-filled breast implants with CTD, reproductive or lactation problems, or breast cancer. However, it is important to note that these studies were not designed to estimate the incidence of rare disease outcomes, nor were they designed to compare silicone gel-filled breast implants to alternative therapies.

Large Post-Approval Studies (*Large Studies*)

Purpose:

The purpose of the *Large Studies* is to determine the incidence of complications and other adverse outcomes, including local complications, connective tissue disease, neurological disease, potential effects on offspring of women with breast implants, potential effects on reproduction and lactation, cancer, suicide, rupture, potential interference of breast implants with mammography, and patient compliance with recommendations for MRI follow-up.

The studies were designed to be large enough to address issues that the *Core Studies* were not powered to answer, as well as to provide a real-world assessment of some outcomes of silicone gel-filled breast implantation surgery.

Study Design:

Both Allergan and Mentor are in the midst of these 10-year, multi-center, prospective follow-up studies in women who received silicone gel-filled breast implants after FDA approval in 2006. Each study includes a control group of women who received saline-filled breast implants during the same time period.

In each of the *Large Studies*, participants are followed annually for 10 years. Data are collected using patient questionnaires (completed online, via mail, or telephone) and clinical follow-up visits (conducted three to four times during the course of the study).

Allergan designed its *Large Study* with 39,390 women with silicone gel-filled breast implants and a control group of 19,605 women with saline-filled breast implants. In October 2008, at Allergan's request, the FDA approved a reduction in the control group sample size to 15,240, based on FDA's calculation that this number of participants would be sufficient to meet the study objectives.

Allergan initiated patient enrollment in the *Large Study* in February 2007 and closed enrollment in March 2010, with a total of 41,342 silicone gel-filled breast implant recipients and 15,646 saline breast implant recipients. The results reported here are taken from Allergan's 2010 annual report. They include data for all participants with 2 years of follow-up.

Mentor's designed its *Large Study* with 41,900 women with silicone gel-filled breast implants and a control group of 1,000 women with saline-filled breast implants. Mentor initiated patient enrollment in the *Large Study* in February 2007, and closed enrollment in July 2009, with a total of 41,975 silicone gel-filled breast implant participants and 1,030 saline breast implant participants. The results reported here are taken from Mentor's 2010 annual report. They include data for all participants with 3 years of follow-up.

Among *Large Study* participants, 97 women enrolled in the Allergan study and 556 women enrolled in the Mentor study were under age 22, which did not meet the enrollment criteria. The tables and analyses of Allergan's data contained in this report include these patients. The tables and analyses of Mentor's data include only the 41,419 patients who met the original enrollment criteria. The FDA has asked Mentor to provide data and analyses on these younger women in future analyses.

[Table 11](#) and [Table 12](#) summarize the number of participants enrolled in Allergan's and Mentor's *Large Studies* by implant type and indication as reported in the 2010 study interim reports. In each company's *Large Study*, the majority of participants received implants for primary augmentation, with revision augmentation, primary reconstruction, and revision reconstruction occurring in decreasing frequency.

Results:

Baseline Social and Demographic Characteristics

Participants in Allergan's *Large Study* had a median age of 35, height of 5'5" and weight of 130 pounds. The majority of subjects were Caucasian (68.6 percent). Most attended or graduated from college (72.1 percent), were married (51.8 percent), and had professional occupations (45.2 percent). At baseline more than half of the participants (57 percent) had never smoked. More than two thirds of the current smokers (67.5 percent) reported smoking 10 or fewer cigarettes per day. The majority of subjects (63.3 percent) consumed no more than three alcoholic drinks per week, and 19.5 percent did not drink at all.

Among participants of known age in Mentor's *Large Study*, 78.2 percent of the silicone gel-filled breast implant participants and 49.8 percent of the saline breast implant participants were at least 30 years old. Among Mentor's participants in the primary augmentation group of known age, 70.4 percent of the silicone gel-filled breast implant recipients and 47.5 percent of the saline breast implant recipients were at least 30 years old. Silicone gel-filled breast implant participants had a median height of 5'5" and median weight of 130 pounds. Saline breast implant participants had a median height of 5'3" and median weight of 129 pounds.

Most participants in Mentor's *Large Study* attended or graduated from college (75.6 percent of silicone gel-filled breast implant recipients and 63.9 percent saline breast implant participants) and were married (59.5 percent silicone gel-filled breast implant recipients and 44.2 percent saline-filled breast implant recipients). For silicone gel-filled breast implant participants, 44.4 percent had ever smoked regularly and 70.7 percent were current alcohol drinkers. For saline breast implant participants, 38 percent had ever smoked regularly and 61.1 percent were current alcohol drinkers.

The FDA asked both manufacturers to closely monitor and report the racial/ethnic distribution of participants during the enrollment period to ensure participation that appropriately represented the demographics of the U.S.

The racial distribution of the Allergan *Large Study* participants at baseline was 71 percent Caucasian, 13 percent Hispanic, five percent Asian, three percent Black/African American and three percent other. There were six percent of participants for whom racial/ethnic information was unavailable.

In the Mentor *Large Study*, the racial/ethnic distribution of the Mentor MemoryGel silicone gel-filled implant recipients was 77.8 percent Caucasian/not of Hispanic origin, 9.9 percent Caucasian of Hispanic origin, 4.5 percent Asian, 2.2 percent Black not of Hispanic origin, 0.4 percent Black of Hispanic origin, 0.7 percent Native America/Alaska Native, 2.5 percent other,

and 2.1 percent unknown or not provided. Among the saline implant group in the Mentor study the race/ethnicity distribution was 56.5 percent Caucasian/not of Hispanic origin, 26.5 percent Caucasian of Hispanic origin, 7.7 percent Asian, 2.8 percent Black not of Hispanic origin, 1.2 percent Black of Hispanic origin, 0.9 percent Native America/Alaska Native, 4.6 percent other. Of note, for participants in the primary augmentation cohort of Mentor's study, for whom race/ethnicity was known, 76.7 percent of the MemoryGel participants and 54.7 percent of the saline participants were Caucasian, not of Hispanic origin.

Follow-Up

Follow-up rates reported to the FDA in the 2010 *Large Study* progress reports fell below targets. In addition, because not all women enrolled in the studies at the same time, follow-up duration varies. In some cases, these factors may limit interpretation of the data.

Allergan *Large Study* follow-up rates are 60.5 percent and 45.1 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively, 2 years after implantation. Follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	53 percent
Revision augmentation	55 percent
Primary reconstruction	75 percent
Revision reconstruction	69 percent

For the Mentor, *Large Study*, follow-up rates 3 years after implantation are 21.1 percent and 9.6 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively. The follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	20 percent
Revision augmentation	19 percent
Primary reconstruction	29 percent
Revision reconstruction	28 percent

Operative Techniques and Implant Characteristics

In the Allergan *Large Study*, 95.9 percent of participants received bilateral implants. Incision sites were most commonly inframammary (54 percent) and periareolar (22.8 percent). Most devices were placed either in a partial (58.9 percent) or complete (29.3 percent) submuscular position. The vast majority of implants had smooth surfaces (91.3 percent). In this study, the most commonly used implant size in both the silicone and saline cohorts was 300-399 cc (42.4 percent). The most common incision sizes were 4- 4.99 cm (32.5 percent) for silicone gel-filled

implants and 3-3.99 cm (43.2 percent) for saline implants, which reflect the fact that saline implants are filled after placement so the incision size can be smaller.

In the Mentor *Large Study*, 95.1 percent of silicone participants and 98.6 percent of saline control participants received bilateral implants. In the primary augmentation cohort, the inframammary surgical approach was used for 58.6 percent of the implants and 26.9 percent of the saline-filled implants. For silicone gel-filled and saline-filled participants, mastectomy scar was the most common surgical approach in the primary reconstruction cohort (72.8 percent and 57.9 percent respectively). The most common placement of the devices was submuscular for all cohorts in both treatment groups.

Local Complications and Adverse Outcomes

Allergan reports the 2-year cumulative incidence of local complications and other adverse outcomes as follows:

- a. Reoperation. 6.5 percent for silicone gel-filled breast implant participants and 4.5 percent for saline breast implant participants.
- b. Rupture. 0.5 percent for silicone gel-filled breast implant participants and 2.5 percent for saline breast implant participants (saline implant deflation).
- c. Capsular Contracture (Grades III/IV). 5.0 percent for silicone gel-filled breast implant participants and 2.8 percent for saline breast implant participants.
- d. Implant removal with or without replacement. 3.4 percent for silicone gel-filled breast implant participants and 2.4 percent for saline breast implant participants.

Mentor reports the 3-year cumulative incidence of local complications and other adverse outcomes for silicone gel-filled breast implant recipients as follows:

- a. Reoperation. 10.8 percent for augmentation, 14.6 percent for revision-augmentation, 20.4 percent for reconstruction, 17.7 percent for revision-reconstruction.
- b. Rupture. 0.2 percent for augmentation, 1.0 percent for revision-augmentation, 0.4 percent for reconstruction, 0.7 percent for revision-reconstruction.
- c. Capsular Contracture (Grades III/IV). 5.3 percent for augmentation, 11.8 percent for revision-augmentation, 9.1 percent for reconstruction, 10.0 percent for revision-reconstruction.
- d. Implant removal with or without replacement. 5.0 percent for augmentation, 7.7 percent for revision-augmentation, 13.5 percent for reconstruction, 11.7 percent for revision-reconstruction.

The *Large Studies* are collecting information on reasons for implant removal. In the Allergan study, the three most frequent reasons for device removal were desire to change size/style,

capsular contracture, and implant malposition. In the Mentor study, the three most frequent reasons for device removal were size change at patient request, infection, and asymmetry. [Table 13](#) and [Table 14](#) provide details of the reasons for device removals.

Rare Outcomes

In the Allergan *Large Study*, forty-three (0.6 percent) silicone gel-filled breast implant participants and 14 (0.4 percent) saline breast implant participants had new reports of CTD at 2 years follow-up. In the silicone gel-filled breast implant group, nine women reported fibromyalgia, four reported rheumatoid arthritis, nine reported fibromyalgia, three reported systemic lupus erythematosus, and 27 reported miscellaneous, undifferentiated, unspecified or “other” CTDs.

At 2 years follow-up, 80 silicone gel-filled breast implant subjects (1.2 percent) have reported a diagnosis of any cancer post-implantation. There were 18 silicone gel-filled breast implant participants with neurological disorders (0.3 percent) at year 2.

In the Mentor *Large Study*, the incidence rates per 10,000 person-years for CTD at 3 years follow-up were: 27.2 for rheumatoid arthritis (83 new cases), 70.9 for osteoarthritis (210 new cases), 3.9 for scleroderma (12 new cases), 4.2 for systemic lupus erythematosus (13 new cases), 5.9 for Sjögren’s Syndrome (18 new cases), 22.4 for other connective tissue diseases (68 new cases), and 26.4 for fibromyalgia (80 new cases).

The incidence rates per 10,000 person-years for newly diagnosed cancer at 3 years follow-up were: 59.7 for all types of cancer (136 new cases), 13.6 for breast cancer (31 new cases), 0.9 for lung cancer (2 new cases), 0.0 for brain cancer, and 45.2 for other cancers (103 new cases). The incidence rate per 10,000 person-years for new neurological disease at 3-years was 36.0 for all types (111 new cases).

Discussion:

Reoperation, implant removal, rupture, capsular contracture, and other complications and adverse outcomes affect a significant proportion of women receiving silicone gel-filled breast implants. To date, the results of the *Large Studies* have not identified any previously unrecognized health concerns nor do they suggest a causal link between silicone gel-filled breast implants and CTD or breast cancer.

Data interpretation is limited due to low follow-up rates and the on-going nature of the study. The FDA has actively worked with the manufacturers to identify methods to improve the rate of study follow-up and to encourage patients and physicians to continue their participation in these studies.

Allergan conducted focus groups to better understand how patients may be motivated to complete follow-up visits and the annual questionnaire. Most respondents agreed that reminder e-mails, mailings, and telephone outreach would encourage them to continue participation.

Based on that feedback, Allergan launched a revised website for their *Large Study* that allows participants to complete the required questionnaire online. New options include personalized

pages, the ability to complete the questionnaire by phone, and the ability to update personal contact information online. In addition, Allergan issued a new direct-to-participant mailer. After these efforts, the annual number of complete questionnaires doubled.

To address their low *Large Study* follow-up rates, Mentor requested that the FDA write letters to patients and physicians. The FDA and Mentor sent more than 40,000 letters to study physicians and patients—these letters are available on the [FDA Post-Approval Studies](#) webpage. The letters encouraged ongoing patient participation and stressed the importance of continued follow up through study completion.

In response to these letters, Mentor and the FDA received significant feedback from study participants. Reasons cited by patients for failure to follow-up included geographical relocation, voluntary study discontinuation, and difficulty accessing the study website. The Mentor patient study webpage has since been modified at FDA's request.

Notably, *Large Study* follow-up rates vary by indication and appear consistent with findings identified in the *Core Studies*. Higher follow-up rates are observed among reconstruction participants, possibly because of their increased access to medical care for on-going monitoring of their underlying medical condition. It appears that once augmentation patients have received their implants and recovered from their surgery, they are less inclined to continue study participation than reconstruction patients.

Device Failure Studies (*Failure Studies*)

Purpose:

The purpose of these studies is to evaluate silicone gel-filled breast implants that have been retrieved and returned to Allergan and Mentor, and to document and catalog the failure modes in order to improve implant design and surgical techniques. Not all returned implants were removed because of local complications or rupture.

Each manufacturer was required to conduct studies of all retrieved devices returned to them until both the *Core Study* and the *Large Study* are completed. The data collection and analysis vary by manufacturer.

These studies are designed to: (1) further evaluate breast implant failures inadvertently caused during implantation, (2) characterize surgical instrument damage to breast implants, (3) evaluate and characterize failures that occur due to localized breast implant shell stress, and (4) determine if surgical factors (e.g., incision size) predispose to device rupture.

Allergan Results:

Since the beginning of its post-approval studies through June 30, 2009, 2,674 devices were returned to and analyzed by Allergan. Nine of these implants were excluded from the summary due to damage that occurred during shipping.

Allergan evaluated 2,665 devices in the laboratory with the following results:

- 87 (3.3 percent) devices could not be analyzed
- 1,429 (53.6 percent) devices were found to be "Intact and Functional," with no openings or other failure characteristics;
- 158 (5.9 percent) had "Gel Related Observations," with defects related to gel-related characteristics without loss of shell integrity.
- 91 (3.4 percent) had "Device Surface Observations," with defects related to the size or appearance of the device but not associated with an opening or deformation of the device.
- 900 (33.8 percent) had openings in the shell. Of the devices with openings:
 - 51 (1.9 percent) devices had fold flaws,
 - 26 devices (1 percent) had manufacturing defects,
 - 487 (18.3 percent) had surgical damage or surgical impact, and
 - 336 (12.6 percent) devices had openings for which the cause could not be identified.

Mentor Results:

Among patients participating in the Mentor *Large* post-approval study, 62 silicone gel-filled breast implants were retrieved; 35 (56.5 percent) were intact or without abnormality, and 27 (43.5 percent) had openings. Among the implants with openings, Mentor reported that 12 were damaged by sharp instruments and 15 had openings of unknown cause.

Among *Core Study* participants, 97 devices were explanted and returned to Mentor for evaluation from August 2000 to August 2009. Seventy-three of the 97 devices (75 percent) were returned intact and without abnormality. Of the 24 devices that ruptured, eight were damaged by sharp instruments, two had partial delamination in the shell or patch juncture, and 14 had a rent of unknown cause.

Discussion:

The most common cause of rupture reported in the device retrieval studies is damage to the implant during the implantation surgery. However, only a small proportion of breast implants are returned to the manufacturers for evaluation. This limits the ability to identify trends in failure modes.

Focus Group Study

Purpose:

The FDA required both manufacturers to complete *Focus Group Studies* to improve the format and content of the labeling. Both manufacturers completed their *Focus Group Studies* in 2007.

Allergan Focus Group Study:

Allergan's *Focus Study* had six focus groups, each of which had up to 10 participants, 18 years of age and older who had a breast implant or were considering breast implants. There were 29 augmentation breast implant participants and 23 reconstruction breast implant participants.

Based on its *Focus Group Study*, Allergan reorganized and modified its product labeling to include implant photos, graphs depicting change in cup size for augmentation, and additional information about patient satisfaction, quality of life, and long-term complications.

Mentor Focus Group Study:

There were four focus groups in Mentor's *Focus Group Study*, each of which had eight to 10 participants. Thirty-five adult women interested in silicone gel-filled breast implants for augmentation or reconstruction participated. Participants completed a self-administered survey designed to collect individual data and to measure their comprehension of information from Mentor's educational brochure. Respondents in both the augmentation and reconstruction groups agreed that the brochure was highly informative and comprehensive. Many respondents felt they learned new information as a result of reading the brochure. Based on the feedback from the focus groups, Mentor modified its brochure to more clearly outline differences between restoration, replacement, reconstruction, and revision and to provide information to help women weigh the risks and complications with the benefits of breast implants.

Annual Physician Informed Decision Survey (*Informed Decision Study*)

Purpose:

The FDA required both manufacturers to institute a formal informed decision process to ensure that: (1) a woman has obtained the patient information brochure with adequate time to read it prior to surgery, and (2) the surgeon has documented that the patient has an adequate understanding of the risks and follow-up recommendations associated with the device.

The FDA also required the manufacturers to provide physician training in the use of their informed decision process as part of physician training program for the implants. In addition, the FDA required each manufacturer to conduct a survey using a new random sample of 50 physicians each year to assess the patient informed consent process.

Results:

Based on the 2009 surveys for each manufacturer, physicians found the patients' brochures informative, useful, and effective in communicating breast implant risks and benefits. However, not all physicians use the brochure. For example, Allergan's survey showed that only 52 percent of physicians provide the brochure as part of the surgery consultation process.

Adjunct Studies

Purpose:

In 1992, when FDA removed all silicone gel-filled breast implants from the market, the FDA continued to permit companies to provide these devices for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Women who received silicone gel-filled breast implants for these purposes were enrolled in *Adjunct Studies* so that data about device performance and safety could be collected. Participant enrollment began in 1992 for Mentor and 1997 for Allergan.

As a condition of approval of silicone gel-filled breast implants in 2006, both manufacturers were required to close enrollment of new patients into the *Adjunct Studies* but continue to follow study participants through their 5-year post-implant evaluations.

Allergan enrolled 83,968 women in its *Adjunct Studies*, including 44,799 who underwent primary reconstruction and 39,169 who underwent breast implant revision. The revision group included women who underwent both revision augmentation and revision reconstruction. Patients had a median age of 42 years (range, 14 to 98).

Mentor enrolled 136,609 women in its *Adjunct Studies*. Reconstruction surgery was performed in 57,828, revision reconstruction surgery in 18,491, and revision augmentation in 60,290 women.

Results:

The 5-year rates for the most common local complications and adverse outcomes observed in the Allergan *Adjunct Study* for patients undergoing primary reconstruction and revision, respectively, were capsular contracture (Baker III/IV) (16.3 percent, 22.6 percent), asymmetry (11.9 percent, 11.3 percent), implant palpability/visibility (7.7 percent, 12.2 percent), and wrinkling (6.2 percent, 9.4 percent).

For Mentor, the most common local complications and adverse outcomes in the primary reconstruction, revision reconstruction, and revision augmentation groups, respectively, were asymmetry (23.1 percent, 11.1 percent, 25.8 percent), wrinkling (13.4 percent, 14 percent, 17.4 percent), and explant (10.7 percent, 9.9 percent, 12.8 percent). Other reported additional procedures included nipple reconstruction, reconstruction revision/staged reconstruction, and capsulectomy. The most common reasons for removal were capsular contracture, infection, patient request for size and implant change, and leakage/rupture/deflation.

Discussion:

The *Adjunct Studies* provide qualitative information about the spectrum of adverse outcomes that occur in this patient population. However, data collection methodology and low follow-up rates (23 percent for Allergan and 16 percent for Mentor 5 years post-implant) limit data interpretation.

Post-Approval Study Conclusions

Overall, the post-approval studies conducted to meet the six conditions of approval demonstrate that the longer a woman has silicone gel-filled breast implants, the more likely she is to experience complications or adverse outcomes. The most common local complications and adverse outcomes associated with silicone gel-filled breast implants include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain and infection. Actual complication rates vary according to the reason for breast implantation.

These observations are consistent with complications and adverse outcomes previously known to

be associated with breast implants.

The post-approval studies to date do not show evidence that silicone gel-filled breast implants cause CTD, reproductive problems, or breast cancer. Low follow-up rates and other study limitations may limit interpretation of the data and preclude the detection of very rare complications.

Both manufacturers have encountered challenges in implementation of their study protocols, and follow-up rates are lower than expected. As follow-up has lagged, the FDA recognizes that these studies may not provide the data necessary to definitively answer questions about rare associations. The FDA has been working with manufacturers to address challenges related to enrollment and follow-up rates. See [FDA Activities](#) for more details.

For more information about breast implant post-approval studies, please visit the [FDA Post-Approval Studies](#) webpage.

V. Postmarket surveillance of adverse events reported on approved silicone gel-filled breast implants

Key Points from Postmarket Surveillance of Adverse Events

- The primary goals of FDA's postmarket medical device surveillance are to identify previously unrecognized adverse events and to help to detect patterns of actual or potential adverse events.
- Allergan and Mentor must submit adverse event reports on silicone gel-filled breast implants received after November 2006 through one of two reporting methods:
 - Medical Device Reports (MDR), or
 - Postmarket Spreadsheet Reports (PSR).
- Patients and healthcare providers can also submit adverse event reports directly to FDA through [MedWatch](#), FDA's safety information and adverse event reporting program.
- Overall, the types of adverse events submitted to the FDA are consistent with results from premarket and post-approval studies. No unexpected outcomes or complications were reported through December 2010, except for rare reports of possible Anaplastic Large Cell Lymphoma (ALCL) associated with breast implants. For additional information on breast implants and ALCL see: [Anaplastic Large Cell Lymphoma \(ALCL\) in Women with Breast Implants: Preliminary FDA Findings and Analyses](#).

Background:

The FDA collects and analyzes adverse event information from a variety of sources as part of its ongoing surveillance of silicone gel-filled breast implants.

Manufacturers and user facilities (such as hospitals and nursing homes) are required to submit device-related reportable events according to the Medical Device Reporting (MDR) regulation (21 CFR Part 803). User facilities are required to report device-related deaths to FDA and device-related deaths and serious injuries to the manufacturer.

Allergan and Mentor must submit adverse event reports for patients who received silicone gel-filled breast implants through one of two reporting methods:

- 1) Medical Device Reports (MDR). Manufacturers must report all deaths and unusual, unique or uncommon adverse events to FDA as individual reports on the FDA Form 3500A within 30 days of becoming aware of the event, or
- 2) Postmarket Spreadsheet Reports (PSR). Manufacturers must report serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials in PSR reports. PSR reports are submitted quarterly, as authorized under 21

CFR Part 803.19(c), as an alternative to the requirement for submitting individual MDR reports on FDA Form 3500A.

Health care professionals, patients and other concerned individuals who do not have a mandatory reporting obligation, can submit reports voluntarily to the FDA through [MedWatch](#), FDA's safety information and adverse event reporting program.

Individual reports submitted by breast implant manufacturers and user facilities are stored in FDA's Manufacturer and User Facility Device Experience (MAUDE) database, a repository for adverse event reports involving medical devices. Voluntary reports from health care professionals and patients are also stored in the MAUDE database. PSR reports are not included in the MAUDE database.

Postmarket Spreadsheet Reporting (PSR):

The FDA designed the PSR program specifically to monitor the postmarket performance of approved silicone gel-filled breast implants. The PSR program, an alternative to the requirement for submitting individual MDR reports, requires manufacturers to submit quarterly reports for serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials (e.g., rupture, capsular contracture).

The PSR program requires manufacturers to collect more specific and more detailed information about these well-known adverse events than would normally be submitted on an individual reporting form. The additional details include the patient's race/ethnicity, whether the patient is enrolled in the *Large Study*, the reason for implanting the device, whether a reoperation (with or without implant removal) was performed as a result of the adverse event, the reason for reoperation, the reason for implant removal, whether the removed implant was replaced and if so, with what type of implant, and the type of surgery performed. Collection of these data will help characterize the known breast implant-related problems and improve data analysis.

Reports from the MDR and PSR reporting systems are described in [Tables 15 - 18](#). The data are grouped according to assigned patient problem codes and device problem codes. Patient and device problem codes are provided by the FDA for use by the manufacturer when submitting an adverse event report. (For more information about codes see [Event Problem Codes](#)).

Results of Postmarket Surveillance of Adverse Events:

Patient and Device Problems Submitted to the FDA as Individual MDRs

Between November 17, 2006 (date of FDA approval) and December 31, 2010, the FDA received 133 individual MDRs associated with Allergan and Mentor silicone gel-filled breast implants. Manufacturers submitted 24 of these reports, user facilities submitted 25 reports, and voluntary reports accounted for 84.

The types of events associated with these reports are two deaths, 84 serious injuries, 21 malfunctions, eight "data element is blank" and 18 "other" (a type of event used by the reporter when the adverse event is not considered a death, injury or malfunction report).

The two death reports referred to the same patient who was diagnosed with anaplastic large cell

lymphoma (ALCL). This patient's pathology report later confirmed that she had systemic ALCL, not ALCL localized to her breast implants. For more information about ALCL and breast implants see: [Anaplastic Large Cell Lymphoma \(ALCL\) in Women with Breast Implants: Preliminary FDA Findings and Analyses](#).

The 133 reports contained a total of 530 patient problem codes and 239 device problem codes. [Table 15](#) and [Table 16](#) list patient problems and device problems that occurred in more than 1 percent of the MDR reports.

Patient and Device Problems Submitted to the FDA through the Postmarket Spreadsheet Reporting (PSR) System

Between November 17, 2006 and December 31, 2010, the FDA received 16,681 reports through the PSR: 16,279 reports of injuries and 402 reports of implant malfunctions. A total of 26,511 patient problems were reported in 16,681 PSR reports.

The most frequent patient adverse events and outcomes reported were reoperations (noted by the code 'surgical procedure'), capsular contracture, pain, infection and breast lumps. The primary reasons for reoperations were rupture, capsular contracture, implant malposition/asymmetry, infection, wrinkling and hematoma. The primary reasons for implant removal were implant rupture, capsular contracture, malposition/asymmetry, infection, wrinkling and extrusion.

A total of 12,327 device problem codes were reported in 16,681 PSR reports. The most frequently reported device problems were device-patient incompatibility, rupture, implant malposition/asymmetry, and device defects that prevented the surgeon from implanting the device (includes codes for 'tears, rips, holes in device,' 'device material that prevented the device from being implanted,' 'design/structure problems,' and 'out of the box failures'). The term 'device-patient incompatibility' is a code used to indicate a biological reaction that the patient has to the implant.

[Table 17](#) and [Table 18](#) list patient problems and device problems that occurred in more than 1 percent of the PSR reports.

Discussion of Adverse Event Data:

There are strengths and limitations to the data collected through FDA's adverse event reporting systems. Strengths of the system include the ability to detect rare or unexpected device-related adverse events, the capacity to identify problems in the real world setting (unlike premarket trials) and collection of information about problems that occur over a long period of device use.

Because the number of patient and device problems reported to the FDA is subject to underreporting, MAUDE and PSR data are not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices.

Specifically, the MAUDE and PSR data are subject to a number of limitations, including:

- The number of events that are reported to the FDA is often much lower than the number of events that actually occur. Whether an event is reported may be influenced

by the severity of the adverse event, how unusual it is or whether there has been a lot of publicity or legal action involving the product.

- It is generally not possible to independently verify the reports received by the FDA. As a result, they may contain incomplete or inaccurate information. The FDA assumes that reports received are truthful.
- The size of the population exposed to the device (denominator) is often not known, so it is difficult to determine adverse event rates and put the number of adverse events in perspective to interpret the data.
- It is difficult to know whether or not the implant caused or contributed to the adverse event based solely on information provided in a report. Establishing a cause and effect relationship is especially difficult if the device is not examined or if the analysis was inadequate.

In summary, the results collected to date through the adverse event reporting system are consistent with the results obtained from the premarket and post-approval studies. With the exception of ALCL occurring in association with breast implants, no new complications or adverse outcomes associated with breast implantation have been identified.

VI. Review of the Literature on the Safety of Silicone Gel-Filled Breast Implants

Key Points from Literature Review

- This section reviews the epidemiologic literature published in peer-reviewed journals since 2005 on the clinical safety and effectiveness of silicone gel-filled breast implants. It focuses on outcomes that have not been addressed to date in post-approval studies.
- Most women report high levels of satisfaction with their body image and the shape, feel and size of their implants.
- Most infections develop in the immediate post-operative period, although infections can develop long after implant. Late infection may be underreported.
- The current body of literature does not support an association between CTD and silicone gel-filled breast implants, but most of the available studies have limitations.
- There is no evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility
- Current evidence does not support an association between mothers with breast implants and difficulty with breast feeding or adverse health events in their children.
- Women with breast implants may be more likely to be diagnosed with anaplastic large cell lymphoma (ALCL). See [Anaplastic Large Cell Lymphoma \(ALCL\) In Women with Breast Implants: Preliminary FDA Findings and Analyses](#).
- Although some studies show an increased risk of suicide in women with breast implants, this is likely due to selection bias. No study has demonstrated a causal relationship between breast implants and suicide.

Background:

At the time of their approval in November 2006, silicone gel-filled breast implants were associated with several well-characterized complications and adverse outcomes, including rupture, reoperation, and capsular contracture. Data concerning these results are presented in the Post-Approval Study (Section V) and Post-Market Surveillance of Adverse Event (Section VI) sections of this report and are not discussed here.

When the FDA approved Allergan and Mentor's silicone gel-filled breast implants in 2006, there were reports of other potential adverse events, but they were infrequent and not fully understood. These included implant-related infections, CTD, cancer, reproductive outcomes, and suicide. In addition, there were limited data on patient satisfaction. These results are discussed in this section.

This section summarizes medical and scientific English literature published primarily from January 1, 2005 through December 31, 2010. The literature search included reviews and meta-analyses of human studies, as well as selected original papers. If significant publications concerning a particular adverse event of interest had not been published during the relevant time period, manuscripts from earlier time periods were evaluated.

Patient Satisfaction and Quality of Life:

Satisfaction of patient expectations remains an important measure of the effectiveness of cosmetic surgery. Patients undergoing breast augmentation surgery have reported high rates of satisfaction with the shape, feel, and size of their silicone gel-filled breast implants.²⁻⁸

Studies show that many women undergo breast augmentation surgery to improve their self-esteem and self-image.^{2,5} More than 90 percent of women with silicone gel-filled breast implants are satisfied that their primary expectations have been met. Body image improves in the majority of women who receive silicone gel-filled breast implants, and this satisfaction lasts for at least two years post-implant.

Post-operative complications such as capsular contracture decrease satisfaction with the procedure, particularly if those complications are visible to other people.²

Infections:

Estimates from scientific and medical literature on the risk of infection following silicone gel-filled breast implantation are derived mainly from prospective studies in Scandinavian countries.^{9,10} Wound infections occur in less than 5 percent of breast implant study participants. Along with hematoma, infections are the most common short-term local complication. Infections generally occur in the immediate period following surgery.⁹ Systemic infections are not typical although toxic shock syndrome has been rarely reported.¹¹

Acute infections associated with breast implants are generally linked to skin pathogens (i.e., group A streptococci, Staphylococcus epidermidis, or Staphylococcus aureus), while long-term infections are often caused by aerobic gram-negative bacilli. Chronic "culture-negative" infections after breast implant procedures are sometimes due to atypical mycobacteria. Although two-thirds of infections develop within the acute post-operative period, some infections may develop years or even decades after surgery. The reported rate of systemic and late infections is approximately 1 percent or less, although it is likely that late infections are under-reported.^{12,13}

Subclinical infection may predispose to long-term complication that follows breast implantation, i.e., capsular contraction that involves the formation and contraction of a collagenous sheath around the implant, thus forming hard, spherical masses in the breasts.

While systemic postoperative wound infections are rare, the effects can be devastating. Among the Mycobacteria, Mycobacterium fortuitum complex represent the opportunistic pathogens that account for 60 to 80 percent of postsurgical wound infections caused by rapidly growing mycobacteria, particularly after breast surgery (with or without prosthetic implants).¹⁴⁻¹⁶ Complications include long term infection occurring months after implantation. Drainage or

implant removal is usually required to ensure bacterial eradication.¹⁷

Connective Tissue Diseases/Rheumatic Conditions:

Connective tissue diseases (CTDs) include a spectrum of conditions such as fibromyalgia, scleroderma, Sjögren's Syndrome, and systemic lupus erythematosus. A number of studies evaluated the possibility of a relationship between silicone gel-filled breast implants and connective tissues diseases.¹⁸⁻³⁷

Estimate of CTD differ. For example, the incidence of fibromyalgia is approximately 1,128 women per 100,000 women in the general population according to one study.³⁸ Comparatively, the incidence of scleroderma in a general population is much lower, occurring in approximately 3 patients per 100,000 per year.³⁹

Because of the incidence and prevalence⁴⁰ of CTDs are quite low,^{38, 39} a very large study of sufficient duration would be required to determine a causal relationship between silicone gel-filled breast implants and CTD.

Most studies have not found an association between connective tissue diseases as a group and silicone gel-filled breast implants. The FDA collaborated on one study in 2001 that found a positive association between extracapsular silicone gel-filled breast implants and fibromyalgia, but significant study design and patient selection weaknesses undermine the study's conclusions.⁴¹

Most studies that have examined specific connective tissue diseases like fibromyalgia, scleroderma and systemic lupus erythematosus have failed to identify an association, although the studies have recognized limitations, such as lack of very long-term duration of follow-up.^{25, 33, 37}

Overall, the current body of evidence does not support an association between silicone gel-filled breast implants and CTD.

Cancer:

Women who receive silicone gel-filled breast implants for augmentation do not appear to be at increased risk of developing breast cancer.^{42, 43} In fact, studies suggest they may be at average or even lower risk – with some estimating a risk reduction of 10 to 50 percent.⁴⁴

Survival rates for women with breast cancer who receive silicone gel-filled breast implants as part of breast reconstruction appear to be unaffected by the presence of an implant.⁴⁴

Some reports have observed an increase in cancer risk for patients with cosmetic breast implants (not specifically silicone gel-filled breast implants), including brain, cervical, vulvar, lung, and non-melanoma skin cancer.⁴⁵ However, these observations appear unrelated to the effects of the implants themselves.^{10, 46} Post-approval studies have not identified an increased cancer risk among silicone gel-filled breast implant recipients.

One possible exception is the rare development of Anaplastic Large Cell Lymphoma (ALCL) in

women with breast implants. Reports in the scientific community have suggested a possible association between ALK-negative ALCL and silicone gel-filled and saline-filled breast implants. In a thorough review of scientific literature published from January 1997 through May 2010, the FDA identified 34 unique cases of ALCL in women with breast implants throughout the world. The FDA's adverse event reporting systems also contain 17 reports of ALCL in women with breast implants. Additional cases have been identified through the FDA's contact with other regulatory authorities, scientific experts, and breast implant manufacturers. In total, the FDA is aware of approximately 60 case reports of ALCL in women with breast implants worldwide. For additional information, see [Anaplastic Large Cell Lymphoma \(ALCL\) In Women with Breast Implants: Preliminary FDA Findings and Analyses](#).

Other than ALCL, the available epidemiologic evidence does not support a clinical association of silicone gel-filled breast implants with an increased cancer risk in humans. Results from several recent published large scale cohort studies with long-term follow-up provide no evidence of an association between breast implants and cancer.^{42, 43, 47}

Screening for Breast Cancer:

Screening mammograms are X-ray images of the breast used to look for changes in the breast tissue that are too small to cause noticeable symptoms; in some cases these represent breast cancers.⁴⁸ Breast implants may make it difficult to see breast tissue on standard mammograms; additional X-ray images, called implant displacement views, can be obtained at the time of a mammogram and should be used to examine the breast tissue more completely in breast implant patients.⁴⁹

The National Cancer Institute advises women with breast implants to receive screening mammography, at experienced centers, at intervals based on their age and risk factors. Women should be sure to notify the mammography facility and the technologist conducting the exam that they have breast implants.

The National Cancer Institute recommendations for breast cancer screening in women with breast implants can be found at <http://www.cancer.gov/cancertopics/factsheet/Detection/mammograms>.

Screening for Rupture:

When a silicone gel-filled implant ruptures, the gel may remain in the shell or in the scar tissue that forms around the implant (intracapsular rupture). In some cases, the silicone migrates outside of scar capsule (extracapsular rupture). It may be difficult or impossible to remove silicone gel that has migrated out of the capsule to other parts of the body.

Different diagnostic tests can be used to detect intracapsular and extracapsular breast implant rupture, including magnetic resonance imaging (MRI), mammography, ultrasound, and computed tomography (CT).

MRI can be used to detect both intracapsular and extracapsular ruptures. In the older models of silicone gel-filled breast implants, MRI can detect more than 90 percent of ruptures.⁵⁰

A recent meta-analysis on the diagnostic accuracy of MRI for detecting silicone gel-filled breast implant ruptures reported lower accuracy in detecting ruptures in asymptomatic patients than in symptomatic patients.⁵¹

One of the post-approval studies required by the FDA looks at the accuracy of MRI in detecting rupture.

The FDA approved labeling for silicone gel-filled implants currently recommends that women get their first breast MRI 3 years after they receive the implants and every 2 years thereafter to detect silent ruptures.

MRIs are not an option, however, for women who have MRI incompatible pacemakers, aneurysm clips, or other implanted metallic foreign bodies, or whose physical size and weight precludes them from having an MRI.⁵⁰

Once implants are removed, there is no medical need for routine screening MRI.

Mammograms can detect extracapsular silicone when an implant ruptures, but they do not detect intracapsular ruptures. In older models of silicone gel-filled breast implants, only 10 to 22 percent of ruptures are extracapsular, so mammograms will miss most ruptures.⁵⁰ If extracapsular silicone is detected by mammography, before making a presumptive diagnosis of implant rupture, the physician should take a careful clinical medical history from the patient to rule out the possibility that the silicone remains from a prior rupture or silicone injection (and thereby unrelated to the current silicone gel-filled breast implant).

The relative value of ultrasound alone to detect intracapsular ruptures is controversial because its accuracy depends on the skill of the ultrasound technologist, the type of equipment used, and the experience of the interpreting physician.⁵⁰ Ultrasound is limited in its ability to detect ruptures in the back wall of the implant and in the breast tissue behind it. Extracapsular silicone has a distinctive appearance on ultrasound and should be recognized if imaged. As with mammography, extracapsular silicone detected on ultrasound may be due to a previous implant rupture or silicone injection. Therefore, a thorough clinical history is important to make an accurate diagnosis.

CT scans can detect intracapsular silicone gel-filled breast implant rupture, but they are limited in their ability to detect extracapsular ruptures. This imaging technique is a useful alternative for women who are unable to have MRIs. However, a disadvantage of CT is that it exposes patients to ionizing radiation.⁵⁰

Effects on Reproductive Outcomes:

There is no significant evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility.

The bulk of the published literature in the field of maternal and child health to date does not suggest a causal relationship between silicone gel-filled breast implants and adverse health outcomes in children born to women with implants.^{10, 52} In addition, silicone gel-filled breast

implants do not appear to be associated with breastfeeding difficulties.^{53, 54}

Suicide:

Retrospective studies consistently suggest an increased rate of suicide in patients undergoing breast implants compared to the general population. However, it is likely that this reflects underlying factors including socioeconomic status and self-esteem. There is no evidence that breast implants cause the observed increase in suicide risk.⁵⁵⁻⁵⁸

VII. Summary of Key Findings

1. Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use.
2. The longer a woman has breast implants, the more likely she is to experience local complications or adverse outcomes. Women with breast implants will need to monitor their breasts for local complications for the rest of their lives.
3. The most frequent complications and adverse outcomes experienced by breast implant patients include capsular contracture, reoperation, and implant removal (with or without replacement). Other frequent complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection, among others. These observations are consistent with the local complications and adverse outcomes that were known at the time of approval.
4. Women with breast implants may have a very small but increased likelihood of being diagnosed with anaplastic large cell lymphoma.
5. In the post-approval *Core Studies*, between 20 to 40 percent of augmentation patients and 40 to 70 percent of reconstruction patients had reoperations during the first 8 to 10 years after they received their implants. Although routine replacement is not necessary, many women will need additional surgery to modify, remove, or replace their implants.
6. There is no apparent association between silicone gel-filled breast implants and connective tissue disease, breast cancer, or reproductive problems. Associations that are very rare or that take many years to manifest may not be detected using currently available data.
7. MRI continues to be the most effective method of detecting silent (asymptomatic) rupture of silicone gel-filled breast implants.
8. Interpretation of the data from the silicone gel-filled breast implant post-approval studies may be limited by low follow-up rates.

VIII. Recommendations for Patients Who Have or Who Are Considering Breast Implants

- Be aware that breast implants are associated with significant local complications, and the longer the devices remain implanted, the more likely you are to experience a complication. Local complications and adverse outcomes include capsular contracture, reoperation, removal, and implant rupture. Many women also experience breast pain, wrinkling, asymmetry, scarring, and infection.
- Continue to receive routine follow-up with your physician. This includes having periodic MRI exams to detect “silent rupture” of the implant.
- Notify your health care provider if you develop any unusual signs or symptoms including pain, asymmetry, hardness or swelling.
- Recognize that breast implants are not lifetime devices. The longer you have your implants, the more likely it will be for you to have them removed.
- If you have enrolled in an Allergan or Mentor post-approval study, continue to participate. These studies are the best way to collect information about the long-term rates of complications.
- Continue routine screening mammography for breast cancer at intervals recommended by your health care provider based on your age and risk factors.

IX. Recommendations for Health Care Providers

- Provide women with copies of patient brochures and informed consent so that they have access to the critical information needed to make informed decisions about receiving and caring for breast implants. [Labeling for Approved Breast Implants](#) for patients and for physicians is available on FDA’s breast implant website.
- Maintain medical vigilance through follow-up and post-approval studies so that the long-term effects of silicone gel-filled breast implants can be better understood. Your contributions provide data that are used to evaluate how new surgical techniques, patient characteristics, and implant characteristics influence the cosmetic and health outcomes of patients undergoing breast implantation.
- Screen for silent rupture using MRI. Women with silicone gel-filled breast implants should undergo MRI screening for silent implant ruptures at 3 years post-implantation, and every 2 years thereafter.
- Report breast implant associated adverse events and deaths to FDA via [MedWatch](#).

X. FDA Activities

The FDA activities surrounding silicone gel-filled breast implants focus on three key goals:

- Fostering the collection of data about implant performance;
- Improving the follow-up rates in current and future post-approval studies; and
- Communicating new safety information when it becomes available so that women can make informed decisions about their healthcare.

To accomplish these goals, the FDA:

- Closely monitors the status and conduct of the on-going required post-approval studies so that data is collected, validated scientifically and disseminated widely;
- Actively encourages and facilitates adverse event reporting by the manufacturers, patients, healthcare providers, and health care facilities;
- Is collaborating with the American Society of Plastic Surgeons (ASPS) and other experts in the clinical and scientific community to develop a registry of women with breast implants and anaplastic large cell lymphoma (ALCL) to better understand the nature and possible factors contributing to their association;
- Will hold a meeting of its Medical Device Advisory Committee in the summer of 2011 to seek input on issues related to postmarket surveillance of silicone breast implants including study design, patient enrollment and follow-up, and data analysis;
- Released, in June 2011, a newly updated breast implant website (www.fda.gov/breastimplants). Key sections of this website describe the risks of breast implants, the questions women should ask their doctors before getting breast implants, and what women should expect during the surgical procedure and recovery.
- Developed a new [Breast Implants Complications Booklet](#) for patients. The booklet includes the latest information from the post-approval studies. It is available on the FDA website.
- Requires breast implant manufacturers to update their labeling each time the data is reanalyzed. The most current [Labeling for Approved Breast Implants](#) is available on the FDA website.

XI. Conclusion

Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use.

Manufacturers and physicians should continue to provide balanced and up-to-date information to women considering breast implants to help inform their decisions.

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XIII. Glossary of Terms

Adverse Event Report: A report submitted to the FDA describing an undesired outcome for which a device association is known or suspected. Also known as a Medical Device Report (MDR).

Adjunct Studies: Specific to silicone gel-filled breast implants, these studies were originally designed by FDA to address the public health need for reconstruction and revision patients. By participating in these studies women and surgeons gained access to the silicone gel-filled breast implants not on the open market.

ALCL: Anaplastic Large Cell Lymphoma, a rare type of T-cell non-Hodgkin's lymphoma. ALCL is a rare type of non-Hodgkin's lymphoma. ALCL is not cancer of the breast tissue. Lymphoma is a cancer of the lymphatic cells of the immune system.

Asymmetry: Lack of proportion of shape, size, and/or position between the two breasts.

Augmentation: A surgical procedure to increase breast size. For this document, it refers to placement of a breast implant. The first time a breast implant is placed to increase breast size, it is called primary augmentation. All subsequent times the implant is replaced, it is called revision augmentation.

Capsular Contracture: A tightening of the fibrous capsule surrounding a breast implant, resulting in firmness or hardening of the breast. One of the most common complications of breast implant surgery.

Capsulectomy: The surgical removal of capsular contracture around the breast implant

Capsulorrhaphy: A surgical procedure to revise the shape and size of the pocket in which the breast implant lies.

Class III device: FDA uses a risk based model to assign devices into one of three classifications: Class I, II, or III. A Class III designation represents the highest risk profile. A Class III device requires premarket approval and a scientific review to ensure the device's safety and effectiveness, in addition to the general controls for lower risk devices.

Cohort: a group of study participants who share similar conditions, characteristics or demographics

Condition of Approval: Postmarket obligation defined by FDA that the manufacturer must comply with as part of the terms for receiving authorization to market a specific device.

Connective Tissue Disease (CTD): any disease that targets the connective tissues of the body; they may be heritable (such as fibromyalgia), autoimmune (such as rheumatoid arthritis) or other (such as scurvy).

Core Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies is to assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications.

Epidemiologic Study: A statistical study on a human population that attempts to link health outcomes with a specific cause.

Extracapsular: Occurring outside the fibrous scar capsule surrounding the breast implant.

Federal Food, Drug, and Cosmetic Act: The law which gives FDA its regulatory authority.

Follow-up rates: the indication of how often the manufacturer maintains contact with the patient after the initial breast implant surgery in the collection of post-implant study data. The follow-up rate reflects the manufactures success in data collection.

Focus Group Studies: A form of quality research in which participants are gathered together and are asked about their perceptions, opinions, beliefs and attitudes towards a specific issue or item. Questions are asked in an interactive group setting where participants are free to talk with other group members.

Iatrogenic Injury/Damage: Injury or damage an implant resulting from a surgical procedure.

Institute of Medicine (IOM): The Institute of Medicine is a US not for profit governmental organization. Its purpose is to provide national advice on issues relating to biomedical science, medicine, and health, and its mission to serve as adviser to the nation to improve health. It works outside the framework of the U.S. federal government to provide independent guidance and analysis.

Intracapsular: Occurring inside the fibrous scar capsule surrounding the breast implant.

Lactation: the act of producing milk from the mammary glands in the breast.

Large Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies was to assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients, following them for 10-years, and comparing them to control groups of saline-filled breast implant patients.

Mammography: An x-ray of the breast tissues

Meta-analysis: A combined evaluation of multiple similar studies

MRI (Magnetic Resonance Imaging): a diagnostic testing process that uses magnets and no ionizing radiation in creating images that provide clear contrast between soft and dense tissues. MRI provides a level of clarity that may not be obtainable by routine x-ray.

Post-Approval Studies: Studies conducted as conditions of approval after the device receives FDA authorization to begin marketing. Post-approval studies provide a means for data collection from a large population over an extended period of time.

Reconstruction: A surgical procedure to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. The first time a breast implant is placed for reconstruction, it is called primary reconstruction. All subsequent times the implant is replaced, it is called revision reconstruction.

Reoperation: Any additional surgical procedure performed on the breast and/or implant after initial breast implantation.

Rupture: Specifically associated with silicone gel-filled breast implants, it represents the condition whereby there is a tear or hole in the implant's outer shell.

Saline-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with saline as the filler.

Silicone Gel-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with a silicone gel filler.

Toxic Shock Syndrome (TSS): A collection of signs and symptoms resulting from infection, often caused by Staphylococcal or Streptococcal bacteria. TSS is both rare and potentially life-threatening.

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TABLE 1. Status of Allergan Natrelle and Mentor MemoryGel silicone gel-filled breast implant post-approval studies.

Study	Allergan		Mentor	
	Enrollment	Follow Up	Enrollment	Follow Up
Core Study	715 patients Enrollment Closed	At 10 years: Overall 65% Primary Aug. 66% Rev Aug. 64% Primary Recon. 75% Rev Recon. 80%	1008 patients Enrollment Closed	At 8 years: Overall 58% Primary Aug. 54% Rev Aug. 59% Primary Recon. 67% Rev Recon. 64%
Large Study	41,342* silicone patients (105% of target) and 15,646 saline patients (103% of target). Enrollment Closed	Below Target: 60.5% at year 2 for silicone; 45.1% at year 2 for saline	41,419** silicone patients (98.6% of target) and 1,030 saline patients (103% of target). Enrollment Closed	Below Target: 21.1% at year 3 for silicone; 9.6% at year 3 for saline
Device Failure Studies	Not Applicable***	No follow-up but study reports are due annually	Not Applicable***	No follow-up but study reports are due annually
Focus Group Study	52 patients Enrollment Closed	No Follow-up of Participants	35 patients Enrollment Closed	No Follow-up of Participants
Informed Decision Process Study	Annual Random Sample of 50 Physicians	No Follow-up of participants	Annual Random Sample of 50 Physicians	No Follow-up of participants
Adjunct Study****	Enrollment Closed	54% at 1-year 30% at 3-year 23% at 5-year	Enrollment Closed	36% at 1-year 24% at 3-year 16% at 5-year

* The enrollment for the Allergan *Large Study* silicone group includes at least 97 women in the augmentation cohorts who are younger than 22 years of age.

**The enrollment for the Mentor *Large Study* silicone group excludes 556 women in the augmentation cohorts who are younger than 22 years of age.

***No enrollment targets were set for the *Device Failure Studies*; all explanted and returned devices are included in these studies.

****The protocols for the *Adjunct Studies* did not include follow-up targets.

TABLE 2. Enrollment in the silicone gel-filled breast implant *Core Studies* by manufacturer and indication.

Company	Study Population	Primary Augmentation	Revision Augmentation	Primary Reconstruction	Revision Reconstruction	Total
Allergan	Overall	455	147	98	15	715
	MRI cohort	147	49	50	5	251
Mentor	Overall	552	145	251	60	1,008
	MRI cohort	202	56	134	28	420

TABLE 3. Core Study complications and adverse outcomes over 10 years post-implantation for Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Asymmetry	3.3% (2.0-5.1)	6.5% (3.2-12.8)	23.2% (15.4-33.9)	6.7% (0.2-31.9)
Breast pain	10.9% (8.2-14.3)	11.7% (7.1-18.9)	6.8% (2.8-16.1)	0%
Breast/skin sensation changes	1.6% (0.8-3.3)	2.2% (0.7-6.6)	0%	0%
Bruising	0.4% (0.1-1.8)	3.0% (1.1-7.8)	1.0% (0.1-7.1)	6.7% (0.2-31.9)
Capsular contracture (Baker III/IV)	19.1% (15.6-23.3)	27.5% (20.3-36.6)	24.6% (16.2-36.2)	6.7% (0.2-31.9)
Delayed wound healing	1.1% (0.5-2.7)	0.7% (0.1-4.8)	1.0% (0.1-7.2)	0%
Hematoma	1.6% (0.7-3.2)	2.1% (0.7-6.3)	1.5% (0.2-10.4)	0%
Implant malposition	6.3% (3.9-8.4)	6.0% (3.1-11.7)	2.3% (0.6-8.9)	13.3% (1.7-40.5)
Implant palpability/visibility	1.9% (1.0-3.8)	6.0% (3.0-11.6)	6.5% (0.4-17.0)	6.7% (0.2-31.9)
Implant removal with or without replacement	20.8% (17.2-25.2-)	32.4% (25.0-41.3)	53.8% (43.65.3)	20% (4.3-48.1)
Implant rupture	10.1% (7.4-13.7)	6.3% (2.8-13.7)	27.2% (17.3-41.3)	6.7% (.2-31.9)
Infection	0.5% (0.1-2.1)	1.4% (0.3-5.4)	3.2% (1.0-9.5)	0%
Irritation	0%	0.7% (0.1-5.0)	0%	0%
Necrosis	0.2% (0-1.6%)	0%	2.3% (0.6-8.8)	0%
Nipple complications	6.3% (4.3-9.1)	1.4% (0.3-5.4)	3.3% (1.1-9.8)	0%
Ptosis	2.0% (1.0-3.9)	4.9% (2.2-10.5)	0%	0%
Redness	0.7% (0.2-2.0)	0.8% (0.1-5.2)	2.1% (0.5-8.3)	0%

Table 3 (continued).

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Reoperation	36.1% (31.6-40.9)	46.0% (38.0-54.9)	71.9% (61.5-81.4)	46.7% (21.3-73.4)
Scarring/hypertrophic scarring	4.2% (2.6-6.5)	6.6% (3.5-12.4)	5.5% (2.3-12.7)	0%
Seroma/fluid accumulation	1.8% (0.9-3.5)	6.0% (3.0-11.7)	2.4% (0.3-15.7)	6.7% (0.2-31.9)
Skin rash	0.9% (0.3-2.3)	0.7% (0.1-4.9)	2.1% (0.5-7.9)	6.7% (0.2-31.9)
Swelling	9.2% (6.8-15.0)	8.3% (4.6-14.5)	7.1% (3.5-14.4)	0%
Wrinkling	1.8% (0.8-3.7)	5.4% (2.6-11.0)	10.2% (5.2-19.6)	0%

* The number of patients evaluated at the 10 year follow-up were: 269 (primary augmentation), 74 (revision augmentation), 44 (primary reconstruction), and 8 (revision reconstruction).

TABLE 4. Core Study complications and adverse outcomes over 8 years post-implantation for Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Breast mass	5.4% (3.7-7.8)	6.5% (3.4-12.0)	5.2% (2.9-9.3)	7.2% (2.8-18.2)
Breast pain	2.5% (1.5-4.3)	3.4% (1.3-8.8)	2.8% (1.2-6.2)	5.2% (1.7-15.3)
Breast/skin sensation changes	2.8% (1.7-4.5)	1.4% (0.4-5.4)	0%	1.8% (0.3-12.0)
Capsular contracture (Baker II)	2.0% (1.1-3.7)	6.2% (3.1-12.1)	4.4% (2.3-8.3)	4.0% (1.0-15.2)
Capsular contracture (Baker III/IV)	10.9% (8.5-13.9)	24.1% (17.7-32.3)	15.3% (11.1-20.9)	23.1% (14.1-36.6)
Delayed wound healing	0%	2.1% (0.7-6.3)	0%	1.7% (0.2-11.3)
Dog ear scars from mastectomy	0%	0%	1.6% (0.6-4.3)	3.4% (0.9-12.8)
Granuloma	0%	2.4% (0.8-7.4)	0%	5.0% (1.6-14.7)
Hematoma	2.9% (1.8-4.8)	2.8% (1.1-7.2)	1.3% (0.4-3.9)	3.4% (0.9-13.0)
Implant extrusion	0%	1.4% (0.4-5.5)	1.2% (0.4-3.7)	1.7% (0.2-11.3)
Implant malposition	0%	2.5% (0.8-7.9)	2.6% (1.2-5.8)	6.7% (2.6-16.9)
Implant removal with or without replacement	7.3% (5.3-9.9)	21.1% (15.0-29.2)	23.3% (18.2-29.4)	29.0% (19.1-42.5)
Implant rupture **	13.6% (7.6-23.6)	15.5% (6.5-34.6)	14.0% (7.6-25.0)	21.3% (7.3-53.3)
Infection	1.6% (0.9-3.1)	1.4% (0.4-5.5)	6.2% (3.8-10.2)	0%
Inflammation of breast	0%	1.4% (0.4-5.5)	0%	1.7% (0.2-11.4)
Lactation difficulties	2.0% (1.1-3.8)	1.6% (0.4-6.1)	0%	0%

Table 4 (continued).

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Metastatic disease	0%	0%	5.7% (3.3-9.6)	4.0% (1.0-15.2)
Miscarriage	2.9% (1.8-4.8)	2.5% (0.8-7.6)	2.3% (1.0-5.6)	0%
New diagnosis of breast cancer	0%	1.8% (0.5-7.2)	1.9% (0.7-5.1)	1.7% (0.2-11.4)
New diagnosis of rheumatic disease	1.8% (1.0-3.5)	1.7% (0.4-6.5)	2.6% (1.1-6.2)	3.4% (0.9-12.9)
Nipple complications	0%	0%	1.3% (0.4-4.1)	0%
Nipple sensation changes	11.8% (9.3-14.8)	14.6% (9.7-21.8)	2.1% (0.9-5.0)	1.7% (0.2-11.3)
Pre-eclampsia at 36 weeks pregnant	0%	1.1% (0.2-7.4)	0%	0%
Reoperation	20.1% (17.0-23.8)	37.8% (30.2-46.6)	38.8% (32.9-45.5)	40.8% (29.5-54.5)
Seroma	1.1% (0.5-2.5)	2.1% (0.7-6.3)	4.8% (2.8-8.4)	1.7% (0.2-11.3)

* The number of patients evaluated at the 10 year follow-up were: 291 (primary augmentation), 77 (revision augmentation), 151 (primary reconstruction), and 36 (revision reconstruction).

** Rupture rates were estimated in MRI cohort at 8 years post-implantation.

TABLE 5. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 10-year follow-up for the Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Allergan	
Complication or Outcome by Study Cohort	4-year FU Rate (%)	10-year FU Rate (%)
Capsular Contracture		
Primary Augmentation	13.2 (10.0-16.3)	19.1 (15.6-23.3)
Revision Augmentation	17.0 (10.7-23.4)	27.5 (20.3-36.6)
Primary Reconstruction	14.1 (7.0-21.2)	24.6 (16.2-36.2)
Revision Reconstruction	6.7 (0.2-31.9)	6.7 (0.2-31.9)
Reoperation		
Primary Augmentation	23.5 (19.5-27.5)	36.1 (31.6-40.9)
Revision Augmentation	35.3 (27.3-43.4)	46.0 (38.0-54.9)
Primary Reconstruction	40.9 (31.0-50.8)	71.9 (61.5-81.4)
Revision Reconstruction	33.3 (11.8-61.6)	46.7 (21.3-73.4)
Removal		
Primary Augmentation	9.6 (6.8-12.4)	20.8 (17.2-25.2)
Revision Augmentation	13.3 (7.6-19.0)	32.4 (25.0-41.3)
Primary Reconstruction	24.8 (15.9-33.6)	53.8 (43.65.3)
Revision Reconstruction	0	20.0 (4.3-48.1)

TABLE 6. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 8-year follow-up for the Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Mentor	
Complication or Outcome by Study Cohort	3-year FU Rate (%)	8-year FU Rate (%)
Capsular Contracture		
Primary Augmentation	8.1 (5.8-10.4)	10.9 (8.5-13.9)
Revision Augmentation	18.9 (12.5-25.4)	24.1 (17.7-32.3)
Primary Reconstruction	8.3 (4.7-11.9)	15.3 (11.1-20.9)
Revision Reconstruction	16.3 (5.0-27.6)	23.1 (14.1-36.6)
Reoperation		
Primary Augmentation	15.4 (12.3-18.4)	20.1 (17.0-23.8)
Revision Augmentation	28.0 (20.4-35.6)	37.8 (30.2-46.6)
Primary Reconstruction	27.0 (21.4-32.6)	38.8 (32.9-45.5)
Revision Reconstruction	29.1 (17.4-40.7)	40.8 (29.5-54.5)
Removal		
Primary Augmentation	4.9 (3.1-6.7)	7.3 (5.3-9.9)
Revision Augmentation	13.4 (7.5-19.3)	21.1 (15.0-29.2)
Primary Reconstruction	12.7 (8.5-16.9)	23.3 (18.2-29.4)
Revision Reconstruction	13.7 (4.9-22.6)	29.0 (19.1-42.5)

TABLE 7. Primary reasons for implant removal for Allergan Natrelle silicone gel-filled breast implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=156*)	Revision Augmentation (N=78*)	Primary Reconstruction (N=56*)	Revision Reconstruction (N=3*)
Asymmetry	7 (4.5%)	1 (1.3%)	12 (21.4%)	2 (66.7%)
Breast cancer mass	2 (1.3%)	2 (2.6%)	0	0
Breast pain	5 (3.2%)	1 (1.3%)	0	0
Breast tissue contour Deformity	1 (0.6%)	0	0	0
Capsular contracture	50 (32.1%)	28 (35.9%)	10 (17.9%)	1 (33.3%)
Hematoma/seroma	0	0	1 (1.8%)	0
Implant extrusion	1 (0.6%)	1 (1.3%)	1 (1.8%)	0
Implant malposition	11 (7.1%)	14 (18.0%)	11 (19.6%)	0
Implant rupture	27 (17.3%)	6 (7.7%)	15 (26.8%)	0
Infection	2 (1.3%)	2 (2.6%)	0	0
Necrosis	0	0	1 (1.8%)	0
Need for biopsy	1 (0.6%)	0	0	0
Patient request for style/size change	31 (19.9%)	11 (14.1%)	4 (7.1%)	0
Ptosis	12 (7.7%)	6 (7.7%)	0	0
Scarring	0	2 (2.6%)	0	0
Wrinkling/rippling	6 (3.9%)	2 (2.6%)	1 (1.8%)	0

* Total number of implant removals in each cohort.

TABLE 8. Primary reasons for implant removal for Mentor MemoryGel silicone gel-filled breast implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=68*)	Revision Augmentation (N=51*)	Primary Reconstruction (N=74*)	Revision Reconstruction (N=2*)
Asymmetry	1 (1.5%)	2 (3.9%)	15 (20.3%)	3 (13.6%)
Breast pain	3 (4.4%)	0	2 (2.7%)	1 (4.5%)
Capsular contracture (Baker II/III/IV)	13 (19.1%)	15 (29.4%)	11 (14.9%)	5 (22.7%)
Hematoma	0	0	1 (1.4%)	0
Infection	2 (2.9%)	1 (2.0%)	2 (2.7%)	0
Implant Extrusion	0	1 (2.0%)	2 (2.7%)	1 (4.5%)
Implant malposition	0	0	4 (5.4%)	0
Implant rupture	3 (4.4%)	4 (7.8%)	8 (10.8%)	1 (4.5%)
Necrosis	2 (2.9%)	0	0	0
Patient request for style/size change	36 (52.9%)	18 (35.3%)	17 (23.0%)	5 (22.7%)
Ptosis	0	0	1 (1.4%)	0
Wrinkling	1 (1.5%)	0	0	1 (4.5%)
Other	7 (10.3%)	9 (17.6%)	11 (14.9%)	5 (22.7%)

* Total number of implant removals in each cohort.

TABLE 9. Primary Reasons for Reoperation for Allergan Natrelle Silicone Gel- filled Breast Implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=221**)	Revision Augmentation (N=108**)	Primary Reconstruction (N=93**)	Revision Reconstruction (N=12**)
Asymmetry	5 (2.3%)	3 (2.8%)	15 (16.1%)	2 (16.7%)
Breast cancer mass	4 (1.8%)	3 (2.8%)	3 (3.2%)	0
Breast pain	3 (1.4%)	1 (0.9%)	0	0
Breast tissue contour Deformity	0	1 (0.9%)	2 (2.2%)	0
Capsular contracture	55 (24.9%)	26 (24.1%)	12 (12.9%)	2 (16.7%)
Delayed wound healing	3 (1.4%)	2 (1.9%)	1 (1.1%)	0
Device injury -- iatrogenic or traumatic	0	1 (0.9%)	0	0
Extrusion	1 (0.5%)	1 (0.9%)	2 (2.2%)	0
Hematoma/seroma	13 (5.9%)	13 (12.0%)	8 (8.6%)	0
Implant malposition	27 (12.2%)	12 (11.1%)	15 (16.1%)	0
Implant palpability/visibility	1 (0.5%)	1 (0.9%)	0	0
Implant rupture	29 (13.1%)	7 (6.5%)	14 (15.1%)	0
Infection	2 (0.9%)	3 (2.8%)	0	0
Necrosis	1 (0.5%)	0	1 (1.1%)	0
Need for biopsy	28 (12.7%)	9 (8.3%)	8 (8.6%)	1 (8.3%)
Nipple complications	1 (0.5%)	3 (2.8%)	1 (1.1%)	5 (41.7%)
Patient request for style/size change	12 (5.4%)	3 (2.8%)	3 (3.2%)	0
Ptosis	25 (11.3%)	9 (8.3%)	4 (4.3%)	1 (8.3%)
Scarring	8 (3.6%)	7 (6.5%)	3 (3.2%)	1 (8.3%)
Wrinkling/rippling	3 (1.4%)	2 (1.9%)	1 (1.1%)	0

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 10. Primary Reasons for Reoperation for Mentor MemoryGel Silicone Gel-filled Breast Implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=146**)	Revision Augmentation (N=78**)	Primary Reconstruction (N=123**)	Revision Reconstruction (N=38**)
Asymmetry	5 (3.4%)	1 (1.3%)	20 (16.3%)	2 (5.3%)
Abnormal screening	1 (0.7%)	0	0	0
Breast cancer	0	1 (1.3%)	1 (0.8%)	0
Breast mass	13 (8.9%)	9 (11.5%)	14 (11.4%)	7 (18.4%)
Breast pain	1(0.7%)	0	2 (1.6%)	1 (2.6%)
Capsular contracture (Baker II/III/IV)	44 (30.1%)	24 (30.8%)	18 (14.6%)	5 (13.2%)
Calcification	2 (1.4%)	0	0	0
Capsular tear	1 (0.7%)	0	0	1 (2.6%)
Delayed wound healing	1 (0.7%)	5 (6.4%)	0	0
Extrusion/Necrosis	2 (1.4%)	2 (2.6%)	2 (1.6%)	1 (2.6%)
Hematoma/Seroma	12 (8.2%)	5 (6.4%)	4 (3.2%)	1 (2.6%)
Implant malposition	4 (2.7%)	1 (1.3%)	8 (6.5%)	0
Implant rupture	2 (1.4%)	4 (5.1%)	10 (8.1%)	1 (2.6%)
Infection	3 (2.1%)	1 (1.3%)	3 (2.4%)	0
Nipple complications	0	0	1 (0.8%)	0
Patient request for style/size change	20 (13.7%)	11 (14.1%)	11 (8.9%)	4 (10.5%)
Ptois	4 (2.7%)	2 (2.6%)	4 (3.3%)	3 (7.9%)
Scarring/hypertrophic scarring	16 (11.0%)	3 (3.8%)	4 (3.3%)	0
Suture complication	1 (0.7%)	0	1 (0.8%)	0
Wrinkling/rippling	1 (0.7%)	1 (1.3%)	0	1 (2.6%)

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 11. Allergan Large Post-Approval Study of Natrelle silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,342)	Saline (N=15,646)	Total Number of Participants (N=56,988)
Primary Augmentation*	29,886 (72.3%)	14,447 (92.3%)	44,333 (77.8%)
Revision Augmentation	6,033 (14.6%)	970 (6.2%)	7,003 (12.3%)
Primary Reconstruction	4,714 (11.4%)	184 (1.2%)	4,898 (8.6%)
Revision Reconstruction	709 (1.7%)	44 (0.3%)	753 (1.3%)
Missing	0	1 (<0.1%)	1 (<0.1%)

* Allergan is still in the process of examining and reporting the number of augmentation patients younger than 22 years of age. The augmentation numbers listed in this table include at least 97 women who were younger than the qualifying age for this study (22 or older).

TABLE 12. Mentor *Large Post-Approval Study* of MemoryGel silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,975)	Saline (N=1,030)	Total Number of Participants (N=43,005)
Primary Augmentation	26,118 (62.2%)	930 (90.3%)	27,048 (62.9%)
Revision Augmentation	8,365 (19.9%)	76 (7.4%)	8,441 (19.6%)
Primary Reconstruction	5,031 (12.0%)	13 (1.3%)	5,042 (11.7%)
Revision Reconstruction	1,757 (4.2%)	9 (0.9%)	1,766 (4.1%)
Missing	148 (0.4%)	2 (0.2%)	150 (0.3%)
Augmentation patients younger than age 22	556 (1.3%)	0 (0%)	556 (1.3%)

TABLE 13. Primary reason for explantation for Allergan Natrelle silicone gel-filled breast implants in the *Large Post-Approval Study* (by implant). Investigator reports contain numbers reported by physicians after clinical evaluation. Patient reports come from patient survey data.

Reason for Explantation	Number of Explants (Investigator Report at Year 1) (N=1310*)	Number of Explants (Patient Report at Year 1) (N=926*)	Number of Explants (Patient Report at Year 2) (N=350*)
Suspected rupture	35 (2.7%)	25 (2.3%)	15 (4.3%)
Infection	79 (6.0%)	78 (8.4%)	27 (7.7%)
Capsular contracture	128 (9.8%)	184 (19.9%)	77 (22.0%)
Implant malposition	119 (9.1%)	110 (11.9%)	48 (13.7%)
Ptosis	38 (2.9%)	69 (7.5%)	13 (3.7%)
Desire for size/style change	664 (50.7%)	299 (32.3%)	118 (33.7%)
Other	247 (18.9%)	161 (17.4%)	52 (14.9%)

* Total number of implant removals.

TABLE 14. Primary reason for explantation during 3 years after implantation for Mentor MemoryGel silicone gel-filled breast implants in the *Large Post-Approval Study*.

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
Asymmetry	21 (5.0%)	39 (13.3%)	108 (23.8%)	37 (25.5%)
Capsular contracture (Baker II/III/IV)	14 (3.3%)	16 (5.5%)	21 (4.6%)	6 (4.1%)
Capsular tear	0	0 (0.0%)	2 (0.4%)	0
Implant palpability	2 (0.5%)	1 (0.3%)	0	0
Implant removal	5 (1.2%)	7 (2.4%)	2 (0.4%)	3 (2.1%)
Implant rupture	7 (1.7%)	12 (4.1%)	2 (0.4%)	0
Lack of projection	0	6 (2.0%)	12 (2.6%)	3 (2.1%)
Position change (dissatisfaction)	3 (0.7%)	0 (0.0%)	4 (0.9%)	3 (2.1%)
Ptois	1 (0.2%)	1 (0.3%)	2 (0.4%)	0
Size change – patient request	169 (40.2%)	91 (31.1%)	92 (20.3%)	18 (12.4%)
Size change – physician assessment	5 (1.2%)	2 (0.7%)	20 (4.4%)	4 (2.8%)
Symmastia	0	0	2 (0.4%)	0
Wrinkling	2 (0.5%)	3 (1.0%)	9 (2.0%)	4 (2.8%)
Breast pain not associated with other complications	3 (0.7%)	2 (0.7%)	4 (0.9%)	2 (1.4%)
Extrusion	11 (2.6%)	14 (4.8%)	32 (7.0%)	9 (6.2%)
Necrosis	0	0	3 (0.7%)	0
Hematoma	1 (0.2%)	1 (0.3%)	0	0
Irritation/Inflammation	3 (0.7%)	0	0	0
Seroma	1 (0.2%)	7 (2.4%)	1 (0.2%)	1 (0.7%)
Infection	37 (8.8%)	23 (7.8%)	34 (8.2%)	9 (6.7%)
New diagnosis of Breast cancer	1 (0.2%)	0	2 (0.4%)	0

Table 14 (continued).

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
New diagnosis of rheumatic disease	0	0	1 (0.2%)	0
Unknown	131 (31.2%)	76 (25.9%)	113 (24.9%)	52 (35.9%)
Other	14 (3.3%)	13 (4.4%)	5 (1.1%)	1 (0.7%)

* Total number of implant removals

TABLE 15. MDR reports of patient problems (based on Patient Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Patient Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=530)
1	Surgical Procedure (generally replacement or removal)	78	15.7
2	Pain	66	12.5
3	Rash/hives/itching/burning sensation	36	6.8
4	Capsular Contracture	33	6.2
5	Therapy/non-surgical treatment	26	4.9
6	Fatigue/weakness	25	4.7
7	Arthralgia/arthritis/myalgia	22	4.2
8	Swelling/edema	22	4.2
9	Palpitations/chest pain	15	2.8
10	Scarring/numbness	14	2.8
11	Disability	9	1.7
12	Infection	9	1.7
13	Breathing difficulties	9	1.7

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 530 “Patient Problem Codes” were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 16. MDR reports of device problems (based on Device Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Device Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=239)
1	Implant removed (both to treat complications and remove at woman's request to change implant size or shape)	70	30.1
2	Rupture	62	26.0
3	Implant replaced	36	15.0
4	Device or device fragment remains in patient	24	10.1
5	Sterility/foreign material	4	1.7
6	Migration of device or device component	3	1.3
7	Implant Extrusion Displacement/Malposition of device	3	1.3

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 239 patient problem codes were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 17. PSR reports of patient problems (based on Patient Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Patient Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=26,511)
1	Surgical Procedure	7,800	29.4
2	Capsular Contraction	4983	18.8
3	Pain	2695	10.2
4	Infection	1,001	3.8
5	Breast lumps	990	3.7
6	Reynaud's phenomenon	364	1.4
8	Inflammation	341	1.3
9	Cancer, Other	331	1.2
10	No consequence to patient	313	1.2
11	Wrinkling	312	1.2
	Other	2558	9.6
	Patient condition unknown	4823	18.2

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 26,511 patient problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

At the time PSR was authorized, the agency defined the types of events that could be submitted under the PSR program and provided the silicone gel-filled breast implants manufacturers with a set of specific patient problem codes and device problem codes to be used for PSR reports. Like all coding systems, accuracy and reliability of coded information depends on the correct assignment of the codes.

TABLE 18. PSR reports of device problems (based on Device Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Device Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=12,327)
1	Device-patient incompatibility	4860	39.4
2	Rupture	4541	36.8
3	Malposition	903	7.3
4	Tears, rips, holes in devices or device material (device never implanted), out of box failure	244	3.1
5	Wrinkling or folds	288	2.3
6	Visibility or palpability	200	1.6
	Other	1157	9.4

*Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 12,327 device problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

At the time PSR was authorized, the agency defined the types of events that could be submitted under the PSR program and provided the silicone gel-filled breast implants manufacturers with a set of specific patient problem codes and device problem codes to be used for PSR reports. Like all coding systems, accuracy and reliability of coded information depends on the correct assignment of the codes.



PHA/MtH/IEA.22

13 January 1992

PHA Information Exchange Service

ALERT**MORATORIUM ON USE OF SILICONE GEL BREAST IMPLANTS**

United States of America. The Food and Drug Administration has called for a moratorium on the use of silicone gel breast implants until recently submitted information on their safety can be thoroughly reviewed by an independent advisory committee. Saline filled implants will not be affected by this action and will remain available to patients.

The new information provides evidence that silicone gel implants could possibly cause autoimmune or connective tissue disorders. Because of these safety concerns, the FDA is requesting surgeons to stop using these implants until the new evidence has been reviewed. The FDA's General and Plastic Surgery Devices Panel will meet in six weeks' time to evaluate the new data and make new recommendations on the use of these products.

Women who have already had a silicone gel implant are advised not to have the implant removed unless they are experiencing problems with it. Any woman who has symptoms that may be related to the implant should consult her doctor for advice.

Approximately one million women in the USA have breast implants, some 80 % for augmentation and some 20 % for breast reconstruction following cancer surgery.

[See also Pharmaceuticals Newsletter Nos.11/12, November/December 1991].

Reference: HHS News P92-1 dated 6 January 1992.

* * *



Human Papillomavirus (HPV) Vaccine Safety

[SAFETY INFORMATION BY VACCINE](#) | [PAGE 7 OF 18](#) | [ALL PAGES](#) ↓

KEY POINTS

- Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.
- Some HPV infections can be persistent and can progress to cancer in both women and men later in life.
- There is a vaccine that can prevent the infections that most commonly cause cancer.

Overview

[Human papillomavirus \(HPV\)](#) is spread through intimate skin-to-skin contact. HPV infections are so common that nearly all men and women will get at least one type of HPV at some time in their lives. HPV infections that do not go away can cause:

- Cervical, vaginal, and vulvar cancers (in women).
- Penile cancer (in men).
- Anal cancer.
- Cancer of the back of the throat (oropharynx).
- Genital warts.

CDC is aware of public concern about the safety of HPV vaccine. Since the vaccine's introduction in 2006, vaccine safety monitoring and studies conducted by CDC, FDA, and other organizations have documented a reassuring safety record.

Available vaccines & manufacturer package inserts

Gardasil 9 and manufacturer insert

- [Gardasil 9](#)  (human papillomavirus 9-valent vaccine, recombinant; 9vHPV) was approved by FDA for use in 2014.
- The safety of Gardasil 9 was studied in clinical trials with more than 15,000 participants before it was licensed and continues to be monitored.
- Gardasil 9 protects against 9 types of cancer-causing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

For HPV vaccine to be most effective, the series should begin prior to exposure to HPV.

Keep Reading:

[Vaccine Information Statement](#)

While only 9vHPV has been available for use in the U.S. since late 2016, safety studies of 4vHPV (Gardasil) have provided important safety information relevant for 9vHPV. Both 9vHPV and 4vHPV are manufactured using a similar process, and contain 4 of the same antigens: HPV types 6, 11, 16, and 18. The 9vHPV vaccine adds 5 additional antigens, providing protection against 9 types of cancer-causing human papillomaviruses. Studies of 2vHPV (Cervarix) have also shown a favorable safety profile. While the vaccines target different HPV types, all three HPV vaccines are similar and made from a single protein of the HPV virus.

Who should & should not get the vaccine

CDC recommends HPV vaccination for everyone through age 26 years, if not vaccinated already. Teens and young adults who start the series at ages 15 through 26 years still need three doses of HPV vaccine. Three doses are also recommended for people with certain

immunocompromising conditions ages 9 through 26 years.

Keep Reading:

[Who should & should not get the vaccine](#)

Common side effects

- Pain, redness, or swelling in the arm where the shot was given.
- Fever.
- Headache or feeling tired.
- Nausea.
- Muscle or joint pain.

When to call 911

Severe allergic reactions following vaccination are rare, but can be life threatening. If someone experiences symptoms of a severe allergic reaction, which can include hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness.

HPV vaccine is safe and effective at preventing HPV-related infections and cancers. Vaccines, like any medicine, can have side effects. Many people who get the HPV vaccine have no side effects at all. The most common side effects are usually mild, like a sore arm from the shot.

Report possible adverse events to VAERS

The Vaccine Adverse Event Reporting System (VAERS) is an early warning system, co-managed by CDC and FDA, that monitors for potential vaccine safety problems. Healthcare providers and vaccine manufacturers are required by law to report certain adverse events (any side effect or health problem after vaccination that is concerning to you, even if you are not sure if the vaccine caused the event) following vaccination to VAERS; patients and caregivers can also submit reports.

Submitting a Vaccine Adverse Event Reporting System (VAERS) Report and Using VAERS Data

Reproductive concerns

HPV vaccines and primary ovarian insufficiency (POI)

Also known as "premature menopause," [POI](#) is a condition in which a woman's ovaries stop functioning before age 40.

Fact

CDC and FDA have not found any proof that HPV vaccines cause reproductive problems in women, including POI. [\[1\]](#) [\[2\]](#) [\[3\]](#)

HPV vaccines and fertility

HPV vaccination prevents infection with the HPV types that most commonly cause cervical cancer. In some cases, women develop cervical cancer before starting or finish having children. Treatment for cervical cancer (removal of the cervix and uterus, chemotherapy, and/or radiation) can keep a woman from being able to become pregnant. Preventing cervical cancer through HPV vaccination reduces this risk.

CDC works closely with the [American Academy of Pediatrics \(AAP\)](#) and the [American Academy of Family Physicians \(AAFP\)](#) on HPV vaccination. Both organizations have information about HPV vaccine available on their websites. [Also, the American College of Obstetrics and Gynecologists \(ACOG\)](#) offers additional resources.

[AAP HPV Vaccine Tools and Resources](#)

[AAFP HPV Vaccine Summary](#)

[ACOG HPV Guidelines and Recommendations](#)

HPV vaccines and pregnancy

HPV vaccines are not approved or recommended for pregnant women. However, some pregnant women receive HPV vaccines because they don't know that they are pregnant at the time of vaccination, or otherwise receive an HPV vaccine when they shouldn't have.

Fact



CDC and vaccine manufacturers have monitored and studied HPV vaccine safety in women who received the vaccine when they were pregnant. The manufacturers for each vaccine established pregnancy registries to follow outcomes for those women who were mistakenly vaccinated. Close monitoring has not found any health concerns. [\[4\]](#) [\[5\]](#) [\[6\]](#) [\[7\]](#) If a woman receives HPV vaccine and later learns that she is pregnant, there is no reason to be alarmed.

Any woman who learns she was pregnant at the time she received an HPV vaccine is encouraged to contact the vaccine manufacturer. This will help us learn how pregnant women respond to the vaccine.

- If a pregnant woman receives a dose of Gardasil 9 no intervention is needed. If she found out she was pregnant when starting the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. She may contact Merck at 1-877-888-4231 if she has questions related to getting the vaccine while pregnant.
- Doctors previously reported Gardasil 9 vaccination during pregnancy using the [Merck Pregnancy Registries](#); the registry is now closed and reporting is no longer needed. Pregnant women who received Gardasil 9 and their physician can also report to the Vaccine Adverse Event Reporting System (VAERS).

A closer look at the safety data

HPV vaccines are safe



Findings from many vaccine safety monitoring systems and more than 160 studies have shown that HPV vaccines have a favorable safety profile—the body of scientific evidence overwhelmingly supports their safety.

Of the reports to VAERS, 6% were classified as "serious." Of the other reports to VAERS relating to HPV, about 22% of the reports were not related to health problems, but were reported for reasons such as improper vaccine storage or the vaccine being given to someone for whom it was not recommended.

Over 100 million doses of HPV vaccines were distributed in the United States from June 2006 through December 2017. To date, most of CDC's HPV vaccine safety monitoring and research has focused on Gardasil because it has accounted for the majority of HPV vaccine doses distributed in the United States. These safety efforts continue, now focusing on Gardasil 9.

Gardasil 9, Gardasil and Cervarix

- In November 2019, initial post-licensure safety monitoring of Gardasil 9 was published in *Pediatrics*. In two separate articles, analyses from the [Vaccine Adverse Event Reporting System \(VAERS\)](#) and the [Vaccine Safety Datalink \(VSD\)](#) were presented. Both included multiple years of data, and did not identify any unexpected safety problems with Gardasil 9. These findings support the favorable safety profile that was established in pre-licensure clinical trials.
 - Analysis from VSD: The Vaccine Safety Datalink conducted near-real time surveillance from October 2015 through October 2017, looking at 11 pre-specified adverse events. During this two-year time period, nearly 840,000 doses were administered to people aged 9-26 years at six VSD sites. No new safety concerns were identified. [\[8\]](#)
 - Analysis from VAERS: Researchers reviewed 7,244 reports submitted to the Vaccine Adverse Event Reporting System following HPV vaccination from December 2014 through December 2017. Of those reports, around 97% were classified as non-serious; around 3% were considered serious. The analysis did not detect any new or unexpected safety concerns. [\[9\]](#)
- In 2014, before Gardasil 9 was licensed by the FDA, its safety was evaluated across seven studies. The safety findings from these pre-licensure studies show that Gardasil 9 has a similar safety profile to Gardasil, an earlier version of the vaccine. The main findings from these studies:
 - The most common side effect reported was pain, swelling, and redness in the arm where the shot was given.
 - These mild side effects may occur more often after Gardasil 9 vaccination than after Gardasil. Women and girls who received Gardasil 9 reported higher rates of swelling and redness where the shot was given than those who received Gardasil. Reports of swelling and redness also increased with each following dose for those receiving Gardasil 9.
- From its licensure in June 2006 through December 2017 more than 80 million doses of Gardasil were distributed in the United States. During the same period, VAERS received 36,142 U.S. reports of adverse events following Gardasil vaccination. Overall, 93% were non-serious reports; 7% have been classified as serious. Gardasil is no longer available in the United States.
 - Although rare, fainting was found to happen after HPV vaccination. In response, FDA changed Gardasil's guidance for doctors to include information about preventing falls and injuries from fainting. CDC and the Advisory Committee on Immunization Practices included this

guidance in the recommendations for HPV vaccination. Based on these recommendations, healthcare professionals should administer HPV vaccinations while the patient is seated or lying down.

- The patient should then remain seated and be observed for 15 minutes. CDC continues to remind doctors and nurses to observe this guidance and to share this information with all their patients.
- In 2014, CDC published a report analyzing health events reported to VAERS following Gardasil vaccination from June 2006 through March 2014. About 92% of the Gardasil reports were classified as non-serious. The most common adverse events reported were: [syncope](#) (fainting); dizziness; nausea; headache; fever; and injection site reactions (pain, swelling, and redness). [\[10\]](#)
- From its licensure in October 2009 through December 2017, about 720,000 doses of Cervarix were distributed in the United States. During the same period, there have been 245 U.S. VAERS reports of adverse events following Cervarix vaccination. Overall, 96% were non-serious reports; 4% have been classified as serious.
 - Cervarix is no longer available in the United States.

Fainting and anaphylaxis

- Syncope (fainting) may be caused by injected vaccines, including HPV vaccines. [\[10\]](#) [\[11\]](#)
 - When fainting was found to happen after vaccination, FDA changed Gardasil’s guidance for doctors to include information about preventing falls and injuries from fainting after HPV vaccination. CDC and the Advisory Committee on Immunization Practices included this guidance in the recommendations for HPV vaccination. CDC continues to remind doctors and nurses to observe this guidance and to share this information with all their patients.
- Very rarely, any vaccine, including HPV vaccine, can cause anaphylaxis. Some people are allergic to certain ingredients in vaccines. As recommended by ACIP, people who experienced a severe allergic reaction (e.g., anaphylaxis) to a previous vaccine dose or to a vaccine component, including yeast, should not receive the HPV vaccine. [\[11\]](#)

Guillain-Barré syndrome (GBS)

- The risk of getting GBS following HPV vaccination is extremely rare. [\[12\]](#) [\[13\]](#) [\[14\]](#)

Postural orthostatic tachycardia syndrome (POTS)

- [POTS](#) [↗](#) is a condition that causes lightheadedness or fainting and a rapid increase in heartbeat upon standing.
- Ongoing safety monitoring has not detected any safety concerns related to POTS following HPV vaccination. [\[14\]](#) [\[15\]](#)
- The [Vaccine Safety Datalink \(VSD\)](#) is currently conducting a study to describe POTS among 9 to 30 year-olds who received any adolescent vaccination.

Complex Regional Pain Syndrome (CRPS)

- CRPS is a rare condition of persistent pain that usually affects arms, legs, hands, or feet after an injury or trauma to that limb.
- Evidence does not support a causal link between HPV vaccines and CRPS. [\[16\]](#) [\[17\]](#)

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

- Chronic fatigue syndrome (ME/CFS) is a disabling and complex illness.
- The Vaccine Safety Datalink (VSD) is currently conducting a study to describe CFS among 9-36 year-olds who received any vaccination.
- Studies show no increased risk of ME/CFS among girls given HPV vaccine. [\[15\]](#)

Death

- Evidence does not suggest a causal link between Gardasil and death. [\[18\]](#)

Gardasil HPV vaccine recall (2013) FAQs

Why was there a recall of the Gardasil HPV vaccine?

On December 16, 2013 CDC was informed by Merck that the company planned to implement a voluntary recall of one lot (lot J007354) of Gardasil [Human Papillomavirus Quadrivalent (types 6, 11, 16, and 18) Vaccine, Recombinant], due to the potential for a small number of vials to contain glass particles as a result of breakage during the manufacturing process. These vials were distributed between August 20, 2013, and October 9, 2013. No other lots were affected.

If my child received one of the affected HPV vaccine vial injections, what could happen?

If a vaccine containing glass particles (tiny enough to get through a needle) is given to a patient, mild reactions routinely seen after vaccination may occur (for instance, redness or swelling at the injection site). There are multiple safety systems in this country that track and monitor vaccine

safety, including the [Vaccine Adverse Event Reporting System \(VAERS\)](#), which allows anyone to report a possible vaccine side effect (also called "adverse event"). To date, no adverse events related to this lot of HPV vaccine have been reported other than mild reactions such as redness and swelling at the injection site. It is not expected that delayed side effects will occur.

If my child received the HPV vaccine injection from this affected lot, does he or she have to be vaccinated again?

If your child received HPV vaccination from this one affected lot, he or she does NOT have to be vaccinated again. The vaccine's effectiveness is not impacted by this problem. The HPV vaccine series is given in 3 shots over 6 months. Be sure that your child gets all 3 shots for full protection.

How will I know if my child received one of the affected HPV vaccinations?

Merck is currently contacting its direct customers (doctors' offices or clinics) who have purchased or received product from the affected lot. People who have recently received an HPV vaccine, including those who received vaccine from the affected lot, do not need to take any action as a result of this recall. Because no action is necessary, CDC is not asking doctors to notify patients who have received vaccine from the affected lot. However, if you want to know if your child received a dose of vaccine from the affected lot, you can ask his or her doctor.

How do I find out more information about this voluntary recall?

Hotline information

For questions about this recall or to report any adverse events following vaccination, please contact: Merck National Service Center at 800-444-2080.



Does CDC recommend HPV vaccination?

Yes. This recall was caused by an isolated problem in the vaccine manufacturing process. HPV vaccine continues to have a strong safety record, and CDC continues to [recommend](#) that all preteen girls and boys receive three doses of this cancer-preventing vaccine at age 11 or 12 years.

How CDC monitors vaccine safety

CDC and FDA are committed to monitoring the safety of vaccines. Once vaccines are licensed or authorized by FDA for use in the United States, CDC, FDA, and other federal agencies work together to monitor them using several safety systems.

Keep Reading:

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CONTENT SOURCE:

National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)

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- HPV vaccine is not recommended for pregnant women. However, receiving HPV vaccine when pregnant is not cause for alarm. If a woman is found to be pregnant after starting the HPV vaccine series, second and/or third doses should be delayed until she is no longer pregnant. Women who are breastfeeding may get the vaccine.

**IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF NORTH CAROLINA
CHARLOTTE DIVISION
CIVIL ACTION NO. 3:22-MD-03036-KDB**

IN RE: GARDASIL PRODUCTS LIABILITY LITIGATION	)	MDL No. 3036
	)	
	)	THIS DOCUMENT RELATES TO:¹
	)	
	)	CASE NO. 3:22-CV-00117, <i>Bergin v.</i>
	)	<i>Merck & Co., Inc. et al.</i>
	)	
	)	AND
	)	
	)	CASE NO. 3:22-CV-00585, <i>America</i>
	)	<i>v. Merck & Co., Inc. et al.</i>
	)	

ORDER ON MOTION FOR PARTIAL JUDGMENT ON THE PLEADINGS

Since August 2022, this Court has been the forum for a multi-district litigation (“MDL”) in which nearly two hundred cases² asserting vaccine injury claims against Defendants Merck & Co., Inc. and Merck, Sharp & Dohme LLC (together, “Merck”) have been consolidated. (Doc. No. 2). Each Plaintiff alleges that he or she has suffered harm caused by vaccination with Gardasil, a Human Papillomavirus (“HPV”) vaccine which seeks to prevent cervical and other cancers believed to be associated with HPV.

Prior to the creation of the MDL, several motions to dismiss pursuant to Federal Rule of Civil Procedure (“Rule”) 12 were either decided or pending in cases which then became

¹ As explained further in this Order, this motion has been filed and considered by the Court as a “bellwether” motion that will be applicable to all cases (unless an exception is made for a particular case for good cause shown) to the extent that similar allegations and claims are asserted.

² At the most recent case management conference, Plaintiffs’ counsel informed the Court that the number of consolidated cases could increase by hundreds more over time.

consolidated in the MDL. All pending motions were stayed by this Court’s First Pretrial Order. However, the Court permitted Merck to file proposed “bellwether” Rule 12 motions in two cases, *Bergin v. Merck & Co., Inc. et al.*, No. 3:22-CV-00117, and *America v. Merck & Co., Inc. et al.*, No. 3:22-CV-00585. (See Doc. Nos. 35 at pp. 2-4; Doc. No. 58 at 7). In February 2023, Merck filed a Motion for Partial Judgment on the Pleadings in *Bergin* and *America* (Doc. No. 68) seeking dismissal of Plaintiffs’ alleged “design defect” and “direct warning” claims based on the argument they are preempted by the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-1, *et seq.* (the “Vaccine Act”) and their “manufacturing defect” and fraud claims for allegedly inadequate pleading. The motion has been fully briefed and the Court held oral argument on the motion on March 11, 2024.

After careful review of the motion, the parties’ briefs and exhibits and their oral arguments, the Court will **in part GRANT** and **in part DENY** the motion for the reasons described below.

I. LEGAL STANDARD

Merck moves for partial judgment on the pleadings under Federal Rule of Civil Procedure 12(c). Rule 12(c) provides that “[a]fter the pleadings are closed—but early enough not to delay trial—a party may move for judgment on the pleadings.” See *In re Bland Companies, Inc. Fair Lab. Standards Act & Wage & Hour Litig.*, 517 F. Supp. 3d 484, 492–93 (W.D.N.C. 2021) (quoting *Burbach Broad. Co. of Del. v. Elkins Radio Corp.*, 278 F.3d 401, 405–06 (4th Cir. 2002)). A motion for judgment on the pleadings is governed by the standard applicable to a motion to dismiss under Rule 12(b)(6) of the Federal Rules of Civil Procedure. *Butler v. United States*, 702 F.3d 749, 751–52 (4th Cir. 2012); *Shipp v. Goldade*, No. 5:19-CV-00085-KDB-DCK, 2020 WL 1429248, at *1 (W.D.N.C. Mar. 19, 2020).

A motion to dismiss under Federal Rule of Civil Procedure 12(b)(6) for “failure to state a claim upon which relief can be granted” tests whether the complaint is legally and factually sufficient. *See* Fed. R. Civ. P. 12(b)(6); *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009); *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007); *Coleman v. Md. Court of Appeals*, 626 F.3d 187, 190 (4th Cir. 2010), *aff’d*, 566 U.S. 30 (2012). A court need not accept a complaint’s “legal conclusions, elements of a cause of action, and bare assertions devoid of further factual enhancement.” *Nemet Chevrolet, Ltd. v. Consumeraffairs.com, Inc.*, 591 F.3d 250, 255 (4th Cir. 2009). The court, however, accepts all well-pled facts as true and draws all reasonable inferences in Plaintiff’s favor. *See Conner v. Cleveland Cty., N. Carolina*, 22 F.4th 412 (4th Cir. 2022); *E.I. du Pont de Nemours & Co. v. Kolon Indus., Inc.*, 637 F.3d 435, 440 (4th Cir. 2011). In so doing, the Court “must view the facts presented in the pleadings and the inferences to be drawn therefrom in the light most favorable to the nonmoving party.” *Pa. Nat’l Mut. Cas. Ins. Co. v. Beach Mart, Inc.*, 932 F.3d 268, 274 (4th Cir. 2019). Construing the facts in this manner, a complaint must contain “sufficient factual matter, accepted as true, to state a claim to relief that is plausible on its face.” *Pledger v. Lynch*, 5 F.4th 511, 520 (4th Cir. 2021) (quoting *Ashcroft*, 556 U.S. at 678). Thus, a motion to dismiss under Rule 12(b)(6) or Rule 12(c) determines only whether a claim is stated; “it does not resolve contests surrounding the facts, the merits of a claim, or the applicability of defenses.” *Republican Party v. Martin*, 980 F.2d 943, 952 (4th Cir. 1992).

In analyzing a Rule 12 motion, a court may consider “documents incorporated into the complaint by reference and matters of which a court may take judicial notice.” *See Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 551 U.S. 308, 322 (2007). In particular, when considering a Rule 12(c) motion, “a court may consider official public records, documents central to plaintiff’s claim,

and documents sufficiently referred to in the complaint ... so long as the authenticity of these documents is not disputed.” *Chapman v. Asbury Auto. Grp., Inc.*, No. 3:13 cv 679, 2016 WL 4706931, at *1, 2016 U.S. Dist. LEXIS 121043 (E.D. Va. Sept. 7, 2016) (quoting *Witthohn v. Fed. Ins. Co.*, 164 F. App'x 395, 396-97 (4th Cir. 2006)); *see also Goines v. Valley Cmty. Servs. Bd.*, 822 F.3d 159 (4th Cir. 2016). “[I]n the event of conflict between the bare allegations of the complaint and any attached exhibit, the exhibit prevails.” *Slater v. Bank of Am.*, No. 1:10-1091, 2012 WL 2997880 at *7, 2012 U.S. Dist. LEXIS 101687 (S.D. W. Va. June 26, 2012) (citing *Fayetteville Investors v. Commercial Builders, Inc.*, 936 F.2d 1462, 1465 (4th Cir. 1991)).

II. RELEVANT FACTS AND PROCEDURAL HISTORY

HPV is a viral infection that is passed between people through skin-to-skin contact. It is the most common sexually transmitted disease. (*See* Doc. No. 76-1 (Bergin Second Amended Complaint (“Bergin SAC”)) at ¶¶ 34-35)).³ There are numerous strains of HPV, with approximately 18 to 24 strains believed to be associated with cervical and/or anal cancer. (Bergin SAC at ¶ 37). Gardasil is a vaccine manufactured and sold by Merck approved by the Food and Drug Administration (“FDA”) as protection against cervical, vulvar, vaginal, and anal cancer and their associated precancerous lesions, as well as genital warts, caused by certain strains of HPV. (*See* Bergin SAC at ¶¶ 49-52; Doc. Nos. 68-2, 68-3 and 68-4 (Gardasil Prescribing

³ The Court notes and Plaintiffs’ counsel acknowledged at oral argument that the operative *Bergin* and *America* complaints are similar, if not identical, with respect to their general allegations and claims against Merck. For convenience, the Court will cite only to the *Bergin* SAC, except as necessary to reflect Ms. America’s allegations related to her particular circumstances.

Information).⁴ An initial formulation of Gardasil targeting four HPV strains was approved in 2006 and a second version (Gardasil 9) adding five more strains associated with cervical and anal cancer was approved in 2014. Believing it to be “safe and effective” in preventing cancer,⁵ the Centers for Disease Control recommends HPV vaccination for both girls and boys through age 26 years. (Bergin SAC at ¶¶ 50, 52, Doc. Nos. 68-7, 68-10). Currently, only Gardasil 9 is sold in the United States. (See Bergin SAC at ¶¶ 44, 46, 51, and 53).

Plaintiff Payton Bergin alleges that in June 2013 and February 2014, when she was 13 years old, she received two injected doses of Gardasil in North Carolina. (Bergin SAC at ¶¶ 344–345, 347). The vaccination was given upon her doctor’s recommendation and with her mother’s consent. (*Id.*). Plaintiff alleges that her mother agreed to her receiving the Gardasil vaccine after being exposed to direct-to-consumer marketing by Merck, including Merck’s “ubiquitous representations concerning the safety and efficacy of Gardasil.” (*Id.* at ¶¶ 345, 349, 502-516).

⁴ As noted, the Court may properly take judicial notice of and consider certain publicly available information related to Gardasil in ruling on Defendants' motion without converting it into a motion for summary judgment. See *Zak v. Chelsea Therapeutics Int'l, Ltd.*, 780 F.3d 597, 607 (4th Cir. 2015); *Stratton v. Merck & Co.*, No. CV 2:21-02211-RMG, 2021 WL 5416705, at *2 (D.S.C. Nov. 17, 2021) (considering publicly available FDA statements and Gardasil label); *Proffitt v. Bristol-Myers Squibb Co.*, No. 1:17-cv-04391, 2018 WL 3318893, at *4 & n.1 (S.D.W. Va. July 5, 2018) (considering alleged defective medication's label on motion for judgment on the pleadings); *Mills v. Bristol-Myers Squibb Co.*, No. CV 11-968-PHX-FJM, 2011 WL 3566131, *3 n.2 (D. Ariz. Aug. 12, 2011) (“We may consider the Plavix label attached as an exhibit to defendants' motion to dismiss ... because it is a matter of public record.”).

⁵ To be clear, for purposes of this motion the Court does not rely on the FDA’s statements concerning the safety and efficacy of Gardasil, which are disputed by Plaintiffs, beyond the existence of the statements and the notice thereby provided to medical providers and the public.

With respect to her injuries, Ms. Bergin alleges that prior to receiving her Gardasil injections, she had no known autoimmune diseases, and no autonomic issues. (*Id.* at ¶ 346). However, following her two Gardasil vaccinations, Ms. Bergin says that she experienced a series of physiological and neurological adverse events, including but not limited to mobility issues, short-term memory loss, chronic fatigue, severe headaches, tiredness, dizziness, fainting, hallucinations, chronic joint pain, amnesic spells, and encephalopathy. (*Id.* at ¶¶ 350-403). Thus, she alleges that Gardasil caused a wide variety of “autoimmune, autonomic, and neurological[] injuries” including “hypersomnia, orthostatic intolerance, autonomic dysfunction, and postural orthostatic tachycardia syndrome (“POTS”)” (*Id.* at ¶ 405).⁶

As required by the Vaccine Act,⁷ Ms. Bergin filed a petition for compensation in the United States Court of Federal Claims related to her alleged injuries, but her claim was later dismissed at her request. (*See* Bergin SAC ¶ 408; *see also* *Bergin v. Sec’y of Health & Hum. Servs.*, No. 17- 241V, 2020 WL 5800718, at *3 (Fed. Cl. Sp. Mstr. Sept. 1, 2020)). She filed her case against Merck in this Court on March 18, 2022.

Plaintiff Ashley America alleges that in October 2014 and April 2015, when she was 18 years old, she received two injected doses of Gardasil in New York. (Doc. No. 76-2 (America

⁶ More broadly, Plaintiffs contend there is a significant body of medical literature that shows Gardasil can cause serious autoimmune and neurological injuries and adverse symptoms similar to those Bergin and America allege they have suffered, a causal link which Merck (and the FDA) deny and is currently the subject of extensive discovery among the parties. *See* Doc. Nos. 76 at fn.1., 68 at 4-5; 68-17 “FDA Information on Gardasil – Presence of DNA Fragments Expected, No Safety Risk”.

⁷ Pursuant to the Vaccine Act, no one may bring “a civil action for damages” against a vaccine manufacturer “for damages arising from a vaccine-related injury” unless she has first filed and exhausted a petition for compensation in the U.S. Court of Federal Claims. *See* 42 U.S.C. § 300aa-11(a)(2)(A).

Amended Complaint (“America AC”) at ¶¶343-345)). She asserts that in obtaining her consent, her doctor informed her Gardasil was a safe and effective vaccine for preventing cervical cancer, which she claims mirrored statements Merck made through its physician and consumer marketing and advertising. (*Id.* ¶¶ 345 & 440-442). With respect to alleged injuries caused by her vaccination, she claims that she experienced various adverse events, including chronic syncope (fainting), chronic dizziness, headaches, and concentration issues. She attributes “various medical conditions” to Gardasil, including “symptoms of POTS,” “non- epileptic seizures, related to autoimmune dysregulation, and neurocardiogenic syncope related to dysregulation of the autonomic nervous system.” (*Id.* ¶¶ 345-351).

Ms. America filed a petition in the U.S. Court of Federal Claims pursuant to the Vaccine Act and, following that court’s ruling, elected to pursue her claims in civil court. (*See id.* ¶ 356; *see also America v. Sec’y of Health & Hum. Servs.*, No. 17-542V, 2022 WL 278151, at *35 (Fed. Cl. Sp. Mstr. Jan. 4, 2022)). On October 10, 2022, Plaintiff filed her case against Merck in the U.S. District Court for the Northern District of New York, which was transferred to this Court on October 26, 2022.

III. DISCUSSION

A. The Scope of the Issues Before the Court and Relevant Authority

As discussed below, this Order resolves various issues concerning Plaintiffs’ alleged claims related to “design defects” in the Gardasil vaccine, the scope of Plaintiffs’ “failure to warn” claims, and the sufficiency of Plaintiffs’ “manufacturing defect” and fraud claims. However, it is also important to clarify the issues that are not before the Court in this motion. All the Plaintiffs in the MDL, including Plaintiffs Bergin and America, allege that they were injured as a result of

receiving the Gardasil vaccine. The most fundamental liability merits issue raised by their claims is the medical/scientific question of whether the Plaintiffs' various alleged injuries were caused by their Gardasil injections. This causation issue is not now before the Court, and the Court expresses no view at this time as to that question.

Second, with respect to Plaintiffs' claims that Merck is liable for failure to properly warn Plaintiffs' prescribing doctors (which are being permitted to proceed), Merck contends that such claims are impliedly preempted by the FDA's approval of the vaccine's "label," which limits how Merck can warn doctors without additional FDA approval – unless Merck has "newly acquired information" as defined in the relevant regulations. *See* 21 C.F.R. § 601.12(f)(2)(i). As with "causation," these issues of "implied preemption" / "newly acquired information" are hotly contested, not yet before the Court, and the Court expresses no view as to their merits by this Order. Rather, the Parties and the Court expect both causation and implied preemption issues to be addressed in summary judgment motions later this year.⁸

Also, further clarification is important with respect to how this Order will be applied to the MDL consolidated cases beyond *Bergin* and *America*. It has been the Court's belief that Merck's Rule 12 motion would, as requested by Merck (and opposed by Plaintiffs), be considered as a "bellwether" motion that would resolve the questions presented as to similar allegations and claims made throughout the consolidated cases. However, the Court has not yet been explicit about that expectation. It will do so now.

⁸ There are other issues that may become relevant to later proceedings, such as the issue of Vaccine Court exhaustion mentioned above, that are not at issue in this motion.

The Court has the authority to apply the ruling here to other consolidated cases, *see* Manual of Complex Litigation § 22.632, and finds that it is both fair and efficient to do so in these circumstances. It would be wasteful and contrary to the spirit of the MDL to require Merck to move to dismiss essentially the same pleadings in every case. Plaintiffs have had the opportunity to express their view that Rule 12 motions were unnecessary and “objected” to the “characterization” of Merck’s motion as a “bellwether” motion. *See* Doc. No. 40 at 3. And, since the Court’s scheduling of the motion (implicitly overruling the objection), no plaintiff has disavowed Plaintiffs Bergin and America’s response, which of course has been prepared by the same counsel they share with those plaintiffs. Therefore, the Court’s ruling here will apply to all substantially similar allegations/claims asserted in the cases subject to the MDL.⁹

Finally, the Court notes that while it has taken an entirely fresh look at the relevant issues and considered Merck’s motion *de novo*, it does not write on a blank slate. Prior to transfer, at least four federal district courts and two California trial courts issued written decisions on motions to dismiss Gardasil complaints. *See Flores v. Merck & Co.*, No. 3:21-CV-00166, 2022 WL 798374, at *3–9 (D. Nev. Mar. 16, 2022); *Herlth v. Merck & Co.*, No. 3:21- CV-438, 2022 WL 788669, at *5–10 (D. Conn. Mar. 15, 2022); *Colbath v. Merck & Co., Inc., et al.*, No. 3:21-cv-120-W, 2022 WL 935195 (S.D. Cal. Mar. 29, 2022); *Stratton v. Merck & Co., Inc., et al.*, 2021 WL 5416705

⁹ Nevertheless, prior to applying the result here to all current and future MDL cases, the Court will allow any party who wants to move to avoid the application of this ruling to her or his claims to do so within 30 days of this Order (or within 30 days of joining the MDL, whichever comes later). In the absence of the granting of such a motion upon a showing of good cause (not to include simply disagreeing with the Court’s ruling or a plaintiff having asserted allegations or claims that are only immaterially different), the Court’s ruling here will apply to all substantially similar allegations/claims asserted in the cases subject to the MDL.

(D.S.C. Nov. 17, 2021); *Shain v. Merck*, Case No. 21STCV35340 (CA Superior Court, Los Angeles County) (August 4, 2022); *Brunker v. Merck*, Case No. 56-2022-00563045 (CA Superior Court, Ventura County) (September 26, 2022). Each of the federal cases granted Merck’s motion to dismiss, at least in part, but the state courts both denied Merck’s “demurrer” under California state procedure. As cited and discussed below, the Court generally finds the collective view of these federal judges from across the country to be persuasive.

However, the different standard applicable to motions to dismiss (“demurrers”) under California law undermines the applicability of those decisions here. Unlike Rule 12 motions under the Federal Rules of Civil Procedure, in California “a general demurrer cannot be sustained as to a portion of a cause of action.” *Brunker*, Doc. No. 76-3, at p.2 (citing *Daniels v. Select Portfolio Servicing Inc.*, 246 Cal.App.4th 1150, 1167 (2016)); *Shain*, Doc. No. 76-4 at 10 (“Ordinarily, a general demurrer does not lie as to a portion of a cause of action and if any part of a cause of action is properly pleaded, the demurrer will be overruled.”).¹⁰ Thus, for example, the California courts were required to reject Merck’s arguments that a Plaintiff’s negligence claim contained preempted “design defect” claims – regardless of the merits of that argument – if the cause of action also included a permissible “failure to warn” allegation. Accordingly, in light of this fundamentally different standard of review, although the state court decisions have been considered, the Court has given them substantially less weight.

¹⁰ Moreover, the Court’s opinion in *Shain* is stated only to be a “tentative ruling,” and the Court could not find any indication on the docket that a “final” ruling has been entered.

B. The Vaccine Act

There is no dispute among the Parties that Gardasil is a childhood vaccine covered by the Vaccine Act. As explained by the Supreme Court in *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 228–30 (2011), Congress enacted the Vaccine Act to “[t]o stabilize the vaccine market and facilitate compensation” to putative plaintiffs by establishing a no-fault compensation program “designed to work faster and with greater ease than the civil tort system.” *Shalala v. Whitecotton*, 514 U.S. 268, 269 (1995). The program allows a person injured by a vaccine, or her legal guardian, to file a petition for compensation against the Secretary of Health and Human Services in the United States Court of Federal Claims, where a special master makes an informal adjudication of the petition, subject to objections reviewed by that court. *See* 42 U.S.C. § 300aa–11, 12.

More specifically, claimants who show that an injury listed in a “Vaccine Injury Table” (which lists compensable adverse side effects of approved vaccines) are *prima facie* entitled to compensation without any showing of causation. A claimant may also recover for unlisted side effects, and for listed side effects that occur at times other than those specified in the Table, but for those the claimant must prove causation. Unlike in tort suits, claimants under the Act are not required to show that the administered vaccine was defectively manufactured, labeled, or designed. Successful claimants receive compensation for medical, rehabilitation, counseling, special education, and vocational training expenses; diminished earning capacity; pain and suffering; and \$250,000 for vaccine-related deaths. Attorney's fees are provided, not only for successful cases, but even for unsuccessful claims that are not frivolous. If the claimant is satisfied with the court’s judgment she can accept it; if not, she can file a tort action against the vaccine manufacturer.

Payments to successful claimants are made from a fund created by an excise tax on each vaccine dose. *See generally, Bruesewitz*, 562 U.S. at 228-229.

Most significant to the pending motion, the “*quid pro quo*” for this no-fault compensation system funded by vaccine manufacturers, is “the provision of significant tort-liability protections for vaccine manufacturers,” which was “designed to stabilize the vaccine market.”¹¹ *Bruesewitz*, 562 U.S. at 229. Several provisions of the Act are relevant here:

(b) Unavoidable adverse side effects; warnings

(1) No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings.

(2) For purposes of paragraph (1), a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with all requirements under the Federal Food, Drug, and Cosmetic Act and section 262 of this title (including regulations issued under such provisions) applicable to the vaccine and related to vaccine-related injury or death for which the civil action was brought unless the plaintiff shows—

(A) that the manufacturer engaged in the conduct set forth in subparagraph (A) or (B) of section 300aa-23(d)(2) of this title, or

(B) by clear and convincing evidence that the manufacturer failed to exercise due care notwithstanding its compliance with such Act and section (and regulations issued under such provisions).

(c) Direct warnings

¹¹ Congress’ concerns about the stability of the vaccine market centered around vaccines against diphtheria, tetanus, and pertussis (“DTP”), which were blamed for children’s disabilities and developmental delays. This led to a massive increase in vaccine-related tort litigation, which destabilized the DTP vaccine market, causing two of the three domestic manufacturers to withdraw and left the remaining manufacturer with potential tort liability that exceeded its annual sales by a factor of 200. *See Bruesewitz*, 562 U.S. at 227.

No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, solely due to the manufacturer's failure to provide direct warnings to the injured party (or the injured party's legal representative) of the potential dangers resulting from the administration of the vaccine manufactured by the manufacturer.

42 U.S.C. § 300aa–22.

Therefore, pursuant to the Act, 1) all design-defect claims against vaccine manufacturers brought by plaintiffs who seek compensation for injury or death caused by vaccine side effects are preempted, *Bruesewitz*, 562 U.S. at 243, and 2) claims alleging liability for failure to properly warn injured plaintiffs or their parents are expressly barred. *See Stratton*, 2021 WL 5416705, at *5; *Flores*, 2022 WL 798374 at *4; *Colbath*, 2022 WL 935195 at *3; *G.M. v. Sanofi Pasteur Inc.*, No. CV 14-9549 FMO (ASX), 2016 WL 7638186, at *4 (C.D. Cal. Mar. 22, 2016) (“To the extent plaintiff alleges that defendant failed to warn her or the public of the risks that the Fluzone vaccine could cause transverse myelitis, such claims are expressly preempted by the Vaccine Act.”).

The Court will discuss how the Vaccine Act (and relevant state law) relates to Plaintiffs’ claims below.

C. The *Bergin* and *America* Complaints

Spanning more than 120 pages and nearly 550 paragraphs, many with multiple subparagraphs, the Bergin SAC asserts claims under North Carolina law for negligence, gross negligence, failure to warn, manufacturing defect, breach of warranty, common law fraud and unfair trade practices. The America AC is nearly as long with 97 pages and seeks to recover for negligence, strict liability for failure to warn and manufacturing defects, breach of warranty and

common law fraud under New York law. Despite this length and breadth,¹² it is challenging for the Court to discern the precise nature of Plaintiff's claims, which in many instances rely on sprawling and conclusory allegations and lump numerous theories of liability together.

For example, in their negligence claims, both Ms. Bergin and Ms. America allege that Merck breached its duties of care in the "research, development, manufacturing, testing, marketing, supply, promotion, advertisement, packaging, labeling, sale, and distribution of Gardasil." Bergin SAC at ¶ 419; America AC at ¶ 368. Indeed, Plaintiffs could just as well have said, "in every manner possible." Accordingly, the Court has attempted to summarize and categorize Plaintiff's more specific allegations with respect to the various issues raised by this motion both to decide the merits of the motion and to give the Parties guidance moving forward as to the scope of the claims that the Court finds may continue.

D. "Design Defect" Claims

Merck's first attack on Plaintiffs' claims is that they reflect, in part, "design defect" claims preempted by the Vaccine Act. *See Bruesewitz*, 562 U.S. at 243. In response, Plaintiffs do not dispute that "design defect" claims are preempted, but rather deny that the complaints make any such claims. While Plaintiffs are correct that the *Bergin* and *America* complaints do not explicitly refer to, and in fact affirmatively disclaim, any "design defect" claims (and told the Court at oral argument that they carefully scrubbed the word "design" from the complaints in response to Merck's earlier successful motions to dismiss), the Court must look at the true nature of the

¹² Other courts have criticized similar Gardasil complaints as "lengthy, difficult to follow, and replete with run-on sentences," while making claims "in blunderbuss fashion." *See Flores*, 2022 WL 798374 at *4; *Herlth*, 2022 WL 788669 at *6.

allegations, not just how Plaintiffs have self-described their claims. *See* Bergin SAC at ¶ 467 (“This is not a design defect claim.”). Viewing the complaints through that substantive lens, it is clear that Plaintiff have asserted a number of preempted “design defect” claims within their “negligence” and “manufacturing defect” causes of action.

1. Gardasil’s Ingredients

Plaintiffs allege that Merck includes numerous “dangerous” ingredients in Gardasil, including HPV LI-DNA fragments, sodium borate (borax), polysorbate 80 and yeast. *See, e.g.*, Bergin SAC at ¶¶ 136-162, 422(u); 469-470 (Gardasil vaccine is “defective and unreasonably dangerous” because it contains “dangerous and undisclosed” “ingredients and toxins”). The FDA is aware of all these components in Gardasil;¹³ therefore, an attack on the ingredients of Gardasil is an attack on the design of Gardasil itself. *See Stratton*, 2021 WL 5416705, at *2. In other words, in challenging what is included in Gardasil – the Gardasil “recipe” – Plaintiffs are simply complaining about how Gardasil is designed. Therefore, such claims are preempted by the Vaccine Act.

2. Gardasil’s Development (Including Clinical Trials)

A second set of “design defect” allegations included in Plaintiffs’ negligence claims is that Merck failed to properly “develop” the Gardasil vaccine, including inadequate or negligently designed clinical trials. *See, e.g.*, Bergin SAC at ¶¶ 422 (a), (c), (d), (e), (f), (g), (h), (i), and (j). As with their challenge to Gardasil’s ingredients, Plaintiffs’ allegations that Gardasil – as a complete

¹³ Plaintiffs’ allegations that these ingredients were not disclosed is contradicted by publicly available documents that show the FDA is aware of the presence of such substances. Doc. Nos. 68-17 (“FDA Information on Gardasil – Presence of DNA Fragments Expected, No Safety Risk”); 68-4 (Gardasil Prescribing Information) (listing other ingredients).

product – was improperly developed is in substance a claim that the vaccine is defectively designed.

This “design defect” claim includes Plaintiffs’ attacks on Merck’s clinical trials. An allegation of “inadequate testing” is not an independent wrong; that is, it is not harmful in and of itself, but rather it allegedly leads to a failure to include the best/safest ingredients in the vaccine.¹⁴ As such, it relates to the design of the vaccine. Plaintiffs suggest that “inadequate” testing is part of its “failure to warn” claim. To be sure, a failure to warn doctors about risks discovered in clinical trials (like risks discovered post approval) could be the subject of a negligence claim not prohibited by the Vaccine Act. *See* § 300aa-22(b)(2)(B).¹⁵ However, claims that Merck simply did not do “enough testing” or did the “wrong kind of testing” yet a vaccine was still approved is an attack on the design of the approved vaccine, not a failure to warn claim.

In sum, Plaintiffs’ claims that Merck was negligent in its “development” of the vaccine, including claims related to clinical trials, are design defect claims barred by the Vaccine Act.

3. Gardasil’s Overall Safety and Efficacy

Finally, Plaintiffs include several allegations in their negligence claims to the effect that Merck is liable for failing to adequately disclose the “lack of efficacy and risk of serious harm” and failure to use care in the “research, manufacturing, labeling, development, etc.” of Gardasil “so as to avoid the risk of serious harm.” *See, e.g.,* Bergin SAC at ¶¶ 414, 422 (b) and (k). As with

¹⁴ To the extent Plaintiffs are claiming that Merck committed a fraud on the FDA, such state law claims are preempted. *See Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 348 (2001) (holding that plaintiffs’ state-law fraud-on-the-FDA claims conflicted with, and are therefore impliedly pre-empted by, federal law).

¹⁵ Again, any duty to warn medical providers may be limited by the “implied preemption” defense discussed earlier and not at issue in this motion.

their allegations related to ingredients and development, Plaintiffs' broad claims that Gardasil is not "safe and effective" is effectively an allegation that the entire design of the vaccine is defective. Therefore, such claims are prohibited by the Vaccine Act, and Merck is entitled to have them dismissed.

E. "Failure to Warn" Claims

Plaintiffs include in their negligence claims numerous allegations that Merck failed to disclose certain important information or warn "Plaintiff, Plaintiff's parent(s), Plaintiff's medical providers and the general public" about Gardasil's risks, etc. *See, e.g.*, Bergin SAC at ¶¶ 421, 422 (l)-(t), (v)-(w), 429. Under the Vaccine Act, whether or not these claims state a valid cause of action turns on the identity of the person whom Plaintiffs contend that Merck failed to properly warn. In short, Plaintiffs may pursue claims against Merck for failure to warn Plaintiffs' medical providers, but may not assert similar claims related to the failure to warn Plaintiffs, their parents or the general public.¹⁶

As discussed above, the Vaccine Act bars liability claims against vaccine manufacturers for failing to provide "direct warnings" to Plaintiffs and their legal representatives (including their parents). The Act provides that "[n]o vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury . . . solely due to the manufacturer's *failure to provide direct warnings to the injured party (or the injured party's legal representative)*." 42 U.S.C. § 300aa- 22(c) (emphasis added). The Vaccine Act "eliminat[es] liability for not providing

¹⁶ At oral argument, when asked to explain under what authority Plaintiffs had standing to assert claims on behalf of the "general public," Plaintiffs acknowledged that those allegations are not intended to assert a separate claim, but rather are intended only to provide support for their claim for punitive damages related to their own claims.

direct warnings to a claimant.” *Holmes v. Merck & Co., Inc.*, 697 F.3d 1080, 1083 (9th Cir. 2012); *see also, e.g., Blackmon v. Am. Home Prods. Corp.*, 328 F. Supp. 2d 659, 666 (S.D. Tex. 2004) (“the Vaccine Act clearly bars claims based on a manufacturer’s failure to provide warnings to the public or to consumers”). Accordingly, the courts in the earlier Gardasil motions dismissed similar claims based on the alleged failure to warn the Plaintiffs or their parents. *See, e.g., Flores*, 2022 WL 798374, at *4 (dismissing “the part[s] of [plaintiff’s] claim[s] that [were] premised on Merck’s failure to warn Flores and her mother” directly); *Stratton*, 2021 WL 5416705, at *5 (“The Court finds that, as to Defendants[’] alleged failure to warn Plaintiff directly, the Vaccine Act bars Plaintiff’s claim.”).¹⁷

Plaintiffs urge the Court to read the Vaccine Act’s prohibition on “direct warning” claims narrowly, arguing that the statute’s use of the word “solely” in Section 22(c) should be interpreted as allowing Plaintiffs’ “direct warning” claims to proceed because they also alleged Merck failed to give sufficient warnings to Plaintiffs’ medical providers. The Court declines the invitation to reach such an absurd result, which Plaintiffs conceded at the hearing no court considering the Vaccine Act has ever adopted. Permitting a claim for failing to warn plaintiffs or their parents that is expressly barred by the statute simply because they have similarly alleged that the vaccine manufacturer failed to adequately warn someone else – a critical exception found nowhere in the

¹⁷ Those courts also found plaintiffs’ direct warning claims barred by the learned intermediary doctrines under Nevada and South Carolina law. *Flores*, 2022 WL 798374, at *5; *Stratton*, 2021 WL 5416705, at *4. New York and North Carolina both recognize the learned intermediary doctrine—which holds that a drug manufacturer’s duty to warn is fulfilled by warning the prescribing physician, not the patient directly—and similarly bar Plaintiffs’ direct warning claims here. *See, e.g., Martin v. Hacker*, 83 N.Y.2d 1, 9, 628 N.E.2d 1308 (1993); N.C. Gen. Stat. § 99B-5(c).

statute – would as a practical matter nullify the prohibition. A better reading, consistent with the clear intent of the Act, is that the word “solely” was included just to emphasize that despite the prohibition on “direct warning” claims, a Plaintiff would still be able to assert a claim for failure to warn the medical providers to whom warnings must be given under the “learned intermediary” doctrine. Simply put, the statute “solely” (i.e. “only”) bars direct warning claims while claims for failing to provide warnings to others are permitted. Holding that the statutory prohibition on direct warning claims is nullified by a claim against medical providers, which the statute intends to allow, would thus turn the use of “solely” in the statute on its head.¹⁸

Therefore, the Court will enforce the Vaccine Act’s bar of “direct warning” claims as written and grant Merck’s motion to dismiss Plaintiffs’ claims that Merck failed to properly warn Plaintiffs and their parent(s).

F. “Manufacturing Defect” Claims

Plaintiffs assert a separate claim for “manufacturing defect” in both *Bergin* and *America*. See Bergin SAC at ¶¶ 466-479, America AC at ¶¶ 402-415. They allege generally and only “upon information and belief” that the Gardasil vaccine was “defective and unreasonably dangerous because [Merck] failed to comply with manufacturing specifications required by the governing manufacturing protocols and also required by the regulatory agencies,” claiming that

¹⁸ Plaintiffs’ additional argument that a vaccine manufacturer should not be permitted to mislead consumers, including Plaintiffs, if it chooses to advertise also must be rejected. First, Plaintiffs have cited to nothing in the Vaccine Act or relevant authority that suggests that Congress intended to eliminate the Act’s protections for vaccine manufacturers as soon as they advertise an approved childhood vaccine (which are vaccinations that public policy would presumably want to encourage through advertising). Further, other federal regulations prevent vaccine manufacturers from dishonest advertising. See 21 C.F.R. § 202.1 *et seq.*

the vaccines contained “ingredients and toxins that were not disclosed in the FDA-approved specifications and/or otherwise not disclosed in the package insert.” Bergin SAC at ¶ 469; America AC at ¶ 405.

“In manufacturing defect cases, the plaintiff proves that the product is defective by ... showing that it does not conform to the manufacturer’s specifications” for products of that type. *Singleton v. Int’l Harvester Co.*, 685 F.2d 112, 115 (4th Cir. 1981). The gravamen of the tort is not defective design but defective execution of the design. *Wankier v. Crown Equip. Corp.*, 353 F.3d 862, 867 (10th Cir. 2003); see *Stratton*, 2021 WL 5416705 at *3. Both North Carolina and New York law describe the claim similarly. See, e.g., *Boudreau v. Baughman*, 368 S.E.2d 849, 860 (N.C. 1988) (“A design defect is an injury-producing hazard accompanying normal use of a product that was intentionally manufactured according to design. A manufacturing defect, on the other hand, is caused by a miscarriage in the manufacturing process that produces an unintended result.” (citations omitted)); *Dunham v. Covidien, LP*, 498 F. Supp. 3d 549, 556 (S.D.N.Y. 2020) (“To state a claim for strict products liability under a manufacturing defect theory, a plaintiff must plead that a specific product unit was defective as a result of some mishap in the manufacturing process itself, improper workmanship, or because defective materials were used in construction, and that the defect was the cause of plaintiff’s injury.” (quotation marks omitted)).

Specifically, “the claim of selection of improper materials is a design defect claim, not a manufacturing defect claim.” *Edwards v. ATRO SpA*, 891 F. Supp. 1074, 1078 (E.D.N.C. 1995), *supplemented*, 891 F. Supp. 1085 (E.D.N.C. 1995). Thus, in the vaccine context, a

manufacturing defect claim alleges that the manufacturer did not follow the vaccine formula or recipe, with the result being a harmful and *different* version of the vaccine. Here, Plaintiffs allege that the vaccine recipe itself, not any specific instances of improper manufacturing, is the problem. *See* America AC at ¶¶ 389, 408; Bergin SAC at ¶¶ 453, 472 (Gardasil reached Plaintiffs “in its intended or reasonably foreseeable manner.”). That is, the alleged failings in the ingredients used in the manufacturing process are, according to Plaintiffs, always dangerous. Indeed, at oral argument, Plaintiff argued that “everybody” who received the Gardasil vaccine is the victim of a manufacturing defect. *See* Bergin SAC at ¶ 142 (noting the presence of challenged ingredient in “every Gardasil vial tested from all over the world.”). A claim that *all* the doses of a vaccine are inherently and unreasonably dangerous when manufactured as intended is not a “manufacturing defect” claim. Rather, it is an allegation of a “design defect,” which is barred by the Vaccine Act as discussed above.

To the extent that Plaintiffs claim that their complaints allege a departure from manufacturing specifications or the inclusion of “unintended” ingredients, those “upon information and belief” allegations are contradicted both by their pleadings, which repeatedly describe the allegedly dangerous “HPV L1-DNA fragments” as “ingredients” in Gardasil, *see* Bergin SAC at ¶¶ 137, 422(u), 471, 517(e), and by publicly available documents that show the ingredients are intended and expected. Doc. No. 68-17 (“FDA Information on Gardasil – Presence

of DNA Fragments Expected, No Safety Risk”);¹⁹ 68-4 (Gardasil Prescribing Information) (listing other ingredients).

Therefore, the Court will grant Merck’s motion to dismiss Plaintiffs manufacturing defect claims.²⁰ *See City of High Point, N. Carolina v. Suez Treatment Sols. Inc.*, 485 F. Supp. 3d 608, 631 (M.D.N.C. 2020) (dismissing claim where plaintiff offered “no allegations that the [product] contained a defect from manufacturing and no allegations concerning the manufacturing process”); *see also Stratton*, 2021 WL 5416705, at *3–4 (dismissing manufacturing defect claim); *Colbath*, 2022 WL 935195, at *5 (same); *Flores*, 2022 WL 798374, at *7 (same); *Herlth*, 2022 WL 788669, at *5–6 (same).

G. Fraud Claims

Mirroring their claims of negligence and failure to warn, Plaintiffs also assert claims against Merck for common law fraud under North Carolina and New York law. Plaintiffs allege that Merck made numerous fraudulent statements and omissions in its “ubiquitous” advertising to the public and marketing to the medical community. *See, e.g.* Bergin SAC at ¶¶ 501-502, 510. However, beyond an allegation that Ms. Bergin’s mother was “exposed to” Merck’s “One Less”

¹⁹ This publicly available FDA statement regarding the “DNA Fragments” challenged by Plaintiffs was issued in October 2011, long before Plaintiffs received their Gardasil vaccine in 2013 and 2014. Therefore, Plaintiffs cannot plausibly contend that the presence of this “ingredient” was undisclosed at the time of their vaccination.

²⁰ Plaintiffs suggest that this Court’s decision in *Lynch v. Nucor Corp.*, No. 323CV00029KDBDCK, 2023 WL 3874034, at *3–4 (W.D.N.C. June 7, 2023) supports their arguments. Not so. In *Lynch*, applying Arizona law, the Court found that Plaintiff’s allegation that the same steel sourced from the defendant performed differently in the front and the back of a “bullet proof” vest that failed, resulting in plaintiff’s death. This permitted a plausible inference that some, but not all, of the steel had been manufactured defectively. Here, Plaintiffs allege that all doses of the vaccine contained the same allegedly dangerous ingredients, manufactured in the same way.

advertising campaign, Plaintiffs do not make any specific allegations as to the who, what, when, where, and how the alleged fraud occurred.

Merck seeks to dismiss Plaintiff's fraud claims on several grounds. First, it argues that to the extent the claims allege a fraudulent failure to adequately warn Plaintiffs, their parents and the public those claims are barred by the Vaccine Act's prohibition on "direct warning" claims. The Court agrees. As discussed above, Section 22(c) of the Act broadly provides that "no manufacturer shall be liable in a civil action for damages..." for failure to warn an injured party or their legal representative. Unlike in Section 22(b)(2)(A), there is no exception for claims of "fraud" or other intentional wrongful conduct. Instead, the statute – again as part of the *quid pro quo* to stabilize the vaccine markets – provides a safe haven for manufacturers in all "civil actions" for any "direct warning" claims. Accepting Plaintiffs' arguments that intentional tort claims, which of course include the possibility of punitive damages, are not included in the statutory prohibition would significantly undermine, if not fully eliminate, the protection intended by the statute. Therefore, Plaintiffs' fraud claims will be dismissed to the extent they assert claims based on any fraud against Plaintiffs, their parents or the public.

With respect to Plaintiffs claims of fraud on medical providers, Merck argues that those claims should be dismissed because they fail to satisfy the heightened pleading requirements of Fed. R. Civ. P. 9(b) that the circumstances of fraud must be plead with particularity. "The Rule 9(b) standard requires a party to, at a minimum, describe the time, place, and contents of the false representations, as well as the identity of the person making the misrepresentation and what he obtained thereby. These facts are often referred to as the who, what, when, where, and how of the alleged fraud." *Bakery & Confectionary Union & Indus. Int'l Pension Fund v. Just Born II, Inc.*,

888 F.3d 696, 705 (4th Cir. 2018); *see Corder v. Antero Res. Corp.*, 57 F.4th 384, 401 (4th Cir. 2023). If the required specific allegations of fraud are not pled then the claim must be dismissed. *See Stratton*, 2021 WL 5416705, at *6 (dismissing Gardasil fraud claim); *see also Flores*, 2022 WL 798374, at *7 (dismissing identical fraud claim); *Herlth*, 2022 WL 788669, at *10 (same).

Plaintiffs have admittedly failed to plead the specific time, place and contents of any of Merck's allegedly fraudulent statements, especially as to medical providers. At oral argument, Plaintiffs acknowledged the absence of allegations of the circumstances of fraud in the complaints, saying that they had not spoken to Plaintiffs' doctors (who they said "didn't like to talk to Plaintiffs' lawyers"). Regardless of the reasons that Plaintiffs have failed to plead their alleged claims of fraudulent misrepresentation with particularity, their clear failure to do so dooms their claims. Accordingly, the Court will dismiss Plaintiffs' fraud claims based on fraudulent misrepresentations to "medical providers" as well as "plaintiffs, parents and the general public" for whom Plaintiffs have also not plead their fraud claims with particularity.

The remaining fraud claims asserted by Plaintiffs allege "fraudulent concealment," that is, the concealment by omission of material facts that were reasonably calculated and intended to deceive and did in fact deceive a person, resulting in damages to the injured party. *See Forbis v. Neal*, 361 N.C. 519, 527 (2007); *Azure Dolphin v. Barton*, 821 S.E.2d 711, 726-28 (N.C. 2018); *Bermuda Container Line Ltd. v. Int'l Longshoremen's Ass'n, AFL-CIO*, 192 F.3d 250, 258 (2d Cir. 1999) (discussing New York law). While the absence of *any* particularized allegations regarding Merck's alleged fraudulent concealment with respect to medical providers makes this a close decision, the Court will allow Plaintiffs' fraudulent concealment claims – which are held to a more lenient standard with respect to the pleading of particularized circumstances – to proceed at this

stage. *See Colbath*, 2022 WL 935195, at *7 (“Because this allegation concerns fraudulent concealment, Plaintiff’s failure to specify the time and place of the omissions will not bar his claim.”); *Corder*, 57 F.4th at 401 (endorsing “relaxed” Rule 9(b) standard for allegations of fraud by omission or concealment, but not eliminating the particularity requirement). Also, in practical effect, discovery on this claim will overlap with Plaintiffs’ already permitted claims that Merck failed to properly warn medical providers and the impact of the differences in proof of this claim of intentional conduct and potential damages will not arise until after Merck has an opportunity to renew its challenge at summary judgment. Accordingly, the Court will deny Merck’s motion to dismiss Plaintiffs’ claims of fraudulent concealment with respect to medical providers without prejudice.

H. Alleged “Shotgun” Claims

Merck asks the Court to dismiss all of Plaintiff’s claims as improper “shotgun” pleadings. A “shotgun pleading” is one that “fails to articulate claims with sufficient clarity to allow the defendant to frame a responsive pleading” or one in which “it is virtually impossible to know which allegations of fact are intended to support which claims for relief.” *Wilkinson v. Wells Fargo Bank, N.A.*, No. 3:19-CV-00580, 2020 WL 2542867, at *3 (W.D.N.C. May 19, 2020). As noted above, the Court questions whether the Complaint is unnecessarily long, repetitive and, in parts, vague, overly general and conclusory in its allegations and claims. Plaintiffs’ counsel candidly acknowledged his regret at the length of the Complaints, but claimed it reflected Plaintiffs’ effort to avoid an argument that their claims had not been sufficiently plead. In any event, notwithstanding the flaws in the Complaint, the Court finds that even to the extent Plaintiffs are on a fishing expedition, Merck is plainly aware of where Plaintiffs’ boat is headed and what they

are trying to catch (as evidenced by the course and detail of the MDL proceedings to date). So, the Court declines to dismiss any portion of Plaintiffs' complaints as a "shotgun pleading."

I. Leave to Amend the Plaintiffs' Complaints

To varying degrees, the earlier courts that ruled on motions to dismiss Gardasil complaints allowed Plaintiffs an opportunity to amend their complaints to replead their claims. Two years later, this MDL litigation stands in a different posture. At oral argument, Plaintiffs recognized that at this late stage of discovery it would be inefficient and likely unproductive to request additional amended pleadings and they declined to do so. The Court agrees that further amended pleading would not be constructive. Therefore, Plaintiffs are not permitted to amend their complaints in response to this Order, other than with Merck's written consent or leave of Court granted for good cause following a separate motion under Fed. R. Civ. P. 15.²¹

IV. **ORDER**

NOW THEREFORE IT IS ORDERED THAT:

1. Defendants' Motion for Partial Judgment on the Pleadings (Doc. No. 68) is **GRANTED in part** and **DENIED in part**;
2. The Court's ruling shall apply to all substantially similar allegations/claims asserted in the cases subject to the MDL; however, Parties who believe they have good cause (as discussed in the Order) to avoid the application of this ruling to her or his claims

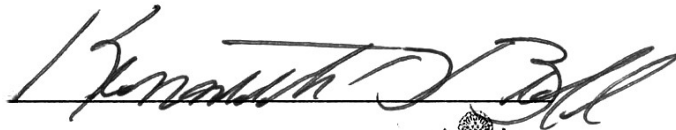
²¹ This ruling with respect to amended pleading is unrelated to the opportunity discussed above for MDL Plaintiffs other than Ms. Bergin and Ms. America to move that this ruling should not be applied to their complaints.

may, within 30 days of this Order (or within 30 days of joining the MDL, whichever comes later), file a motion seeking relief from this Order; and

3. Except as ordered here, this case shall move forward to further proceedings in accordance with the Court's current case management orders and the Parties' agreements.

SO ORDERED ADJUDGED AND DECREED.

Signed: March 20, 2024

A handwritten signature in black ink, appearing to read "Kenneth D. Bell", written over a horizontal line.

Kenneth D. Bell
United States District Judge



In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

* * * * *

JENNIFER ROBI,

Petitioner,

v.

SECRETARY OF HEALTH
AND HUMAN SERVICES,

Respondent.

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No. 13-734V

Special Master Christian J. Moran

Filed: April 15, 2015

Decision on the record; insufficient
proof of causation; human
papillomavirus (“HPV”) vaccine;
influenza (“flu”) vaccine.

Sol P. Ajalat, Ajalat & Ajalat, North Hollywood, CA, for petitioner;
Debra A. Filteau Begley, United States Dep’t of Justice, Washington, D.C., for
respondent.

UNPUBLISHED DECISION DENYING COMPENSATION¹

Jennifer Robi filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-10 through 34 (2006), on September 25, 2013. Her petition alleged that she developed an acquired demyelination neuropathy or an aggravation of existing fibromyalgia from the receipt of the human papillomavirus (“HPV”) vaccines administered to her on March 4, 2010, June 29, 2010, and January 20, 2011, and influenza (“flu”) vaccines administered on October 1, 2010, and September 12, 2011. The information in the record, however, does not show entitlement to an award under the Program.

¹ The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this ruling on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

I. Procedural History

On September 26, 2013, Ms. Robi filed medical records, as required by 42 U.S.C. § 300aa-11(c) and Vaccine Rule 2(c)(2)(A). She continued to file additional medical records periodically. During status conferences, the parties discussed the need for petitioner to obtain a report from an expert, opining that a vaccination harmed her.

A status conference was held on October 28, 2014. Ms. Robi indicated that she had consulted with a rheumatologist/ immunologist. She stated that her expert would need at least 60 days to review the relevant medical records. The undersigned prepared a list of proposed instructions for Ms. Robi's expert. The parties were ordered to file any comments to the proposed instructions in two weeks. Additionally, Ms. Robi was ordered to file a status report indicating the date she transmitted her medical records to her expert and a date of completion for the report.

In her status report filed on January 5, 2015, Ms. Robi stated that she had undergone extensive diagnostic testing with no tentative diagnosis besides fibromyalgia. A status conference was held on February 3, 2015, the parties discussed the case and Ms. Robi requested 45 days to file her motion for a ruling on the record.

On March 13, 2015, Ms. Robi filed her motion for a ruling on the record. Respondent filed her response on March 27, 2015. Accordingly, this case is now ready for adjudication.

II. Analysis

To receive compensation under the National Vaccine Injury Compensation Program (hereinafter "the Program"), Ms. Robi must prove either 1) that she suffered a "Table Injury" – i.e., an injury falling within the Vaccine Injury Table – corresponding to her vaccination, or 2) that she suffered an injury that was actually caused by a vaccine. See §§300aa-13(a)(1)(A) and 300aa-11(c)(1). An examination of the record did not uncover any evidence that Ms. Robi suffered a "Table Injury." Thus, she is necessarily pursuing a causation-in-fact claim.

Under the Act, a petitioner may not be given a Program award based solely on the petitioner's claims alone. Rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1). In

this case, because the medical records do not support Ms. Robi's claim, a medical opinion must be offered in support. Ms. Robi, however, has offered no such opinion.

Accordingly, it is clear from the record in this case that Ms. Robi has failed to demonstrate either that she suffered a "Table Injury" or that her injuries were "actually caused" by a vaccination. **Thus, this case is dismissed for insufficient proof. The Clerk shall enter judgment accordingly.**

Any questions may be directed to my law clerk, Christina Gervasi, at (202) 357-6360.

IT IS SO ORDERED.

S/Christian J. Moran
Christian J. Moran
Special Master



HPV VACCINE IS CANCER PREVENTION

HPV Vaccine Safety and Effectiveness

HPV vaccination provides safe, effective, and long-lasting protection against cancers caused by HPV.

HPV vaccination prevents cancer

Human papillomavirus (HPV) infects about 13 million people, including teens, each year. While most HPV infections go away on their own, infections that don't go away can lead to certain types of cancer. Every year, about 36,000 men and women develop a cancer caused by HPV. **HPV vaccination could prevent more than 90% of these cancers from ever developing.** The vaccine is made from one protein from the virus and is not infectious, meaning it *cannot* cause HPV infection or cancer.

HPV vaccination is safe

With more than 135 million doses distributed in the United States, HPV vaccine has a reassuring safety record that is backed by over 15 years of monitoring and research. As with all approved vaccines, CDC and FDA closely monitor the safety of HPV vaccines.

Any detected safety concerns are reported to health officials, healthcare professionals, and the public. Data continue to show that HPV vaccination is safe and effective.

HPV vaccination works

The HPV vaccine works extremely well. Since HPV vaccination was introduced over in the U.S. in 2006, infections with HPV types that cause most HPV cancers and genital warts have dropped 88 percent among teen girls. Research has also shown that fewer women are developing cervical precancers (abnormal cells on the cervix that can lead to cancer).

HPV vaccination provides long-lasting protection

Studies show that the protection provided by HPV vaccine is long lasting. People who received HPV vaccination remained protected from the virus for more than 10 years, with no evidence of the protection decreasing over time.

HPV vaccination can have side effects

Like any vaccine or medicine, HPV vaccination can have side effects. The most common side effects are mild and include pain, redness, or swelling in the arm where the shot is given; dizziness, fainting, nausea, and headache. Fainting after any vaccine, including HPV vaccine, is more common among adolescents. To prevent fainting and injuries from fainting, anyone receiving HPV vaccine should be seated or lying down during vaccination and for 15 minutes after getting the shot.

HPV vaccination doesn't negatively affect fertility

HPV vaccine does not cause fertility problems. However, not getting HPV vaccine leaves people vulnerable to HPV cancers and precancers. People who develop a cancer caused by HPV will need treatment that can sometimes limit their ability to have children, such as a hysterectomy, chemotherapy, or radiation. Treatment for cervical precancer could also put women at risk for problems with their cervix, which can sometimes cause preterm delivery.

How can I get help paying for vaccines?

The Vaccines for Children (VFC) program provides vaccines for children ages 18 years and younger, who are uninsured, Medicaid-eligible, American Indian or Alaska Native. Learn more at

www.cdc.gov/vaccines/programs/vfc/parents/qa-detailed.html

Stereotypes cannot be invoked to extend the meaning of self-identifying expression of one's own sexual orientation, and thereby become a vehicle for discrimination against homosexuals. Such stereotypes, baseless assumptions, and unsupported generalizations reflecting a discredited view of homosexuality as criminal, immoral and improper are discordant with current law and public policy. Accordingly, they cannot serve to define contemporary social mores and morality. Boy Scouts' adherence to "traditional moral values," its "belief in moral values," and its uncontroverted purpose to "encourage the moral development of its members," *ante* at 613, 734 A.2d at 1223, remain undisturbed and undeterred by Dale's open avowal of his homosexuality.

III

For the foregoing reasons, I concur in the opinion of the Court.

HANDLER, concurring in the result.

For affirmance and remandment—
Chief Justice PORITZ and Justices
HANDLER, POLLOCK, O'HERN,
GARIBALDI, STEIN, and COLEMAN—
7.

Opposed—None.



1

160 N.J. 652

**In the Matter of Dwayne C. VAUGHN,
an Attorney at Law.**

Supreme Court of New Jersey.

Aug. 6, 1999.

Prior report: 157 N.J. 160, 723 A.2d 611.

ORDER

This matter having been duly presented to the Court, it is ORDERED that **WAYNE C. VAUGHN** of **STONE MOUNTAIN, GEORGIA**, who was admitted to the bar of this State in 1981, and who was temporarily suspended from the practice of law effective March 15, 1999, by

Order of this Court dated February 11, 1999, be restored to the practice of law, effective immediately.



2

161 N.J. 1

Saray PEREZ, Cheryl Bailey, Kimberly Bartlett, Anna Cesareo and Soraya Arias, Plaintiffs—Appellants,

v.

WYETH LABORATORIES INC., a subsidiary of American Home Products Corporation; American Home Products Corporation; Wyeth—Ayerst Laboratories Division of American Home Products Corporation; Wyeth—Ayerst International Inc.; Wyeth—Ayerst Laboratories Company and Dow Corning France, S.A., Defendants—Respondents.

Supreme Court of New Jersey.

Argued March 2, 1999.

Decided Aug. 9, 1999.

Patients who had undergone surgical insertion of contraceptive capsules brought products liability action against manufacturer of drug. The Superior Court, Law Division, Middlesex County, entered summary judgment against consumers. Consumers appealed. The Superior Court, Appellate Division, 313 N.J.Super. 511, 713 A.2d 520, affirmed. Consumers petitioned for review. The Supreme Court, O'Hern, J., held that: (1) "learned intermediary" doctrine does not apply to direct marketing of prescription drugs to consumer; (2) rebuttable presumption exists that when manufacturer complies with Food and Drug Administration (FDA) advertising, labeling, and warning requirements, manufacturer has satisfied its duty to warn consumer about potentially harmful side ef-

fects of its product; and (3) when drug manufacturer has advertised₂ its drug directly to consumers, role of physician in prescribing drugs does not break the chain of causation for manufacturer's failure to warn patient of harmful side effects.

Reversed and remanded.

Pollock, J., filed dissenting opinion in which Garibaldi, J., joined.

1. Drugs and Narcotics ⇨18

"Learned intermediary" doctrine, under which manufacturer generally discharges its duty to warn ultimate user of prescription drugs by supplying physician with information about drug's dangerous propensities, does not apply to direct marketing of prescription drugs to consumers. Restatement (Third) of Torts: Products Liability § 6(d); N.J.S.A. 2A:58C-4.

2. Physicians and Surgeons ⇨15(8)

A patient must be informed of material risks, which exist when a reasonable patient, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether to forego the proposed therapy or to submit to it.

3. Drugs and Narcotics ⇨18

Pharmaceutical manufacturer generally discharges its duty to warn the ultimate users of prescription drugs by supplying physicians with information about the drug's dangerous propensities, when manufacturer simply supplies physician information about product and does not advertise directly to patient.

4. Drugs and Narcotics ⇨21

In area of direct-to-consumer advertising of pharmaceuticals, rebuttable presumption exists that when manufacturer complies with Food and Drug Administration (FDA) advertising, labeling, and warning requirements, manufacturer has satisfied its duty to 1₃ warn consumer about potentially harmful side effects of its product.

5. Drugs and Narcotics ⇨18

When drug manufacturer has advertised its drug directly to consumers, role of physician in prescribing drugs does not break the chain of causation for manufacturer's failure to warn patient of harmful side effects.

6. Negligence ⇨380, 422

A proximate cause need not be the sole cause of harm; it suffices if it is a substantial contributing factor to the harm suffered.

7. Negligence ⇨375

Proximate or legal causation is that combination of logic, common sense, justice, policy, and precedent that fixes a point in a chain of events, some foreseeable and some unforeseeable, beyond which the law will bar recovery.

8. Negligence ⇨1713

Ordinarily, issues of proximate cause are considered to be jury questions.

Richard Galex, East Brunswick, for plaintiffs-appellants (Galex, Tortoreti & Tomes, attorneys).

John W. Vardaman, a member of the District of Columbia bar, Washington, DC, for defendants-respondents (Porzio, Bromberg & Newman, attorneys; Anita R. Hotchkiss, Lauren E. Handler, Connie A. Matteo and Linda Pissott Reig, Morristown, on the brief).

John F. Brenner, Newark, submitted a brief on behalf of amicus curiae, Pharmaceutical Research and Manufacturers of America (McCarter & English, attorneys; Mr. Brenner and Jerry P. Sattin, on the brief).

The opinion of the Court was delivered by

1₄O'HERN, J.

Our medical-legal jurisprudence is based on images of health care that no longer exist. At an earlier time, medical advice

was received in the doctor's office from a physician who most likely made house calls if needed. The patient usually paid a small sum of money to the doctor. Neighborhood pharmacists compounded prescribed medicines. Without being pejorative, it is safe to say that the prevailing attitude of law and medicine was that the "doctor knows best." *Logan v. Greenwich Hosp. Ass'n*, 191 Conn. 282, 465 A.2d 294, 299 (1983).

Pharmaceutical manufacturers never advertised their products to patients, but rather directed all sales efforts at physicians. In this comforting setting, the law created an exception to the traditional duty of manufacturers to warn consumers directly of risks associated with the product as long as they warned health-care providers of those risks.

For good or ill, that has all changed. Medical services are in large measure provided by managed care organizations. Medicines are purchased in the pharmacy department of supermarkets and often paid for by third-party providers. Drug manufacturers now directly advertise products to consumers on the radio, television, the Internet, billboards on public transportation, and in magazines. For example, a recent magazine advertisement for a seasonal allergy medicine in which a person is standing in a pastoral field filled with grass and goldenrod, attests that to "TAKE [THE PRODUCT]" is to "TAKE CLEAR CONTROL." Another recent ad features a former presidential candidate, encouraging the consumer to "take a little courage" to speak with "your physician." The first ad features major side effects, encourages the reader to "talk to your doctor," and lists a brief summary of risks and contraindications on the opposite page. The second ad provides a phone number and the name of the pharmaceutical com-

pany, but does not provide the name of the drug.

The question in this case, broadly stated, is whether our law should follow these changes in the marketplace or reflect the images of the past. We believe that when mass marketing of prescription drugs seeks to influence a patient's choice of a drug, a pharmaceutical manufacturer that makes direct claims to consumers for the efficacy of its product should not be unqualifiedly relieved of a duty to provide proper warnings of the dangers or side effects of the product.

I

The Norplant System (Norplant)

This appeal concerns Norplant, a Food and Drug Administration (FDA)-approved, reversible contraceptive that prevents pregnancy for up to five years. The Norplant contraceptive employs six thin, flexible, closed capsules that contain a synthetic hormone, levonorgestrel.¹ The capsules are implanted under the skin of a woman's upper arm during an in-office surgical procedure characterized by the manufacturer as minor. A low, continuous dosage of the hormone diffuses through the capsule walls and into the bloodstream. Although the capsules are not usually visible under the skin, the outline of the fan-like pattern can be felt under the skin. Removal occurs during an in-office procedure, similar to the insertion process.

We have no doubt of the profound public interest in developing new products for reproductive services. We intend no disparagement of the product when we recite plaintiffs' claims concerning the efficacy of Norplant. The procedural posture that brings this case before us requires that we accept as true plaintiffs' version of the

1. The Norplant System was made available for marketing in the United States by Wyeth-Ayerst Laboratories (Wyeth) in 1990. The "Wyeth" defendants include Wyeth Laboratories, Inc., a subsidiary of American Home Products Corporation; American Home Products Corporation; Wyeth-Ayerst Laboratories

Division of American Home Products Corporation; Wyeth-Ayerst International Inc.; and Wyeth-Ayerst Laboratories Company. The complaint against Dow Corning France, S.A., was dismissed for lack of personal jurisdiction in January 1996.

facts. The motion to dismiss was in the nature of a motion for judgment on the pleadings.

¹⁶According to plaintiffs, Wyeth began a massive advertising campaign for Norplant in 1991, which it directed at women rather than at their doctors. Wyeth advertised on television and in women's magazines such as *Glamour*, *Mademoiselle* and *Cosmopolitan*. According to plaintiffs, none of the advertisements warned of any inherent danger posed by Norplant; rather, all praised its simplicity and convenience. None warned of side effects including pain and permanent scarring attendant to removal of the implants. Wyeth also sent a letter to physicians advising them that it was about to launch a national advertising program in magazines that the physicians' patients may read.

Plaintiffs cite several studies published in medical journals that have found Norplant removal to be difficult and painful. One study found that thirty-three percent of women had removal difficulty and forty percent experienced pain. Another study found that fifty-two percent of physicians reported complications during removal. Medical journals have catalogued the need for advanced medical technicians in addition to general surgeons for Norplant removal. Plaintiffs assert that none of this information was provided to consumers.

2. Bellwether plaintiffs are not created pursuant to any formal rule. As explained by the Fifth Circuit in *In re Chevron, U.S.A., Inc.*, 109 F.3d 1016, 1019-20 (1997):

The term bellwether is derived from the ancient practice of belling a wether (a male sheep) selected to lead his flock. The ultimate success of the wether selected to wear the bell was determined by whether the flock had confidence that the wether would not lead them astray, and so it is in the mass tort context.

The notion that the trial of some members of a large group of claimants may provide a basis for enhancing prospects of settlement or for resolving common issues or claims is a sound one that has achieved general acceptance by both bench and bar. References to bellwether trials have long been included in the Manual for Complex Litigation. See MANUAL FOR COMPLEX LITIGATION § 33.27-28 (3d ed.

In 1995, plaintiffs began to file lawsuits in several New Jersey counties claiming injuries that resulted from their use of Norplant. Plaintiffs' principal claim alleged that Wyeth, distributors of Norplant in the United States, failed to warn adequately about side effects associated with the contraceptive. Side effects complained of by plaintiffs included weight gain, headaches, dizziness, nausea, diarrhea, acne, vomiting, fatigue, facial hair growth, numbness in the arms and legs, irregular menstruation, hair loss, leg cramps, anxiety and nervousness, vision problems, anemia, mood swings and depression, high blood pressure, and removal complications that resulted in scarring.

Class action certification was denied. All New Jersey Norplant cases were consolidated in Middlesex County. Eventually, twenty-five New Jersey Norplant cases involving approximately fifty ¹⁷Norplant users were pending in the Superior Court in Middlesex County.

After a case management conference, plaintiffs' counsel sought a determination of whether the learned intermediary doctrine applied. Pursuant to that conference, five bellwether plaintiffs² were selected to challenge defendant's motion for summary judgment concerning the learned intermediary doctrine. See *Perez v.*

1995)... If a representative group of claimants are tried to verdict, the results of such trials can be beneficial for litigants who desire to settle such claims by providing information on the value of the cases as reflected by the jury verdicts. Common issues or even general liability may also be resolved....

....
[B]efore a trial court may utilize results from a bellwether trial for a purpose that extends beyond the individual cases tried, it must, prior to any extrapolation, find that the cases tried are representative of the larger group of cases or claims from which they are selected[,] ... based on competent, scientific, statistical evidence so as to permit a finding that there is a sufficient level of confidence that the results obtained reflect results that would be obtained from trials of the whole....

Wyeth Labs., Inc., 313 N.J.Super. 646, 650, 713 A.2d 588 (Law Div.1997). The trial court dismissed plaintiffs' complaints, concluding that even when a manufacturer advertises directly to the public, and a woman is influenced by the advertising campaign, "a physician is not simply relegated to the role of prescribing the drug according to the woman's wishes." *Id.* at 658, 713 A.2d 588. Consequently, the court held that the learned intermediary doctrine³ applied. *Ibid.* According to the court, the physician retains the duty to weigh the benefits and risks associated with a drug before deciding whether the drug is appropriate for the patient. *Ibid.* Because N.J.S.A. 2A:58C-4 of the Products Liability Act, N.J.S.A. 2A:58C-1 to -11, measures warning adequacy based on the knowledge and characteristics of the health-care provider, the court was not "concerned with the effect that a warning had on the . . . consumer-plaintiff." *Id.* at 659, 713 A.2d 588. The court found, however, that plaintiffs failed to provide expert testimony to rebut the statutory presumption under N.J.S.A. 2A:58C-4, that the manufacturer's warning is adequate when it has been approved by the FDA, as is the case here. The court found that plaintiffs failed to rebut the presumption by demonstrating that the manufacturer's warnings to the physicians were inadequate or that a warning as to the difficulty of removal would have altered the health-care providers' decisions to implant Norplant. *Id.* at 659-60, 713 A.2d 588. Although the trial court listed pain and scarring associated with removal among plaintiffs' complaints, *id.* at 650-52, 713 A.2d 588, when addressing proximate cause the court subsequently stated that "none of the bellwether plaintiffs complained of difficult removals or that they have significant scarring." *Id.* at 660 n. 5, 713 A.2d 588. Consequently, the court concluded that plaintiffs had failed to prove failure to warn and proximate cause, and dismissed plaintiffs' complaints. *Id.* at 660, 713 A.2d 588.

Plaintiffs appealed. Plaintiffs challenged the court's failure to hear expert testimony on the adequacy of the warnings

and the decision concerning proximate cause because "it was specifically agreed that the production of expert testimony would await the outcome of the decision on the issue of the learned intermediary doctrine." The Appellate Division affirmed the trial court's grant of summary judgment in favor of defendants and its determination that the learned intermediary doctrine applied. 313 N.J.Super. 511, 713 A.2d 520 (1998). The court supplemented the trial court's opinion, comparing Section 6d of the *Restatement (Third) of Torts: Products Liability* (1997) (*Restatement*) to N.J.S.A. 2A:58C-4,⁴ the similar provision of New Jersey's Products Liability Act. Section 6(d) of the *Restatement* provides:

(d) A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to:

- (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or
- (2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.

As noted by the Appellate Division, the new *Restatement* is similar to N.J.S.A. 2A:58C-4, which defines an adequate warning as

one that a reasonably prudent person in the same or similar circumstances would have provided with respect to the danger and that communicates adequate information on the dangers and safe use of the product, . . . in the case of prescription drugs, taking into account the characteristics of, and the ordinary knowledge common to, the prescribing physician.

The court noted that Section 6(d)(2) of the *Restatement* may require a warning when

the physician or health-care provider has a "diminished role as an evaluator or decision maker," in which case the manufacturer would have a duty to warn patients directly. 313 *N.J.Super.* at 515, 713 A.2d 520 (citing *Restatement (Third)*, § 6d comment b).³ Consequently, the court agreed with the trial court that if the warning was "legislatively deemed adequate and has been given to the proper party," no warning defect under *N.J.S.A. 2A:58C-4* had been established. *Ibid.*

We granted plaintiffs' petition for certification. 156 *N.J.* 410, 719 A.2d 642 (1998).

II

In *Feldman v. Lederle Laboratories*, 97 *N.J.* 429, 479 A.2d 374, (1984) (*Feldman I*), we considered the relationship between principles of products liability law and pharmaceutical products. In *Feldman I*, we declined to "hold as a matter of law and policy that all prescription drugs that are unsafe are unavoidably so." *Id.* at 447, 479 A.2d 374. We explained:

Drugs, like any other products, may contain defects that could have been avoided by better manufacturing or design. Whether a drug is unavoidably unsafe should be decided on a case-by-case basis; we perceive no justification for giving all prescription drug manufacturers a blanket immunity from strict liability manufacturing and design defect claims under [*Restatement (Second) Torts* § 402A] comment k [(1965)].

Moreover, even if a prescription drug were unavoidably unsafe, the comment k immunity would not eliminate strict liability for failure to provide a proper warning. As Justice Pollock stated in *O'Brien v. Muskin Corp.*, 94 *N.J.* 169, 183, 463 A.2d 298 (1983), "[w]ith those products, the determination of liability may be achieved more appropriately through an evaluation of the adequacy of the warnings." [] Thus, a manufacturer

who knows or should know of the danger or side effects of a product is not relieved of its duty to warn. Rather, as the comment expressly states, it is only the unavoidably unsafe product "accompanied by proper * * * warning" that is not defective. (Emphasis added.)

[*Ibid.* (citations omitted).]

As explained in *Niemiera by Niemiera v. Schneider*, 114 *N.J.* 550, 559, 555 A.2d 1112 (1989):

In New Jersey, as elsewhere, we accept the proposition that a pharmaceutical manufacturer generally discharges its duty to warn the ultimate user of prescription drugs by supplying physicians with information about the drug's dangerous propensities. See, e.g., *Bacardi v. Holzman*, 182 *N.J.Super.* 422, 442 A.2d 617 (App.Div.1981). This concept is known as the "learned intermediary" rule because the physician acts as the intermediary between the manufacturer and the consumer. The phrase appears to have been coined in the case of *Sterling Drug, Inc. v. Cornish*, 370 F.2d 82, 85 (8th Cir.1966).

We observed that there were circumstances, such as in *Davis v. Wyeth Laboratories, Inc.*, 399 F.2d 121 (9th Cir.1968), in which the manufacturer should not be relieved of a duty to warn. *Niemiera, supra*, 114 *N.J.* at 559, 555 A.2d 1112. In *Davis*, the manufacturer of a polio vaccine was held to have an independent duty to warn the consumer because in mass immunization clinics such as where the plaintiff received a polio vaccine, there was "no physician present to weigh the risks and benefits of the drug therapy for each patient." *Ibid.* (quoting *Reyes v. Wyeth Labs., Inc.*, 498 F.2d 1264 (5th Cir.), cert. denied, 419 U.S. 1096, 95 S.Ct. 687, 42 L.Ed.2d 688 (1974)); see also *Stephens v. G.D. Searle & Co.*, 602 F.Supp. 379

3. Although the New Jersey statute refers only to a prescribing "physician," the court assumed that other health-care providers such as dentists, optometrists, podiatrists, nurse practitioners, home health care service firms

and physician's assistants, or other professionals licensed to prescribe or administer drugs, would be included. *Perez, supra*, 313 *N.J.Super.* at 515-16, 713 A.2d 520.

(E.D.Mich.1985) (manufacturer of oral contraceptive has duty to warn consumers directly of risks and side effects); *Samuels v. American Cyanamid Co.*, 130 Misc.2d 175, 495 N.Y.S.2d 1006 (Sup.Ct.1985) (pharmaceutical company had duty to warn recipient of "travel" vaccines when company knew vaccines were ordinarily given without meaningful balancing of risks and benefits by informed intermediary).

We were satisfied in *Niemiera*, *supra*, that sufficient reasons existed with respect to the DPT vaccine (for diphtheria, pertussis and tetanus) to conclude that the "learned intermediary" doctrine should apply." *Id.* at 560, 555 A.2d 1112. The question in this appeal is whether sufficient reasons exist to warrant its application under these facts. Norplant appears to be a hybrid prescription medical device exhibiting characteristics both of a medical device implanted in the body and of a drug. For convenience, most of our discussion will use the terminology relevant to prescription drugs, the context in which most such claims may arise.

III

Direct-to-Consumer Advertising

It is paradoxical that so pedestrian a concern as male-pattern baldness should have signaled the beginning of direct-to-consumer marketing of prescription drugs. Upjohn Company became the first drug manufacturer to advertise directly to consumers when it advertised for Rogaine, a hair-loss treatment. Jon D. Hanson & Douglas A. Kysar, *Taking Behavioralism Seriously: Some Evidence of Market Manipulation*, 112 *Harv. L.Rev.* 1420, 1456 (1999). The ad targeted male consumers by posing the question, "Can an emerging bald spot . . . damage your ability to get along with others, influence your chance of obtaining a job or date or even interfere with your job performance?" *Ibid.* (footnotes omitted).¹² A related ad featured an attractive woman asserting suggestively, "I know that a man who can afford Rogaine is a man who can afford me." *Ibid.* (footnote omitted).

Advertising for Rogaine was the tip of the iceberg. Since drug manufacturers began marketing directly to consumers for products such as prescription drugs in the 1980s, "almost all pharmaceutical companies have engaged in this direct marketing practice." *Ibid.* (footnote omitted). Consider the following example:

A hot-air balloon floats lazily across the backdrop of a beautiful, cloudless, sunny sky. Cole Porter sings in the background, "Blue skies smiling at me[.] Nothing but blue skies do I see." A kind voice instructs the viewer to "see your doctor about Claritin (R)" because a "clear answer is out there." This advertisement for Claritin (R), a nondrowsy prescription antihistamine, aired prior to the . . . (FDA's) release of new direct-to-consumer (DTC) broadcast advertising guidelines in August 1997. The viewer often was bewildered because the "clear answer" about what Claritin (R) treated was not in the otherwise well-produced thirty-second television advertisement.

[Kelly N. Reeves, *Direct-to-Consumer Broadcast Advertising: Empowering the Consumer or Manipulating a Vulnerable Population?*, 53 *Food & Drug L.J.* 661, 661 (1998) (footnotes omitted).]

These campaigns "bring to 'bear all the slick pressure of which Madison Avenue is capable.'" Hanson & Kysar, *supra*, 112 *Harv. L.Rev.* at 1456 (footnote omitted).

Pressure on consumers is an integral part of drug manufacturers' marketing strategy. From 1995 to 1996, drug companies increased advertising directed to consumers by ninety percent. Bob Van Voris, *Drug Ads Could Spell Legal Trouble[.] Consumer Campaigns May Result in Greater Liability*, *Nat'l L.J.*, July 21, 1997, at B1. In 1997, advertising costs of pharmaceutical products surpassed the half-billion dollar mark for the first time, "easily outpacing promotional efforts directed to physicians." Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing*

the Regulatory and Liability Issues, 32 *Ga. L.Rev.* 141, 141 (1997) (footnote omitted). "John F. Kamp, senior vice president of the American Association of Advertising Agencies, said that prescription drug companies spent \$1.3 billion on print and broadcast advertising aimed at consumers last year, up from \$843 million in 1997...." Robert Pear, *Drug Companies Getting* ¹³*F.D.A. Reprimands for False or Misleading Advertising*, N.Y. Times, Mar. 28, 1999, at 28. These efforts are not just an essential part of manufacturers' marketing plans; they are an extremely successful one. As of December 1998, "because of its testimonials" in print and broadcast media by renowned personalities, sales of a product that treats male impotence had increased to \$788 million, with approximately 7.5 million prescriptions having been written. Jay P. Speivack, *Direct Ads May Create Liability Dangers. Consumer Advertising by Drug Manufacturers Has Reopened the Issue of Expanded Liability*, *Nat'l L.J.*, Mar. 15, 1999, at B7 n. 1.

Without vouching for every decimal point in the discussion, the following is a summary of changes in pharmaceutical marketing.

[Significant technological] advances in [medical] treatment have been accompanied by significant increases in the cost of health care. It is estimated that in 1996, Americans spent more than \$1 trillion on health care products and services. Health care is the single largest business in the United States, representing 14% of the gross domestic product. Health care expenses comprise the largest single area of non-government spending.

Corresponding with the financial burdens attendant to our modern health care system, a fundamental change has taken place in the way Americans pay for their health care [from individually-funded to third-party-funded health care].... These fundamental changes have drastically altered the delivery of health care services.

....

As [pharmaceutical] manufacturers attempt to appropriately position their products in the chain of delivery, new techniques are often employed to supplement traditional marketing efforts which have historically consisted of direct physician education, information provided in medical references, educational seminars, and research grants....

Among the most controversial of the new marketing techniques employed by pharmaceutical manufacturers is direct-to-consumer prescription advertising in a variety of formats and media. Pharmaceutical remedies for varied problems such as allergies, nail fungus, hypertension, hair loss, and depression are placed directly before the consumer in magazines, television, and via the Internet. The utilization of direct consumer marketing raises questions and issues addressing manufacturer liability for failure to adequately warn of risks possibly associated with pharmaceutical use.

¹⁴....

The American Medical Association (AMA) has long maintained a policy in opposition to product-specific prescription ads aimed at consumers. A 1992 study by the *Annals of Internal Medicine* reports that a peer review of 109 prescription ads found 92 per cent of the advertisements lacking in some manner. [Michael C. Allen, *Medicine Goes Madison Avenue: An Evaluation of the Effect of Direct-to-Consumer Pharmaceutical Advertising on the Learned Intermediary Doctrine*, 20 *Campbell L.Rev.* 113, 113-116 (1997) (footnotes omitted).]

The difficulties that accompany this [type of advertising] practice are manifest. "The marketing gimmick used by the drug manufacturer often provides the consumer with a diluted variation of the risks associated with the drug prod-

uct.” Even without such manipulation, “[t]elevision spots lasting 30 or 60 seconds are not conducive to ‘fair balance’ [in presentation of risks].” Given such constraints, pharmaceutical ads often contain warnings of a general nature. However, “[r]esearch indicates that general warnings (for example, see your doctor) in [direct-to-consumer] advertisements do not give the consumer a sufficient understanding of the risks inherent in product use.” Consumers often interpret such warnings as a “general reassurance” that their condition can be treated, rather than as a requirement that “specific vigilance” is needed to protect them from product risks.

[Hanson & Kysar, *supra*, 112 *Harv. L.Rev.* at 1456.]

IV

How Has the Law Responded to These Changes?

A. The new *Restatement (Third) of Torts* has left the issue to “developing case law.”

Parallel to the developments in drug marketing, the American Law Institute was in the process of adopting the *Restatement (Third) of Torts: Products Liability* (1997). The comment to Section 6 explains that subsection (d)(1) sets forth the traditional rule of the learned intermediary that drug and medical device manufacturers are liable for failing to warn of a drug’s risks only when the manufacturer fails to warn the health-care provider of risks attendant to a specific drug. *Restatement, supra*, § 6(d) comment a. That same comment also notes that subsection (d)(2) reflects decisional law and provides limited exceptions to the traditional rule by requiring manufacturers to warn patients in certain circumstances. *Ibid.* Because situations may exist when the health-care provider assumes a “much-diminished role as an evaluator or decisionmaker,” it is appropriate to impose a duty on the manufacturer to warn the patient directly. *Id.* at § 6d comment b. Despite the early effort to provide an exception to the doctrine

in the case of direct marketing of pharmaceuticals to consumers, the drafters left the resolution of that issue to “developing case law.” *Id.* at § 6d comment e. One commentator described the *Restatement’s* approach as a “tepid endorsement” of the learned intermediary doctrine. Charles J. Walsh et al., *The Learned Intermediary Doctrine: The Correct Prescription for Drug Labeling*, 48 *Rutgers L.Rev.* 821, 869 (1994). Thus, under the new *Restatement*, “warnings may have to be provided to a health-care provider or even to the patient,” depending on the circumstances. William A. Dreier, *The Restatement (Third) of Torts: Products Liability and the New Jersey Law—Not Quite Perfect Together*, 50 *Rutgers L.J.* 2059, 2097 (1998). This is an entirely appropriate resolution. Judge Cardozo, a shaper of both the common law and of the *Restatements* of law drafted by the American Law Institute, saw each role as complementary:

Cardozo saw the Institute as continuing his own work as a common law judge: to show that new decisions that modernized law had their roots in ancient notions of the purpose of law to accomplish justice through an ongoing reformulation of the governing rules.

[Andrew L. Kaufman, *Cardozo* 174 (1998).]

B. The New Jersey Products Liability Act does not legislate the boundaries of the learned intermediary doctrine.

As noted, the New Jersey Products Liability Act provides:

An adequate product warning or instruction is one that a reasonably prudent person in the same or similar circumstances would have provided with respect to the danger and that communicates adequate information on the dangers and safe use of the product, taking into account the characteristics of, and the ordinary knowledge common to, the persons by whom the product is intended to be used, or in the case of prescription drugs, taking into account

the characteristics of, and the ordinary knowledge common to, the prescribing physician. If the warning or instruction given in connection with a drug or device or food or food additive has been approved or prescribed by the federal Food and Drug Administration under the "Federal Food, Drug, and Cosmetic Act," 52 Stat. 1040, 21 U.S.C. § 301 *et seq.*, . . . a rebuttable presumption shall arise that the warning or instruction is adequate. . . .

[N.J.S.A. 2A:58C-4.]

¹⁶The Senate Judiciary Committee Statement that accompanied L. 1987, c. 197 recites: "The subsection contains a general definition of an adequate warning and a special definition for warnings that accompany prescription drugs, since, *in the case of prescription drugs, the warning is owed to the physician.*" See N.J.S.A. 2A:58C-1 (providing the Committee Statement) (emphasis added). At oral argument, counsel for Wyeth was candid to acknowledge that he could not "point to a sentence in the statute" that would make the learned intermediary doctrine applicable to the manufacturers' direct marketing of drugs, but rather relied on the Committee Statement. Although the statute provides a physician-based standard for determining the adequacy of the warning due to a physician, the statute does not legislate the boundaries of the doctrine. For example, the Act does not purport to repeal a holding such as *Davis v. Wyeth Labs, supra*, which required that manufacturers directly warn patients in mass inoculation cases. Rather, the statute governs the content of an "adequate product warning," when required. As noted, *supra* at 11-12, 734 A.2d at 1251, in 1987, direct-to-consumer marketing of prescription drugs was in its beginning stages. The Committee Statement observes that "the warning is owed to the physician" because drugs were then marketed to the physician. We believe that the part of the provision establishing "a presumption that a warning or instruction is adequate on drug or food products if the warning has been approved or prescribed by the Food and Drug Administra-

tion," *Committee Statement, supra*, will provide the benchmark for this decision.

Our dissenting member suggests that we should await legislative action before deciding that issue. As we explained in *Kelly v. Gwinnell*,

[t]his Court has decided many significant issues without any prior legislative study. In any event, if the Legislature differs with us on issues of this kind, it has a clear remedy. . . .

We are satisfied that our decision today is well within the competence of the judiciary. Defining the scope of tort liability has traditionally been accepted as the responsibility of the courts.

¹⁷[96 N.J. 538, 555-56, 476 A.2d 1219 (1984) (footnote and internal citations omitted).]

If we decline to resolve the question, we are making the substantive determination that the learned intermediary doctrine applies to the direct marketing of drugs, an issue recently debated but left unanswered by the drafters of the *Restatement*. Either course, then, requires us to adopt a principle of law. The question is which is the better principle.

C. Direct advertising of drugs to consumers alters the calculus of the learned intermediary doctrine.

[1] In *Reyes, supra*, the respected Judge John Minor Wisdom explained the rationale behind the learned intermediary doctrine. His perspective reflects the then-prevalent attitude about doctor-patient relationships:

This special standard for prescription drugs is an understandable exception to the Restatement's general rule that one who markets goods must warn foreseeable ultimate users of dangers inherent in [the] products. . . . Prescription drugs are likely to be complex medicines, esoteric in formula and varied in effect. As a medical expert, the prescribing physician can take into account the propensities of the drug, as well as the susceptibilities of [the] patient.

[The physician's] task [is to weigh] the benefits of any medication against its potential dangers. The choice [the physician] makes is an informed one, an individualized medical judgment bottomed on a knowledge of both patient and palliative. Pharmaceutical companies then, who must warn ultimate purchasers of dangers inherent in patent drugs sold over the counter, in selling prescription drugs are required to warn only the prescribing physician, who acts as a "learned intermediary" between manufacturer and consumer.

[498 F.2d at 1276 (footnote and citation omitted).]

A more recent review summarized the theoretical bases for the doctrine as based on four considerations.

First, courts do not wish to intrude upon the doctor-patient relationship. From this perspective, warnings that contradict information supplied by the physician will undermine the patient's trust in the physician's judgment. Second, physicians may be in a superior position to convey meaningful information to their patients, as they must do to satisfy their duty to secure informed consent. Third, drug manufacturers lack effective means to communicate directly with patients, making it necessary to rely on physicians to convey the relevant information. Unlike [over the counter products], pharmacists usually dispense prescription drugs from bulk containers rather than as unit-of-use packages in which the manufacturer may have enclosed labeling. Finally, because of the complexity of risk information about prescription drugs, comprehension problems would complicate any effort by manufacturers¹⁸ to translate physician labeling for lay patients. For this reason, even critics of the rule do not suggest that pharmaceutical companies should provide warnings only to patients and have no tort duty to warn physicians.

[Noah, *supra*, 32 Ga. L.Rev. at 157-59 (footnotes omitted).]

These premises: (1) reluctance to undermine the doctor patient-relationship; (2) absence in the era of "doctor knows best" of need for the patient's informed consent; (3) inability of drug manufacturer to communicate with patients; and (4) complexity of the subject; are all (with the possible exception of the last) absent in the direct-to-consumer advertising of prescription drugs.

First, with rare and wonderful exceptions, the "Norman Rockwell" image of the family doctor no longer exists." *Id.* at 180 n. 78 (citing Paul D. Rheingold, *The Expanding Liability of the Drug Manufacturer to the Consumer*, 40 *Food Drug Cosm. L.J.* 135, 136 (1985)). Informed consent requires a patient-based decision rather than the paternalistic approach of the 1970s. *See Largey v. Rothman*, 110 N.J. 204, 206, 540 A.2d 504 (1988) (discussing *Canterbury v. Spence*, 464 F.2d 772 (D.C.Cir.), *cert. denied*, 409 U.S. 1064, 93 S.Ct. 560, 34 L.Ed.2d 518 (1972)). The decision to take a drug is "not exclusively a matter for medical judgment." *See* Teresa Moran Schwartz, *Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule*, 46 *Food Drug Cosm. L.J.* 829, 831 (1991) (citing Margaret Gilhooley, *Learned Intermediaries, Prescription Drugs, and Patient Information*, 30 *St. Louis. U. L.J.* 633, 652 (1986)).

Second, because managed care has reduced the time allotted per patient, physicians have considerably less time to inform patients of the risks and benefits of a drug. Sheryl Gay Stolberg, *Faulty Warning Labels Add to Risk in Prescription Drugs*, N.Y. Times, June 4, 1999, at A27. "In a 1997 survey of 1,000 patients, the F.D.A. found that only one-third had received information from their doctors about the dangerous side effects of drugs they were taking." *Ibid.*

Third, having spent \$1.3 billion on advertising in 1998, *supra* at 12-13, 734 A.2d at 1251 - 52, drug manufacturers can hardly be said to "lack effective means to com-

municate directly ¹¹⁰with patients,” Noah, *supra*, 32 *Ga. L.Rev.* at 158, when their advertising campaigns can pay off in close to billions in dividends.

Consumer-directed advertising of pharmaceuticals thus belies each of the premises on which the learned intermediary doctrine rests.

First, the fact that manufacturers are advertising their drugs and devices to consumers suggests that consumers are active participants in their health care decisions, invalidating the concept that it is the doctor, not the patient, who decides whether a drug or device should be used. Second, it is illogical that requiring manufacturers to provide direct warnings to a consumer will undermine the patient-physician relationship, when, by its very nature, consumer-directed advertising encroaches on that relationship by encouraging consumers to ask for advertised products by name. Finally, consumer-directed advertising rebuts the notion that prescription drugs and devices and their potential adverse effects are too complex to be effectively communicated to lay consumers. Because the FDA requires that prescription drug and device advertising carry warnings, the consumer may reasonably presume that the advertiser guarantees the adequacy of its warnings. Thus, the common law duty to warn the ultimate consumer should apply.

[Susan A. Casey, Comment, *Laying an Old Doctrine to Rest: Challenging the Wisdom of the Learned Intermediary Doctrine*, 19 *Wm. Mitchell L.Rev.* 931, 956 (1993) (footnotes omitted).]

When all of its premises are absent, as when direct warnings to consumers are mandatory, the learned intermediary doctrine, “itself an exception to the manufacturer’s traditional duty to warn consumers directly of the risk associated with any product, simply drops out of the calculus, leaving the duty of the manufacturer to be determined in accordance with general principles of tort law.” *Edwards v. Basel*

Pharms., 116 *F.3d* 1341, 1343 (10th Cir. 1997) (discussing question of adequacy of nicotine patch warning under Texas law certified in *Edwards v. Basel Pharms.*, 933 *P.2d* 298 (Okla.1997)). We acknowledge that the Fifth Circuit recently held that under Texas law, the learned intermediary doctrine does apply in the context of Norplant. *In re Norplant Contraceptive Products Liab. Litig.*, 165 *F.3d* 374, 379–80 (1999). Nonetheless, we agree with the Tenth Circuit’s approach.

Concerns regarding patients’ communication with and access to physicians are magnified in the context of medicines and medical devices furnished to women for reproductive decisions. In *MacDonald v. Ortho Pharmaceutical Corp.*, 394 *Mass.* 131, 475 *N.E.2d* 65, *cert. denied*, 474 *U.S.* 920, 106 *S.Ct.* 250, 88 *L.Ed.2d* 258 (1985), the plaintiff’s use of oral contraceptives allegedly resulted in a stroke. The Massachusetts Supreme Court explained several reasons why contraceptives differ from other prescription drugs and thus “warrant the imposition of a common law duty on the manufacturer to warn users directly of associated risks.” *Id.* at 136–37, 475 *N.E.2d* 65. For example, after the patient receives the prescription, she consults with the physician to receive a prescription annually, leaving her an infrequent opportunity to “explore her questions and concerns about the medication with the prescribing physician.” *Id.* at 137, 475 *N.E.2d* 65. Consequently, the limited participation of the physician leads to a real possibility that their communication during the annual checkup is insufficient. *Id.* at 138, 475 *N.E.2d* 65. The court also explained that because oral contraceptives are drugs personally selected by the patient, a prescription is often not the result of a physician’s skilled balancing of individual benefits and risks but originates, instead, as a product of patient choice. *Id.* at 137, 475 *N.E.2d* 65. Thus, “the physician is relegated to a . . . passive role.” *Ibid.*

[2] Patient choice is an increasingly important part of our medical-legal jurisprudence. New Jersey has long since abandoned the “professional standard” in favor of the objectively-prudent-patient rule, recognizing the informed role of the patient in health-care decisions. *Largey, supra*, 110 N.J. at 212, 540 A.2d 504. Accordingly, a patient must be informed of material risks, which exist “when a reasonable patient, in what the physician knows or should know to be the patient’s position, would be ‘likely to attach significance to the risk or cluster of risks’ in deciding whether to forego the proposed therapy or to submit to it.” *Id.* at 211–12, 540 A.2d 504 (quoting *Canterbury, supra*, 464 F.2d at 787). When a patient is the target of direct marketing, one would think, at a minimum, that the law would require that the patient not be misinformed about the product. It is one thing not to inform a patient about the potential side effects of a product; it is another thing to misinform the patient by deliberately withholding potential side effects while marketing the product as an efficacious solution to a serious health problem. Further, when one considers that many of these “life-style” drugs or elective treatments cause significant side effects without any curative effect, increased consumer protection becomes imperative, because these drugs are, by definition, not medically necessary.

In the development of products liability law, the role of advertising has been a significant factor in defining the duties of sellers.

An early, but important, example is *Henningsen v. Bloomfield Motors Inc.*, [32 N.J. 358, 161 A.2d 69 (1960)] the seminal case marking “the date of the fall of the citadel of privity,” in which the Court recognized the “advent of large scale advertising by manufacturers” as a basis for reconsidering the long-standing privity rule in warranty cases. The general principle recognized in *Henningsen*—that a manufacturer’s duty runs directly to the consumer when it markets its products directly to the

consumer—is as applicable today to prescription drug manufacturers who advertise their products as it was to automobile manufacturers three decades ago in *Henningsen*.

[Schwartz, *supra*, 46 *Food Drug Cosm. L.J.* at 840–41 (footnotes omitted).]

[3] Obviously, the learned intermediary doctrine applies when its predicates are present. “In New Jersey, as elsewhere, we accept the proposition that a pharmaceutical manufacturer generally discharges its duty to warn the ultimate users of prescription drugs by supplying physicians with information about the drug’s dangerous propensities.” *Niemiera, supra*, 114 N.J. at 559, 555 A.2d 1112. Had Wyeth done just that, simply supplied the physician with information about the product, and not advertised directly to the patients, plaintiffs would have no claim against Wyeth based on an independent duty to warn patients. The question is whether the absence of an independent duty to warn patients gives the manufacturer the right to misrepresent to the public the product’s safety.

D. Prescription drug manufacturers that market their products directly to consumers should be subject to claims by consumers if their advertising fails to provide an adequate warning of the product’s dangerous propensities.

In reaching the conclusion that the learned intermediary doctrine does not apply to the direct marketing of drugs to consumers, we must necessarily consider that when prescription drugs are marketed and labeled in accordance with FDA specifications, the pharmaceutical manufacturers should not have to confront “state tort liability premised on theories of design defect or warning inadequacy.” Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 *Harv. L.Rev.* 773, 773 (1990). We draw much of this summary concerning the specifics of FDA pharmaceutical

regulation from the brief of *amicus curiae*, the Pharmaceutical Research and Manufacturers of America. Because such regulations may change from day to day, our commentary concerning the current regulations may soon become moot.

The FDA is authorized to regulate advertisements for prescription drugs pursuant to 21 U.S.C.A. Section 352(n) of the Food, Drug and Cosmetic Act, 21 U.S.C.A. Sections 301–397. Advertisements subject to Section 352(n) include “advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.” 21 C.F.R. § 202.1(l)(1). Although the FDA has regulated drug advertising since 1963, those regulations initially addressed only advertising directed at health-care providers. Noah, *supra*, 32 *Ga. L.Rev.* at 142–43. Aware of the potential threat to consumers when pharmaceutical companies first sought to advertise to non-health-care professionals, the FDA, in the early 1980s

initially imposed a [voluntary] moratorium on such advertising so that it could study the issue more carefully; but, in 1985, it lifted the moratorium, content to apply its existing regulations to this new practice. Perhaps spurred by the rapid growth of direct consumer advertising and the inherent shortcomings of rules designed to control advertising to physicians, coupled with the emergence of brand new media such as the Internet for disseminating promotional messages, the Agency has now proposed to modify its approach.

[*Id.* at 142–43.]

Section 352(n) of the Act contains the “brief summary requirement,” which is a misnomer considering that the summary is anything but brief. Accordingly, all advertisements must include a description of “side effects, contraindications, and effectiveness as shall be required in regulations . . .” 21 U.S.C.A. § 352(n)(3).

¹²⁵The regulations addressing prescription drugs also require that the brief summary

provide “all the risk-related information in a product’s approved package labeling,” which is usually a package insert or product package insert. 62 *Fed.Reg.* 43,171 (Aug. 12, 1997) (citing 21 C.F.R. § 202.1(e)(1) and (e)(3)(iii)). As noted by *amicus curiae*, the FDA “[r]egulations are exhaustive, addressing issues as broad as the requirement that ads be fairly balanced (21 C.F.R. § 202.1(e)(6)) and as narrow as how graphs must be labeled (21 C.F.R. § 202.1(e)(7)(iv)) and the type size used to set forth a medicine’s established name (21 C.F.R. § 202.1(b)(2)).”

In August 1997, the FDA released a Draft Guidance, which specifically addresses consumer-directed broadcast advertisements such as radio, television and telephone communications. 21 *Fed.Reg.* 43,172 (Aug. 12, 1997). Broadcast advertisements must contain a “major statement” of the major risks of the drug. *Ibid.* Instead of presenting a brief summary with the broadcast, which is not as feasible as in the print media, the Guidance proposes an alternative requirement known as the “adequate provision” requirement. *Ibid.* That provision provides that the manufacturer “may make adequate provision for the dissemination of the approved package labeling in connection with the broadcast presentation (§ 202.1(e)(1)).” *Ibid.* The Guidance explains that four components must be present to meet the “adequate provision” requirement in broadcasts—a toll-free number that provides information concerning where consumers might find information about package labeling; an alternative mechanism for obtaining package labeling information for consumers who do not have access to technology such as the Internet; a statement directing consumers to pharmacists and/or physicians; and an Internet web-page address. See *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (visited June 14, 1999) <<http://www.fda.gov/cder/guidance/index.htm>>. Within two years of the release of the Guidance, the FDA “intends

to evaluate the effects of the guidance....” 62 *Fed.Reg.* 43,172. These FDA actions indicate that the agency views direct-to-consumer advertising²⁴ as a means of providing consumers with improved access to important information about prescription drugs.⁴

FDA regulations are pertinent in determining the nature and extent of any duty of care that should be imposed on pharmaceutical manufacturers with respect to direct-to-consumer advertising. *Cf. Alloway v. Bradlees, Inc.*, 157 N.J. 221, 236, 723 A.2d 960 (1999) (discussing relevance of federal OSHA standards in determining duty of care to impose on general contractor for injuries incurred by subcontractor’s employee on worksite). Presently, any duty to warn physicians about prescription drug dangers is presumptively met by compliance with federal labeling. *See N.J.S.A. 2C:58-4*. That presumption is not absolute. *See, e.g., Feldman v. Lederle Labs., Inc.*, 125 N.J. 117, 156-7, 592 A.2d 1176 (1991) (*Feldman II*) (concluding that under unique circumstances of case, compliance with FDA determination not to require drug warning due to lack of “unequivocal factual evidence of adverse reaction in man,” despite evidence of adequacy of product labeling, did not create conclusive presumption that labeling contained adequate warning) *cert. denied*, 505 U.S. 1219, 112 S.Ct. 3027, 120 L.Ed.2d 898 (1992). Nevertheless, FDA regulations serve as compelling evidence that a manufacturer satisfied its duty to warn the physician about potentially harmful side effects of its product.

[4] We believe that in the area of direct-to-consumer advertising of pharmaceuticals, the same rebuttable presumption should apply when a manufacturer complies with FDA advertising, labeling and warning requirements. That approach harmonizes the manufacturer’s duty to

doctors and to the public when it chooses to directly advertise its products, and simultaneously recognizes the public interest in informing patients about new pharmaceutical²⁵ developments. Moreover, a rebuttable presumption that the duty to consumers is met by compliance with FDA regulations helps to ensure that manufacturers are not made guarantors against remotely possible, but not scientifically-verifiable, side-effects of prescription drugs, a result that could have a “significant anti-utilitarian effect.” *See Feldman II, supra*, 125 N.J. at 162, 592 A.2d 1176 (Garibaldi, J., dissenting); *see also* Michael D. Green, *Statutory Compliance and Tort Liability: Examining the Strongest Case*, 30 *U. Mich. J.L. Ref.* 461, 466-67 (1997) (noting that over deterrence in drug advertising context could impede and delay manufacturers from research and development of new and effective drugs, force beneficial drugs from market, lead to shortages in supplies and suppliers of pharmaceuticals, and create unnecessary administrative costs).

We believe that this standard is fair and balanced. For all practical purposes, absent deliberate concealment or nondisclosure of after-acquired knowledge of harmful effects, compliance with FDA standards should be virtually dispositive of such claims. By definition, the advertising will have been “fairly balanced.” This presumptive effect is in accordance with legislative intent that we discern from the punitive damages provision of the Products Liability Act. *See L. 1987, c. 142, § 5(c)*. That provision prohibits, in the case of the sale of pharmaceutical products, an award of punitive damages if there has been compliance with FDA labeling and pre-marketing requirements, impliedly reserving compensatory damages for those rare cases when the presumption is overcome. *N.J.S.A. 2A:58C-5(c)*.

4. *But see* Robert Cohen, *Regulation on Drugs Unraveling on the Web*, *Star-Ledger*, July 6, 1999, at 1 (noting that although prescription “drug bazaars” on the Internet “are undermining federal drug safety laws, tearing apart

the doctor-patient relationship and breaking state pharmacy and medical regulations,” federal officials are uncertain how to “get control of the latest e-commerce phenomenon.”).

V

The final issues in this case concern proximate cause, that is, whether misinformation actually affected these patients and, if so, whether the intervention of the physician (without whom the product may not reach the patient) breaks the chain of causation.

Concerning the first issue, defendants argue that we should refrain from deciding whether the learned intermediary doctrine 126applies because these plaintiffs did not say that they had been influenced by defective advertising of Norplant. We decline to do so for two reasons. First, plaintiffs claim to have been lulled into the view that the only issue for decision at this phase of the case was the application of the learned intermediary doctrine. Moreover, were we to decline to resolve the application of the learned intermediary doctrine, the remainder of the fold would have to relitigate the issue even if their bellwethers were no longer available to lead them.⁵ See *supra* at 7 n. 2, 734 A.2d at 1248 n. 2. We believe it best to resolve the threshold issue of whether the learned intermediary doctrine applies in the case of direct-to-consumer marketing of pharmaceutical goods and to remand the matter for further proceedings. The issue on remand will be whether, on a summary judgment motion, there is sufficient evidence for a reasonable jury to determine in the cases of the bellwether plaintiffs, or any remaining plaintiffs, that the absence of information or presence of misinformation in Norplant advertising was in violation of FDA requirements and whether such violations, if any, were a substantial factor in bringing about the harm suffered.

[5] The more difficult question is whether the role of the physician breaks the chain of causation. Although the physician writes the prescription, the physician's role in deciding which prescription drug is selected has been altered. With

the arrival of direct-to-consumer advertising, patients now enter physicians' offices with "preconceived expectations about treatment because of information obtained from DTC [direct-to-consumer] advertisements." Tamar V. Terzian, *Direct-to-Consumer Prescription Drug Advertising*, 25 *Am. J.L. & Med.* 149, 157 (1999). Consequently,

[p]hysicians may relent to patient pressure, even if it is not in the best interest of the patient. In fact, physicians state that they are increasingly asked and pressured by their patients to prescribe drugs that the patient has seen advertised. 127For example, the diet drug combinations known as fen-phen was prescribed despite little hard scientific evidence of its potential side-effects. Physicians are under attack for prescribing the pills too often and too readily to inappropriate patients. Physicians argue that it is not their fault; rather, they claim pushy patients, prodded by DTC advertisements, pressed, wheedled, begged and berated them for quick treatments. This scenario comes at a time when physicians cannot afford to lose patients, because their income is already strained by managed care cost cutting. Physicians complain that it is impossible to compete with pharmaceutical companies' massive advertising budgets, and resign themselves to the fact that if consumers make enough noise, they will eventually relent to patient pressure.

[*Id.* at 157-58 (footnotes omitted).]

We disagree that these "ads change the physician into 'simply a functionary, filling out prescriptions[,]'" but we must examine whether the changed relationship affects the finding of proximate cause. See Van Voris, *supra*, *Nat'l L.J.*, at B1 (quoting Michael Traynor, adviser to the *Restatement* project).

sure to advertising of Norplant.

5. Several of the bellwether plaintiffs submitted supplemental affidavits concerning expo-

[6–8] We have described proximate cause as an expression as much of policy as it is an expression of the effect of sequential events. A proximate cause need not be the sole cause of harm. It suffices if it is a substantial contributing factor to the harm suffered.

“Proximate or legal causation is that combination of ‘logic, common sense, justice, policy and precedent’ that fixes a point in a chain of events, some foreseeable and some unforeseeable, beyond which the law will bar recovery.” *People Express Airlines, Inc. v. Consolidated Rail Corp.*, 100 N.J. 246, 264, 495 A.2d 107 (1985) (quoting *Caputzal v. Lindsay Co.*, 48 N.J. 69, 77–78, 222 A.2d 513 (1966)); see also *Kuzmich v. Ivy Hill Park Apartments, Inc.*, 147 N.J. 510, 540–41, 688 A.2d 1018 (1997) (Stein, J., dissenting) (same); *Contey v. New Jersey Bell Tel. Co.*, 136 N.J. 582, 587, 643 A.2d 1005 (1994) (“We have . . . defined the limits of proximate cause as an instrument of fairness and policy.”) (internal quotation omitted); *Brown v. United States Stove Co.*, 98 N.J. 155, 173, 484 A.2d 1234 (1984) (“The assessment as to whether conduct can be considered sufficiently causally connected to accidental harm so as to justify the imposition of liability also implicates concerns for overall fairness and sound public policy.”); *Rappaport v. Nichols*, 31 N.J. 188, 205, 156 A.2d 1 (1959) (“We are fully mindful that policy considerations and the balancing of the conflicting interests are the truly vital factors in the molding and application of the common law principles of negligence and proximate causation.”).

Ordinarily, issues of proximate cause are considered to be jury questions. See *Martin v. Bengue, Inc.*, 25 N.J. 359, 374 136 A.2d 626 (1957). However, in unique cases our courts have rejected the imposition of liability as a matter of law for highly extraordinary consequences . . .

¹²[*Garrison v. Township of Middletown*, 154 N.J. 282, 307–08, 712 A.2d 1101 (1998) (Stein, J., concurring).]

As a matter of policy then, we could hold that even if deceptive advertising were a substantial contributing factor influencing a patient’s choice of a medicine, the intervening role of the physician should insulate the manufacturer who has engaged in deceptive trade practices. In other contexts, we have not insulated manufacturers when another might have given better warning. *Freund v. Cellofilm Properties, Inc.*, 87 N.J. 229, 245, 432 A.2d 925 (1981); see also *Campos v. Firestone Tire & Rubber Co.*, 98 N.J. 198, 208, 485 A.2d 305 (1984), citing *Bexiga v. Havir Mfg. Corp.*, 60 N.J. 402, 410, 290 A.2d 281 (1972) (holding that manufacturer may be responsible for failing to include safety precautions on its machine despite its expectation that someone would install these safety devices, because public interest required that duty of assuring such installation should not be left to others); and *Davis supra*, 399 F.2d at 131 (holding that prescription drug manufacturer may have duty to see that warnings of drug’s risks, distributed to medical profession, in fact reached drug’s ultimate consumers).

Furthermore, a manufacturer who fails to warn the medical community of a particular risk may nonetheless be relieved of liability under the learned intermediary doctrine if the prescribing physician either did not read the warning at all, and thus did not rely on any information from the manufacturer in prescribing the product, or if the physician was aware of the risk from other sources and considered the risk in prescribing the product. Under these circumstances, the learned intermediary’s conduct is deemed to be the superseding or intervening cause that breaks the chain of liability between the manufacturer and the user.

[Richard J. Heafey & Don M. Kennedy, *Products Liability: Winning Strategies and Techniques* § 10.03 (1999) (footnotes omitted).]

The superseding cause rationale

is appealing because it is based on the familiar tort concept that a tortfeasor is liable only for the injuries that he or she proximately causes. Despite its appeal, one problem with using the causation rationale is the inherent difficulty of establishing causation in failure-to-warn cases as compared with other product liability claims. In a typical defective design case, a plaintiff points to the existence of a viable alternative design and asserts that the manufacturer's failure to use that design proximately caused the plaintiff's injury. Failure-to-warn claims, however, entail a different sort of showing. A plaintiff suing under a failure-to-warn theory must presumably establish that she would have heeded an adequate warning if one were given. Due to the individualized nature of the inquiry into what warning ¹²⁹would have caused the plaintiff to alter her behavior, Professors Henderson and Twerski suggest that predicting how additional information would have affected any given individual may be well nigh impossible.

[Lloyd C. Chatfield II, *Medical Implant Litigation and Failure to Warn: A New Extension for the Learned Intermediary Rule*, 82 Ky. L.J. 575, 582-83 (1993-94) (footnotes omitted).]

On balance, we believe that the patient's interest in reliable information predominates over a policy interest that would insulate manufacturers. "Products liability law is based on concepts of fairness, feasibility, practicality and functional responsibility. We have always stressed the public's interest in motivating individuals and commercial entities to invest in safety to protect workers." *Zaza v. Marquess and Nell, Inc.*, 144 N.J. 34, 64, 675 A.2d 620 (1996). Within bounds, that policy extends to consumers of pharmaceuticals.

Obviously, the physician is almost always the essential link between the patient

and the pharmaceutical. Most ads for drugs caution the patient to consult with a physician. Because of that essential link, under the learned intermediary rule drug manufacturers were found not liable even if they did not provide an adequate warning to those physicians who eventually prescribed a drug, to inform them of the risk.⁶

Courts have differed in their application of the learned intermediary doctrine in cases in which the defendant claimed that the prescribing physician knew of the risk that the manufacturer did not warn about. Some courts have applied a presumption that the physician would not have prescribed the product if an adequate warning had been given. The defendant may then rebut the presumption with evidence that the physician's decision would not have been affected by such a warning. Other courts have refused to create such a presumption, and have required the plaintiff to prove that an adequate warning would actually have changed the physician's decision. The courts have also differed in the quantum of proof a defendant must establish to show that the physician would have prescribed the drug even if the manufacturer had warned of the risk.

[Heafey & Kennedy, *supra*, at § 10.03 (footnotes omitted).]

¹³⁰However, we must consider as well a case in which a diabetic patient might have been influenced by advertising to request a drug from a physician without being warned by the manufacturer or the physician of the special dangers posed to a diabetic taking the drug. If an overburdened physician does not inquire whether the patient is a diabetic, the question remains whether the manufacturer should be relieved entirely of responsibility. In the case of direct marketing of drugs, we believe that neither the physician nor the

6. The sale of pharmaceuticals is changing even faster than the manufacturers themselves might have anticipated. Doctors in "cyberspace" write prescriptions for patients whom they have never seen. Sometimes the

"learned intermediary" owns the pharmacy. Sheryl Gay Stolberg, *Internet Prescriptions Boom in the 'Wild West' of the Web*, N.Y. Times, June 27, 1999, at A1.

manufacturer should be entirely relieved of their respective duties to warn. Pharmaceutical manufacturers may seek contribution, indemnity or exoneration because of the physician's deficient role in prescribing that drug. In each case, a jury must resolve the close questions of whether a breach of duty has been a proximate cause of harm, *Cowan v. Doering*, 111 N.J. 451, 545 A.2d 159 (1988), and how that causative harm, if found, may be apportioned among culpable defendants. In our experience, jurors are extremely skilled at sorting out the justly and legally responsible parties. See *Estate of Chin v. St. Barnabas Med'l Ctr.*, 160 N.J. 454, 734 A.2d 778 (1999) (explaining how jury assessed evidence to determine relative fault of physician and attending nurses when medical device manufacturer was relieved of liability). As our dissenting member observes, it is still the physician in whom the patient reposes the greatest trust for health-care decisions. *Post* at 36, 734 A.2d at 1266. We are certain that today's ruling will not alter the existing fair balance of trust and responsibility for patient health care as between physician and pharmaceutical manufacturer.

VI

To sum up, the dramatic shift in pharmaceutical marketing to consumers is based in large part on significant changes in the health-care system from fee-for-service to managed care. Managed care companies negotiate directly with pharmaceutical companies and then inform prescribers which medications are covered by the respective plans. Because managed care has made it more difficult for pharmaceutical companies to communicate with prescribers,³¹ the manufacturers have developed a different strategy, marketing to consumers.

Pharmaceutical companies have a right to communicate with the public. These companies hope to increase their market share by making their product well known to both patients and physicians. Pharmaceutical executives, aware of the high levels of spending on DTC efforts,

are trying to determine how to best spend their funds to obtain the highest return on their investment. Since the FDA Guidance was released, pharmaceutical companies have taken consumer advertising crash courses. Pharmaceutical companies are already seeing results in strong sales growth, due to DTC advertising.

[Terzian, *supra*, 25 *Am. J.L. & Med.* at 160-61.]

The direct marketing of drugs to consumers generates a corresponding duty requiring manufacturers to warn of defects in the product. The FDA has established a comprehensive regulatory scheme for direct-to-consumer marketing of pharmaceutical products. Given the presumptive defense that is afforded to pharmaceutical manufacturers that comply with FDA requirements, we believe that it is fair to reinforce the regulatory scheme by allowing, in the case of direct-to-consumer marketing of drugs, patients deprived of reliable medical information to establish that the misinformation was a substantial factor contributing to their use of a defective pharmaceutical product.

Before concluding, we acknowledge that the procedural posture of this case casts defendant's product in an unfair light. Because the case arises on a motion for summary judgment, we are obliged to view the issues in the light most favorable to the claimants. We have no doubt that substantial proofs will be marshaled to show that Norplant is a safe and efficacious product and that Wyeth's advertising, if any, was fairly balanced. An agreed statement of facts submitted to the trial court suggested as much. And Norplant probably does not afford the best context in which to address the general question whether direct-to-consumer marketers of pharmaceutical products are unqualifiedly relieved of a duty to warn consumers of the dangerous propensities of a product. After all, in the case of Norplant, the role of the physician can never be insubstantial because only a physician may implant the

device. Just as it is difficult to legislate a rule for every foreseeable³² circumstance, so too it is difficult to create a special rule of law for a hybrid product such as Norplant.

We are called upon, however, to resolve a question of law that will apply equally as well to an unprincipled marketer of pharmaceutical products as to a principled marketer. To place the issue in context, consider if prescription diet drugs were heavily advertised without warning of a known potential for heart damage.

Health hazards associated with prescription diet treatments in the 1990s . . . provide a modern example of the continuing threat posed by the premature approval of drugs. This threat is exacerbated by unprecedented access to information for an increasing number of patients. With access to more and more information about new drugs, consumers not only become empowered to direct their own treatment, but often become demanding as well, pressuring physicians to prescribe drugs that are expensive and sometimes ineffective at best, and harmful or even deadly at worst.

[Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debate*, 79 *B.U. L.Rev.* 93, 98-99 (1999) (footnotes omitted).]

That is the normative situation for which we must decide if a pharmaceutical manufacturer is free to engage in deceptive advertising to consumers. We believe that the answer in such a case should be no. Any question of fairness in imposing on the direct marketer of a product such as Norplant a duty to warn the targeted consumers will be resolved in the proximate cause analysis.

Finally, we return briefly to the main theme of the dissent, *post* at 35-36, 734 A.2d at 1266, that our decision is inconsistent with legislative mandate. We are certain that legislative codification of the learned intermediary doctrine—which generally relieves a pharmaceutical manufacturer of an independent duty to warn the

ultimate user of prescription drugs, as long as it has supplied the physician with information about a drug's dangerous propensities—does not confer on pharmaceutical manufacturers a license to mislead or deceive consumers when those manufacturers elect to exercise their right to advertise their product directly to such consumers.

³³The judgment of the Appellate Division is reversed and the matter is remanded to the Law Division for further proceedings.

POLLOCK, J., dissenting

With disarming understatement, the majority opinion raises profound questions about the purpose of judicial opinions, the role of courts, and the separation of powers. In raising those questions, the majority rejects the Legislature's endorsement of the learned intermediary doctrine as set forth in *N.J.S.A. 2A:58C-4*. The majority opinion sustains itself only by ignoring the plain language of an unambiguous statute, the New Jersey Products Liability Act, *N.J.S.A. 2A:58C-1 to -7* (NJPLA), and by substituting its own policy preference for that of the Legislature. Contrary to the majority opinion, the point of this dissent is not that the Court should await legislative action. *Ante* at 16, 734 A.2d at 1254. Rather, the point is that the Legislature has already acted. Believing that the Court is bound by the NJPLA, I respectfully dissent.

Initially, the Law Division held that the duty of defendants Wyeth Laboratories Inc., American Home Products Corporation, Wyeth-Ayerst Laboratories Division of American Home Products Corporation, Wyeth-Ayerst International Inc., and Wyeth-Ayerst Laboratories Company ("defendants" or "Wyeth") extended not to plaintiffs, but to their physicians or other health-care professionals. 313 *N.J.Super.* 646, 658, 713 A.2d 588 (1997). The Appellate Division affirmed. 313 *N.J.Super.* 511, 516, 713 A.2d 520 (1998).

On a related issue, the Law Division held that defendants adequately warned

the bellwether plaintiffs' physicians or other health-care professionals of the risks associated with Norplant. 313 *N.J.Super.* at 658, 713 A.2d 588. The Appellate Division likewise affirmed that holding. 313 *N.J.Super.* at 518, 713 A.2d 520.

The majority reverses the judgment of the Appellate Division. I would affirm.

¹³⁴To place the issue in perspective, a brief summary of relevant principles of products liability law may be helpful. At common law, a manufacturer is strictly liable for a defective product. *Feldman v. Lederle Laboratories, Inc.*, 97 N.J. 429, 441-42, 479 A.2d 374 (1984) (*Feldman I*). The manufacturer, however, is not liable if the product is "unavoidably unsafe" and is "accompanied by proper warning." *Id.* at 447, 479 A.2d 374. In general, the manufacturer must communicate this warning directly to the consumer. *Niemiera v. Schneider*, 114 N.J. 550, 559, 555 A.2d 1112 (1989). With prescription drugs, the "manufacturer generally discharges its duty to warn the ultimate user . . . by supplying physicians with information about the drug's dangerous propensities." *Ibid.* This rule, known as the learned intermediary doctrine, reflects the common law's awareness of the unique role that physicians serve in warning their patients of the risks associated with prescription drugs. See *Sterling Drug, Inc. v. Cornish*, 370 F.2d 82, 85 (8th Cir.1966). New Jersey courts consistently have recognized the vitality of the learned intermediary doctrine. See, e.g., *Bacardi v. Holzman*, 182 N.J.Super. 422, 442 A.2d 617 (App.Div. 1981); *Torsiello v. Whitehall Laboratories*, 165 N.J.Super. 311, 322-23, 398 A.2d 132 (App.Div.) ("[W]hile it is the customer who is entitled to the warning in respect of non-prescription drugs, only the prescribing physician need be warned as to the risks involved in a prescription drug."), *certif. denied*, 81 N.J. 50, 404 A.2d 1150 (1979). In 1987, the Legislature codified the learned intermediary doctrine in the NJPLA. L. 1987, c. 197, § 4 (effective July 22, 1987). Thus, although the learned intermediary doctrine remains a common-

law rule in most states, it is now a statutory rule in New Jersey.

Before the enactment of the NJPLA, this Court had issued numerous products liability opinions based primarily on the common law. In those opinions, we emphasized the rights of injured persons and consumers in a mass-marketing economy. New Jersey manufacturers, including pharmaceutical companies, thought we had gone too far. The Legislature agreed and enacted ¹³⁵the NJPLA. As the passed bill memorandum to Governor Kean explained:

The New Jersey manufacturers that have lobbied heavily for the enactment of this bill argue that in certain areas the New Jersey Supreme Court has gone beyond the laws of other states. These groups state that this bill will "bring New Jersey back into the mainstream" of product liability law. New Jersey manufacturers argue that because certain areas of New Jersey product liability law provide more protection for the consumer than other states, injured consumers from out-of-state are likely to bring a lawsuit against the New Jersey manufacturers in New Jersey. Thus, to the extent this bill conforms the New Jersey product liability law to the law of the majority of states, New Jersey will no longer be a "favorable forum" to out-of-state injured parties.

[Passed Bill Memorandum to Governor Thomas H. Kean on S-2805, at 3 (July 10, 1987).]

Of special interest to the pharmaceutical companies and the Legislature was the learned intermediary doctrine.

Analysis of the status of the learned intermediary doctrine thus depends on the intent of the Legislature. *Merin v. Maglaci*, 126 N.J. 430, 435, 599 A.2d 1256 (1992). When a statute is clear, a court need not look beyond the statutory language to discover the legislative intent. *State v. Kittrell*, 145 N.J. 112, 123, 678 A.2d 209 (1996). The language of the NJPLA is clear.

The NJPLA states that a manufacturer has a duty to include an "adequate warning or instruction" with a product. Otherwise, the product may be considered defective. According to the statute, an "adequate warning" is

one that a reasonably prudent person in the same or similar circumstances would have provided with respect to the danger and that communicates adequate information on the dangers and safe use of the product, taking into account the characteristics of, and the ordinary knowledge common to, the persons by whom the product is intended to be used, or *in the case of prescription drugs, taking into account the characteristics of, and the ordinary knowledge common to, the prescribing physician.*

[N.J.S.A. 2A:58C-4 (emphasis added).]

The majority finds ambiguity in the NJPLA, stating that "[a]lthough the statute provides a physician-based standard for determining the adequacy of the warning due to a physician, the statute does not legislate the boundaries of the doctrine." *Ante* at 16, 734 A.2d at 1254. According to the Senate Committee statement ¹³⁶accompanying the NJPLA, however, a drug manufacturer's duty to warn is owed to the physician, not the consumer:

[A] manufacturer or seller is not liable in a warning-defect case if an adequate warning is given when the product has left the control of the manufacturer or seller. . . . The subsection contains a general definition of an adequate warning and a special definition for warnings that accompany prescription drugs, since, *in the case of prescription drugs, the warning is owed to the physician.*

[Senate Judiciary Committee, *Statement to Senate Bill No. 2805* (L. 1987, c. 197), N.J.S.A. 2A:58C-1a (emphasis added).]

The NJPLA provides that "committee statements that may be adopted or included in the legislative history of this act shall be consulted in the interpretation and construction of this act." N.J.S.A. 2A:58C-1a;

Roberts v. Rich Foods Inc., 139 N.J. 365, 374, 654 A.2d 1365 (1995). Through that extraordinary mandate, the Legislature sought to preclude judicial circumvention of the plain meaning of the statute.

Today's decision demonstrates that the Legislature's efforts were unavailing. The majority has mischaracterized both the statute and the rationale for the learned intermediary doctrine. Contrary to the majority opinion, the statute directs that the warning is owed to the physician not "because drugs were then marketed to the physician," *ante* at 16, 734 A.2d at 1254, but because the physician is in the best position to make an individualized evaluation of the risks of drugs and warn the patient of those risks. The patient, moreover, cannot obtain the drugs without a prescription written by a physician.

Underlying the majority opinion is the assumption that the Legislature in 1987 could not have anticipated the mass-marketing of prescription drugs. That assumption, however, has no basis in the record. In fact, the drug companies and the Legislature, like the Federal Food and Drug Administration (FDA), were aware of such marketing. *See Direct-to-Consumer Advertising of Prescription Drugs*, 50 *Fed.Reg.* 36,677 (1985) (commenting that "the public discussion on direct-to-consumer advertising of prescription drugs has provided interested individuals and organizations ample opportunity to consider and express opinions on the issue"). As ¹³⁷the majority opinion states: "Aware of the potential threat to consumers when pharmaceutical companies first sought to advertise to non-health-care professionals, the FDA, in the early 1980s 'initially imposed a [voluntary] moratorium on such advertising so that it could study the issue more carefully; but in 1985, it lifted the moratorium, content to apply its existing regulations to this new practice.'" *Ante* at 22, 734 A.2d at 1258 (quoting Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 *Ga. L. Rev.* 141, 142-43 (1997)).

The majority's imposition of expanded duties on drug manufacturers contravenes the legislative history of the NJPLA. That history demonstrates that the statute was intended to strengthen the protections afforded manufacturers:

It is important to recognize that this bill not only conforms New Jersey product liability law to the law of the majority of states but, in some instances, changes New Jersey law in favor of the manufacturer in a way that is not currently recognized by the law of the majority of states. Thus, the effect of the enactment of this bill would be to shift the status of the law of New Jersey on certain issues from its current position of being more favorable to the injured consumer than the majority of states to being more favorable to the manufacturer than the majority of states.

[Passed Bill Memorandum to Governor Thomas H. Kean on S-2805, *supra*, at 3.]

Judges, although they may disagree with a legislative policy, are bound to respect it. In adapting the common law to society's needs, this Court may not have favored manufacturers, including pharmaceutical companies, as enthusiastically as has the Legislature. The issue, however, is not whether the Court shares the Legislature's enthusiasm or even whether the majority would prefer to amend the common-law learned intermediary doctrine. Because of the enactment of the NJPLA, the issue is whether the majority should respect the learned intermediary doctrine as declared by the Legislature.

As the majority recognizes, the modern law of product liability began with Justice Francis's opinion in *Henningsen v. Bloomfield Motors Inc.*, 32 N.J. 358, 161 A.2d 69 (1960), *ante* at 21, 734 A.2d at 1257; *see Prosser & Keeton on Torts* § 97 (5th ed.1984) (describing *Henningsen* as "the most rapid and altogether spectacular overturn of an established rule in the entire history of the law of torts"). Given the prominence of that opinion, written by

Justice Francis while serving on this Court with Chief Justice Joseph Weintraub, Justice Francis's eulogy at the proceedings before this Court in memory of Chief Justice Weintraub is worth recalling. Justice Francis eloquently described the distinction that the late Chief Justice drew between respecting the will of the Legislature and adapting the common law to the needs of the time. Speaking of Chief Justice Weintraub, Justice Francis stated:

Throughout his years on the Court, he remained acutely aware of the line of demarcation between the judicial and legislative branches of government, and of the duty of the judicial branch to refrain from encroaching on the area of operation of the legislative branch. So if a statutory rule or doctrine were in question before the Court, even if it appeared to be inadequate to serve the needs of the times, he would declare that the remedy was in the hands of the Legislature, and the Courts should not interfere.

[72 N.J. XIX, XXVIII-XXIX (1977)].

That demarcation remains valid today.

Given the statutory basis for the learned intermediary doctrine in New Jersey, recourse to the *Restatement (Third) of Torts: Products Liability* § 6 (1998) ("*Restatement*") is gratuitous. Furthermore, the *Restatement* generally endorses the traditional rule that a drug manufacturer's duty to warn is owed to the health-care provider, not the consumer. *Id.* § 6(d)(1). The *Restatement* suggests, however, that it may be appropriate to impose a duty to warn the patient directly "when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings." *Id.* § 6(d)(2). Here, the *Restatement* does not apply for two reasons. First, as prestigious as any *Restatement* may be, it cannot supersede a governing statute. Second, the surgical implantation of Norplant requires the significant involvement of a health-care provider who must make an individualized evaluation of the risk to the patient. Such involvement stands in con-

trast to ³⁹the “diminished role as an evaluator or decision maker” that is a predicate for liability under the *Restatement*. See *id.* § 6(d) comment a. That involvement also distinguishes the implantation of Norplant from the administration of mass inoculations, see *ante* at 10–11, 734 A.2d at 1250–51, which proceed without an individualized evaluation of the risks to the patient.

Contrary to the majority opinion, the question is not “whether the absence of an independent duty to warn patients gives the manufacturer the right to misrepresent to the public the product’s safety.” *Ante* at 21, 734 A.2d at 1257. No defendant claims such a right. Neither does the FDA, which regulates prescription drug advertising, allow it. For example, FDA regulations require that print and broadcast advertisements promoting prescription drugs be “balanced.” 21 C.F.R. § 202.1(e)(6). Additionally, the FDA has issued a Draft Guidance that requires prescription drug broadcast advertisements to include a thorough “major statement” in “consumer-friendly” language about a drug’s major risks. 62 Fed.Reg. 43,171; see also *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (visited July 14, 1999) <<http://www.fda.gov/cder/guidance/index.htm>>.

On the facts, moreover, Norplant is a poor vehicle to import so momentous a change. Unlike other drugs that concern the majority, the record reveals that Norplant cannot be purchased in a supermarket, see *ante* at 4, 734 A.2d at 1247, is not promoted by health maintenance organizations, see *ante* at 18, 734 A.2d at 1255, approved by compliant physicians to placate overbearing patients, see *ante* at 20, 734 A.2d at 1257, or implanted over the Internet, *ante* at 4, 29 n. 6, 734 A.2d at 1257, 1262 n. 6. Through the incorporation of presumed facts, the majority has created a phantom record to support the creation of its exception to the learned intermediary doctrine. That exercise has led the majority to wander from the confines of the present case.

Norplant is not an over-the-counter drug; it can be obtained only with a doctor’s prescription. To insert Norplant, a physician or other health-care professional anesthetizes an area in a patient’s⁴⁰ upper arm, makes a one-eighth-inch incision, and implants six capsules just below the patient’s skin. Similar surgery is required to remove the capsules.

The use of Norplant thus requires the significant involvement of the prescribing physician. Even Norman Rockwell, see *ante* at 18, 734 A.2d at 1255, would recognize the procedure as one performed in accordance with the traditional physician-patient relationship. Presumably, Wyeth’s mass-marketing campaign has increased the demand for Norplant and led many women to request it by name. In some contexts, the extent to which pharmaceutical companies seek to influence consumers, like the extent to which they seek to influence physicians, may be disturbing. Here, however, the mass-marketing campaign apparently was ineffectual; none of the bellwether plaintiffs saw any advertising about Norplant. The invasiveness of the Norplant procedure, moreover, would give any patient pause and a physician cause to evaluate the risks. As the Law Division stated, “a physician is not simply relegated to the role of prescribing the drug according to the woman’s wishes.” 313 N.J.Super. 646, 648, 713 A.2d 588 (Law Div.1997).

Earlier this year, the Fifth Circuit Court of Appeals held, in a case involving Norplant, that “as long as a physician-patient relationship exists, the learned intermediary doctrine applies.” *In re Norplant Contraceptive Prods. Liab. Litig.*, 165 F.3d 374, 379 (5th Cir.1999). The court rejected the creation of an exception to the learned intermediary doctrine for mass-marketed drugs. Specifically, the court stated that “Norplant is nevertheless a prescription drug . . . [and] physicians play a significant role in prescribing Norplant and in educating their patients about the benefits and disadvantages to using it.” *Ibid.*

The majority identifies four premises underlying the learned intermediary doctrine that it asserts are inapplicable when a manufacturer advertises the drug directly to consumers: "(1) reluctance to undermine the doctor-patient relationship; (2) absence in the era of 'doctor knows best' of need for the patient's 14informed consent; (3) inability of drug manufacturer to communicate with patients; and (4) complexity of the subject." *Ante* at 18, 734 A.2d at 1255. Contrary to the majority, *ante* at 18–19, 734 A.2d at 1255–56, those four considerations remain relevant to the implantation of Norplant.

First, the Norplant System must be implanted surgically. Implicit in the performance of a surgical procedure is respect for the physician-patient relationship. "[T]he physician is in the best position to take into account the propensities of the drug and the susceptibilities of the patient, and to give a highly individualized warning to the ultimate user based on the physician's specialized knowledge." *Spychala v. G.D. Searle & Co.*, 705 F.Supp. 1024, 1031–32 (D.N.J.1988). Second, the physician is the only person who can communicate with the patient to obtain the patient's informed consent to the procedure. Third, a pharmaceutical company, such as Wyeth, cannot provide an adequate warning to each individual consumer about the potential side-effects and risks associated with the device. Each patient has individualized risks associated with surgical procedures. Lastly, the Norplant implant, far more than other birth control devices, is a complex contraceptive system that requires detailed instructions and warnings.

To soften the impact of its opinion, the majority creates a rebuttable presumption that a warning is adequate if it complies with FDA regulations. *Ante* at 25, 734 A.2d at 1259. Regrettably, the Court has not granted the parties the opportunity to address the creation, nature, or sufficiency of such a presumption. To the extent that such a presumption is essential to the majority's rationale, the parties should have been given that opportunity. *See Office of Employee Relations v. Communications*

Workers, 154 N.J. 98, 108, 711 A.2d 300 (1998); *see also Canesi v. Wilson*, 158 N.J. 490, 539–41, 730 A.2d 805 (1999) (Pollock, J., dissenting). Similarly, the parties should have been accorded the opportunity to address the issue of proximate cause, *see ante* at 25, 734 A.2d at 1260, as well as that of contribution and indemnity from 142physicians, *see ante* at 30, 734 A.2d at 1262–63. In a judicial proceeding, the test of a hypothesis through the adversary process serves as a safeguard when addressing issues of broad public concern, such as those introduced by the majority.

To conclude, when enacting the NJPLA, the Legislature chose to confine the expansion of product liability law. The majority's preference for a different policy does not justify ignoring the one chosen by the Legislature.

GARIBALDI, J., joins in this dissent.

For reversal and remandment—Chief Justice PORITZ and Justices HANDLER, O'HERN, STEIN and COLEMAN—5.

For affirmance—Justices POLLOCK and GARIBALDI—2.



161 N.J. 42

142In the Matter of Paul A. DYKSTRA,
An Attorney at Law.

Supreme Court of New Jersey.

Aug. 17, 1999.

Prior report: 157 N.J. 636, 725 A.2d 1121.

ORDER

This matter having been duly presented to the Court, it is ORDERED that PAUL A. DYKSTRA of HASBROUCK HEIGHTS, who was admitted to the bar of this State in 1974, and who was suspended from the practice of law for a period of three months effective April 19,

Facts about an implantable contraceptive: Memorandum from a WHO Meeting*

This Memorandum reviews the results of research undertaken in animals and human subjects on the implantable contraceptive, Norplant, and where relevant, its components, levonorgestrel and Silastic. Results from clinical trials, including effectiveness and side-effects, are evaluated and service delivery aspects commented on. The Memorandum concludes with a statement regarding the use of Norplant as an option for long-term reversible contraception.

Through its Special Programme of Research, Development, and Research Training in Human Reproduction, the World Health Organization provides advice to Member States and responds to questions from governments, other organizations of the United Nations system, and the scientific community on the safety and effectiveness of existing and new methods of fertility regulation. In response to a request from the United Nations Fund for Population Activities (UNFPA) to evaluate proposals for the introduction into family planning programmes of the new implantable contraceptive, Norplant, a consultation was convened by the Special Programme to review all data available from animal and human studies on this method of fertility regulation.

The only implantable contraceptive that can currently be considered for introduction into family planning programmes is Norplant, which was developed by the Population Council, New York, USA, primarily through its International Committee for Contraception Research (ICCR). It is registered under the Population Council's trademark as a subdermal implant for the release of levonorgestrel and is manufactured under licence from the Population Council by Huhtamäki Oy/Leiras Pharmaceuticals, Finland. It was approved for contraceptive use in November 1983 by the Finnish National Board of Health and is presently under consideration by the Swedish National Board of Health and Welfare. Submissions are expected to be made to the drug regulatory agencies of some 40 additional countries within the next two years.

About 20 years ago it was shown that Silastic (polydimethylsiloxane) could be used for the long-term

delivery of lipophilic drugs (1), and it was subsequently proposed for use in the delivery of contraceptive steroids (2). After studies with several steroids (3-7), the ICCR selected levonorgestrel as the drug with which the Silastic subdermal implant would be developed further (6, 8). Levonorgestrel is used extensively as a progestogen for contraception in both combined progestogen-estrogen and progestogen only oral contraceptive pills (9) and in other injectable and implantable systems, intrauterine devices, and vaginal rings currently under development (10).

Since 1975, clinical studies on Norplant have been initiated in several centres by ICCR. In more recent years, other investigators, funded by other agencies, have also become involved. To date, studies have been undertaken in the following countries: Brazil, Chile, Colombia, Denmark, Dominican Republic, Ecuador, Egypt, Finland, India, Indonesia, Jamaica, Sweden, Thailand, and the United States of America.

The Norplant system consists of six capsules, each containing 36 mg of levonorgestrel and having a diameter of 2.4 mm and a length of 3.4 cm. The six capsules appear to release levonorgestrel at a rate of approximately 80 µg per 24 h during the first 6-18 months of use. This rate declines over the next few months and thereafter the capsules deliver approximately 30 µg of levonorgestrel per 24 h. This latter rate of release is maintained for at least 5 years. The capsules are inserted subdermally, usually in the inner aspect of the upper arm or in the palmar aspect of the forearm, by means of a specially designed 10-gauge trocar which is introduced through a single 2-mm incision.

A second-generation system is also being developed by the Population Council which utilizes only two implants and is known as Norplant-2. This system consists of two rods in which levonorgestrel is homogeneously dispersed within a Silastic matrix and

* This Memorandum was drafted by the signatories listed on p.492, on the occasion of a Consultation convened by the World Health Organization in Geneva in October 1984. Requests for reprints should be addressed to the Director, Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland. A French translation of this Memorandum will appear in a later issue of the *Bulletin*.

covered by a layer of Silastic. The rods are 2.4 mm in diameter and 4.4 cm long and have been shown to deliver amounts of levonorgestrel equivalent to those released by Norplant. Norplant-2 is currently being tested in phase III clinical trials.

The only other implantable system for contraception that could be available to family planning programmes this decade is the Capnor device, developed by the Contraceptive Development Branch of the US National Institute of Child Health and Human Development in collaboration with the WHO Special Programme of Research, Development, and Research Training in Human Reproduction (10). Capnor consists of a single biodegradable capsule that delivers levonorgestrel for a period of approximately 18 months. This system is at an early stage of development; preliminary clinical trials have been completed (11, 12) and studies will shortly be expanded to cover safety and efficacy.

ANIMAL STUDIES

The Toxicology Review Panel of the Special Programme has reviewed the animal data available on the two components of the system, levonorgestrel and Silastic, as well as on Norplant itself. Toxicological studies on levonorgestrel have been conducted in accordance with the requirements of the United Kingdom Committee on the Safety of Medicines and the United States Food and Drug Administration (FDA), among others. It should be noted that these studies refer to both the racemic mixture, *d,l*-norgestrel and to its biologically active enantiomer, levonorgestrel, which comprises 50% of the racemic mixture. Originally, *d,l*-norgestrel was used in hormonal contraceptives but in more recent times it has largely been replaced by levonorgestrel.

Acute toxicity

The acute toxicity of *d,l*-norgestrel is over 5000 mg/kg of body weight (LD_{50}) as determined by oral administration in dogs and by various routes of administration in adult mice and rats. The LD_{50} value is 950 mg/kg of body weight in neonatal mice and

more than 1260 mg/kg of body weight in neonatal rats. The dose administered to women by implants may be estimated to be about 1 μ g/kg of body weight per day. No toxicity relevant to the human was seen in animal studies, which indicates a wide margin of safety.

Subacute and chronic toxicity

A considerable amount of information is available from long-term studies of *d,l*-norgestrel and levonorgestrel in mice, rats, dogs, and monkeys. The chronic toxicity studies with levonorgestrel, in dogs and monkeys, are summarized in Table 1. These studies, conducted by Wyeth Laboratories, USA, were reported in detail to the FDA, and have been incorporated in files on Norplant submitted by the Population Council to the FDA, and by Huhtamäki Oy/Leiras Pharmaceuticals to the Finnish National Board of Health.

The Toxicology Review Panel noted that studies in the beagle dog showed no adverse effects relevant to human use, but nevertheless restated its opinion that the beagle dog is an unsuitable toxicological model for the study of progestogens. The studies were completed before the Panel's opinion on the relevance of the beagle model was first published in 1982 (13).

One 10-year study in the rhesus monkey, in which the animals received the drug orally in capsules, has recently been completed. The highest dose given was equivalent to 1000 times the human implant dose. No toxic effects attributable to the treatment were found.

Extensive chronic toxicological studies have been conducted to evaluate the systemic effects of levonorgestrel. Dosing schedules have included daily administration, as well as cyclic administration comparable to the human use of contraceptives. The studies have served as a basis for the approval by the FDA of oral contraceptives with the following composition: 500 μ g of *d,l*-norgestrel with 50 μ g of ethinylestradiol; 300 μ g of *d,l*-norgestrel with 30 μ g of ethinylestradiol; 150 μ g of levonorgestrel with 30 μ g of ethinylestradiol; and 75 μ g of *d,l*-norgestrel alone.

Table 1. Chronic toxicity studies on levonorgestrel

Species	Highest dose (mg/kg of body weight)	Route	Multiple of daily implant dose	Duration
Dog	0.5, cyclic	Capsules	500	7 years
Dog	0.125, cyclic	Capsules	125	7 years
Monkey	1.0, cyclic	Capsules	1000	10 years

Effects on reproduction

Teratological and reproduction studies have been undertaken in rats and rabbits. Both *d,l*-norgestrel and levonorgestrel have been used in doses corresponding to more than 100 times and 50 times the human dose, respectively. No adverse effects that would suggest a risk for humans were found. In another study, in which covered rods releasing 3.5 µg of levonorgestrel per 24 h were inserted between implantation sites in the uterus of the pregnant rabbit, there was no evidence of any teratological effects on the progeny (ICCR, unpublished data). Masculinization was observed in offspring of rats, but this has been reported with other progestogens and is not considered to be relevant to human subjects. No other fetal abnormalities or malformations were found and the duration of gestation was not altered. Offspring reserved for subsequent breeding were normal with respect to survival age and reproductive capacity. Three dose levels of *d,l*-norgestrel were given to lactating rats, the highest dose being 150 times the human dose. No significant effect was seen in the mothers, in the young, or on lactation.

Relevance of animal tests to the implant dosage form

Long-term animal tests of levonorgestrel have been carried out using oral administration. Several factors must be considered in weighing the relevance of these tests to the implant mode of administration. These include the relative bioavailability of the drug by different routes of administration and the relative constancy of exposure to the drug. When plasma levels of the drug have been measured, the bioavailability by the oral route has been reported as 9% for the rat, 22% for the dog, 9% for the monkey, but 87% for the human (14). Plasma levels of levonorgestrel in Norplant users are lower than those observed with oral administration and do not fluctuate. In view of these considerations the toxicological studies involving oral administration were considered pertinent to the safety of the drug released from the implanted drug delivery system.

Safety of silicone rubber in implants

Silicone rubber materials have been used to make implants of various kinds, such as heart valves and drainage tubes, for use in humans over long periods. It was estimated that, by 1974, 200 000 shunts had been implanted in patients with hydrocephalus, and many thousands more have been used in the subsequent 10 years. The Silastic tubing used to make the shunts is of the same type and diameter as that used in the Norplant capsules.

Even though it is well established that impervious or semipermeable subcutaneous implants induce local sarcomas in rats (15), this observation is not considered to be relevant to man in the light of the very extensive and long-term use of Silastic in humans, during which malignant tumours have not been observed.

Conclusions

The Toxicology Review Panel concluded that the toxicological and teratological data from animal studies on both levonorgestrel and Silastic provide a sufficient indication that Norplant may be considered safe for use in humans.

HUMAN STUDIES

A substantial number of clinical trials have been undertaken on Norplant, including several major phase III studies supported by the ICCR and other agencies. Use-effectiveness and side-effects have been evaluated in studies that have continued for more than 5 years. However, because the method is only now becoming widely available, there have, as yet, been no epidemiological studies of long-term safety.

Release rates

The amount of levonorgestrel released from implants has been calculated from the difference between the steroid content at time of placement and the amount remaining after a known period of use. An analysis of steroid loss from 42 sets of implants used for periods ranging from 1.3 to 6.3 years gave an average release rate of 30 µg per 24 h (16). These data were later supplemented by similar analyses from an additional 117 sets of capsules recovered at various time intervals up to about 8 years from subjects in several clinics. The data suggest an initial release rate of approximately 80 µg per 24 h, which declines over the first 6–18 months to an approximately constant release rate of about 30 µg per 24 h.

Peripheral blood levels of levonorgestrel

Several studies have reported data on peripheral blood levels of levonorgestrel (16–21). Extensive data from unpublished studies were also made available to the consultation by the ICCR. In all of the studies, analyses for levonorgestrel were carried out by radioimmunoassay. The results show that immediately after implantation of the devices there is a rapid rise in peripheral levonorgestrel levels, to 3–4.5 nmol/litre after 24 hours. From results derived from other

studies on levonorgestrel, levels of this magnitude are likely to be more than sufficient to inhibit ovulation (22, 29). During the subsequent 6–18 months, the mean plasma levels gradually decline to 1–1.5 nmol/litre. The mean values in individual subjects appear to remain constant thereafter for a further 5 years, after which there is a substantial decrease.

As with all other constant delivery systems for levonorgestrel, there is considerable between-subject variation in circulating levels of levonorgestrel. One of the factors that contribute to this variation is the large difference in sex-hormone binding globulin (SHBG) levels observed between normal individuals (23, 26). Unlike several other progestogens, levonorgestrel has a high binding affinity to SHBG, and there is thus a correlation between circulating levels of SHBG and levonorgestrel. Levonorgestrel also suppresses SHBG levels, resulting in a decrease in both SHBG and levonorgestrel levels. Moreover, subjects starting with a high level of SHBG show a greater suppression in SHBG and hence levonorgestrel than those with lower initial levels of SHBG. Thus significant between-subject variation in peripheral levonorgestrel levels is found (24–26). Two studies on Norplant users have shown similar results (27; ICCR, unpublished data).

Following the removal of the implants, plasma levonorgestrel becomes unmeasurable within a few days. A removal half-life of some 18 hours can be calculated (ICCR, unpublished data), which is in good agreement with that reported by other investigators for other modes of administration of levonorgestrel (17, 28, 29).

Effects on ovarian function

The ovarian response to levonorgestrel released from the Norplant implants shows considerable variation, both within and between subjects, as has been observed with other low-level levonorgestrel delivery systems (29). When periods of treatment were evaluated in 6-week segments, elevated plasma progesterone levels (> 10 nmol/litre) were observed in 44% of the segments, but the mean increase in progesterone level was less than that observed in ovulatory cycles in normal menstruating women. There was also a marked suppression of the luteinizing hormone surge. It is not known whether the periodic increases in progesterone levels seen in Norplant users and in subjects using other low-dose progestogen formulations (29) reflect the occurrence of ovulation, since monitoring by ultrasound has as yet yielded inconclusive results. In other treatment segments, increases in estradiol were observed, which varied in amplitude (up to 2 nmol/litre) and duration (5–20 days), in the

absence of elevated progesterone levels, indicating follicular activity and no ovulation (17, 18).

Effects on cervical mucus

The effect of levonorgestrel on cervical mucus also contributes to its contraceptive efficacy. During Norplant use, the cervical mucus becomes viscous and scanty, and in a few subjects from whom it was possible to obtain cervical mucus, poor sperm penetration was seen compared with control subjects. In another study, post-coital tests have also shown poor sperm penetration (ICCR, unpublished data).

Effects on the endometrium

Endometrial biopsies from 41 women who used Norplant for between 6 and 110 weeks have been studied (30). Using the criteria of Noyes et al. (31), 5 endometria were normal, 12 were diagnosed as irregular secretory, and 24 demonstrated suppressed activity. These findings are similar to those obtained with other low-dose progestogen delivery systems (29). There was no evidence of endometrial inflammation, atrophy, hyperplasia, carcinoma, or other pathological processes.

Other endocrine effects

Although one study claimed a significant increase in peripheral androstenedione and some increase in testosterone levels after 6 months' use of Norplant (32), two other studies demonstrated contrary results (27, 33). One of these, a cross-sectional study, showed significantly lower testosterone levels in users of Norplant after 51 months than in IUD users (33), while the other, a longitudinal study, showed a decline in testosterone, androstenedione, and SHBG levels (27). Increases in prolactin levels have been observed, but were within normal limits (34).

With regard to effects on adrenal function, a decrease in peripheral levels of cortisol, of approximately 30% over 12 months, has been observed, although the values were within the normal range and remained so during 3 years of observation (35). Similar results were obtained in another study over one year (36). The adrenal response to adrenocorticotrophic hormone (ACTH) stimulation has been shown to be normal (37). Regarding thyroid function, no alterations have been observed in thyroxine and thyroid-stimulating hormone (TSH) levels; a decrease was found in triiodothyronine levels, although the levels remained within the normal range (33). Thus, Norplant does not appear to disturb significantly the function of the thyroid and adrenal glands.

Metabolic effects

Several cross-sectional and longitudinal studies have been undertaken to determine the metabolic and biochemical effects of Norplant at intervals of up to 3 years.

Studies on lipid metabolism have given inconsistent results: triglycerides were reported to be significantly decreased, as were cholesterol and low-density lipoprotein (LDL)-cholesterol levels, with up to 37 months of use (33, 38, 39; ICCR, unpublished data). Widely discrepant changes in high-density lipoprotein (HDL)-cholesterol have been reported, however, including: no change (33); decrease (39); and no change initially, but a significant increase at 12 months (38). Two laboratories reported decreases in HDL-cholesterol levels and in total cholesterol, giving an unchanged cholesterol/HDL-cholesterol ratio (ICCR, unpublished data). In the centre reporting increased HDL-cholesterol levels, the cholesterol/HDL-cholesterol ratio was reduced at 6 months and further at 12 months. A recent study with rods releasing equivalent amounts of levonorgestrel has shown alterations in some subfractions of lipoproteins; HDL-2a, HDL-2b, and HDL-3 were reduced after 1–2 months of use; these decreases were less pronounced at 6 months and there was a return to normal levels after 12 months (40). The studies carried out so far used different methodologies, techniques of quality control, and populations, and further studies are still needed to clarify the effects of levonorgestrel released from Norplant on lipids and lipoproteins.

Liver function has been evaluated at several centres (41; ICCR, unpublished data). Slight non-significant increases in total serum protein and albumin were observed. A reduction in ceruloplasmin levels at 6 months was reported, as well as small increases in bilirubin and bile acids in the first month; these levels returned to normal over the next 5 months (41). No other changes in liver function were seen. In two other cross-sectional studies (33, 42), after 51 months of use, liver function was not significantly different from that observed in control subjects using intra-uterine devices.

Measurements of urea nitrogen, uric acid, sodium, potassium and calcium (33, 42; ICCR, unpublished data) showed no changes. A significant decrease in inorganic phosphorus was observed, but levels remained within the normal range (33). No changes in immunoglobulins have been observed.

Mean blood glucose levels have been shown to be elevated, but within the normal range, after 12–51 months of Norplant use (ICCR, unpublished data). In one study, oral glucose tolerance tests were done at intervals of 6 months for 3 years in 9 subjects (35). Abnormal glucose tolerance was observed in 2 women

with familial diabetes and, in both, glucose tolerance returned to normal at the next test. While the data are limited, Norplant appears to have no deleterious effect on carbohydrate metabolism.

Coagulation studies before treatment, and at 1, 3, and 6 months were undertaken in one study (43). Two groups of subjects taking oral contraceptives were used as controls. Nine clotting factors and nine other haematological parameters were measured. An increase in factor VII and a decrease in antithrombin III were the only significant changes observed in Norplant users after 6 months; these changes were significantly less than those observed in the groups taking oral contraceptives. Moreover, the oral contraceptive users showed significant changes in many of the other factors measured, whereas the Norplant users did not.

Use-effectiveness and discontinuation rates

Experience with more than 14 000 insertions of Norplant has shown a low pregnancy rate and a high continuation rate (44–48; ICCR, unpublished data). The aggregate interim results from a number of clinical trials conducted by the ICCR, involving 992 women, indicate a gross cumulative pregnancy rate at 5 years of 2.6 per 100 woman-years. The annual pregnancy rates during the first 5 years ranged from 0.2 to 1.3. Data on 100 women entering the 6th year show a pregnancy rate of 2.9 (with a standard error of ± 1.4), which suggests a reduction in efficacy although the rate is not significantly different from the rates for the first 5 years.

In a clinical trial in 3 countries conducted between the years 1978 and 1983, the continuation rate at 1 year was 81.4 per 100 women and at 4 years was 49.1 per 100 women (44). In a number of other studies undertaken in developing countries, continuation rates at 1 year were higher (45–48). Continuation rates were lowest among younger women and those desiring a pregnancy (44). These continuation rates are comparable to those commonly quoted for the IUD.

The major medical reason for termination has been menstrual irregularities, the aggregate cumulative rate for several centres being 14.1 per 100 women at 4 years (44). It should be noted that these data are from clinical trials and therefore may not be representative of discontinuation rates that might be seen in programme use. It is difficult to compare the results of these studies with those on other contraceptive methods since the contraceptive in question has a known duration of action of 5 years and the acceptors are thus likely to be highly motivated to continue contraceptive use for such a period.

A total of 11 pregnancies have been reported to be due to method failure. Of these, there were 2 ectopic

pregnancies, both from the same centre, giving an incidence of ectopic pregnancy of 0.8 per 1000 woman-years (44). Although the number of events is small, the method does not appear to increase the incidence of ectopic pregnancy. However, should a pregnancy occur in a woman using Norplant, attention must be paid to the possibility of an ectopic pregnancy.

In a cohort of 992 women, a mean increase in weight of 1.4 kg occurred during the first year of use of Norplant. However, although weight was increased in 52% of the women, 35% of the subjects showed a decrease (49). No significant changes in systolic or diastolic blood pressure were found during the first 3 years of use of Norplant; no data are available for a longer duration of use. In the studies reported by ICCR, headache was the second predominant spontaneously reported complaint after bleeding disturbances, accounting for 3.2% of the discontinuations during the first 3 years of use (44). However, it has not appeared to be a problem in most clinical trials of Norplant in other countries (45-48).

Bleeding patterns

As with other progestogen-only contraceptives, the major side-effect of Norplant is the disruption of the menstrual cycle; about 40% of Norplant users report a regular bleeding pattern during the first year of use. Most abnormal bleeding episodes are characterized by an increased frequency, an increased number of bleeding days, or irregular bleeding and spotting. Heavy bleeding episodes are uncommon and the prevalence of abnormal bleeding decreases with duration of use.

In a study of a cohort of 104 Norplant users who completed 4 years of use, 25% reported bleeding episodes lasting more than 11 days in the first year, while only 10% had such bleeding episodes during the second, third and fourth years of use (44). In another cohort of 54 women, 50% of users reported bleeding and spotting for more than 96 days during the first year of use; only 20% reported this during the third year (50). While the menstrual problems do diminish markedly with time, these complaints are the major reason for discontinuation in the first year of use (45, 48, 51, 52).

In a small study, the mean amount of monthly blood loss in Norplant users decreased, although not significantly, from 30 ml pretreatment to 24 ml during the first year of use (53). Mean haemoglobin levels increased slightly but significantly in Norplant users and evidence of anaemia from the use of Norplant, even in women with frequent bleeding episodes, has been rare (49). If a user develops severe and prolonged bleeding, removal of the capsules

should be considered. Normal regular menstrual bleeding can be expected to resume shortly after, unless the bleeding has another pathogenesis.

Insertion and removal of Norplant

Extensive clinical experience has been accumulated on the insertion and removal of Norplant. More than 14 000 women have had these capsules inserted and 10-15% have had them removed. The experience gained has indicated that, to minimize the risk of infection, both insertion and removal should be performed in a clinic setting. It is of utmost importance that sterile techniques be maintained throughout both procedures.

Norplant should be inserted during the first 7 days after the onset of menstruation in order to minimize the risk of insertion during an undiagnosed pregnancy. Insertion can also be done immediately after abortion and in non-breast-feeding women immediately postpartum. At this stage of knowledge, it is not possible to make a recommendation on the use of Norplant in lactating women.

The preferred sites of insertion are the upper arm or the forearm. It is important that the capsules be inserted superficially, as deeper insertion makes removal more difficult. In one study, removal was difficult in 12% of the subjects primarily because the capsules had been inserted too deeply (ICCR, unpublished data). Sutures are not required to close the small incision and the scar is usually minimal, although keloid formation has been reported to occur occasionally (ICCR, unpublished data). Local complications following insertion are uncommon and the cumulative local infection rate is 0.3%. Expulsion of capsules is rare and has occurred only in the presence of infection. Only one instance of migration of a capsule has been reported (ICCR, unpublished data).

The capsules should be removed after 5 years of use as the effectiveness of the method declines after this time. However, in the event that a woman does not return for scheduled removal, no deleterious effects would be expected, other than the risk of unplanned pregnancy. If a woman wants to continue this method of contraception, a new set of implants may be inserted. Removal of the capsules is more time-consuming than the insertion: for example, in one clinic the mean time for insertion was 7 minutes, and for removal, 21 minutes (ICCR, unpublished data).

When the capsules are removed because of complications related to the method or if the woman wants to conceive, blood levels of levonorgestrel decline rapidly, becoming undetectable within two days, and ovulation resumes promptly. Of patients having Norplant removed in order to conceive, 40% had become pregnant by 3 months, 76% by 1 year and

90% by 24 months (44). These rates are similar to normal rates of fecundity. The implants should be removed whenever requested by the woman or in the case of an accidental pregnancy that the woman wishes to carry to term.

Contraindications for the use of Norplant

Since Norplant is a new method of contraception, there has been insufficient time for large-scale, long-term studies of rare adverse effects; thus, contraindications and possible warnings regarding Norplant use must be based on extrapolation from information on other hormonal methods. Until further information is available it is considered inadvisable to use Norplant as a method of contraception in women undergoing anticoagulant therapy, or with undiagnosed abnormal uterine bleeding, known or suspected pregnancy, haemorrhagic diathesis, or active hepatocellular disease.

SERVICE DELIVERY ASPECTS

Service delivery issues arising from the introduction of Norplant must be addressed if utilization of this method in family planning programmes is to be successful. Although clinical trials have provided extensive experience with Norplant, there is limited information on service aspects, which will be needed by both family planning programme administrators and clinic staff. The cost-effectiveness of the method relative to other methods of contraception remains to be determined.

Since Norplant utilizes a new mode of drug delivery, requiring insertion and later removal, considerable attention must be given to training for these procedures. Available information suggests that both physicians and other health personnel can easily be trained to insert and remove the capsules (51). In addition, clinic staff should be familiar with the bleeding disturbances that are particularly common during the first year, and need to be trained to counsel users accordingly. It is important to identify specific centres that can serve as national or regional resources for the training of health personnel. Similarly, referral or back-up facilities need to be identified, especially in rural areas.

From the outset, it is essential that government health agencies be involved in the introduction of the method. Experience with the introduction of other new methods of contraception has shown the essential role that "pre-introductory trials" play in this process. These trials can be of use in identifying training requirements and other method-related service delivery issues.

CONCLUSIONS

The Norplant subdermal implant is a very efficient method of contraception, which remains effective for at least 5 years. This long duration of contraceptive action is particularly advantageous to women who wish an extended period of contraceptive protection, irrespective of whether a subsequent pregnancy is planned.

Animal studies on levonorgestrel, the progestogen released by the implant, provide a sufficient indication that the drug may be considered safe for use in humans. Extensive clinical studies have so far not shown any major adverse side-effects. Silastic, from which the capsule is made, has been used in human subjects since 1950 for extended periods and has shown no adverse effects.

The clinical trial data available to date on more than 4000 women have shown high continuation rates, ranging from 60% to 95% at the end of the first year, and about 50% at the end of the fifth year. As with other progestogen-only contraceptives, the most common side-effect and the principal reason for discontinuation is bleeding irregularities. These occur at some time in the majority of women using this method, although bleeding problems tend to diminish with increasing duration of use. Women have reported irregular bleeding, spotting and, to a lesser extent, amenorrhoea. Heavy and prolonged bleeding has rarely occurred.

Because of the constant release of small amounts of the contraceptive drug (approximately 30 µg per 24 h after the first 6–18 months of use), the total amount of drug to which the body is exposed is small, being less than 100 mg of levonorgestrel over 5 years. Thus, potential side-effects of the contraceptive steroid are minimized and there appears to be little significant effect on metabolic or other physiological parameters. Furthermore, exposure to the drug can be terminated at any time by removal of the device.

This modality is just beginning to be widely introduced, thus little information has been generated on rare or long-term effects. It is recommended that appropriate surveillance activities be developed to evaluate its long-term safety. As with other hormonal contraceptive methods, additional research is also needed on the use of Norplant during lactation, since few data are available on the effect of levonorgestrel on the growth and development of children exposed to the steroid via breast milk.

The insertion and removal of Norplant, whether by trained physicians or by other health personnel, require appropriate clinic facilities. It is essential that adequate training programmes be established for clinic personnel prior to introduction of Norplant into a family planning programme.

"Pre-introductory" trials, prior to widespread introduction, are important for providing training and information about service delivery issues, and to assess the local acceptability of the method. It is important to note that the skill of the provider at insertion will largely determine the ease of removal.

In summary, the participants in the Consultation

concluded that Norplant provides an effective and reversible long-term method of fertility regulation. It is considered suitable for use in family planning programmes, along with other currently available contraceptive preparations and devices, since it provides an important option for women desiring long-term contraception.

*
* *

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F. #2018R00733

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U.S. DISTRICT COURT E.D.N.Y.
★ MAY 23 2019 ★

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
----- X

BROOKLYN OFFICE

UNITED STATES OF AMERICA

- against -

WESLEY BLAKE BARBER and
CHRISTOPHER WALKER,

Defendants.

----- X

THE GRAND JURY CHARGES:

INDICTMENT

CR 19 239

Cr. No.
(T. 18, U.S.C., §§ 371, 981(a)(1)(C),
1343, 1349, 1952(a)(3)(A), 2 and 3551
et seq.; T. 21, U.S.C., § 853(p); T. 28,
U.S.C., § 2461(c))

DEARIE, J.

ORENSTEIN, M.J.

INTRODUCTION

At all times relevant to this Indictment, unless otherwise indicated:

I. The Defendants and Relevant Entities

1. The defendant CHRISTOPHER WALKER was a licensed physician and urogynecologist who performed surgeries on women to remove transvaginal mesh ("TVM") implants ("removal surgeries"). WALKER performed these surgeries in connection with MedSurg Holdings LLC d/b/a MedSurg Consultants LLC ("MedSurg"), a business he owned and operated.

2. The defendant WESLEY BLAKE BARBER, together with others, operated and owned Surgical Assistance Inc. ("Surgical Assistance") and Medical Funding Consultants LLC ("Medical Funding Consultants") (together, the "Barber Entities"). The Barber Entities facilitated the coordination of removal surgeries and purchased and resold medical debts for profit.

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ORNSTEIN M.

3. Various companies were in the business of, among other things, providing financing in connection with removal surgeries, including by offering loans that were secured by financial awards from personal injury lawsuits (“Contingent Loans”) or by purchasing the right to collect debts for expenses owed by patients who had removal surgeries (“Medical Debts”). These companies included Company-1, an entity the identity of which is known to the Grand Jury, and its affiliates (collectively, “Funding Company-1”), which operated in Brooklyn, New York, and other locations; and Company-2, an entity the identity of which is known to the Grand Jury, and its affiliates (collectively, “Funding Company-2”), which operated in Boca Raton, Florida, and other locations.

II. The Fraudulent Scheme

4. Since approximately 2008, manufacturers of TVM implants have been engaged in lawsuits relating to the use of TVM implants and alleged harm that these implants caused. On or about February 7, 2012, a Multi-District Litigation (“MDL”) was formed and numerous TVM lawsuits were consolidated in the District Court in the Southern District of West Virginia. On or about June 14, 2013, one of the manufacturer-defendants in the MDL announced that it had entered into a Master Settlement Agreement (“MSA”) with certain counsel regarding a particular number of filed – and some unfilled – TVM cases handled or controlled by participating counsel. As part of the MSA, the parties agreed upon monetary recoveries to be provided to current and future claimants who fell into particular categories. Women who had undergone removal surgeries were entitled to receive a larger settlement than those whose mesh insert remained implanted. Other manufacturers entered into similar settlement agreements that were also publicly announced.

5. Following the announcement of the MSA, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, participated in a fraudulent scheme in order to profit from the MSA and other TVM-related lawsuits.

(a) First, members of the conspiracy facilitated the identification of victims – women throughout the United States who had the mesh insert implanted transvaginally and might have been willing to undergo removal surgeries and commence lawsuits against the manufacturer of the mesh insert (the “Victims”). Among the Victims were Jane Doe #1, Jane Doe #2 and Jane Doe #3, individuals whose identities are known to the Grand Jury and who resided in the Eastern District of New York. Once the Victims were identified, individuals associated with medical funding facilitators, including the Barber Entities, contacted the Victims to determine whether the Victims would travel to meet with one of their pre-selected surgeons and undergo removal surgeries. To entice the Victims to undergo a removal surgery that would lead to a higher settlement payment from the TVM manufacturers, the defendants, together with others, falsely and fraudulently (i) described the risks of the TVM implants and the need for removal of the TVM implants, (ii) strongly implied that the women would need to travel out of state to use pre-selected doctors (rather than the Victims’ local doctors), and (iii) misled the Victims about their ability (or inability) to rely upon their health insurance to cover any medical expenses associated with the removal surgery.

(b) Second, companies, including Funding Company-1 and Funding Company-2, financed the removal surgeries for the Victims, either through Contingent Loans or by purchasing Medical Debts. Certain agreements entered into by the Victims included provisions in which the women agreed to repay the costs of the removal surgery plus interest,

which accrued at exorbitant rates, if the women ultimately received a settlement or favorable judgment against the mesh manufacturer. In certain funding arrangements, the Victims were responsible for the medical bills associated with the removal surgeries even if they did not receive a settlement.

(c) Third, once surgical funding was secured, the Victims were contacted again and arrangements were made for the women to travel to visit a doctor who would perform the removal surgery (often by traveling hundreds of miles and with very little consultation in advance of the surgery). For example, WALKER performed removal surgeries on Jane Doe #1 and Jane Doe #3.

(d) Fourth, with no disclosure to the Victims who underwent the removal surgeries, WALKER, together with others, paid kickbacks and bribes in exchange for BARBER's and the Barber Entities' referral of patients to WALKER.

COUNT ONE
(Wire Fraud Conspiracy)

6. The allegations contained in paragraphs one through five are realleged and incorporated as if fully set forth in this paragraph.

7. In or about and between June 2013 and March 2016, both dates being approximate and inclusive, within the Eastern District of New York and elsewhere, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, did knowingly and intentionally conspire to devise a scheme and artifice to defraud and to obtain money and property by means of one or more materially false and fraudulent pretenses, representations and promises, and for the purpose of executing such scheme and artifice, to transmit and cause to be transmitted, by means of wire communication in

interstate commerce, writings, signs, signals and sounds, contrary to Title 18, United States Code, Section 1343.

(Title 18, United States Code, Sections 1349 and 3551 et seq.)

COUNTS TWO THROUGH FOUR
(Wire Fraud)

8. The allegations contained in paragraphs one through five are realleged and incorporated as if fully set forth in this paragraph.

9. On or about the dates set forth below, within the Eastern District of New York and elsewhere, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, did knowingly and intentionally devise a scheme and artifice to defraud and to obtain money and property by means of one or more materially false and fraudulent pretenses, representations and promises, and for the purpose of executing such scheme and artifice, transmit and cause to be transmitted, by means of wire communication in interstate commerce, writings, signs, signals and sounds, as described below.

<u>COUNT</u>	<u>APPROXIMATE DATE</u>	<u>DESCRIPTION</u>
TWO	May 27, 2014	Email on behalf of a Florida-based law firm to Jane Doe #1 in New York providing, among other things, a document from Surgical Assistance
THREE	June 7, 2014	Email from a Washington-based electronic communications provider to New York-based Funding Company-1 providing a chart of the status of various individuals, including Jane Doe #3

<u>COUNT</u>	<u>APPROXIMATE DATE</u>	<u>DESCRIPTION</u>
FOUR	July 14, 2014	Email from "blake@medicalfundingconsultants.com," based in Florida, directing New York-based Funding Company-1 to send another individual the "contract for the [last name of Jane Doe #3] case"

(Title 18, United States Code, Sections 1343, 2 and 3551 et seq.)

COUNT FIVE
(Travel Act Conspiracy)

10. In or about and between January 2014 and March 2016, both dates being approximate and inclusive, within the Eastern District of New York and elsewhere, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, did knowingly and willfully conspire to use, and cause the use of, one or more facilities in interstate commerce, with intent to promote, manage, establish, carry on and facilitate the promotion, management, establishment and carrying on of an unlawful activity, to wit: payment and acceptance of bribes and kickbacks in exchange for the referral of patients, in violation of the laws of the State or States in which the unlawful activity was committed, and thereafter perform such promotion, management, establishment, carrying on and facilitation of the promotion, management, establishment and carrying on of such unlawful activity, contrary to Title 18, United States Code, Section 1952(a)(3)(A).

11. In furtherance of the conspiracy and to effect its objects, within the Eastern District of New York and elsewhere, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, committed and caused to be committed, among others, the following:

OVERT ACTS

(a) On or about May 23, 2014, Jane Doe #1 traveled from New York to Florida for a TVM removal surgery.

(b) On or about May 27, 2014, Jane Doe #2 traveled from New York to Florida for a TVM removal surgery.

(c) On or about September 17, 2014, Jane Doe #3 traveled from New York to Florida for a TVM removal surgery.

(d) A check dated October 3, 2014 was issued from Funding Company-1 and made payable to MedSurg.

(e) A check dated October 21, 2014 in the amount of \$16,000 was issued from MedSurg to Surgical Assistance for Jane Doe #3 and three other Victims.

(Title 18, United States Code, Sections 371 and 3551 et seq.)

COUNT SIX

(Travel Act Violation – Jane Doe #3)

12. On or about September 17, 2014, within the Eastern District of New York and elsewhere, the defendants WESLEY BLAKE BARBER and CHRISTOPHER WALKER, together with others, did knowingly and intentionally use, and cause the use of, one or more facilities in interstate commerce, with intent to promote, manage, establish, carry on and facilitate the promotion, management, establishment and carrying on of an unlawful activity, to wit: payment and acceptance of bribes and kickbacks in exchange for the referral of Jane Doe #3 to WALKER, in violation of Florida Statute Sections 817.505 and 456.054, and thereafter did perform and attempt to perform such promotion, management,

establishment, carrying on and facilitation of the promotion, management, establishment and carrying on of such unlawful activity.

(Title 18, United States Code, Sections 1952(a)(3)(A), 2 and 3551 et seq.)

CRIMINAL FORFEITURE ALLEGATION

13. The United States hereby gives notice to the defendants that, upon their conviction of any of the offenses charged herein, the government will seek forfeiture in accordance with Title 18, United States Code, Section 981(a)(1)(C) and Title 28, United States Code, Section 2461(c), which require any person convicted of such offenses to forfeit any property, real or personal, constituting, or derived from, proceeds obtained directly or indirectly as a result of such offenses.

14. If any of the above-described forfeitable property, as a result of any act or omission of the defendants:

- (a) cannot be located upon the exercise of due diligence;
- (b) has been transferred or sold to, or deposited with, a third party;
- (c) has been placed beyond the jurisdiction of the court;
- (d) has been substantially diminished in value; or
- (e) has been comingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of the defendants up to the value of the forfeitable property described in this forfeiture allegation.

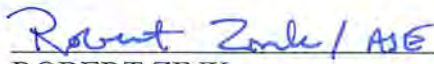
(Title 18, United States Code, Section 981(a)(1)(C); Title 21, United States Code, Section 853(p); Title 28, United States Code, Section 2461(c))

A TRUE BILL


FOREPERSON

RICHARD P. DONOGHUE
UNITED STATES ATTORNEY
EASTERN DISTRICT OF NEW YORK

BY: 
ACTING UNITED STATES ATTORNEY
PURSUANT TO 28 C.F.R. § 136


ROBERT ZINK
ACTING CHIEF, FRAUD SECTION
CRIMINAL DIVISION
U.S. DEPARTMENT OF JUSTICE

F.#: 2018R00733
FORM DBD-34
JUN. 85

No. _____

UNITED STATES DISTRICT COURT

EASTERN *District of* NEW YORK

CRIMINAL DIVISION

THE UNITED STATES OF AMERICA

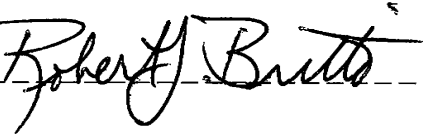
vs.

WESLEY BLAKE BARBER and CHRISTOPHER WALKER,
Defendants.

INDICTMENT

(T. 18, U.S.C., §§ 371, 981(a)(1)(C), 1343, 1349, 1952(a)(3)(A), 2 and 3551 et seq.;
T. 21, U.S.C., § 853(p); T. 28, U.S.C. § 2461(c))

A true bill



Foreperson

Filed in open court this _____ day,

of _____ A.D. 20 _____

Clerk

Bail, \$ _____

Elizabeth Geddes, Assistant U.S. Attorney (718) 254-6430

Andrew Estes, Trial Attorney (718) 254-6250



PRESS RELEASE

Patient Recruiter and Physician Plead Guilty in Bribery and Kickback Scheme in Connection with Transvaginal Mesh Litigation

Friday, September 17, 2021

For Immediate Release

U.S. Attorney's Office, Eastern District of
New York

Defendants Corrupted the Physician-Patient Relationship through Bribes and Kickbacks for Patient Referrals

Earlier today, in federal court in Brooklyn, Christopher Walker, a licensed urogynecologist, pleaded guilty to participating in a scheme involving the payment of bribes and kickbacks to obtain referrals of female patients across the United States for surgeries to remove transvaginal mesh (TVM) implants. Wesley Blake Barber, an owner of Surgical Assistance Inc., pleaded guilty on September 14, 2021 to participating in the same scheme. Both proceedings took place before United States District Judge Raymond J. Dearie.

Jacquelyn M. Kasulis, Acting United States Attorney for the Eastern District of New York, Assistant Attorney General Kenneth A. Polite Jr. of the Justice Department's Criminal Division, and Michael J. Driscoll, Assistant Director-in-Charge, Federal Bureau of Investigation, New York Field Office (FBI) announced the guilty pleas.

“With these guilty pleas, both defendants have admitted to participating in a reprehensible bribery and kickback scheme to exploit women across the country in connection with costly transvaginal mesh removal surgeries,” stated Acting United States Attorney Kasulis. “This Office, the Department of Justice and the FBI are committed to investigating and prosecuting medical professionals and others who take advantage of vulnerable victims for their own illegal gain and personal profit.”

According to court filings and facts presented at the plea proceeding, Barber and Walker sought to profit in connection with lawsuits filed throughout the United States relating to alleged harm that TVM implants had caused female patients. The scheme sought to take advantage of the fact that female patients who had their TVM implants surgically removed were entitled to receive larger settlements than female patients whose inserts remained implanted. As part of the scheme, Walker and others paid kickbacks and bribes to Barber in exchange for the referral of female patients for these surgeries, including patients who traveled across the United States to undergo the surgeries.

When sentenced, Walker faces up to 10 years in prison and has agreed to forfeit approximately \$800,000. Barber faces up to 5 years in prison and has agreed to forfeit approximately \$1.1 million.

The government’s case is being prosecuted by Assistant United States Attorneys Elizabeth Geddes and Sarah Evans and Trial Attorney Andrew Estes of the Criminal Division’s Fraud Section.

The Defendants:

WESLEY BLAKE BARBER

Age: 51

Detroit, Michigan

CHRISTOPHER WALKER

Age: 49

Windermere, Florida

E.D.N.Y. Docket No. 19-CR-239 (RJD)

Contact

John Marzulli

United States Attorney’s Office

(718) 254-6323

Updated September 17, 2021

Topic

HEALTH CARE FRAUD

Component

[USAO - New York, Eastern](#)

Related Content

PRESS RELEASE

Former Long Island Business Owner Charged with Orchestrating \$22 Million Health Care Fraud, Kickback and Money Laundering Scheme

Earlier today, at the federal courthouse in Brooklyn, an indictment was unsealed charging Oleg Beretsky with conspiring to commit health care fraud, violating the federal Anti-Kickback Statute, conspiring to violate...

March 18, 2025

PRESS RELEASE

Long Island Medical Doctor Convicted of Illegally Distributing Oxycodone Pills

"As proven, Dr. Hassad was a drug dealer who disgracefully dispensed highly addictive oxycodone pills without any regard for the well-being of the patient but with plenty of interest in...

December 11, 2024

PRESS RELEASE

**United States Settles Claim Against New York Dermatology Practice
Whose Medical Doctor Refused to Perform a Medical Procedure on an
HIV-Positive Patient**

“This settlement reflects this Office’s commitment to robust enforcement of the ADA and ensuring that patients with HIV have access to medical care,” stated United States Attorney Peace.

December 3, 2024



Eastern District of New York

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Brooklyn NY 11201



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PRESS RELEASE

Surgical Funding Facilitator and Physician Charged in Alleged Nationwide Scheme to Defraud Women in Connection with Transvaginal Mesh Litigation

Friday, May 24, 2019

For Immediate Release

Office of Public Affairs

A surgical funding facilitator and a licensed urogynecologist were charged in a six-count indictment unsealed today for their roles in an alleged scheme to defraud women across the United States in connection with surgeries to remove transvaginal mesh (TVM) implants related to mass tort litigation.

Assistant Attorney General Brian A. Benczkowski of the Justice Department's Criminal Division, U.S. Attorney Richard P. Donoghue of the Eastern District of New York and Assistant Director in Charge William F. Sweeney Jr. of the FBI's New York Field Office made the announcement.

Wesley Blake Barber, 49, of Detroit, Michigan, the owner of Surgical Assistance Inc. and Medical Funding Consultants LLC, and Christopher Walker, M.D., 49, of Orlando, Florida, and owner of MedSurg Holdings LLC, were charged in an indictment filed in the Eastern District of New York with one count of conspiracy to commit wire fraud, three counts of wire fraud, one count of conspiracy to violate the Travel Act and one count of violating the Travel Act. Both defendants were arrested this morning. Barber is expected to appear this afternoon before U.S. Magistrate

Judge Rebecca Rutherford of the Northern District of Texas at the federal courthouse in Dallas, and Walker is expected to appear before U.S. Magistrate Judge Gregory Kelly of the Middle District of Florida at the federal courthouse in Orlando. The case has been assigned to U.S. District Judge Raymond J. Dearie of the Eastern District of New York.

According to the indictment, Barber and Walker sought to profit in connection with lawsuits filed around the country relating to alleged harm that TVM implants caused women. The alleged scheme sought to take advantage of settlements in these lawsuits in which women who had their TVM implants surgically removed were entitled to receive larger settlements than women whose inserts remained implanted. As part of the scheme, women around the country were allegedly enticed into agreeing to undergo removal surgeries after scheme participants allegedly fraudulently told the women, among other things, about the risks of the TVM implants and the need to travel long distances and incur significant debt in order to undergo the surgeries. In addition, Walker and others allegedly paid kickbacks and bribes to Barber in exchange for the referral of these women for surgeries.

The charges in the indictment are merely allegations, and all defendants are presumed innocent until proven guilty beyond a reasonable doubt in a court of law.

The investigation was conducted by the FBI. Trial Attorney Andrew Estes of the Criminal Division's Fraud Section and Assistant U.S. Attorney Elizabeth Geddes of the Eastern District of New York are prosecuting the case.

The Criminal Division's Fraud Section leads the Medicare Fraud Strike Force. Since its inception in March 2007, the Medicare Fraud Strike Force, which maintains 14 strike forces operating in 23 districts, has charged nearly 4,000 defendants who have collectively billed the Medicare program for more than \$14 billion.

Updated February 5, 2025

Topic

HEALTH CARE FRAUD

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Press Release Number: 19-582

Related Content

PRESS RELEASE

Executive Vice President of Insurance Brokerage Pleads Guilty in \$133M Affordable Care Act Fraud Scheme

A Florida executive pleaded guilty today for his role in a scheme to submit fraudulent applications to enroll consumers in Affordable Care Act insurance plans (ACA plans) that were fully...

April 18, 2025

PRESS RELEASE

Physician Convicted at Trial for Illegal Distribution of Opioids and Healthcare Fraud Conspiracies

A federal jury convicted a medical doctor yesterday for his participation in conspiracies to commit health care fraud and wire fraud and to unlawfully distribute controlled substances.

April 16, 2025

PRESS RELEASE

Louisiana Chiropractor Convicted of Health Care Fraud and Unemployment Insurance Fraud

A federal jury convicted a Louisiana chiropractor yesterday for his role in health care fraud and unemployment insurance fraud schemes totaling millions of dollars.



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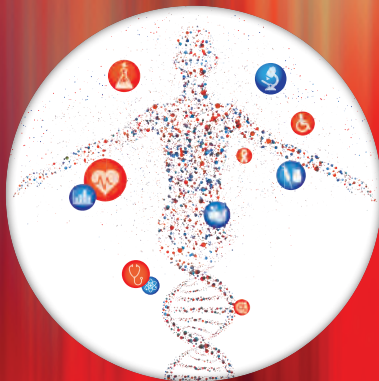


**U.S. FOOD & DRUG
ADMINISTRATION**

MENOPAUSE

Medicines to Help You

Some women choose to treat their menopause symptoms with hormone medicines. This booklet lists some basic information about the FDA-approved hormone medicines for menopause. Use this booklet to help you talk to your healthcare provider about whether hormone medicines are right for you.



Menopause (sometimes called “the change of life”) is a normal time in a woman’s life when her period stops. During menopause, a woman’s body makes less of the hormones estrogen and progesterone. Lower hormone levels may lead to symptoms like night sweats, hot flashes, and vaginal dryness along with thin bones.

Some women choose to treat their menopause symptoms with hormone medicines sometimes called Hormone Therapy. There are different types of hormone medicines used during and after menopause:

- Estrogen-Only Medicines
- Progestin-Only Medicines
- Combination Estrogen and Progestin Medicines
- Combination Estrogen and Other Medicines

This booklet does not talk about non-hormone medicines for menopause. Ask your healthcare provider about the FDA-approved non-hormone medicine for menopause called Brisdelle (paroxetine).

FDA Office of Women’s Health
www.fda.gov/menopause

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Side Effects

Hormone medicines can have side effects. Serious health problems can happen in women who take menopause hormone therapy.

- For some women, hormone medicines may raise their chances of blood clots, heart attacks, strokes, and breast cancer.
- For some women who are 65 years old or older, hormone medicines may raise their chances of dementia.
- For women who still have their uterus, taking estrogen-only medicines raises their chance of getting cancer of the lining of the uterus or endometrial cancer. These women need to take progestin to prevent endometrial cancer.

Do not take hormone therapy if you:

- have problems with vaginal bleeding
- have or have had certain cancers such as breast cancer or uterine cancer
- have or have had a blood clot, stroke or heart attack
- have a bleeding disorder
- have liver disease
- have allergic reactions to hormone medicine

This booklet does not list all of the side effects and warnings for each hormone medicine. Ask your healthcare provider about all of the benefits and risks of taking hormone medicines. Also check the FDA website to learn more about each medicine listed in this booklet.

<https://www.accessdata.fda.gov/scripts/cder/daf/>

Estrogen-Only Medicines

BRAND NAME	GENERIC NAME	PRODUCT TYPE
Alora	estradiol	Patch
Cenestin	synthetic conjugated estrogens	Pill
Climara	estradiol	Patch
Delestrogen	estradiol valerate	Injection (Shot)
Divigel	estradiol	Gel
Elestrin	estradiol	Gel
Enjuvia	synthetic conjugated estrogens	Pill
Esclim	estradiol	Patch
Estrace	estradiol	Pill, Vaginal Cream
Estraderm	estradiol	Patch
Estrasorb	estradiol	Skin Cream (Emulsion)
Estring	estradiol	Vaginal Insert
EstroGel	estradiol	Gel
Evamist	estradiol	Skin Spray (Transdermal)
Femring	estradiol acetate	Vaginal Ring
Femtrace	estradiol acetate	Pill
Menest	esterified estrogen	Pill
Menostar (only used to prevent osteoporosis)	estradiol	Patch
Minivelle	estradiol	Patch
Ogen	estropipate	Pill, Vaginal Cream
Ortho-Est	estropipate	Pill
Osphena (not estrogen only)	ospemifene	Pill
Premarin	conjugated estrogens	Pill, Vaginal Cream, Injection (Shot)
Vagifem	estradiol	Vaginal Tablet
Vivelle	estradiol	Patch
Vivelle-Dot	estradiol	Patch

Estrogen-Only Medicines

Do not use if you:

- have unusual vaginal bleeding
- have or have had certain cancers such as breast cancer or uterine cancer
- have or have had blood clots in the legs or lungs
- have a bleeding disorder
- have had a stroke or heart attack
- have liver problems
- have serious reactions to estrogen medicines
- think you are pregnant

Serious Side Effects

- Stroke or blood clots
- Endometrial cancer in women who still have their uterus and who do not use progestin with estrogen-only medicines
- Dementia in women 65 years and older
- Gallbladder disease or high triglyceride (cholesterol) levels that could lead to problems with your pancreas
- Vision loss caused by a blood clot in the eye
- Liver problems
- High blood pressure
- Severe allergic reactions

Less Serious, Common Side Effects

- Headaches
- Painful or tender breasts
- Vaginal spotting
- Stomach cramps/bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

For more information about the risks and side effects for each drug, check:
<https://www.accessdata.fda.gov/scripts/cder/daf/>

Progestin-Only Medicines

BRAND NAME	GENERIC NAME	PRODUCT TYPE
Prometrium	micronized progesterone	Pill
Provera	medroxyprogesterone acetate	Pill

Progestin-Only Medicines

Progestin-Only Medicines

Estrogen-only medicines are usually taken with progestin-only medicines to lower the chance of getting endometrial cancer in women who still have their uterus.

The side effects listed below are for women who take a progestin-only medicine and an estrogen-only medicine.

Do not use if you:

- have unusual vaginal bleeding
- have or have had certain cancers such as breast cancer or uterine cancer
- have or have had blood clots in the legs or lungs
- have a bleeding disorder
- have had a stroke or heart attack
- have liver problems
- have serious reactions to estrogen medicines
- think you are pregnant

Serious Side Effects

- Heart attack or stroke
- Blood clots
- Breast cancer
- Dementia in women 65 years and older
- Gallbladder disease or high triglyceride (cholesterol) levels that could lead to problems with your pancreas
- Vision loss caused by a blood clot in the eye
- Liver problems
- High blood pressure
- Severe allergic reactions

Less Serious, Common Side Effects

- Headaches
- Painful or tender breasts
- Vaginal spotting
- Stomach cramps/bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

For more information about the risks and side effects for each drug, check:

<https://www.accessdata.fda.gov/scripts/cder/daf/>

Combination Estrogen and Progestin Medicines

BRAND NAME	GENERIC NAME	PRODUCT TYPE
Activella	estradiol/norethindrone acetate	Pill
Angeliq	estradiol/drospirenone	Pill
Climara Pro	estradiol/levonorgestrel	Patch
Combipatch	estradiol/norethindrone acetate	Patch
Femhrt	norethindrone acetate/ethinyl estradiol	Pill
Prefest	estradiol/norgestimate	Pill
Prempro	conjugated estrogen/medroxyprogesterone	Pill

Combination Estrogen and Progestin Medicines

Do not use if you:

- have unusual vaginal bleeding
- have or have had certain cancers such as breast cancer or uterine cancer
- have or have had blood clots in the legs or lungs
- have a bleeding disorder
- have had a stroke or heart attack
- have liver problems
- have serious reactions to estrogen medicines
- think you are pregnant

Serious Side Effects

- Heart attack or stroke
- Blood clots
- Breast cancer
- Dementia in women 65 years and older
- Gallbladder disease or high triglyceride (cholesterol) levels that could lead to problems with your pancreas
- Vision loss caused by a blood clot in the eye
- Liver problems
- High blood pressure
- Severe allergic reaction

Less Serious, Common Side Effects

- Headaches
- Painful or tender breasts
- Vaginal spotting
- Stomach cramps/bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

For more information about the risks and side effects for each drug, check:

<https://www.accessdata.fda.gov/scripts/cder/daf/>

Combination Estrogen and Other Medicines

BRAND NAME	GENERIC NAME	PRODUCT TYPE
Duavee	conjugated estrogen/bazedoxifene	Pill

You should not use Duavee if you are taking medicines that have estrogen, progestin, or both hormones.

Do not use if you:

- have unusual vaginal bleeding
- have or have had certain cancers such as breast cancer or uterine cancer
- have or have had blood clots in the legs or lungs
- have a bleeding disorder
- have had a stroke or heart attack
- have liver problems
- have had a serious allergic reaction to estrogen medicines
- think you are pregnant or may become pregnant
- are breastfeeding (nursing)

Serious Side Effects

- Stroke or blood clots
- Dementia in women 65 years and older
- Gallbladder disease or high triglyceride (cholesterol) levels that could lead to problems with your pancreas
- Vision loss caused by a blood clot in the eye
- Liver problems
- High blood pressure
- Severe allergic reaction

Less Serious, Common Side Effects

- Muscle spasms
- Nausea
- Diarrhea
- Upset stomach/stomach pain
- Throat pain
- Dizziness
- Neck pain

For more information about the risks and side effects for each drug, check:

<https://www.accessdata.fda.gov/scripts/cder/daf/>

Important Questions to Ask About Menopause Hormone Medicines

Are hormones right for me? Why?

What are the benefits?

What are the serious risks and common side effects?

How long should I use hormone therapy?

What is the lowest dose that will work for me?

Are there any non-hormone medicines that I can take?



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To get other women's health materials, go to: www.fda.gov/womens

This booklet was developed by the FDA Office of Women's Health.

This booklet should not be used in place of talking to your healthcare provider or reading the label for your medicine.

The drug and risk information may change. Check the FDA website for the latest facts for each product listed in this booklet.



Prempro Settlements to Result in \$1.2B Payments for Breast Cancer: Report



📅 June 20, 2012 👤 Staff Writers 💬 [Add Your Comments](#)

Pfizer is expected to pay a total of about \$1.2 billion to settle lawsuits claiming that [side effects of Prempro caused women to develop breast cancer](#).

The drugmaker has already paid out \$896 million to settle approximately 6,000 Prempro breast cancer lawsuits, and Pfizer has now set aside an additional \$330 million to cover the remaining 4,000, according to a recent filing with the Securities and Exchange Commission (SEC).

The Prempro settlements come after six years of trials, in which several plaintiffs were awarded tens of millions of dollars, including punitive damages for the drug maker's actions in withholding information about the risk of breast cancer from Prempro.



DO YOU KNOW ABOUT...

HAIR DYE CANCER LAWSUITS FOR SALON PROFESSIONALS

Hair dye lawsuits are being pursued for salon professionals who were routinely exposed to hair dye chemicals and diagnosed with bladder cancer or breast cancer. See if you qualify for a hair dye cancer lawsuit settlement.

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[SEE IF YOU QUALIFY FOR COMPENSATION](#)

Commonly referred to as hormone replacement therapy (HRT), Prempro contains a combination of the drugs Provera and Premarin, which artificially boost hormone levels in women undergoing menopause due to surgery or in postmenopausal women. It was originally introduced by Wyeth, which was acquired by Pfizer in 2009.

About 10,000 women have filed a lawsuit after allegedly developing breast cancer from Prempro. In the litigation, 11 out of the 21 cases presented to a jury have resulted in a verdict in favor of the plaintiff.

In the early years those trials were against Wyeth, which originally developed Prempro, and Wyeth performed poorly in those cases. But in 2009 the company was acquired by Pfizer, which has won the last eight out of 10 trial verdicts.

If Pfizer is able to resolve all claims for the amount of money that has been set aside, each case will receive about \$150,000 in compensation. However, some plaintiffs are likely to reject such offers, and Pfizer has noted that the remaining 4,000 claims may cost more to settle than the money set aside.

Most of the complaints were filed after a 2002 study by the National Institutes of Health found that women receiving HRT were at a higher risk of breast cancer, strokes and heart attacks. By that time, Prempro and other HRT drugs had been used by more than 6 million women.

Tags: [Breast Cancer](#), [Cancer](#), [Pfizer](#), [Prempro](#), [Wyeth](#)

Image Credit: |

MORE LAWSUIT STORIES



Ozempic Side Effects Caused Stomach Paralysis and Severe Abdominal Pain, Lawsuit Claims

April 18, 2025



Zyn Nicotine Pouches Lawsuit Alleges Tobacco Product Is Marketed to Minors

April 18, 2025



Radiation from CT Scans Given in 2023 Alone May Cause More Than 100,000 Future Cancer Cases: Study

April 18, 2025

44 Comments

Vera January 31, 2025

In 1995 I took the drug Prempro by Pfizer for four years and in 1999 was diagnosed with breast cancer. A couple of lymph nodes were also affected. In January 2000 I had a lumpectomy and the nodes were removed followed by chemo and radiation. I didn't know about any lawsuits then; until I came upon this article today by chance. Is there any way I can get in on this lawsuit?

Rhonda December 23, 2024

My mom was diagnosed in 2000 with breast cancer, 38 lymph nodes involved. She had taken Prempro for 9 years, she heard on the radio that it caused breast cancer. She threw it in the trash, went to the doctor and had her diagnosis. She fought it until 2010 and died in October. We were contacted by an attorney in Texas who said she was part of about 200 women who were harmed by Prempro. In the end we received a settlement, but in no way does it make up for her life being ruined and then taken. I would like to burn that drug companies headquarters to the ground with them inside. They knew how bad it was and hid that information from doctors so they could make more money. They are murderers plain and simple and yet they walk the streets, may they burn in hell.

Robert February 27, 2024

Is this class action lawsuit still open

Phyllis February 23, 2024

In 1999-2000 I was diagnosed with stage 2 breast cancer with 2-3 lymph nodes involved. I was told by my Drs it was caused by taking the Pfizer drug Prempro which I took for 6 years. I had a lumpectomy, aggressive chemo and radiation. I was in a study at Karmanos Cancer Center in Detroit Mi. I have had the DNA test which was negative for heredity.

Phyllis February 22, 2024

1999-2000 I was diagnosed with stage 2 breast cancer with 2-3 lymph nodes involved. I was told by my Drs. It was caused from taking Pfizer/ Prempro hormone therapy. I took Prempro for 6 years. I had a lumpectomy, Aggressive Chemo, and Radiation. I was in a study at Karmanos Cancer Center in Detroit Michigan. I've had the Bracka test and it was not hereditary.

Juanita July 5, 2023

Found out I had breast cancer stage three 2011 when the lawsuit was filed and I saw it online try to get a lawyer I was on it between 10 and 15 years and nobody seem to want to help me. I don't

know if because of my color or what I would think somebody would jump at the chance, but nobody did anybody else have this problem?

Brenda M June 18, 2023

Cancer

Michelle May 29, 2023

Prempro user diagnosed with breast cancer

Carolyn May 13, 2023

I took Prempro for 6 months in 2022. I am 71 yrs old with hot flashes and heat intolerance. During my routine mammogram in January 2023, they found cancer. A biopsy confirmed invasive carcinoma. I have never had an abnormal mammogram before.

Judy May 1, 2023

I too was on Prempro for several years before developing breast cancer. The day of my positive diagnosis, my gynecologist called and said to stop taking it. I had a lumpectomy on my left breast and have never felt the same about myself. I believe this contributed to my divorce. No one in my extended family as far back as we can go had breast cancer!

Elke March 24, 2023

I'm a victim of Prempro as well. I was diagnosed with breast cancer stage 2, in 2001 after the urging of my gynecologist that I must take this product to prevent a heart attack or stroke since my husband passed away due to a massive heart attack. I was on the product for 11 years. Is there a chance of a new class action law suit, since even today so many people are still suffering that have not yet been compensated ?!

Lisa November 29, 2022

I developed breast cancer in 2006 after taking Premarin for about 12 years. Can I still sue?

Mike November 26, 2022

My wife filed and no response is she elected for the lawsuit

Carole August 22, 2022

One of my coworkers told me about Prempro and how it helped with her hot flashes. I discussed it with my OB/GYN and she prescribed Prempro to me in the late 1990's, which I took for several years. In 2008 I was diagnosed with Ductal Carcinoma and had two lumpectomy surgeries on left breast. A couple of years later, the coworker I mentioned, she also was diagnosed with breast cancer and had to have a mastectomy. In 2019, I had to have a quadruple bypass heart surgery. In 2021, I was diagnosed with Lobular Cancer in right breast. This resulted in a Mastectomy of right breast in January of 2022.

Joyce July 20, 2022

1994 I was given Prempro, estrogen-progesterone. In 1998 I developed Aggressive Carcinoma cancer, right breast. I then had a radical modified mastectomy. Three months of Chemo. It changed my life, for the rest of my life. Thank you for taking the time to read this. Joyce

Angela June 5, 2022

I was diagnosed with breast cancer in 2017 after taking prempro. Diagnosed with bone cancer in 2019. I've had many surgeries since and live in constant pain. Thank you for the help.

Maria April 26, 2022

Currently have stage 2 breast cancer due to this medication please help me and my family!

Dean April 18, 2022

Is it too late to file?

Maria March 11, 2022

I took Finasteride from 2019 until March 2021. In November 2021 I was diagnosed with breast cancer. What can I do to receive compensation?

Big Pharma: A Big List of Crimes February 7, 2022

[...] 2012: Pfizer was ordered to pay a total of about \$1.2 billion to settle lawsuits claiming that side effects of Prempro caused women to develop breast cancer. The drug maker had already paid out \$896 million to settle approximately 6,000 Prempro breast cancer lawsuits, and Pfizer now set aside an additional \$330 million to cover the remaining 4,000, according to a filing with the SEC. The Prempro settlements came after six years of trials, in which several plaintiffs were awarded tens of millions of dollars, including punitive damages for the drug maker's actions in withholding information about the risk of breast cancer from Prempro. [...]

Cynthia March 20, 2021

I am reaching out to anyone who knows lawyers in Birmingham / Montgomery AL accepted clients through the ReLion Group, my mother signed up with these lawyers and she met with these attorneys. however, before settlements could be paid our mother passed away, we have not gotten any communications from these attorneys, and we need to reach out,

lawrence July 31, 2020

My mother was on this HRT Treatment and she got breast cancer – she wasn't even informed by her GP of the potential cancerous side effects. This was over 20 years ago now. If only we had this info back then

Tammy May 16, 2020

I Started Premarin 2011 and never was told anything about risk, was diagnosed with Invasive Ductal Carcinoma Stage 1 in 2016 at that time my Oncology's told me to stop immediately as was cause it I was 53 never smoked and had no family history of breast cancer, I had a Double Mastectomy 8 weeks after stop taken it, and have 19 surgery's in the past 3 years, In debt to my ears my credit and was suicidal and had to go threw years of counseling. I lost my home, jobs.

Nita April 20, 2020

2011 stage 3 cancer full removal left breast on prempo 10 -13 yrs plus Removal under arm 13 Lymphnodes

Stella February 27, 2020

I took Premarin 0.625 and 0.125 for a time span of at least 10 years for post menopausal issues. My PCP prescribed it for hot flashes and other associated issues. I was diagnosed with breast cancer and had 2 surgeries within 60 days of each other. I was informed that Premarin was cancer food by my oncologist. I stopped taking it of course. There is no history of cancer anywhere in my family. I have breast deformity and pain issues, permanent issues. I was a very active 70 year old. I had hysterectomy at 24 with one ovary left. My life will never be the same. I want them to pay for what we are going through!

patty January 12, 2020

My mom took the HRT and was diagnosed with stage 4 breast cancer in 2001/2002. Trying to find information on how to get her involved in this suit because this cancer has devastated her health and her life.

Lenea September 11, 2019

LeneaS70 @ gmail. com Big fat sour onion's to Pfizer the manufacturer and supplier Prempro, and the doctors who prescribe it First of all for over ten years there has been tens of thousands of lawsuits connecting prempro to breast cancer, and hundreds of millions of dollars has been

out, to its victims of this God awful medicine, when it's so Crystal Clear the problem this medication is creating, how can it possibly still be on the market Please do your own research and make the best decision for your own Self ----- ~~~ New problem concerning Prempro ~~~ Approximately 70% plus of women in the approximate age of 50 have fibroids in they uterus, and in many cases these are not a problem and they quit growing once a woman enters into menopause, creating no significant problem through their life There's a growing group of us that believe prempro is acting like a fertilizer and these fibroids are growing too extreme size, and forcing full hysterectomies We are in search of anyone who had a sonogram of there uterus prior to taking the medication Prempro manufactured by Pfizer Please – anyone contact me through Facebook Messenger We are very confident this is the beginning of a class action suit Our prescription drugs in this world are severely broken

Karen August 14, 2019

I too was diagnosed in November of 2018 with Invasive Ductal Carcinoma Stage 1. I took Prempro for many years, at least 5. I have three sisters none of them took hormones none of them have cancer. I did not test positive for the so called cancer gene. Where do I stand with this as far as a lawsuit against the pharmaceutical company that made and distributed this drug?

Linda February 2, 2019

After taking Prempro for two years to help prevent osteoporosis, discovered I had stage 2 breast cancer. I opted to have a mastectomy, reconstruction surgery and chemo. I ended up having to have three surgeries. My sister was also on this drug at the same time, and she too got breast cancer. We are the first in our family to ever get this cancer. I now have metastasized breast cancer which has gone to my bone and gave me fractures in my vertebrae. This has destroyed my life and also my sister, who unfortunately lost hers. I feel I should be compensated for this careless disregard of human life by the drug company.

Nadya July 18, 2017

2 months ago I was diagnosed with invasive ductal carcinoma stage One last month I went on surgery on my right breast. and now I need to go on going radiation, I took the genomic health test and it came positive which tells that the cancer will come back(Recurrence score results) that says

that I have to worry for the rest of my life if I am going to live or not? that is a terrible feeling. I was on hormone therapy and it was never mentioned not even once about the risk of breast cancer.

Fran June 9, 2017

I was given prim pro about 15 months ago by my doctor to treat my menopause and subsequently developed an aggressive type of Breast Cancer. I'm currently going through chemo therapies. Doctors tell me my cancer might have been caused by prim Pro. I wish never ever had taken this medication.

Susan Lanette May 24, 2017

I took prim pro for 5 to 6 years and ended up getting breast cancer and had no history of breast cancer in my family and my doctor told me it might have been caused by this medication

Sandi October 24, 2016

I too have been on many different HRT treatments. I took these around 10 years ago, after taking them I have had 2 different skin cancers and 9 years ago I had breast cancer I had all the treatments. I had to be away from my home and go through this by my self because treatment were not available where I lived. But I thought this way I would get rid of it for good. Be able to rise my boys and see my grandchildren grow up. Not true because here I go again, last week I had my Mammo and have been called back for more tests. We all know what that means. Never thought of this all being from meds a doctor gave me to make things better. HRT the give that keep giving.

Patricia October 16, 2016

Took prempo for 5years maybe more. Probably stopped in 2006. Not sure of dates. I have gerd. Heart attach 2014. Lobular breast cancer rt breast Feb 2016. Had lumpectomy but biopsy showed more cancer and was told i needed mastectomy. Had that two weeks later. I am undergoing breast reconstruction now. Last surgery is Oct 25 2016. I have thought about prempo and my cancer. I took it for many years and at the time I couldn't live without it. It helped me get through Menopause. Now i take arimedex.

marsha June 16, 2016

I was told in 2012 i had breast cancer. I was told. It was because of the hormones i had taken i took prempo. And was not told it would. Cause breast cancer i think they should pay for not warning us about this

kathy February 11, 2015

I need to know if I qualify for inclusion on these lawsuits. I was on prempo 1998 to 1999> I was diagnosed with breast cancer in January of 2001, and had surgery in February 2001. I did not know that this lawsuit was ongoing, and I feel as though I should be included. My oncologist had told me that I should never been on the hormone replacement drugs.

Jacquelyn September 18, 2014

I taken prempo for more than 3-4 years and now I've been diagnosed with breast cancer can someone tell me if I can be included in these suits?

Rosemary June 24, 2014

Diagnosed with invasive breast cancer in 2013. Never was warned about getting it from prempo.

DONNA May 12, 2014

I was given Prempro ten years ago and wasn't asked if I take medicine for a thyroid condition and I have been diagnosed with Lichen Scleriosis which amazingly I acquired right after the use of Prempro, I itch constantly everyday on my vagina, it is terrible, I get ulcerative sores, can't have sex anymore, it is terrible, no relief at all from anything I have tried.

Faith February 7, 2014

I am the middle of 3 sisters and am also the only one who took Prempro and the only one who has had breast cancer. I had the chemo and the radiation.....ugly experiences both. I am thankful to be a survivor but wonder why pharmaceutical companies can continue to produce and market these drugs that have negative side effects that outweigh any benefit from the drug. I've really started questioning and researching everything the doctors offer at this point!

Louie October 23, 2013

It shouldn't matter long you were on the evil drug. If you got cancer they should pay.

Sharon October 31, 2012

I have had four surgeries on my right breast – nothing left there but skin. Surgeon refused to remove the breast after the third surgery – said still a good breast. As a result of the radiation, developed acid reflux. Lost 30 pounds in 1 year – only 138 to begin with. Tried to take the Arimidex, but could hardly walk down the halls. Put on Tamoxifen, developed suicidal thoughts. Was a fairly health person before this all developed. Only pill I ever took was the HRT. Have an older sister and two younger sisters, who never took HRT and they don't have breast cancer. None in my family at all. When are these companies going to start taking care of the people they destroy?

Dee August 8, 2012

I took Prempro and etc., for more than 5-years. When I found out about its side affect in 2003, I voluntarily stopped taking it. In August 2004, I was diagnosed with ductal-breast cancer. After my mastectomy, I refused to take Tomaxafin, too. Whereas, I am the ONLY female in my family who has breast cancer. Hopefully, these pharmaceutal companies will stop playing Russian Roulette with people lives and the court system. Because they are guilty: Pay up and Shut up!!! What is greater than destroying a person's health or life. Regardless, CANCER is a death sentence: PERIOD!!!

Dian July 11, 2012

invasive ductal carcinoma stage two, 6 months of chemo, radiation and breast removal

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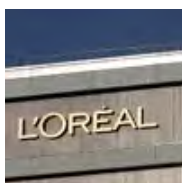
A product liability lawsuit filed against Novo Nordisk accuses the drug maker of failing to provide adequate warnings of Ozempic side effects, like stomach paralysis.

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More Than 12,000 Hair Relaxer Cancer Lawsuits Filed Against L'Oreal, Other Cosmetics Companies

(Posted: 3 days ago)

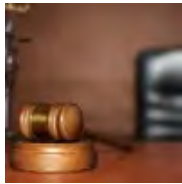
Nearly a dozen different cosmetics companies face more than 12,000 hair relaxer lawsuits, involving claims that chemical straighteners caused women to develop uterine cancer, endometrial cancer, ovarian cancer and other injuries.

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**Women's Health Initiative
Clinical Trial and Observational Study**

**Semi-Annual Progress Report
March 1, 2002 to August 31, 2002**

**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 5, 2002

WHI Semi-Annual Progress Report

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Executive Summary

This report, summarizing data accumulated through August 31, 2002, presents the current status of the three clinical trial components and the Observational Study (OS) of the Women's Health Initiative (WHI). The primary areas for this report are adherence to the interventions, completeness of follow-up, safety and outcome rates for these study components.

The Hormone Replacement Therapy (HRT) component randomized 27,347 women into two trials, one of unopposed estrogen (ERT) for the 10,739 women who previously had a hysterectomy and a parallel one 16,608 of estrogen plus progestin (PERT) in women with a uterus. The PERT trial was stopped early, in July of this year, at the recommendation of the DSMB. Because of this change, the current report provides adherence data only for the ERT trial. The average follow-up is now approximately 5.5 years. Drop-out rates have been generally stable but somewhat higher than design assumptions. "Drop-in" rates are also larger than projected. Analyses of intermediate effects, including blood biomarker analyses, bone density and blood pressure are provided. Vital status is known within the last 18 months for all but 3.8% of women. 3.2% of HRT participants are deceased. The current event rates for CHD, breast cancer, colorectal cancer, and hip fractures are approximately 70%, 85%, 75%, and 35%, respectively, of projected rates. Event rates by age, race/ethnicity and hysterectomy status are provided for all monitored outcomes.

The Dietary Modification (DM) component randomized 48,836 women. Intervention adherence is monitored by the difference between the Intervention and Control arms in Food Frequency Questionnaire (FFQ) percent energy from fat (C-I). Studywide, the FFQ mean difference between Intervention and Control women is 10.9% energy from fat at AV-1 decreasing to 7.7% at AV-7. The corresponding design assumptions for the C-I comparisons were 13% at year 1, diminishing to 0.25% per year though adequate power can be maintained as long as this difference remains at or above 10%. For fruit and vegetable intake, the mean difference between the arms of the trial remains consistently in excess of 1 more serving per day. Compared to Control women, Intervention women consumed almost 1 more serving per day of grains at AV-1, decreasing to one-half serving from AV-4 – AV-7. Currently 3.7% of the DM participants are lost-to-follow-up or have stopped follow-up, and 2.6% of participants are deceased. The average follow-up time for DM women is approximately 5.6 years. The current incidence rates of breast cancer, colorectal cancer, and CHD are approximately 115%, 75%, and 60%, respectively, of what was assumed in the study design. Event rate comparisons by age and race/ethnicity are presented for all monitored outcomes.

The Calcium and Vitamin D (CaD) component randomized 36,282 women previously recruited to the trial. Adherence to CaD supplements, defined as those women known to be consuming 80% or more of the prescribed dose, has remained steady since the last report and is now 56%-65%, though still lower than desirable. Follow-up rates for CaD participants are better than for the other CT components in part because of the delayed randomization into this trial component; as only 1.9% of participants are lost to follow-up or have stopped follow-up, and 2.2% of the participants are known to be deceased. Virtually all of the remaining participants have completed a *Form 33 – Medical History Update* in the last 18 months. With just over 4.5 years of average follow-up, the current rates of hip fractures, invasive breast cancer, and colorectal cancer are approximately 40%, 110%, and 80%, respectively, of what was assumed in the study design. Event rates by age and race/ethnicity are shown for all monitored outcomes.

Observational Study recruitment ended with 93,676 women enrolled. Follow-up rates suggest strong retention overall as only 3.7% are considered lost to follow-up or have stopped follow-up, and <1% have not provided recent outcomes data. Responses to mailings are generally high ($\geq 93\%$). Approximately 84% of the 3-year clinic visits due have been conducted, as judged by task completeness. Event rates by age, race/ethnicity and follow-up time (pre- vs. post-year 3 visit) are presented for all adjudicated outcomes.

Additional information on the timeliness and quality of outcomes ascertainment is provided. Clinical center performance monitoring is summarized and a tabulation of ancillary studies and clinical center participation in these studies is also provided.

1. Preliminary Remarks

This report documents study activities of the Women's Health Initiative (WHI) Clinical Trial (CT) and Observational Study (OS) through August 31, 2002. Topics include intervention adherence, follow-up, safety, outcomes and specialized scientific efforts. Updates are provided for each study component separately with a separate section on outcomes devoted to data quality, processing and timeliness issues.

During the past 6 months, the major WHI activities have been those surrounding the historic events of the early stopping and publication of results of the randomized trial of combined estrogen plus progestin (PERT)¹. This was an intensive effort for all of WHI. The report was published on the world-wide-web on July 9, 2002, just five and a half weeks after the DSMB recommendation to stop the trial. By that time, all 27,000 women in the hormone program had been mailed a letter from Dr. Lenfant, Director, NHLBI, describing this decision with informational materials presenting primary study results in lay terms. The remaining 130,000 WHI participants were provided similar materials within a few weeks thereafter. Clinical centers then made personal contacts with all PERT trial participants. Final outcomes data were collected, and the participants were unblinded and provided an opportunity to discuss study findings.

The participant response to this has been overwhelmingly positive. WHI participants have expressed their pride in being a part of this history-making event and of helping answer these questions. They were very appreciative of being informed of the results by WHI before hearing it through other sources. The value of their participation, not only in the PERT trial but in other study components, has been reinforced through the media coverage. There have been anecdotal reports of a few women in the estrogen alone trial (ERT) expressing anxiety in continuing with the intervention but overall, the early stopping of PERT has been a retention boost to the entire study.

WHI Investigators have been active in presenting these results to various communities and also in developing additional reports. There are 10 priority papers under development devoted to coronary heart disease, stroke, venous thromboembolism, breast cancer, gynecologic cancers, colorectal and other cancers, fractures, quality of life/cognition, diabetes, and gynecologic symptoms. These reports will present the more detailed analyses of the completed trial database (data and health events through July 7, 2002), using centrally adjudicated outcomes. The work of the HRT-CVD biomarkers study is progressing. The writing committees for the corresponding committees will use the data from the PERT trial in their developing manuscripts.

Routine activities of the other trials have proceeded in parallel. Major efforts involved included:

- Implementation of the Personalized Evaluation of Fat Intake (PEFI) in the summer of 2002.

¹ Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results of the Women's Health Initiative Randomized Controlled Trial. JAMA 2002; 283:321-333.

- Planning for a clinical center nutritionist workshop in December 2002 to discuss adherence issues
- Further development of close-out planning, including special emphasis on possible early close-out of other trial components.

All reports summarize clinical center (CC) data provided to the CCC by August 31, 2002. All data presented are derived from WHILMA, the study database. Data managed in WHILMA are those defined by standardized data collection procedures and instruments (see *WHI Manuals, Vol. 2 - Procedures* and *Vol. 3 - Forms*).

Clinical center locations and Principal Investigators are listed in *Table 1.1*.

Table 1.1
WHI Clinical Centers and Principal Investigators

Institution	Principal Investigator	Location
Albert Einstein College of Medicine	Sylvia Wassertheil-Smoller, PhD	Bronx, NY
Baylor College of Medicine	Jennifer Hays, PhD	Houston, TX
Brigham and Women's Hospital	Joann Manson, MD DrPH	Boston, MA
Emory University	Larry Phillips, MD	Atlanta, GA
Fred Hutchinson Cancer Research Center	Shirley Beresford, PhD	Seattle, WA
George Washington University	Judith Hsia, MD	Washington, DC
Kaiser Foundation Research Institute	Bette Caan, PhD	Oakland, CA
Kaiser Foundation Research Institute	Cheryl Ritenbaugh, PhD	Portland, OR
Medical College of Wisconsin	Jane Morley Kotchen, MD MPH	Milwaukee, WI
MedStar Research Institute	Barbara Howard, PhD	Washington, D.C.
Memorial Hospital of Rhode Island	Annlouise Assaf, PhD	Pawtucket, RI
Northwestern University	Linda Van Horn, PhD RD	Chicago/Evanston, IL
Ohio State University	Rebecca Jackson, MD	Columbus, OH
Research Foundation of SUNY, Stony Brook	Dorothy Lane, MD MPH	Stony Brook, NY
Rush Presbyterian- St. Luke's Medical Center	Henry Black, MD	Chicago, IL
Stanford University	Marcia Stefanick, PhD	San Jose, CA
State University of New York, Buffalo	Maurizio Trevisan, MD MS	Buffalo, NY
University of Alabama at Birmingham	Cora Lewis, MD MSPH	Birmingham, AL
University of Arizona	Tamsen Bassford, MD	Tucson/Phoenix, AZ
University of California, Davis	John Robbins, MD	Sacramento, CA
University of California, Irvine	Allan Hubbell, MD	Irvine, CA
University of California, Los Angeles	Howard Judd, MD	Los Angeles, CA

Table 1.1 (continued)
WHI Clinical Centers and Principal Investigators

Institution	Principal Investigator	Location
University of California, Los Angeles	Rowan Chlebowski, MD PhD	Torrance, CA
University of California, San Diego	Robert Langer, MD MPH	La Jolla/Chula Vista, CA
University of Cincinnati	Margery Gass, MD	Cincinnati, OH
University of Florida	Marian Limacher, MD	Gainesville/Jacksonville, FL
University of Hawaii	David Curb, MD	Honolulu, HI
University of Iowa	Robert Wallace, MD	Iowa City/Bettendorf, IA
University of Massachusetts	Judith Ockene, PhD	Worcester, MA
University of Medicine and Dentistry	Norman Lasser, MD PhD	Newark/New Brunswick, NJ
University of Miami	Mary-Jo O'Sullivan, MD	Miami, FL
University of Minnesota	Karen Margolis, MD	Minneapolis, MN
University of Nevada	Robert Brunner, PhD	Reno, NV
University of North Carolina at Chapel Hill	Gerardo Heiss, MD MPH	Chapel Hill, NC
University of Pittsburgh	Lewis Kuller, MD DrPH	Pittsburgh, PA
University of Tennessee	Karen Johnson, MD	Memphis, TN
University of Texas	Robert Schenken, MD	San Antonio, TX
University of Wisconsin	Catherine Allen, PhD	Madison, WI
Wake Forest University	Gregory Burke, MD MS	Winston-Salem/ Greensboro, NC
Wayne State University	Susan Hendrix, DO	Detroit, MI

2. HRT Component

The intervention activities of the estrogen plus progestin trial (PERT) were stopped in July 2002, following the recommendation of the DSMB. PERT trial participants were informed with a centralized mailing beginning July 8, with personal contacts by clinic staff over the next few weeks. A procedure was put in place to collect final outcomes for the intervention period, to unblind the women, explain the study results, and provide information on the transition to a follow-up phase without intervention. These participants are no longer being dispensed study medications but the remaining elements of the WHI protocol are continuing. At the same time, participants in the estrogen only arm (ERT) were informed of the PERT study findings and the continuing need for their participation was reinforced.

A few changes to this report have been implemented, reflecting the change in the PERT trial status. For this report we have omitted the reports of adherence to PERT study medicine, and endometrial aspiration results since there are few additional data from the last report. Additional changes will be incorporated as post-intervention data accumulate.

2.1 Recruitment

27,347 women were randomized into the HRT component (99.4% of goal). Of these, 10,739 women had a prior hysterectomy (39%) and were randomized to ERT or placebo in equal proportions. The remaining 16,608 women with an intact uterus were randomized to PERT or its placebo, again in equal proportions for most of the recruitment period. *Table 2.1* documents the age and racial/ethnic distribution for each trial.

2.2 Adherence

Adherence to study medications is determined at clinic visits by weighing returned bottles, if available, or by self-report in the small proportion of women with missed pill collection. *Table 2.2 – HRT Adherence Summary* gives descriptive data on all women who are considered due for each contact for participants with hysterectomy (ERT vs. placebo) trial. At this point, essentially all participants (99.7%) were randomized more than four years ago, 8,243 (77%) more than five years, 4,516 (42%) more than six and only 1,965 women (18%) have been in the study more than seven years. Experience in the eighth year is too sparse yet to be reliable. The current estimates of rates of stopping pills in follow-up years five through seven are between 4% and 6% per year. The adherence summaries for AV-4 through AV-7 are 58%, 55%, 52%, and 48%. *Figure 2.1* presents the secular trends in adherence rates for each visit type for the entire ERT trial cohort. A change in the methodology for calculating adherence (described previously) has not been applied retrospectively to the results prior to the February 2002 report. The increase between the previous two cycles is likely to be an artifact of this change.

Drop-out and drop-in rates are presented in *Table 2.3* along with associated design assumptions for combined stopping pills and death or loss to follow-up. Results for each interval as well as the overall cumulative loss to intervention are provided. In AV-4 through AV-8 the difference between the observed and projected cumulative stopping intervention rates appear to be somewhat divergent. At AV-6, where the estimates should be stable, 41.3% had dropped out, as compared to a projected 32.7%. The cumulative rate at AV-7, though less reliable, is 45.5%, as compared to the design projection of 36.7%. Overall, approximately 48% of the ERT trial cohort has stopped their study

pills at some point but 56% were active at their last contact.

A small proportion (1.5% per year) of the HRT participants were expected to stop study hormone pills and begin taking hormones outside of the trial. Among hysterectomized women the observed (design) cumulative rates are 2.9% (1.5%) at AV-1, 7.0% (4.4%) at AV-3, and 9.8% (8.7%) at AV-6, notably larger than expected. Reported reasons for stopping pills are listed in *Table 2.4*. Tabulations of these reasons by age and race/ethnicity are presented in *Table 2.5*.

2.3 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. Reports of bleeding and breast changes by contact type and hysterectomy strata are shown in *Tables 2.6* and *2.7*, respectively. Reports of bleeding in women on PERT reached a high of nearly 50% at 6 months (SAV-1), declining to approximately 7% after AV-5. Reports of breast changes peaked at 6 weeks after randomization and have declined to less than 2% in both strata.

2.4 Laboratory Studies

Tables 2.8 and *2.9* present the results of blood specimen analyses from a small (8.6%) cohort of HRT women selected randomly at baseline for these prospective analyses. These results are essentially the same as our last report and are shown here only for completeness. The subsample analyzed incorporated over-sampling of minorities. The results in *Table 2.8* are weighted to reflect the overall WHI-CT distribution of race/ethnicity. In *Table 2.9*, similar results are provided for each racial/ethnic group, though some groups have rather small sample sizes.

2.5 Intermediate Outcomes

Bone mineral density (BMD) measures are collected in three clinical centers (Pittsburgh, Birmingham, and Tucson) at baseline and at follow-up years 1, 3, 6, and 9. These data, shown in *Table 2.10* suggest small but significant increases in BMD between baseline and AV-1, with larger differences observed over greater follow-up time (AV-3 and AV-6) for whole body and spine. For hip, the largest increase occurs at AV-3. The pattern of treatment effects is similar in both hysterectomy strata. *Table 2.11* presents BMD data for Black/African American, Hispanic/Latino, and White women participating in the HRT component at these three centers.

2.6 Vital Status

Table 2.12 presents data on the vital status and the participation status of participants in the HRT trial. A detailed description of CCC and clinic activities to actively locate participants who do not complete their periodic visits is given in *Section 6 – Outcomes Processing*. For operational purposes, we define CT participants to have an “unknown” participation status if there is no outcomes information from the participant for 18 months and no other contacts for 6 months. There is a substantial difference in the rate of lost to follow up participants between the women without a uterus (2.0%) and the women with a uterus (1.1%). The difference was much smaller 6 months ago. Presumably this is the result of the recent closure of the intervention of the E+P component. Currently, 3.8% of the HRT participants are lost-to-follow-up or have stopped follow-up, and 3.2% of the participants are known to be deceased. Virtually all of the remaining participants have completed a *Form 33 – Medical History Update* in the last 18 months. The design assumed that 3% per year would be lost-to-follow-up or dead. Currently, the average follow-up for HRT participants

is about 5.5 years, suggesting that approximately 15.4% could be expected to be dead or lost-to-follow-up. Our overall rates compare favorably to design assumptions. Follow-up in women with a uterus is slightly better than in women who have had a hysterectomy.

2.7 Outcomes

Table 2.13 contains counts of the number of locally verified, major WHI outcomes for HRT participants by age and race/ethnicity. The estimates of annualized incidence rates for many event types in several racial/ethnic subgroups should be viewed with caution as the small number of events observed to-date results in unstable estimates. Approximately 4% of the self-reported outcomes have not yet been verified, so the numbers in this table can be seen as a lower bound of the actual number of outcomes that have occurred.

Compared to the design assumptions, we have observed about 70% of the expected number of CHD events, 85% of the expected number of breast cancers, 75% of the expected number of colorectal cancers, and about 35% of the expected number of hip fractures.

We have classified the strokes among HRT participants in one of six classes of the Glasgow scale, based on the condition of the participant at discharge:

1. Good recovery – participant can lead a full and independent life with or without minimal neurological deficit.
2. Moderately disabled – participant has neurological or intellectual impairment but is independent.
3. Severely disabled – participant conscious but totally dependent on others to get through daily activities.
4. Vegetative survival – participant has no obvious cortical functioning.
5. Dead. (All participants who died within one month of their stroke were classified in this category, irrespective of their actual cause of death.)
6. Unable to categorize based on available documentation.

The subclass *Non-disabling stroke* contains strokes with Glasgow scale class 1 and 2; *Fatal/disabling stroke* contains strokes with Glasgow scale class 3 through 5; *Unknown status from stroke* contains strokes with Glasgow scale 6 and strokes for which the Glasgow classification was not yet complete.

Table 2.14 compares the rates of the same locally verified outcomes according to baseline hysterectomy strata. For most cardiovascular outcomes the event rates are slightly larger for the women without a uterus, while for most cancers the rates are slightly larger for women with a uterus. The differences in cardiovascular disease rates are consistent with the risk profile differences we have previously observed.

Table 2.15 presents the distribution of stroke diagnostic categories for HRT participants by hysterectomy status. The distribution of the subtype of stroke appears to be similar for the women

with and without a uterus.

Table 2.16 compares the Glasgow scale for strokes between hysterectomy strata. From this table it appears that the largest number of strokes fall in Glasgow classes 1 and 2, the less disabling strokes, but a substantial number of participants die within one month of a stroke.

Table 2.17 contains counts of the number of self-reports by age and race/ethnicity for some outcomes that are not locally verified in WHI. As most of the self-reported outcomes are somewhat over-reported (see *Section 6.3 – Outcomes Data Quality*), the numbers in this table should be taken as an upper bound on the number of events that have occurred in HRT participants.

2.8 WHI Memory Study (WHIMS)

The WHI Memory Study is an ancillary study in the HRT component, funded by Wyeth Ayerst through a grant to Dr. Sally Shumaker, Wake Forest University. The aim of this study is to determine whether hormone replacement therapy reduces the incidence of dementia in women over 65 years of age. 7,526 women were enrolled in the 39 participating centers, representing approximately 61% of the age-eligible cohort and 28% of the entire HRT study. Baseline characteristics of WHIMS participants are shown in *Table 2.18* hysterectomy status.

2.9 Issues

The closing of the PERT trial has been the focus of study activities over the past 6 months. In addition to informing all HRT participants and transitioning the PERT participants to a follow-up only phase, investigators and staff have been working diligently to communicate the results underlying the early stopping recommendation to the medical community and general population, including a publication and many opportunities to present these results in public forums. This publication has generated considerable interest and questions regarding the design of the trial (choice of agents, dosing, study population), size and statistical significance of the effects, and rationale for early stopping. The investigators are working to respond to these issues in multiple forums, including providing JAMA with a response to letters to the editor and providing both the FDA and Wyeth with a dataset from the JAMA publication.

Operationally, considerable effort is being devoted to completing the trial database and developing a full set of trial results. The complete database will include all events occurring through July 7, 2002, since participant were informed of study results and began to be unblinded on July 8. The reports of these events was approximately 70% complete as of August 31. The effort to adjudicate these events, both locally and centrally, is a current study-wide priority. Another data source under development is the HRT-CVD biomarker study, an effort initiated previously but now of greater interest and urgency.

There was considerable concern that ERT trial participants would drop out of the study after learning of the PERT trial results. Currently we have no evidence of any change in the rate of drop-outs over time. Many anecdotes regarding PERT trial participants have been relayed to the CCC indicating how well received this information was in general, particularly because participants were given information before it was made public. There have been fewer reports from ERT trial participants but it is assumed that the release of these results have given much needed visibility to the program and reinforced the importance of these studies to all WHI participants.

Looking forward, the investigators have planned 10 priority papers geared toward looking at the effects of PERT on CHD, stroke, venous thromboembolism, breast cancer, gynecologic cancers, colorectal and other cancers, fractures, quality of life and cognitive function, gynecologic symptoms, and diabetes using the final trial database. A final summary paper examining overall risks and benefits in the complete dataset is also anticipated. The plan is to complete these manuscripts over the next nine to twelve months.

Table 2.1
Hormone Replacement Therapy Component Age – and Race/Ethnicity – Specific Recruitment

Data as of: August 31, 2002

HRT Participants	Total Randomized	% of Overall Goal	Distribution	Design Assumption
<u>Age</u>				
Overall	27,347			
50-54	3425	125%	13%	10
55-59	5408	99%	20%	20
60-69	12364	100%	45%	45
70-79	6150	90%	22%	25
Without Uterus	10,739			
50-54	1396	113%	13%	10
55-59	1916	78%	18%	20
60-69	4852	88%	45%	45
70-79	2575	84%	24%	25
With Uterus	16,608			
50-54	2029	135%	12%	10
55-59	3492	116%	21%	20
60-69	7512	111%	45%	45
70-79	3575	95%	22%	25
<u>Race/Ethnicity</u>				
Overall	27,347			
American Indian	130		<1%	
Asian	527		2%	
Black	2738		10%	
Hispanic	1537		6%	
White	22030		81%	
Unknown	385		1%	
Without Uterus	10,739			
American Indian	75		1%	
Asian	164		2%	
Black	1616		15%	
Hispanic	651		6%	
White	8084		75%	
Unknown	149		1%	
With Uterus	16,608			
American Indian	55		<1%	
Asian	363		2%	
Black	1122		7%	
Hispanic	886		5%	
White	13946		84%	
Unknown	236		1%	

Table 2.2
HRT Adherence Summary for Participants Without a Uterus

Data as of: August 31, 2002

Contact	Due N	Conducted N %	Conducted in Window N %	Stopped HRT during interval N %	Missed Pill Collection N %	Total with Collections N %	Medication Rate ¹ <50% N %	Medication Rate ¹ 50%-80% N %	Medication Rate ¹ 80% + N %	Adherence Summary ² %
Semi-Annual Visit - 1	10739	10448 97	8785 82	381 4	96 1	10627 99	741 7	957 9	8929 84	83
Annual Visit - 1	10739	10349 96	8536 79	476 4	133 1	10190 99	916 9	1108 11	8166 80	76
Annual Visit - 2	10739	10063 94	7944 74	1005 9	211 2	9594 98	966 10	1190 12	7438 78	70
Annual Visit - 3	10739	10043 94	7445 69	809 8	225 3	8525 97	842 10	1046 12	6637 78	63
Annual Visit - 4	10705	9787 91	6758 63	661 6	204 3	7671 97	617 8	939 12	6115 80	58
Annual Visit - 5	8243	7418 90	5022 61	448 6	146 3	5444 97	418 8	647 12	4379 80	55
Annual Visit - 6	4516	4051 90	2583 57	221 5	85 3	2769 97	194 7	319 12	2256 81	52
Annual Visit - 7	1965	1713 87	1054 54	69 4	27 2	1116 98	83 7	121 11	912 82	48
Annual Visit - 8	545	456 84	285 52	28 5	15 5	297 95	19 6	38 13	240 81	47

¹ Medication rate calculated as number of pills taken divided by number of days since bottle(s) were dispensed.

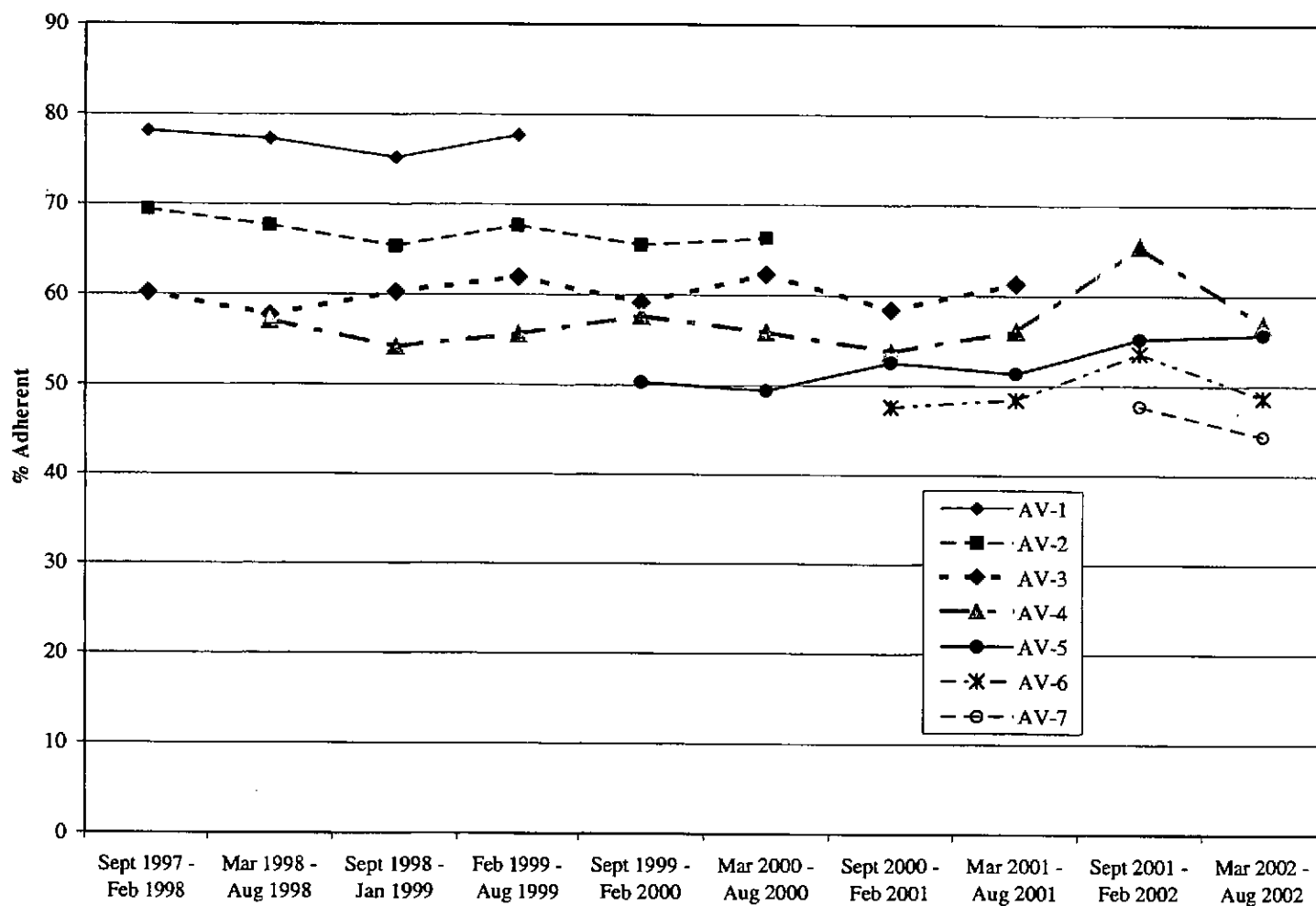
² Adherence summary calculated as number of women consuming $\geq 80\%$ of pills / # due for visit.

Note: Deceased women are excluded from all medication adherence calculations, but are included in the number "Due."

Figure 2.1
HRT Adherence Summary
% Participants Due for a Visit Who Took at Least 80% of Study Pills¹

Data as of August 31, 2002

Participants Without Uterus



¹ Adherence calculations changed as of the September 2001 – February 2002 interval.

Table 2.3
HRT Drop-Out and Drop-In Rates (%) by Follow-Up Time

Data as of: August 31, 2002

	Design		Without Uterus			
	Int	Cum	Stopped ¹	Dead/ Lost ²	Int ³	Cum ⁴
Drop-Outs⁵						
AV-1	8.8	8.8	7.8	0.4	8.3	8.3
AV-2	5.9	14.2	9.4	0.9	10.3	17.7
AV-3	5.9	19.2	7.7	1.3	9.0	25.2
AV-4	5.9	24.0	6.3	1.7	8.0	31.2
AV-5	5.9	28.5	5.6	1.9	7.5	36.3
AV-6	5.9	32.7	5.0	2.8	7.8	41.3
AV-7	5.9	36.7	3.7	3.6	7.3	45.5
AV-8	5.9	40.4	5.4	5.5	10.9	51.5
Drop-Ins⁶						
AV-1	1.5	1.5			2.9	2.9
AV-3	2.9	4.4			4.2	7.0
AV-6	4.4	8.7			3.0	9.8

¹ Estimated rate of stopping hormones in the interval.

² Death or lost to follow-up rate in the interval.

³ Combined rate of stopping and death or lost to follow-up in the interval.

⁴ Estimated cumulative rate of stopping and death or lost to follow-up.

⁵ Drop-out rates derived from Form 7 by date. Cumulative rates calculated as life-table estimates.

⁶ Cumulative Drop-in rates derived from medication inventory collected at AV-1, AV-3, AV-6, AV-9.
Interval estimates back-calculated from cumulative rates.

Table 2.4
Reasons for Stopping HRT¹: HRT Participants Without Uterus

Data as of August 31, 2002

Reasons ²	(N = 4684)	
Personal/family		
Demands of work	82	1.8%
Family illness, emergency or other family demands ³	199	4.2%
Financial problems	9	0.2%
Lack of cooperation/support from family/friends ⁴	47	1.0%
Living in nursing home	9	0.2%
Issues of interest in study ⁵	107	2.3%
Travel		
Too far to CC	166	3.5%
Moved out of area or refuses to be followed to another CC	34	0.7%
Other travel issues ⁶	97	2.1%
Visits & Procedures		
Doesn't like visits, calls	58	1.2%
Mammogram Issues ⁷	27	0.6%
Doesn't like gynecologic procedures	13	0.3%
Doesn't like required forms or safety procedures ⁸	81	1.7%
Problems with other procedures ⁹	11	0.2%
Worried about health effects of medical tests/procedures	18	0.4%
Wants test results ¹⁰	1	<0.1%
Problems with CC ¹¹	31	0.7%

(continues)

¹ Does not include reasons reported by women who stopped and later restarted HRT.

² Multiple reasons may be reported for a woman.

³ Combines "Family illness, emergency or other family demands", "Death in the family or of a close friend", and "Caregiver responsibilities demanding time, effort, lifestyle changes".

⁴ Combines "Lack of cooperation/support from family and/or friends" and "Family/friends request that she withdraw".

⁵ Combines "Conflicting priorities other than work or family", "Feels discouraged regarding participation overall", "Loss of interest, boredom", "Feels it is not an important study", and "In another study in conflict with WHI intervention".

⁶ Combines "Transportation problems (other than distance)", "Traffic", "Parking at CC", and "CC neighborhood/safety".

⁷ Combines "Doesn't like mammograms (DM, HRT)" and "Cost of mammograms (DM, HRT)".

⁸ Combines "Doesn't like filling out forms (other than those required for safety)", and "Doesn't like required safety forms and/or procedures (HRT, CaD)".

⁹ Combines "Doesn't like having blood drawn", "Doesn't like ECG (DM, HRT)", and "Doesn't like other procedures (other than those required for safety)".

¹⁰ Combines "Wants results of blood analyses", and "Wants results of bone mineral density measurement (BD sites only)".

¹¹ Combines "Problem with the CC", "Problem with CC staff person (other than DM Group Nutritionist)", and "Staff change/turnover".

Table 2.4 (continued)
Reasons for Stopping HRT¹: HRT Participants Without Uterus

Data as of August 31, 2002

Reasons ²	(N = 4684)	
Symptoms		
Vaginal Bleeding	6	0.1%
Breast Symptoms ³	183	3.9%
Vaginal Changes	14	0.3%
Hot flashes/night sweats	33	0.7%
Other ⁴	1042	22.2%
Health Conditions		
Breast Cancer	85	1.8%
Complex or atypical hyperplasia	0	0.0%
Endometrial cancer	2	<0.1%
Venous thromboembolism ⁵	52	1.1%
High triglycerides (> 1000 mg/dL)	2	<0.1%
Malignant melanoma	11	0.2%
Gallbladder disease	7	0.1%
Heart Attack	59	1.3%
Stroke	89	1.9%
Meningioma	4	0.1%
Depression	11	0.2%
Cholesterol (high or concern about levels)	9	0.2%
Osteoporosis	37	0.8%
Cognitive/memory changes	22	0.5%
Other ⁶	475	10.1%

(continues)

¹ Does not include reasons reported by women who stopped and later restarted HRT.

² Multiple reasons may be reported for a woman.

³ Combines "Breast tenderness (HRT)" and "Other breast changes (HRT)".

⁴ Combines "Experiencing health problems or symptoms not due to intervention", "Reports other health problems or symptoms from the WHI intervention", "Reports health problems or symptoms from the WHI intervention", "Hair/skin changes", "Bloating/Gas", "Constipation", "Other gastrointestinal problems", "Headaches", "Weight loss/gain", "Low energy/too tired", "Possible allergic reaction", and "Other symptoms not listed above".

⁵ Combines "Deep vein thrombosis", and "Pulmonary embolism".

⁶ Combines "Removed from intervention due to WHI symptom management", "Removed from intervention due to adverse health event", "Communication problem", "Hypercalcemia", "Kidney failure/dialysis", "Renal calculi", "Arthritis", "Diabetes", "Loss of vision and/or hearing", and "Other health conditions not listed above".

Table 2.4 (continued)
Reasons for Stopping HRT¹: HRT Participants Without Uterus

Data as of August 31, 2002

Reasons ²	(N = 4684)	
Intervention		
Doesn't like randomized nature of intervention	87	1.9%
Expected some benefit from intervention	40	0.9%
Feels guilty, unhappy, or like a failure for not meeting study goals of intervention	3	0.1%
Takes too many pills	35	0.7%
Other pill issues ³	134	2.9%
CaD Issues ⁴	28	0.6%
DM Issues ⁵	5	0.1%
Taking active HRT ⁶	196	4.2%
Will not be on any HRT ⁷	373	8.0%
Taking SERMs or other hormone medications ⁸	44	0.9%
Other Health Issues		
Worried about cost if adverse effects occur	11	0.2%
Expected more health care	12	0.3%
Advised not to participate by health care provider ⁹	626	13.4%
Study conflicts with other health issues ¹⁰	588	12.6%
Other		
Other reasons not listed above	991	21.2%
Refuses to give a reason	74	1.6%

¹ Does not include reasons reported by women who stopped and later restarted HRT.

² Multiple reasons may be reported for a woman

³ Combines "Doesn't like taking pills (HRT, CaD)", "Doesn't like taste of pills (HRT, CaD)", and "Unable to swallow pills (HRT, CaD)".

⁴ Combines "Wants to take her own calcium (CaD)", "Feels diet is already sufficient in calcium/Vitamin D (CaD)", "Taking more than the maximum allowable IU of Vit D (CaD)", and "Taking Calcitriol (CaD)".

⁵ Combines "Doesn't like DM requirements", "Problem with DM Group Nutritionist or group members (DM)", "Doesn't like DM eating pattern", "Doesn't like attending DM intervention classes (DM)", "Doesn't like self-monitoring (DM)", "Doesn't like budgeting fat grams (DM)", "Has concerns regarding long-term risks/benefits of low fat diet (DM)", "Unhappy that not losing weight (DM)", "Not in control of meal preparation (DM)", "Too difficult to meet or maintain dietary goals (DM)", "Doesn't like eating low fat diet (DM)", "Doesn't like eating 5 vegetables/fruits per day (DM)", "Doesn't like eating 6 grains per day (DM)", "Feels fat gram goal is unrealistic (DM)", and "Eating pattern conflicts with personal health beliefs (DM)".

⁶ Combines "Has made a personal decision to go on active HRT (HRT)" and "Advised to go on active HRT by health care provider (HRT)".

⁷ Combines "Has made a personal decision that she does not want to be on HRT (HRT)" and "Advised to not be on active HRT by health care provider (HRT)".

⁸ Combines "Has made a personal decision to go on SERM (e.g., Evista/raloxifene, tamoxifen) (HRT)", "Advised to go on SERM (e.g., Evista/raloxifene, tamoxifen) by health care provider (HRT)", and "Taking testosterone medications (HRT)".

⁹ Combines "Advised not to participate by health care provider" and "Advised not to participate by health care provider for other reason".

¹⁰ Combines "Study conflicts with health care needs" and "Study conflicts with other health issues".

Table 2.5
Reasons for Stopping HRT¹ by Age at Screening and Race/Ethnicity: HRT Participants Without Uterus

Data as of August 31, 2002

	Age at Screening									
	All		50 - 54		55 - 59		60 - 69		70 - 79	
	N	% ²	N	% ²	N	% ²	N	% ²	N	% ²
Women Stopping HRT	4684	43.6%	611	43.8%	800	41.8%	2058	42.4%	1215	47.2%
REASONS FOR STOPPING³	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴
Family illness, emergency, or other family demands ⁵	199	4.2%	24	3.9%	41	5.1%	93	4.5%	41	3.4%
Vaginal bleeding	6	0.1%	2	0.3%	2	0.3%	1	<0.1%	1	0.1%
Breast symptoms ⁶	183	3.9%	13	2.1%	23	2.9%	74	3.6%	73	6.0%
Taking active HRT ⁷	196	4.2%	29	4.7%	45	5.6%	81	3.9%	41	3.4%
Will not be on any HRT ⁸	373	8.0%	29	4.7%	47	5.9%	187	9.1%	110	9.1%
Advised not to participate by health care provider ⁹	626	13.4%	86	14.1%	101	12.6%	266	12.9%	173	14.2%
Study conflicts with other health issues ¹⁰	588	12.6%	83	13.6%	96	12.0%	262	12.7%	147	12.1%

	Race/Ethnicity									
	American Indian/ Alaskan Native		Asian/Pacific Islander		Black/African American		Hispanic/Latino		White	
	N	% ²	N	% ²	N	% ²	N	% ²	N	% ²
Women Stopping HRT	32	42.7%	60	36.6%	737	45.6%	333	51.2%	3460	42.8%
REASONS FOR STOPPING³	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴
Family illness, emergency, or other family demands ⁵	1	3.1%	2	3.3%	44	6.0%	25	7.5%	124	3.6%
Vaginal bleeding	0	0.0%	0	0.0%	2	0.3%	1	0.3%	3	0.1%
Breast symptoms ⁶	1	3.1%	2	3.3%	26	3.5%	15	4.5%	137	4.0%
Taking active HRT ⁷	1	3.1%	0	0.0%	22	3.0%	11	3.3%	159	4.6%
Will not be on any HRT ⁸	1	3.1%	5	8.3%	56	7.6%	19	5.7%	286	8.3%
Advised not to participate by health care provider ⁹	5	15.6%	10	16.7%	68	9.2%	36	10.8%	498	14.4%
Study conflicts with other health issues ¹⁰	5	15.6%	11	18.3%	68	9.2%	29	8.7%	467	13.5%
Unknown									62	41.6%

¹ Does not include reasons reported by women who stopped and later restarted HRT.

² Percentages are of HRT participants without uterus in the same age or race/ethnicity category.

³ Multiple reasons may be reported for a woman.

⁴ Percentages are of HRT participants without uterus in the same age or race/ethnicity category who stopped HRT.

⁵ Combines "Family illness, emergency or other family demands", "Death in the family or of a close friend", and "Caregiver responsibilities demanding time, effort, lifestyle changes".

⁶ Combines "Breast tenderness (HRT)" and "Other breast changes (HRT)".

⁷ Combines "Has made a personal decision to go on active HRT (HRT)" and "Advised to go on active HRT by health care provider (HRT)".

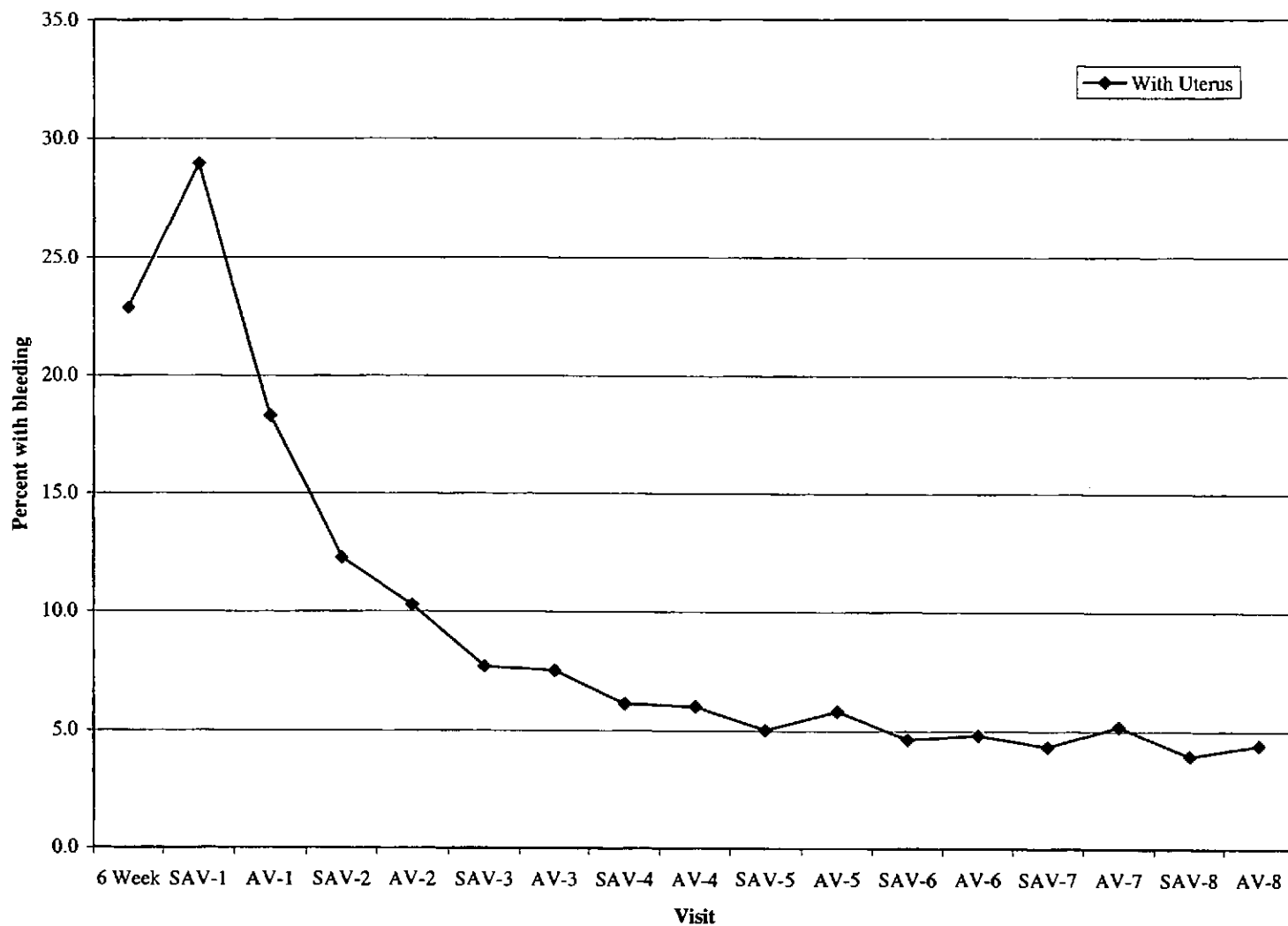
⁸ Combines "Has made a personal decision that she does not want to be on HRT (HRT)" and "Advised to not be on active HRT by health care provider (HRT)".

⁹ Combines "Advised not to participate by health care provider" and "Advised not to participate by health care provider for other reason".

¹⁰ Combines "Study conflicts with health care needs" and "Study conflicts with other health issues".

Table 2.6
Reports of Bleeding

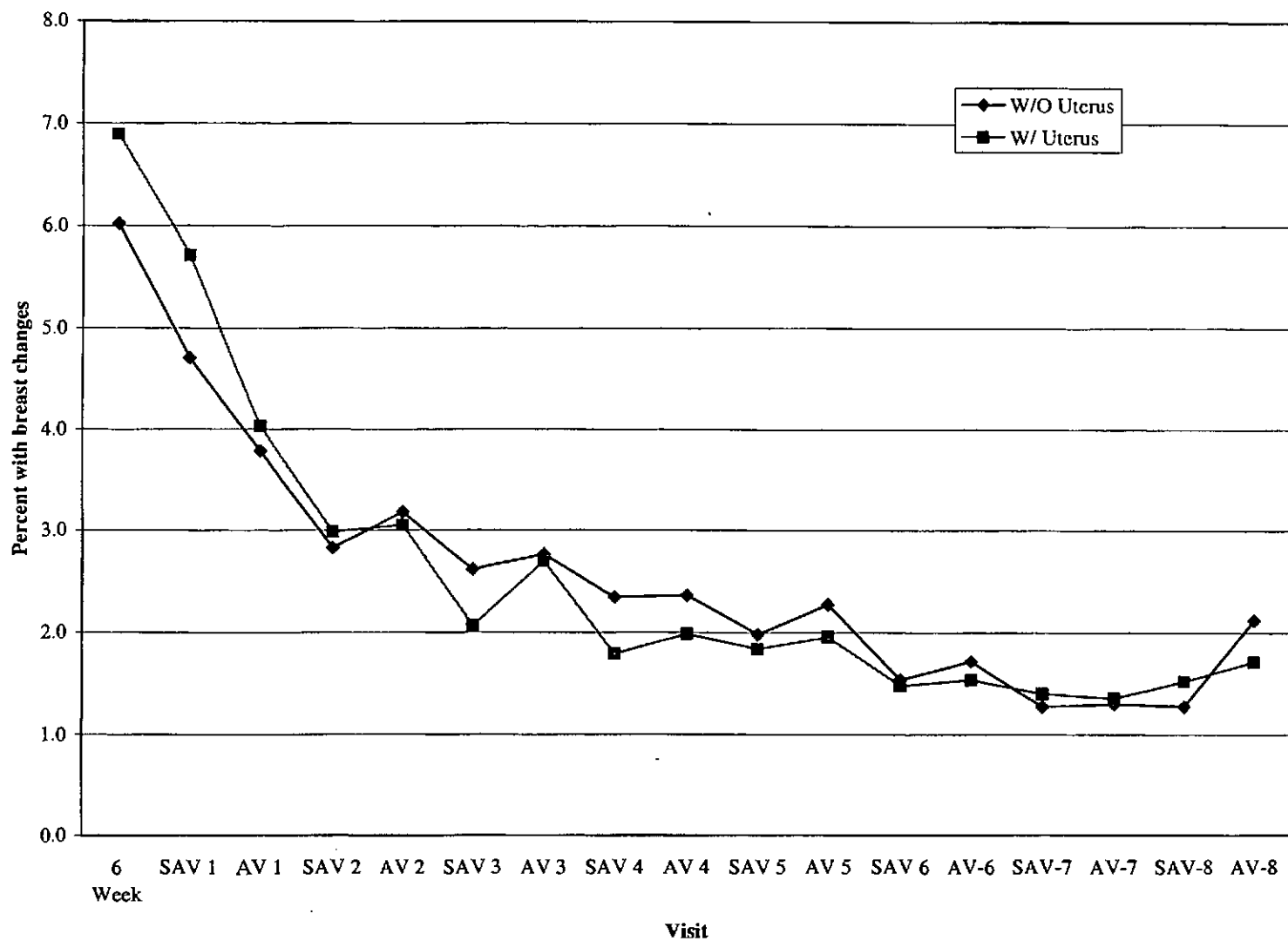
Data as of: August 31, 2002



Contact	With Uterus	
Semi-Annual Visit 3 – Number with Bleeding	1195	(7.7%)
Annual Visit 3 – Number with Bleeding	1186	(7.5%)
Semi-Annual Visit 4 – Number with Bleeding	951	(6.1%)
Annual Visit 4 – Number with Bleeding	934	(6.0%)
Semi-Annual Visit 5 – Number with Bleeding	699	(5.0%)
Annual Visit 5 – Number with Bleeding	679	(5.8%)
Semi-Annual Visit 6 – Number with Bleeding	406	(4.6%)
Annual Visit 6 – Number with Bleeding	299	(4.8%)
Semi-Annual Visit 7 – Number with Bleeding	181	(4.3%)
Annual Visit 7 – Number with Bleeding	133	(5.2%)
Semi-Annual Visit 8 – Number with Bleeding	59	(3.9%)
Annual Visit 8 – Number with Bleeding	30	(4.4%)

Table 2.7
Reports of Breast Changes

Data as of: August 31, 2002



Contact	Without Uterus		With Uterus	
Semi-Annual Visit 3 – Number with Breast Changes	220	(2.6%)	275	(2.1%)
Annual Visit 3 – Number with Breast Changes	229	(2.8%)	355	(2.7%)
Semi-Annual Visit 4 – Number with Breast Changes	182	(2.3%)	223	(1.8%)
Annual Visit 4 – Number with Breast Changes	177	(2.4%)	243	(2.0%)
Semi-Annual Visit 5 – Number with Breast Changes	131	(2.0%)	197	(1.8%)
Annual Visit 5 – Number with Breast Changes	125	(2.3%)	173	(2.0%)
Semi-Annual Visit 6 – Number with Breast Changes	62	(1.5%)	97	(1.5%)
Annual Visit 6 – Number with Breast Changes	49	(1.7%)	70	(1.5%)
Semi-Annual Visit 7 – Number with Breast Changes	24	(1.3%)	42	(1.4%)
Annual Visit 7 – Number with Breast Changes	15	(1.3%)	25	(1.4%)
Semi-Annual Visit 8 – Number with Breast Changes	9	(1.3%)	16	(1.5%)
Annual Visit 8 – Number with Breast Changes	7	(2.1%)	8	(1.7%)

Table 2.8
Blood Specimen Analysis: HRT Participants

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean ¹	S.D. ¹	N	Mean ¹	S.D. ¹
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	1163	0.07	0.07	1468	0.09	0.08
AV-1	1022	0.07	0.06	1365	0.08	0.08
AV3	838	0.06	0.06	1151	0.07	0.08
AV-1 – Baseline	1000	-0.01	0.06	1332	-0.01	0.06
AV-3 – Baseline	822	-0.01	0.06	1123	-0.01	0.07
Beta-Carotene (µg/ml)						
Baseline	1162	0.29	0.27	1468	0.34	0.33
AV-1	1021	0.26	0.25	1366	0.31	0.30
AV3	838	0.25	0.25	1151	0.32	0.38
AV-1 – Baseline	999	-0.03	0.22	1333	-0.04	0.21
AV-3 – Baseline	821	-0.04	0.24	1123	-0.03	0.32
Alpha-tocopherol (µg/ml)						
Baseline	1163	16.09	7.04	1468	16.31	7.70
AV-1	1022	17.70	8.91	1366	16.81	7.42
AV3	838	17.84	8.33	1151	18.26	8.25
AV-1 – Baseline	1000	1.63	6.25	1333	0.51	5.73
AV-3 – Baseline	822	1.85	6.81	1123	2.02	7.33
Gamma-tocopherol (µg/ml)						
Baseline	1163	2.48	1.65	1468	2.24	1.40
AV-1	1022	2.22	1.84	1366	1.84	1.24
AV3	838	1.99	1.49	1151	1.67	1.25
AV-1 – Baseline	1000	-0.30	1.13	1333	-0.37	0.93
AV-3 – Baseline	822	-0.55	1.19	1123	-0.58	1.17
Beta-Cryptoxanthine (µg/ml)						
Baseline	1163	0.08	0.08	1468	0.09	0.10
AV-1	1022	0.08	0.07	1365	0.09	0.09
AV3	838	0.08	0.07	1151	0.10	0.09
AV-1 – Baseline	1000	0.00	0.06	1332	-0.01	0.07
AV-3 – Baseline	822	0.00	0.07	1123	0.00	0.09
Lycopene (µg/ml)						
Baseline	1163	0.40	0.20	1468	0.41	0.20
AV-1	1022	0.39	0.19	1366	0.40	0.19
AV3	838	0.35	0.18	1151	0.38	0.21
AV-1 – Baseline	1000	-0.01	0.17	1333	-0.01	0.17
AV-3 – Baseline	822	-0.05	0.20	1123	-0.03	0.21
Lutein and Zeaxanthin (µg/ml)						
Baseline	1163	0.20	0.10	1468	0.21	0.09
AV-1	1022	0.20	0.10	1366	0.21	0.10
AV3	838	0.19	0.10	1151	0.20	0.09
AV-1 – Baseline	1000	0.00	0.07	1333	0.00	0.06
AV-3 – Baseline	822	-0.01	0.07	1123	-0.01	0.08
Retinol (µg/ml)						
Baseline	1163	0.60	0.15	1468	0.60	0.15
AV-1	1022	0.63	0.16	1366	0.61	0.15
AV3	838	0.62	0.15	1151	0.60	0.16
AV-1 – Baseline	1000	0.03	0.11	1333	0.01	0.10
AV-3 – Baseline	822	0.02	0.13	1123	0.01	0.13

(continues)

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

Table 2.8 (continued)
Blood Specimen Analysis: HRT Participants

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean ¹	S.D. ¹	N	Mean ¹	S.D. ¹
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	1121	128.49	28.82	1415	123.49	28.32
AV-1	973	139.42	35.19	1319	129.64	31.02
AV-3	805	136.01	33.79	1095	128.62	31.65
AV-1 – Baseline	927	10.40	25.42	1248	5.94	22.53
AV-3 – Baseline	766	8.32	30.71	1036	5.43	27.63
Factor VII C (%) ²						
Baseline	1101	129.99	28.24	1396	125.15	27.13
AV-1	961	136.32	31.68	1308	124.89	27.96
AV-3	803	135.45	34.47	1090	127.55	32.20
AV-1 – Baseline	899	6.23	23.93	1220	-0.58	21.84
AV-3 – Baseline	748	7.39	29.00	1016	2.50	27.33
Fibrinogen (mg/dl)						
Baseline	1118	312.18	63.50	1413	306.41	59.37
AV-1	971	301.34	61.46	1316	299.11	59.45
AV-3	805	294.65	59.69	1095	290.34	57.50
AV-1 – Baseline	923	-11.50	52.68	1243	-7.95	53.17
AV-3 – Baseline	763	-17.85	61.89	1034	-15.77	56.80
Hormones / Other						
Glucose (mg/dl)						
Baseline	1160	105.16	35.35	1466	100.47	26.73
AV-1	1020	102.91	31.69	1362	98.72	24.59
AV-3	857	102.16	31.94	1167	98.77	26.67
AV-1 – Baseline	995	-2.76	21.30	1326	-1.94	17.24
AV-3 – Baseline	840	-3.49	26.17	1138	-2.39	20.73
Insulin (μIU/ml)						
Baseline	1139	12.88	10.62	1421	11.42	6.86
AV-1	1004	12.16	8.14	1317	11.37	7.18
AV-3	813	13.67	11.48	1107	12.49	7.32
AV-1 – Baseline	964	-0.74	5.98	1264	-0.09	5.56
AV-3 – Baseline	784	0.62	9.09	1046	1.18	6.64

(continues)

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

² Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.8 (continued)
Blood Specimen Analysis: HRT Participants

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean ¹	S.D. ¹	N	Mean ¹	S.D. ¹
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	1163	162.97	99.73	1469	146.01	74.89
AV-1	1020	176.31	132.80	1365	149.20	74.99
AV-3	856	170.16	82.87	1165	152.48	82.27
AV-1 – Baseline	997	13.67	73.57	1332	3.01	55.53
AV-3 – Baseline	838	6.88	81.77	1137	6.62	65.69
Total Cholesterol (mg/dl)						
Baseline	1163	229.63	41.21	1469	224.84	36.85
AV-1	1020	223.25	40.59	1365	215.84	35.23
AV-3	856	218.59	36.29	1165	214.97	35.37
AV-1 – Baseline	997	-6.04	29.85	1332	-8.79	28.18
AV-3 – Baseline	838	-10.90	34.20	1137	-8.82	31.99
LDL-C (mg/dl)						
Baseline	1139	142.06	36.82	1444	138.73	32.93
AV-1	998	128.48	35.85	1340	127.13	32.49
AV-3	838	126.86	34.57	1142	126.92	33.10
AV-1 – Baseline	966	-13.26	27.27	1298	-11.34	25.66
AV-3 – Baseline	811	-15.59	31.98	1100	-10.78	29.55
HDL-C (mg/dl)						
Baseline	1157	55.59	14.52	1464	56.92	14.38
AV-1	1018	59.92	16.83	1365	59.13	14.89
AV-3	851	58.49	16.59	1163	58.27	15.28
AV-1 – Baseline	993	4.11	9.36	1327	2.29	8.16
AV-3 – Baseline	830	3.05	10.24	1131	1.33	9.47
HDL-2 (mg/dl)						
Baseline	1133	16.92	7.52	1423	17.72	7.57
AV-1	995	19.35	8.80	1332	19.05	8.12
AV-3	838	16.44	6.82	1143	16.29	6.41
AV-1 – Baseline	952	2.05	5.05	1263	1.20	4.67
AV-3 – Baseline	804	-0.59	5.57	1082	-1.55	5.42
HDL-3 (mg/dl)						
Baseline	1134	38.75	8.41	1423	39.14	8.11
AV-1	997	40.86	9.49	1333	40.11	8.18
AV-3	838	41.97	10.67	1143	41.87	9.52
AV-1 – Baseline	954	2.10	5.77	1264	1.03	5.21
AV-3 – Baseline	805	3.60	7.33	1082	2.74	6.64
Lp(a) (mg/dl)						
Baseline	1141	26.81	26.19	1449	27.34	27.77
AV-1	1005	25.40	27.00	1351	25.25	27.27
AV-3	829	21.83	21.88	1129	21.72	22.16
AV-1 – Baseline	970	-1.12	10.84	1303	-2.01	10.88
AV-3 – Baseline	799	-4.75	15.21	1089	-4.87	14.82

(continues)

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

Table 2.9
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	32	0.06	0.04	30	0.05	0.04
AV-1	27	0.07	0.08	25	0.05	0.03
AV-3	19	0.05	0.05	23	0.05	0.03
AV-1 - Baseline	27	0.01	0.06	24	-0.01	0.03
AV-3 - Baseline	19	-0.02	0.04	22	-0.01	0.04
Beta-Carotene (µg/ml)						
Baseline	32	0.33	0.38	30	0.25	0.20
AV-1	27	0.34	0.39	25	0.30	0.32
AV-3	19	0.30	0.26	23	0.25	0.29
AV-1 - Baseline	27	-0.02	0.24	24	0.03	0.17
AV-3 - Baseline	19	-0.06	0.27	22	0.01	0.20
Alpha-tocopherol (µg/ml)						
Baseline	32	18.70	9.89	30	13.04	4.96
AV-1	27	19.18	10.00	25	14.86	8.17
AV-3	19	18.92	7.17	23	13.00	4.00
AV-1 - Baseline	27	1.33	6.21	24	2.08	8.17
AV-3 - Baseline	19	1.66	7.37	22	0.19	3.22
Gamma-tocopherol (µg/ml)						
Baseline	32	2.47	1.64	30	3.06	1.80
AV-1	27	2.64	2.73	25	2.34	0.99
AV-3	19	2.08	1.72	23	2.16	0.80
AV-1 - Baseline	27	0.04	1.81	24	-0.76	1.95
AV-3 - Baseline	19	-0.50	1.21	22	-0.51	1.06
Beta-Cryptoxanthine (µg/ml)						
Baseline	32	0.09	0.11	30	0.06	0.03
AV-1	27	0.08	0.06	25	0.07	0.05
AV-3	19	0.09	0.07	23	0.08	0.06
AV-1 - Baseline	27	-0.01	0.10	24	0.01	0.04
AV-3 - Baseline	19	-0.01	0.11	22	0.02	0.06
Lycopene (µg/ml)						
Baseline	32	0.37	0.22	30	0.39	0.16
AV-1	27	0.40	0.21	25	0.42	0.18
AV-3	19	0.37	0.21	23	0.33	0.16
AV-1 - Baseline	27	0.03	0.21	24	0.05	0.16
AV-3 - Baseline	19	0.02	0.20	22	-0.03	0.19
Lutein and Zeaxanthin (µg/ml)						
Baseline	32	0.21	0.10	30	0.18	0.09
AV-1	27	0.25	0.15	25	0.18	0.09
AV-3	19	0.21	0.15	23	0.18	0.08
AV-1 - Baseline	27	0.03	0.09	24	0.00	0.05
AV-3 - Baseline	19	0.00	0.11	22	-0.01	0.05
Retinol (µg/ml)						
Baseline	32	0.62	0.20	30	0.52	0.12
AV-1	27	0.65	0.19	25	0.55	0.16
AV-3	19	0.63	0.14	23	0.57	0.15
AV-1 - Baseline	27	0.05	0.07	24	0.03	0.09
AV-3 - Baseline	19	0.06	0.12	22	0.04	0.12

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	30	144.43	37.09	27	118.30	32.15
AV-1	26	154.77	44.02	25	126.84	35.71
AV-3	19	145.26	47.09	24	122.75	30.44
AV-1 – Baseline	24	13.08	28.42	21	1.95	20.69
AV-3 – Baseline	18	10.00	29.57	21	3.10	23.59
Factor VII C (%) ¹						
Baseline	30	141.67	30.83	27	117.67	33.09
AV-1	25	141.24	30.15	25	126.44	32.24
AV-3	19	143.32	41.56	24	124.38	42.77
AV-1 – Baseline	23	6.70	16.45	21	3.90	23.09
AV-3 – Baseline	18	12.17	34.07	21	6.90	34.93
Fibrinogen (mg/dl)						
Baseline	30	325.93	67.56	27	312.41	79.21
AV-1	26	315.69	83.44	25	307.40	76.47
AV-3	19	313.26	52.91	24	283.08	58.72
AV-1 – Baseline	24	-9.04	75.45	21	-13.33	52.01
AV-3 – Baseline	18	-9.94	63.22	21	-34.71	57.48
Hormones / Other						
Glucose (mg/dl)						
Baseline	32	112.22	42.33	30	116.17	51.66
AV-1	27	112.30	42.55	25	113.44	60.34
AV-3	20	104.05	37.03	25	109.80	52.89
AV-1 – Baseline	27	-3.59	41.95	24	0.67	28.55
AV-3 – Baseline	20	-5.50	47.84	24	-2.50	31.91
Insulin (μIU/ml)						
Baseline	32	13.63	8.05	30	12.61	8.81
AV-1	27	13.22	7.68	24	12.52	7.35
AV-3	18	12.77	5.92	22	11.63	6.05
AV-1 – Baseline	27	-0.86	3.72	23	-0.26	2.88
AV-3 – Baseline	18	0.27	6.77	21	0.04	5.82

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	31	186.87	107.13	30	154.20	84.64
AV-1	27	214.63	159.36	25	161.12	100.16
AV-3	20	206.35	125.93	25	158.68	83.16
AV-1 – Baseline	26	35.85	98.82	24	10.88	56.74
AV-3 – Baseline	19	34.63	72.30	24	7.04	43.56
Total Cholesterol (mg/dl)						
Baseline	31	239.94	46.31	30	218.70	42.32
AV-1	27	230.78	47.19	25	208.32	41.70
AV-3	20	226.75	41.33	25	211.20	42.96
AV-1 – Baseline	26	-4.23	27.84	24	-2.83	19.24
AV-3 – Baseline	19	-3.11	27.32	24	-0.96	25.44
LDL-C (mg/dl)						
Baseline	28	143.11	28.19	30	133.93	38.98
AV-1	23	125.13	38.01	24	122.21	39.54
AV-3	18	133.39	39.21	25	123.88	41.47
AV-1 – Baseline	22	-15.77	25.61	23	-7.04	20.73
AV-3 – Baseline	18	-13.83	30.00	24	-3.25	25.32
HDL-C (mg/dl)						
Baseline	31	54.71	13.06	30	53.90	14.50
AV-1	27	59.44	15.82	25	56.28	13.48
AV-3	20	57.25	15.10	25	55.64	13.81
AV-1 – Baseline	26	5.04	7.68	24	2.67	7.85
AV-3 – Baseline	19	4.79	8.64	24	1.00	7.68
HDL-2 (mg/dl)						
Baseline	31	16.55	5.86	30	16.27	6.51
AV-1	26	19.42	7.17	25	16.76	5.80
AV-3	19	16.16	4.67	25	15.04	5.79
AV-1 – Baseline	25	2.68	3.67	24	0.50	4.31
AV-3 – Baseline	18	0.06	4.12	24	-1.63	3.56
HDL-3 (mg/dl)						
Baseline	32	38.06	7.75	30	37.63	8.72
AV-1	26	40.69	9.38	25	39.52	9.30
AV-3	19	41.16	11.30	25	40.60	8.96
AV-1 – Baseline	26	2.69	4.87	24	2.17	4.50
AV-3 – Baseline	19	3.84	6.60	24	2.63	6.00
Lp(a) (mg/dl)						
Baseline	31	35.90	39.11	30	21.83	32.28
AV-1	26	32.08	43.78	25	14.32	15.48
AV-3	19	26.05	28.02	23	18.87	26.63
AV-1 – Baseline	26	-0.50	14.62	24	-2.00	5.50
AV-3 – Baseline	18	-10.89	24.08	22	-5.59	12.85

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	50	0.12	0.10	124	0.12	0.07
AV-1	45	0.09	0.07	115	0.11	0.08
AV-3	36	0.08	0.08	91	0.10	0.06
AV-1 - Baseline	45	-0.04	0.09	113	-0.01	0.07
AV-3 - Baseline	36	-0.04	0.07	89	-0.03	0.07
Beta-Carotene (µg/ml)						
Baseline	50	0.57	0.53	124	0.54	0.37
AV-1	45	0.40	0.33	115	0.44	0.27
AV-3	36	0.41	0.38	91	0.46	0.37
AV-1 - Baseline	45	-0.13	0.30	113	-0.10	0.30
AV-3 - Baseline	36	-0.10	0.29	89	-0.09	0.39
Alpha-tocopherol (µg/ml)						
Baseline	50	20.49	8.12	124	18.62	8.88
AV-1	45	21.30	8.68	115	19.55	10.14
AV-3	36	22.61	9.76	91	21.47	13.96
AV-1 - Baseline	45	0.90	5.79	113	0.69	6.09
AV-3 - Baseline	36	2.16	8.02	89	2.83	10.79
Gamma-tocopherol (µg/ml)						
Baseline	50	1.67	1.24	124	1.55	1.06
AV-1	45	1.36	1.15	115	1.26	0.99
AV-3	36	1.25	1.10	91	1.24	0.94
AV-1 - Baseline	45	-0.27	0.71	113	-0.26	0.76
AV-3 - Baseline	36	-0.38	1.07	89	-0.35	0.95
Beta-Cryptoxanthine (µg/ml)						
Baseline	50	0.16	0.14	124	0.24	0.37
AV-1	45	0.17	0.19	115	0.23	0.34
AV-3	36	0.20	0.26	91	0.24	0.25
AV-1 - Baseline	45	0.01	0.14	113	-0.02	0.25
AV-3 - Baseline	36	0.03	0.23	89	-0.02	0.30
Lycopene (µg/ml)						
Baseline	50	0.42	0.25	124	0.40	0.21
AV-1	45	0.35	0.19	115	0.36	0.19
AV-3	36	0.30	0.19	91	0.33	0.18
AV-1 - Baseline	45	-0.06	0.19	113	-0.04	0.19
AV-3 - Baseline	36	-0.11	0.18	89	-0.09	0.20
Lutein and Zeaxanthin (µg/ml)						
Baseline	50	0.30	0.14	124	0.29	0.11
AV-1	45	0.28	0.13	115	0.28	0.12
AV-3	36	0.25	0.12	91	0.28	0.14
AV-1 - Baseline	45	-0.03	0.08	113	-0.01	0.09
AV-3 - Baseline	36	-0.05	0.10	89	-0.01	0.12
Retinol (µg/ml)						
Baseline	50	0.62	0.13	124	0.60	0.15
AV-1	45	0.65	0.15	115	0.61	0.18
AV-3	36	0.65	0.15	91	0.60	0.16
AV-1 - Baseline	45	0.03	0.11	113	0.01	0.11
AV-3 - Baseline	36	0.04	0.14	89	0.00	0.12

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	47	127.23	23.78	122	122.39	27.53
AV-1	43	143.30	41.46	111	127.50	26.93
AV-3	33	126.30	24.90	90	129.29	29.99
AV-1 – Baseline	41	18.83	33.34	108	3.82	21.88
AV-3 – Baseline	32	5.34	27.30	87	5.99	22.35
Factor VII C (%) ¹						
Baseline	47	126.96	24.75	122	124.72	24.52
AV-1	43	134.42	24.89	111	123.19	27.23
AV-3	33	127.85	25.43	89	124.48	27.16
AV-1 – Baseline	41	9.29	19.47	108	-1.48	16.86
AV-3 – Baseline	32	9.47	25.49	86	-1.09	19.70
Fibrinogen (mg/dl)						
Baseline	47	290.96	62.19	122	298.55	57.06
AV-1	43	286.44	65.15	111	286.46	54.74
AV-3	33	258.52	51.22	90	280.60	62.35
AV-1 – Baseline	41	-5.37	57.30	108	-13.99	49.10
AV-3 – Baseline	32	-27.00	43.76	87	-21.06	60.99
Hormones / Other						
Glucose (mg/dl)						
Baseline	50	105.40	28.34	124	101.58	24.24
AV-1	45	105.78	36.28	115	100.99	22.78
AV-3	37	99.86	25.72	95	99.49	16.57
AV-1 – Baseline	45	-0.58	12.59	113	-0.92	12.16
AV-3 – Baseline	37	-6.86	14.67	93	-1.83	17.35
Insulin (μIU/ml)						
Baseline	49	12.06	8.12	116	10.70	7.71
AV-1	44	11.75	9.46	109	10.05	7.03
AV-3	34	14.24	11.86	90	11.59	6.83
AV-1 – Baseline	43	-0.88	5.54	107	-0.43	5.33
AV-3 – Baseline	33	1.04	5.62	84	1.66	7.66

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	50	176.18	84.55	124	146.48	71.67
AV-1	45	197.38	102.02	114	160.58	102.70
AV-3	37	183.19	91.74	95	162.34	137.11
AV-1 – Baseline	45	19.93	79.99	112	12.00	80.72
AV-3 – Baseline	37	10.22	77.03	93	11.19	116.78
Total Cholesterol (mg/dl)						
Baseline	50	231.80	32.71	124	222.26	33.71
AV-1	45	219.98	33.82	114	211.69	32.20
AV-3	37	202.54	33.18	95	211.80	32.96
AV-1 – Baseline	45	-14.82	21.84	112	-10.92	26.78
AV-3 – Baseline	37	-27.22	31.76	93	-9.11	27.56
LDL-C (mg/dl)						
Baseline	48	138.19	30.66	123	132.40	30.46
AV-1	44	118.75	35.98	111	120.50	29.88
AV-3	36	109.86	34.90	93	120.25	29.90
AV-1 – Baseline	42	-22.83	28.41	109	-12.96	27.33
AV-3 – Baseline	35	-29.43	35.07	91	-10.41	27.90
HDL-C (mg/dl)						
Baseline	50	58.50	17.42	124	59.96	16.19
AV-1	45	63.56	18.58	114	60.40	15.75
AV-3	37	58.78	15.63	95	60.18	14.19
AV-1 – Baseline	45	3.76	8.35	112	0.88	8.49
AV-3 – Baseline	37	0.51	6.85	93	0.56	9.54
HDL-2 (mg/dl)						
Baseline	49	17.73	9.38	123	18.96	8.87
AV-1	44	20.20	9.85	111	20.06	8.55
AV-3	37	15.92	6.54	92	17.20	5.89
AV-1 – Baseline	43	1.51	6.54	109	1.32	4.52
AV-3 – Baseline	36	-2.06	5.08	89	-1.72	5.73
HDL-3 (mg/dl)						
Baseline	49	40.43	9.13	123	40.78	8.42
AV-1	44	43.39	11.30	112	40.27	7.98
AV-3	37	42.86	9.68	92	43.20	8.83
AV-1 – Baseline	43	1.95	5.88	110	-0.39	5.94
AV-3 – Baseline	36	2.72	4.98	89	2.30	6.45
Lp(a) (mg/dl)						
Baseline	50	20.74	14.22	122	19.81	18.78
AV-1	45	16.62	14.70	114	17.31	17.67
AV-3	37	14.00	12.53	92	14.18	13.85
AV-1 – Baseline	45	-4.73	7.81	111	-3.04	12.22
AV-3 – Baseline	37	-5.89	11.29	90	-4.72	11.09

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	395	0.07	0.08	282	0.06	0.06
AV-1	343	0.06	0.08	262	0.06	0.07
AV-3	258	0.06	0.08	207	0.05	0.06
AV-1 - Baseline	334	0.00	0.06	257	0.00	0.05
AV-3 - Baseline	250	-0.01	0.08	203	0.00	0.06
Beta-Carotene (µg/ml)						
Baseline	394	0.36	0.38	282	0.30	0.25
AV-1	342	0.35	0.37	263	0.29	0.26
AV-3	258	0.34	0.42	207	0.27	0.22
AV-1 - Baseline	333	-0.01	0.21	258	-0.02	0.19
AV-3 - Baseline	249	-0.02	0.29	203	-0.03	0.22
Alpha-tocopherol (µg/ml)						
Baseline	395	14.36	6.52	282	14.39	6.35
AV-1	343	14.37	5.40	263	14.66	6.56
AV-3	258	14.55	5.85	207	15.38	6.68
AV-1 - Baseline	334	0.12	5.07	258	0.06	5.05
AV-3 - Baseline	250	0.82	5.74	203	1.06	6.28
Gamma-tocopherol (µg/ml)						
Baseline	395	2.50	1.38	282	2.53	1.42
AV-1	343	2.33	1.38	263	2.29	1.31
AV-3	258	2.16	1.33	207	2.20	1.55
AV-1 - Baseline	334	-0.17	0.91	258	-0.21	0.94
AV-3 - Baseline	250	-0.33	1.13	203	-0.35	1.12
Beta-Cryptoxanthine (µg/ml)						
Baseline	395	0.09	0.06	282	0.09	0.07
AV-1	343	0.09	0.07	263	0.09	0.06
AV-3	258	0.09	0.06	207	0.09	0.08
AV-1 - Baseline	334	0.00	0.06	258	0.00	0.06
AV-3 - Baseline	250	0.00	0.05	203	0.01	0.08
Lycopene (µg/ml)						
Baseline	395	0.39	0.21	282	0.40	0.21
AV-1	343	0.38	0.21	263	0.38	0.21
AV-3	258	0.34	0.22	207	0.35	0.20
AV-1 - Baseline	334	0.00	0.18	258	-0.02	0.19
AV-3 - Baseline	250	-0.04	0.22	203	-0.04	0.21
Lutein and Zeaxanthin (µg/ml)						
Baseline	395	0.24	0.12	282	0.23	0.11
AV-1	343	0.25	0.12	263	0.24	0.11
AV-3	258	0.22	0.11	207	0.22	0.09
AV-1 - Baseline	334	0.00	0.08	258	0.01	0.08
AV-3 - Baseline	250	-0.02	0.09	203	-0.01	0.08
Retinol (µg/ml)						
Baseline	395	0.56	0.16	282	0.56	0.16
AV-1	343	0.57	0.15	263	0.57	0.15
AV-3	258	0.54	0.13	207	0.57	0.18
AV-1 - Baseline	334	0.01	0.10	258	0.01	0.08
AV-3 - Baseline	250	-0.01	0.12	203	0.01	0.14

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	383	113.26	22.95	268	113.54	26.49
AV-1	334	119.15	28.31	254	118.29	30.43
AV-3	245	119.00	27.17	198	118.60	30.72
AV-1 – Baseline	317	5.64	20.62	239	4.70	18.58
AV-3 – Baseline	230	5.86	23.75	184	5.54	22.24
Factor VII C (%) ¹						
Baseline	373	117.99	28.00	262	116.98	29.20
AV-1	330	119.30	27.11	253	115.93	27.30
AV-3	245	118.07	26.60	197	118.37	30.96
AV-1 – Baseline	303	1.76	19.50	232	-1.88	20.49
AV-3 – Baseline	221	0.81	22.45	178	0.30	26.01
Fibrinogen (mg/dl)						
Baseline	382	328.07	66.21	268	318.81	65.87
AV-1	333	323.92	66.78	254	314.64	64.60
AV-3	245	310.20	69.56	197	304.05	63.94
AV-1 – Baseline	316	-2.01	52.20	239	-4.26	47.77
AV-3 – Baseline	229	-19.75	55.20	183	-12.24	68.17
Hormones / Other¹						
Glucose (mg/dl)						
Baseline	394	111.38	42.90	283	106.94	38.02
AV-1	343	108.62	40.78	261	109.82	41.39
AV-3	266	106.32	35.05	209	109.85	43.88
AV-1 – Baseline	333	-1.14	36.72	256	0.63	26.09
AV-3 – Baseline	258	-3.86	31.66	205	0.43	26.89
Insulin (μIU/ml)						
Baseline	386	15.99	25.09	279	13.16	8.24
AV-1	341	14.38	13.52	261	13.18	7.77
AV-3	255	17.01	26.86	201	14.60	9.79
AV-1 – Baseline	324	-0.86	8.40	253	-0.14	6.24
AV-3 – Baseline	242	-1.38	20.42	194	1.94	8.50

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	395	119.97	54.59	283	118.84	60.74
AV-1	343	122.01	50.37	263	119.79	59.57
AV-3	266	116.78	46.08	209	121.56	61.99
AV-1 – Baseline	334	4.30	38.53	258	-2.10	39.83
AV-3 – Baseline	258	0.93	43.88	205	-0.44	52.99
Total Cholesterol (mg/dl)						
Baseline	395	224.05	42.33	283	221.35	41.99
AV-1	343	220.02	41.01	263	214.95	38.34
AV-3	266	213.18	39.80	209	212.54	39.46
AV-1 – Baseline	334	-4.89	29.09	258	-6.82	24.91
AV-3 – Baseline	258	-10.38	35.49	205	-7.34	30.00
LDL-C (mg/dl)						
Baseline	394	143.33	40.35	281	140.54	38.87
AV-1	343	134.12	39.02	260	132.36	37.67
AV-3	266	130.35	37.40	207	132.20	39.19
AV-1 – Baseline	334	-9.86	27.40	255	-8.78	22.85
AV-3 – Baseline	257	-13.03	33.24	203	-6.74	28.25
HDL-C (mg/dl)						
Baseline	394	56.73	13.77	282	56.71	13.47
AV-1	343	61.44	15.73	263	59.24	14.51
AV-3	266	59.45	14.89	209	56.62	13.76
AV-1 – Baseline	334	4.08	9.64	257	2.60	8.37
AV-3 – Baseline	257	2.40	10.11	205	0.10	8.40
HDL-2 (mg/dl)						
Baseline	392	17.52	7.15	276	17.12	7.17
AV-1	341	20.25	8.62	261	18.81	8.19
AV-3	261	16.68	5.98	207	15.32	5.21
AV-1 – Baseline	330	2.25	5.46	250	1.58	5.16
AV-3 – Baseline	253	-1.16	5.74	199	-1.44	5.17
HDL-3 (mg/dl)						
Baseline	392	39.20	8.14	276	39.55	7.49
AV-1	343	41.26	9.00	261	40.23	7.78
AV-3	261	42.91	9.81	207	41.14	9.35
AV-1 – Baseline	331	1.80	5.81	250	0.74	4.84
AV-3 – Baseline	253	3.54	6.98	199	1.46	6.52
Lp(a) (mg/dl)						
Baseline	388	40.45	31.50	277	38.83	28.83
AV-1	341	38.48	31.37	262	37.15	27.76
AV-3	259	34.35	27.02	207	31.32	22.96
AV-1 – Baseline	327	-1.15	13.04	252	-2.08	10.95
AV-3 – Baseline	246	-4.97	22.13	197	-4.65	19.10

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	177	0.09	0.11	222	0.10	0.09
AV-1	148	0.08	0.06	185	0.09	0.07
AV-3	123	0.06	0.07	158	0.07	0.07
AV-1 - Baseline	144	-0.02	0.11	183	-0.01	0.08
AV-3 - Baseline	121	-0.03	0.13	157	-0.03	0.10
Beta-Carotene (µg/ml)						
Baseline	177	0.32	0.49	222	0.32	0.31
AV-1	148	0.27	0.26	185	0.28	0.23
AV-3	123	0.23	0.25	158	0.28	0.28
AV-1 - Baseline	144	-0.07	0.38	183	-0.05	0.25
AV-3 - Baseline	121	-0.11	0.42	157	-0.07	0.36
Alpha-tocopherol (µg/ml)						
Baseline	177	15.52	7.30	222	15.78	6.81
AV-1	148	16.91	7.56	185	16.56	7.41
AV-3	123	16.27	7.11	158	17.29	8.43
AV-1 - Baseline	144	1.42	6.23	183	0.76	5.12
AV-3 - Baseline	121	0.20	6.68	157	1.38	6.74
Gamma-tocopherol (µg/ml)						
Baseline	177	2.29	1.37	222	2.23	1.37
AV-1	148	2.12	1.44	185	1.96	1.33
AV-3	123	1.97	1.22	158	1.92	1.49
AV-1 - Baseline	144	-0.22	0.98	183	-0.28	0.95
AV-3 - Baseline	121	-0.35	1.11	157	-0.36	1.17
Beta-Cryptoxanthine (µg/ml)						
Baseline	177	0.12	0.17	222	0.12	0.11
AV-1	148	0.11	0.11	185	0.12	0.11
AV-3	123	0.11	0.08	158	0.13	0.11
AV-1 - Baseline	144	-0.02	0.15	183	-0.01	0.09
AV-3 - Baseline	121	0.00	0.10	157	-0.01	0.10
Lycopene (µg/ml)						
Baseline	177	0.40	0.19	222	0.45	0.21
AV-1	148	0.38	0.18	185	0.40	0.19
AV-3	123	0.35	0.20	158	0.37	0.19
AV-1 - Baseline	144	-0.03	0.15	183	-0.05	0.17
AV-3 - Baseline	121	-0.05	0.19	157	-0.09	0.21
Lutein and Zeaxanthin (µg/ml)						
Baseline	177	0.19	0.09	222	0.22	0.10
AV-1	148	0.20	0.09	185	0.22	0.11
AV-3	123	0.18	0.08	158	0.20	0.09
AV-1 - Baseline	144	0.00	0.06	183	-0.01	0.08
AV-3 - Baseline	121	-0.01	0.07	157	-0.03	0.08
Retinol (µg/ml)						
Baseline	177	0.53	0.13	222	0.56	0.14
AV-1	148	0.55	0.13	185	0.56	0.15
AV-3	123	0.54	0.12	158	0.55	0.13
AV-1 - Baseline	144	0.02	0.08	183	0.00	0.09
AV-3 - Baseline	121	0.00	0.11	157	-0.01	0.11

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	170	122.91	25.34	209	124.94	27.93
AV-1	134	128.32	26.46	179	129.13	28.73
AV-3	123	130.59	28.74	147	131.42	28.79
AV-1 – Baseline	124	9.34	24.44	168	4.43	22.81
AV-3 – Baseline	117	7.26	28.49	140	5.26	28.42
Factor VII C (%) ¹						
Baseline	164	126.37	29.10	202	124.85	27.65
AV-1	131	126.92	24.66	174	123.49	26.08
AV-3	124	128.19	26.92	146	126.86	29.56
AV-1 – Baseline	118	3.15	26.69	158	-0.80	19.87
AV-3 – Baseline	113	2.55	28.53	134	0.51	26.75
Fibrinogen (mg/dl)						
Baseline	170	318.05	66.36	209	316.09	63.72
AV-1	134	311.28	60.61	178	315.65	61.87
AV-3	124	302.65	66.82	148	302.05	60.67
AV-1 – Baseline	124	-5.34	54.42	167	-6.71	52.31
AV-3 – Baseline	118	-16.12	56.05	141	-16.81	54.67
Hormones / Other						
Glucose (mg/dl)						
Baseline	176	104.09	30.87	222	106.05	35.26
AV-1	148	106.64	36.96	185	104.92	30.63
AV-3	127	106.45	29.46	161	108.14	37.73
AV-1 – Baseline	142	2.91	23.64	183	-1.09	17.83
AV-3 – Baseline	124	-0.05	26.54	160	-0.50	22.31
Insulin (μIU/ml)						
Baseline	174	14.00	8.69	220	13.60	7.88
AV-1	146	13.73	9.11	182	13.21	6.62
AV-3	118	15.07	8.32	154	13.97	7.45
AV-1 – Baseline	140	-0.39	6.26	180	-0.41	6.00
AV-3 – Baseline	115	1.61	7.22	152	0.00	8.14

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	178	162.16	67.43	222	166.98	86.24
AV-1	148	169.21	67.99	185	181.77	123.47
AV-3	126	169.68	66.86	161	192.13	144.12
AV-1 – Baseline	144	8.65	51.64	183	14.21	94.14
AV-3 – Baseline	124	0.69	65.66	160	27.31	110.22
Total Cholesterol (mg/dl)						
Baseline	178	219.26	37.88	222	224.51	37.44
AV-1	148	212.66	34.96	185	215.15	35.35
AV-3	126	208.44	33.04	161	215.30	35.20
AV-1 – Baseline	144	-6.39	27.28	183	-11.76	23.84
AV-3 – Baseline	124	-11.19	34.34	160	-11.58	29.47
LDL-C (mg/dl)						
Baseline	176	132.35	32.60	216	137.42	35.02
AV-1	147	122.43	31.51	178	127.15	33.73
AV-3	125	118.77	28.84	152	125.70	34.41
AV-1 – Baseline	141	-9.70	26.16	174	-14.01	24.32
AV-3 – Baseline	122	-13.18	30.87	148	-15.01	28.71
HDL-C (mg/dl)						
Baseline	177	54.01	12.96	222	53.64	14.08
AV-1	148	56.93	14.89	185	53.79	13.04
AV-3	125	55.57	14.36	161	54.37	13.62
AV-1 – Baseline	143	2.54	9.43	183	0.64	7.14
AV-3 – Baseline	123	1.94	10.08	160	0.89	8.88
HDL-2 (mg/dl)						
Baseline	177	15.97	6.45	218	15.61	6.68
AV-1	147	17.88	7.89	185	16.59	6.73
AV-3	124	15.24	6.03	160	15.18	5.70
AV-1 – Baseline	142	1.36	5.25	180	0.89	4.43
AV-3 – Baseline	122	-0.72	5.58	156	-0.59	5.34
HDL-3 (mg/dl)						
Baseline	177	38.03	7.75	218	37.58	7.65
AV-1	147	39.03	8.12	185	37.19	7.57
AV-3	124	40.19	9.22	160	39.23	8.71
AV-1 – Baseline	142	1.18	5.43	180	-0.31	4.77
AV-3 – Baseline	122	2.65	6.63	156	1.63	6.39
Lp(a) (mg/dl)						
Baseline	175	17.59	17.80	222	21.97	22.40
AV-1	145	16.40	17.78	184	19.75	20.96
AV-3	121	12.75	11.95	160	19.64	20.87
AV-1 – Baseline	140	-0.73	7.22	182	-1.79	10.78
AV-3 – Baseline	118	-1.40	8.15	159	-3.46	13.60

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	484	0.07	0.06	777	0.09	0.08
AV-1	436	0.06	0.05	749	0.08	0.08
AV-3	383	0.06	0.05	648	0.07	0.08
AV-1 - Baseline	427	-0.01	0.05	727	-0.01	0.06
AV-3 - Baseline	377	-0.01	0.05	629	-0.01	0.08
Beta-Carotene (µg/ml)						
Baseline	484	0.27	0.22	777	0.34	0.34
AV-1	436	0.24	0.22	749	0.31	0.31
AV-3	383	0.23	0.21	648	0.32	0.40
AV-1 - Baseline	427	-0.02	0.20	727	-0.04	0.21
AV-3 - Baseline	377	-0.04	0.22	629	-0.03	0.32
Alpha-tocopherol (µg/ml)						
Baseline	484	16.18	6.94	777	16.52	7.83
AV-1	436	18.04	9.19	749	17.02	7.36
AV-3	383	18.18	8.48	648	18.62	8.10
AV-1 - Baseline	427	1.86	6.39	727	0.54	5.80
AV-3 - Baseline	377	2.07	6.90	629	2.18	7.36
Gamma-tocopherol (µg/ml)						
Baseline	484	2.51	1.70	777	2.22	1.40
AV-1	436	2.23	1.91	749	1.80	1.21
AV-3	383	2.00	1.52	648	1.60	1.18
AV-1 - Baseline	427	-0.32	1.15	727	-0.40	0.92
AV-3 - Baseline	377	-0.60	1.20	629	-0.62	1.18
Beta-Cryptoxanthine (µg/ml)						
Baseline	484	0.08	0.07	777	0.09	0.07
AV-1	436	0.07	0.06	748	0.08	0.07
AV-3	383	0.08	0.06	648	0.09	0.08
AV-1 - Baseline	427	0.00	0.04	726	-0.01	0.06
AV-3 - Baseline	377	0.00	0.07	629	0.00	0.07
Lycopene (µg/ml)						
Baseline	484	0.40	0.20	777	0.41	0.19
AV-1	436	0.39	0.19	749	0.40	0.19
AV-3	383	0.35	0.18	648	0.39	0.21
AV-1 - Baseline	427	-0.01	0.17	727	-0.01	0.17
AV-3 - Baseline	377	-0.05	0.20	629	-0.02	0.22
Lutein and Zeaxanthin (µg/ml)						
Baseline	484	0.19	0.09	777	0.20	0.09
AV-1	436	0.20	0.09	749	0.21	0.09
AV-3	383	0.18	0.10	648	0.19	0.09
AV-1 - Baseline	427	0.00	0.06	727	0.00	0.06
AV-3 - Baseline	377	-0.01	0.07	629	-0.02	0.08
Retinol (µg/ml)						
Baseline	484	0.61	0.14	777	0.61	0.15
AV-1	436	0.64	0.15	749	0.62	0.14
AV-3	383	0.63	0.15	648	0.61	0.16
AV-1 - Baseline	427	0.03	0.11	727	0.01	0.10
AV-3 - Baseline	377	0.02	0.14	629	0.01	0.13

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	466	130.54	29.03	756	124.77	28.36
AV-1	413	142.32	35.17	722	131.18	31.03
AV-3	367	138.56	34.18	613	129.74	31.78
AV-1 – Baseline	398	10.84	25.67	684	6.25	23.04
AV-3 – Baseline	351	8.69	31.75	581	5.40	28.42
Factor VII C (%) ¹						
Baseline	463	131.66	27.89	750	126.27	26.73
AV-1	409	139.00	32.05	717	126.12	27.93
AV-3	364	137.94	35.11	611	128.85	32.34
AV-1 – Baseline	392	6.86	24.44	673	-0.44	22.25
AV-3 – Baseline	347	8.15	29.68	574	2.94	27.62
Fibrinogen (mg/dl)						
Baseline	464	310.11	62.68	754	304.41	57.78
AV-1	412	298.22	59.62	720	296.60	58.17
AV-3	366	292.89	57.36	613	288.37	55.83
AV-1 – Baseline	395	-13.02	52.01	680	-8.11	53.98
AV-3 – Baseline	348	-17.56	63.14	579	-15.67	55.14
Hormones / Other						
Glucose (mg/dl)						
Baseline	483	104.40	34.60	773	99.20	23.96
AV-1	434	101.79	29.67	747	96.81	20.23
AV-3	388	101.43	31.74	653	96.75	22.28
AV-1 – Baseline	425	-3.37	18.03	721	-2.36	15.78
AV-3 – Baseline	382	-3.66	25.27	632	-2.85	19.72
Insulin (μIU/ml)						
Baseline	473	12.47	7.13	742	11.11	6.52
AV-1	423	11.81	7.05	712	11.09	7.10
AV-3	369	13.19	7.83	617	12.19	6.93
AV-1 – Baseline	407	-0.75	5.63	672	-0.06	5.49
AV-3 – Baseline	357	0.78	6.63	572	1.14	6.26

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	484	167.85	104.44	776	148.16	75.10
AV-1	434	182.58	141.40	749	150.63	70.86
AV-3	388	176.29	84.03	651	153.91	76.43
AV-1 – Baseline	425	14.68	77.27	726	2.72	53.47
AV-3 – Baseline	381	7.51	86.62	631	6.42	61.65
Total Cholesterol (mg/dl)						
Baseline	484	230.56	41.19	776	225.46	36.16
AV-1	434	224.01	40.78	749	216.14	34.82
AV-3	388	220.06	35.73	651	215.36	34.84
AV-1 – Baseline	425	-6.00	30.26	726	-8.92	28.82
AV-3 – Baseline	381	-10.63	34.07	631	-8.92	32.57
LDL-C (mg/dl)						
Baseline	469	142.35	36.70	760	138.85	31.99
AV-1	418	128.17	35.47	738	126.68	31.58
AV-3	374	127.11	34.28	641	126.54	32.13
AV-1 – Baseline	405	-13.65	27.27	708	-11.57	25.97
AV-3 – Baseline	360	-15.71	31.76	610	-11.14	29.77
HDL-C (mg/dl)						
Baseline	480	55.47	14.64	772	57.06	14.40
AV-1	432	59.82	17.04	749	59.41	14.94
AV-3	384	58.54	16.97	649	58.63	15.54
AV-1 – Baseline	422	4.19	9.38	722	2.40	8.18
AV-3 – Baseline	375	3.22	10.33	625	1.49	9.64
HDL-2 (mg/dl)						
Baseline	459	16.89	7.60	743	17.89	7.59
AV-1	415	19.30	8.87	721	19.21	8.14
AV-3	378	16.48	6.99	635	16.45	6.58
AV-1 – Baseline	390	2.06	4.96	672	1.17	4.63
AV-3 – Baseline	356	-0.49	5.56	591	-1.64	5.45
HDL-3 (mg/dl)						
Baseline	459	38.70	8.48	743	39.14	8.18
AV-1	415	40.84	9.58	721	40.26	8.24
AV-3	378	41.94	10.88	635	42.06	9.57
AV-1 – Baseline	390	2.17	5.79	672	1.19	5.26
AV-3 – Baseline	356	3.68	7.47	591	2.96	6.66
Lp(a) (mg/dl)						
Baseline	472	25.65	25.24	764	26.46	27.75
AV-1	426	24.39	26.22	737	24.41	27.46
AV-3	375	20.94	21.12	625	20.86	21.99
AV-1 – Baseline	410	-1.06	10.74	705	-1.96	10.81
AV-3 – Baseline	362	-4.83	14.40	599	-4.96	14.40

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Unknown Race/Ethnicity

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Micronutrients						
Alpha-Carotene (µg/ml)						
Baseline	25	0.10	0.05	33	0.11	0.13
AV-1	23	0.10	0.09	29	0.09	0.10
AV-3	19	0.09	0.07	24	0.07	0.08
AV-1 - Baseline	23	0.00	0.07	28	-0.03	0.05
AV-3 - Baseline	19	-0.01	0.06	23	-0.05	0.08
Beta-Carotene (µg/ml)						
Baseline	25	0.35	0.32	33	0.42	0.45
AV-1	23	0.35	0.25	29	0.35	0.31
AV-3	19	0.36	0.45	24	0.36	0.34
AV-1 - Baseline	23	-0.03	0.16	28	-0.07	0.29
AV-3 - Baseline	19	0.01	0.22	23	-0.03	0.21
Alpha-tocopherol (µg/ml)						
Baseline	25	17.48	8.26	33	16.71	7.64
AV-1	23	18.94	11.06	29	17.21	6.22
AV-3	19	19.93	10.62	24	18.16	6.99
AV-1 - Baseline	23	0.97	5.11	28	0.09	5.64
AV-3 - Baseline	19	1.50	5.54	23	0.03	5.27
Gamma-tocopherol (µg/ml)						
Baseline	25	2.19	1.14	33	1.90	1.08
AV-1	23	2.00	0.87	29	1.73	1.06
AV-3	19	1.65	1.06	24	1.48	0.96
AV-1 - Baseline	23	-0.14	0.99	28	-0.08	0.70
AV-3 - Baseline	19	-0.43	1.36	23	-0.43	0.79
Beta-Cryptoxanthine (µg/ml)						
Baseline	25	0.09	0.08	33	0.11	0.12
AV-1	23	0.11	0.07	29	0.08	0.06
AV-3	19	0.09	0.08	24	0.09	0.08
AV-1 - Baseline	23	0.01	0.05	28	-0.02	0.08
AV-3 - Baseline	19	0.01	0.04	23	-0.03	0.09
Lycopene (µg/ml)						
Baseline	25	0.48	0.21	33	0.36	0.21
AV-1	23	0.44	0.23	29	0.33	0.22
AV-3	19	0.30	0.12	24	0.29	0.20
AV-1 - Baseline	23	-0.06	0.24	28	0.00	0.16
AV-3 - Baseline	19	-0.15	0.18	23	-0.03	0.15
Lutein and Zeaxanthin (µg/ml)						
Baseline	25	0.20	0.10	33	0.20	0.14
AV-1	23	0.20	0.11	29	0.22	0.12
AV-3	19	0.20	0.11	24	0.18	0.09
AV-1 - Baseline	23	-0.01	0.07	28	0.01	0.10
AV-3 - Baseline	19	0.00	0.10	23	-0.03	0.11
Retinol (µg/ml)						
Baseline	25	0.59	0.14	33	0.58	0.13
AV-1	23	0.64	0.19	29	0.60	0.13
AV-3	19	0.59	0.12	24	0.60	0.14
AV-1 - Baseline	23	0.06	0.13	28	0.00	0.12
AV-3 - Baseline	19	0.02	0.11	23	0.03	0.13

(continues)

Table 2.9 (continued)
Blood Specimen Analysis: Unknown Race/Ethnicity

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Clotting Factor						
Factor VII Activity, Antigen (%)						
Baseline	25	124.88	22.36	33	120.91	21.99
AV-1	23	133.00	26.98	28	130.21	27.60
AV-3	18	133.94	22.92	23	131.96	28.21
AV-1 – Baseline	23	8.43	26.66	28	8.82	16.06
AV-3 – Baseline	18	12.06	23.28	23	8.43	22.78
Factor VII C (%) ¹						
Baseline	24	123.79	22.90	33	123.64	21.38
AV-1	23	130.57	20.25	28	127.11	27.36
AV-3	18	146.94	30.04	23	130.39	32.67
AV-1 – Baseline	22	7.41	19.63	28	3.71	18.73
AV-3 – Baseline	17	23.35	20.64	23	5.13	29.63
Fibrinogen (mg/dl)						
Baseline	25	317.08	55.39	33	324.70	71.74
AV-1	23	294.04	64.72	28	307.32	59.63
AV-3	18	293.56	77.70	23	292.65	72.59
AV-1 – Baseline	23	-24.48	53.87	28	-23.04	51.03
AV-3 – Baseline	18	-20.67	73.91	23	-34.96	52.58
Hormones / Other						
Glucose (mg/dl)						
Baseline	25	98.32	19.88	34	100.62	26.89
AV-1	23	103.04	28.07	29	99.59	19.11
AV-3	19	103.37	26.24	24	100.92	19.67
AV-1 – Baseline	23	4.17	14.54	29	-2.83	14.46
AV-3 – Baseline	19	8.58	15.90	24	-3.08	17.55
Insulin (μIU/ml)						
Baseline	25	10.15	6.58	34	10.24	4.97
AV-1	23	10.90	7.41	29	10.97	6.59
AV-3	19	12.14	6.86	23	11.93	3.80
AV-1 – Baseline	23	0.61	6.25	29	0.11	3.45
AV-3 – Baseline	19	2.98	5.27	23	1.24	4.19

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 2.9 (continued)
Blood Specimen Analysis: Unknown Race/Ethnicity

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Lipoproteins						
Triglyceride (mg/dl)						
Baseline	25	155.40	89.00	34	157.29	73.88
AV-1	23	168.13	68.18	29	161.72	75.02
AV-3	19	155.11	63.58	24	156.17	61.65
AV-1 – Baseline	23	11.57	62.43	29	2.21	38.74
AV-3 – Baseline	19	8.42	31.67	24	-10.21	52.33
Total Cholesterol (mg/dl)						
Baseline	25	238.76	41.89	34	221.15	35.46
AV-1	23	236.48	36.92	29	220.34	38.73
AV-3	19	219.95	38.86	24	219.42	33.09
AV-1 – Baseline	23	-4.96	28.61	29	-1.17	29.84
AV-3 – Baseline	19	-12.16	34.25	24	-7.67	26.22
LDL-C (mg/dl)						
Baseline	24	152.25	37.79	34	135.24	33.35
AV-1	23	143.65	35.75	29	132.62	41.10
AV-3	19	131.05	31.86	24	129.71	32.45
AV-1 – Baseline	22	-10.27	23.25	29	-2.62	29.46
AV-3 – Baseline	19	-17.58	30.37	24	-11.46	30.71
HDL-C (mg/dl)						
Baseline	25	55.32	12.58	34	54.47	14.86
AV-1	23	59.17	13.34	29	55.31	15.06
AV-3	19	57.89	13.27	24	58.50	16.08
AV-1 – Baseline	23	4.61	7.45	29	0.93	4.78
AV-3 – Baseline	19	3.63	10.58	24	5.88	7.81
HDL-2 (mg/dl)						
Baseline	25	16.48	6.76	33	16.03	8.12
AV-1	22	18.73	7.25	29	17.00	9.21
AV-3	19	16.42	6.27	24	16.88	6.29
AV-1 – Baseline	22	1.91	5.08	28	0.57	4.14
AV-3 – Baseline	19	0.47	5.83	23	1.43	5.53
HDL-3 (mg/dl)						
Baseline	25	38.84	7.11	33	38.00	7.80
AV-1	22	41.50	6.84	29	38.31	7.28
AV-3	19	41.47	7.76	24	41.63	10.72
AV-1 – Baseline	22	3.00	4.86	28	0.18	3.38
AV-3 – Baseline	19	3.16	6.78	23	4.39	5.66
Lp(a) (mg/dl)						
Baseline	25	20.64	22.31	34	27.41	25.20
AV-1	22	20.23	23.22	29	23.00	19.88
AV-3	18	15.28	12.95	22	25.86	22.36
AV-1 – Baseline	22	-0.55	3.20	29	-3.55	15.82
AV-3 – Baseline	18	-1.67	3.83	22	-5.27	12.56

Table 2.10
Bone Mineral Density¹ Analysis: HRT Participants

Data as of: August 31, 2002

	Without Uterus			With Uterus		
	N	Mean	S.D.	N	Mean	S.D.
Whole Body Scan						
Baseline	930	1.01	0.11	1017	0.99	0.10
AV1	838	1.01	0.11	926	1.00	0.10
AV3	766	1.03	0.12	854	1.02	0.10
AV6	422	1.03	0.12	471	1.03	0.11
AV1 % Change from baseline BMD ²	833	0.41	2.79	921	0.26	2.35
AV3 % Change from baseline BMD ³	761	2.08	4.28	846	1.97	3.79
AV6 % Change from baseline BMD ⁴	419	2.19	5.27	465	2.76	5.51
Spine Scan						
Baseline	906	0.97	0.16	991	0.95	0.16
AV1	818	0.99	0.16	896	0.97	0.16
AV3	753	1.00	0.17	834	0.99	0.17
AV6	410	1.01	0.17	460	1.00	0.17
AV1 % Change from baseline BMD ²	814	1.91	4.55	892	2.06	4.34
AV3 % Change from baseline BMD ³	749	3.53	6.16	828	4.09	6.04
AV6 % Change from baseline BMD ⁴	407	4.48	7.75	458	5.22	7.60
Hip Scan						
Baseline	934	0.86	0.14	1024	0.84	0.13
AV1	841	0.86	0.14	928	0.84	0.13
AV3	774	0.88	0.15	860	0.86	0.14
AV6	429	0.88	0.14	481	0.86	0.13
AV1 % Change from baseline BMD ²	838	0.72	3.31	925	0.63	3.17
AV3 % Change from baseline BMD ³	768	2.22	4.86	854	2.17	4.78
AV6 % Change from baseline BMD ⁴	426	0.84	5.59	473	1.36	5.74

¹ Measured in (g/cm³).

² AV1 % Change from baseline BMD is defined as ((AV1-Baseline)/Baseline)x100.

³ AV3 % Change from baseline BMD is defined as ((AV3-Baseline)/Baseline)x100.

⁴ AV6 % Change from baseline BMD is defined as ((AV6-Baseline)/Baseline)x100.

Table 2.13
Locally Verified Outcomes (Annualized Percentages) by Age for Hormone Replacement Therapy

Data as of: August 31, 2002

Outcomes	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	27347	3425	5408	12364	6150
Mean follow-up (months)	66.4	71.5	68.6	65.5	63.6
Cardiovascular					
CHD ¹	568 (0.38%)	34 (0.17%)	48 (0.16%)	255 (0.38%)	231 (0.71%)
CHD death ²	133 (0.09%)	7 (0.03%)	13 (0.04%)	49 (0.07%)	64 (0.20%)
Total MI ³	479 (0.32%)	29 (0.14%)	37 (0.12%)	220 (0.33%)	193 (0.59%)
Clinical MI	462 (0.31%)	28 (0.14%)	37 (0.12%)	211 (0.31%)	186 (0.57%)
Evolving Q-wave MI ⁴	17 (0.01%)	1 (<0.01%)	0 (0.00%)	9 (0.01%)	7 (0.02%)
Possible evolving Q-wave MI ⁴	95 (0.06%)	11 (0.05%)	11 (0.04%)	35 (0.05%)	38 (0.12%)
Angina	771 (0.51%)	32 (0.16%)	95 (0.31%)	359 (0.53%)	285 (0.87%)
CABG/PTCA	765 (0.51%)	31 (0.15%)	83 (0.27%)	371 (0.55%)	280 (0.86%)
Carotid artery disease	131 (0.09%)	2 (0.01%)	14 (0.05%)	72 (0.11%)	43 (0.13%)
Congestive heart failure	440 (0.29%)	24 (0.12%)	47 (0.15%)	180 (0.27%)	189 (0.58%)
Stroke	458 (0.30%)	14 (0.07%)	43 (0.14%)	211 (0.31%)	190 (0.58%)
Non-disabling stroke	267 (0.18%)	11 (0.05%)	24 (0.08%)	127 (0.19%)	105 (0.32%)
Fatal/disabling stroke	111 (0.07%)	2 (0.01%)	6 (0.02%)	46 (0.07%)	57 (0.17%)
Unknown status from stroke	80 (0.05%)	1 (<0.01%)	13 (0.04%)	38 (0.06%)	28 (0.09%)
PVD	124 (0.08%)	6 (0.03%)	12 (0.04%)	62 (0.09%)	44 (0.13%)
DVT	261 (0.17%)	15 (0.07%)	38 (0.12%)	115 (0.17%)	93 (0.29%)
Pulmonary embolism	164 (0.11%)	8 (0.04%)	26 (0.08%)	74 (0.11%)	56 (0.17%)
CHD ¹ /Possible evolving Q-wave MI	658 (0.43%)	45 (0.22%)	59 (0.19%)	288 (0.43%)	266 (0.82%)
Coronary disease ⁵	1692 (1.12%)	95 (0.47%)	186 (0.60%)	769 (1.14%)	642 (1.97%)
DVT/PE	346 (0.23%)	17 (0.08%)	50 (0.16%)	161 (0.24%)	118 (0.36%)
Total cardiovascular disease	2543 (1.68%)	129 (0.63%)	279 (0.90%)	1188 (1.76%)	947 (2.90%)
Cancer					
Breast cancer ⁶	597 (0.39%)	55 (0.27%)	101 (0.33%)	291 (0.43%)	150 (0.46%)
Invasive breast cancer	478 (0.32%)	44 (0.22%)	82 (0.27%)	229 (0.34%)	123 (0.38%)
Non-invasive breast cancer	121 (0.08%)	11 (0.05%)	19 (0.06%)	64 (0.09%)	27 (0.08%)
Ovarian cancer	60 (0.04%)	2 (0.01%)	11 (0.04%)	34 (0.05%)	13 (0.04%)
Endometrial cancer ⁷	50 (0.05%)	1 (0.01%)	10 (0.05%)	24 (0.06%)	15 (0.08%)
Colorectal cancer	218 (0.14%)	10 (0.05%)	24 (0.08%)	107 (0.16%)	77 (0.24%)
Other cancer ⁸	766 (0.51%)	57 (0.28%)	107 (0.35%)	356 (0.53%)	246 (0.75%)
Total cancer	1645 (1.09%)	125 (0.61%)	247 (0.80%)	787 (1.17%)	486 (1.49%)
Fractures					
Hip fracture	176 (0.12%)	3 (0.01%)	4 (0.01%)	57 (0.08%)	112 (0.34%)
Vertebral fracture	187 (0.12%)	6 (0.03%)	20 (0.06%)	78 (0.12%)	83 (0.25%)
Other fracture ⁸	2233 (1.47%)	253 (1.24%)	343 (1.11%)	1056 (1.56%)	581 (1.78%)
Total fracture	2509 (1.66%)	259 (1.27%)	362 (1.17%)	1153 (1.71%)	735 (2.25%)
Deaths					
Cardiovascular deaths	259 (0.17%)	10 (0.05%)	23 (0.07%)	99 (0.15%)	127 (0.39%)
Cancer deaths	377 (0.25%)	19 (0.09%)	37 (0.12%)	181 (0.27%)	140 (0.43%)
Other known cause	124 (0.08%)	9 (0.04%)	17 (0.05%)	45 (0.07%)	53 (0.16%)
Unknown cause	51 (0.03%)	4 (0.02%)	6 (0.02%)	21 (0.03%)	20 (0.06%)
Not yet adjudicated	72 (0.05%)	2 (0.01%)	7 (0.02%)	34 (0.05%)	29 (0.09%)
Total death	883 (0.58%)	44 (0.22%)	90 (0.29%)	380 (0.56%)	369 (1.13%)

¹ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Total MI" includes clinical MI and evolving Q-wave MI.

⁴ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁵ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁶ Excludes four cases with borderline malignancy.

⁷ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁸ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

Table 2.13 (continued)
Locally Verified Outcomes (Annualized Percentages) by Race/Ethnicity for Hormone Replacement Therapy

Data as of: August 31, 2002

Outcomes	Race/Ethnicity					
	American Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	130	527	2738	1537	22030	385
Mean follow-up (months)	64.1	63.0	65.5	63.6	66.9	62.7
Cardiovascular						
CHD ¹	3 (0.43%)	7 (0.25%)	51 (0.34%)	17 (0.21%)	477 (0.39%)	13 (0.65%)
CHD death ²	2 (0.29%)	3 (0.11%)	22 (0.15%)	4 (0.05%)	99 (0.08%)	3 (0.15%)
Total MI ³	2 (0.29%)	6 (0.22%)	37 (0.25%)	14 (0.17%)	409 (0.33%)	11 (0.55%)
Clinical MI	2 (0.29%)	6 (0.22%)	36 (0.24%)	14 (0.17%)	394 (0.32%)	10 (0.50%)
Evolving Q-wave MI ⁴	0 (0.00%)	0 (0.00%)	1 (0.01%)	0 (0.00%)	15 (0.01%)	1 (0.05%)
Possible evolving Q-wave MI ⁴	0 (0.00%)	1 (0.04%)	11 (0.07%)	4 (0.05%)	78 (0.06%)	1 (0.05%)
Angina	4 (0.58%)	12 (0.43%)	79 (0.53%)	34 (0.42%)	635 (0.52%)	7 (0.35%)
CABG/PTCA	5 (0.72%)	7 (0.25%)	66 (0.44%)	30 (0.37%)	648 (0.53%)	9 (0.45%)
Carotid artery disease	1 (0.14%)	1 (0.04%)	5 (0.03%)	0 (0.00%)	124 (0.10%)	0 (0.00%)
Congestive heart failure	3 (0.43%)	6 (0.22%)	64 (0.43%)	11 (0.14%)	351 (0.29%)	5 (0.25%)
Stroke	3 (0.43%)	8 (0.29%)	58 (0.39%)	14 (0.17%)	370 (0.30%)	5 (0.25%)
Non-disabling stroke	2 (0.29%)	5 (0.18%)	28 (0.19%)	10 (0.12%)	219 (0.18%)	3 (0.15%)
Fatal/disabling stroke	1 (0.14%)	2 (0.07%)	15 (0.10%)	2 (0.02%)	90 (0.07%)	1 (0.05%)
Unknown status from stroke	0 (0.00%)	1 (0.04%)	15 (0.10%)	2 (0.02%)	61 (0.05%)	1 (0.05%)
PVD	2 (0.29%)	0 (0.00%)	11 (0.07%)	2 (0.02%)	109 (0.09%)	0 (0.00%)
DVT	1 (0.14%)	1 (0.04%)	23 (0.15%)	4 (0.05%)	231 (0.19%)	1 (0.05%)
Pulmonary embolism	3 (0.43%)	1 (0.04%)	16 (0.11%)	1 (0.01%)	142 (0.12%)	1 (0.05%)
CHD ¹ /Possible evolving Q-wave MI	3 (0.43%)	8 (0.29%)	61 (0.41%)	21 (0.26%)	551 (0.45%)	14 (0.70%)
Coronary disease ⁵	9 (1.30%)	22 (0.80%)	188 (1.26%)	64 (0.79%)	1386 (1.13%)	23 (1.14%)
DVT/PE	4 (0.58%)	1 (0.04%)	29 (0.19%)	4 (0.05%)	307 (0.25%)	1 (0.05%)
Total cardiovascular disease	15 (2.16%)	32 (1.16%)	273 (1.83%)	80 (0.98%)	2114 (1.72%)	29 (1.44%)
Cancer						
Breast cancer ⁶	0 (0.00%)	14 (0.51%)	51 (0.34%)	21 (0.26%)	507 (0.41%)	4 (0.20%)
Invasive breast cancer	0 (0.00%)	10 (0.36%)	40 (0.27%)	15 (0.18%)	409 (0.33%)	4 (0.20%)
Non-invasive breast cancer	0 (0.00%)	4 (0.14%)	11 (0.07%)	6 (0.07%)	100 (0.08%)	0 (0.00%)
Ovarian cancer	0 (0.00%)	0 (0.00%)	5 (0.03%)	0 (0.00%)	54 (0.04%)	1 (0.05%)
Endometrial cancer ⁷	1 (0.34%)	0 (0.00%)	0 (0.00%)	1 (0.02%)	48 (0.06%)	0 (0.00%)
Colorectal cancer	0 (0.00%)	7 (0.25%)	22 (0.15%)	12 (0.15%)	174 (0.14%)	3 (0.15%)
Other cancer ⁸	5 (0.72%)	12 (0.43%)	64 (0.43%)	26 (0.32%)	648 (0.53%)	11 (0.55%)
Total cancer	6 (0.86%)	33 (1.19%)	136 (0.91%)	58 (0.71%)	1394 (1.13%)	18 (0.89%)
Fractures						
Hip fracture	0 (0.00%)	2 (0.07%)	7 (0.05%)	3 (0.04%)	163 (0.13%)	1 (0.05%)
Vertebral fracture	0 (0.00%)	2 (0.07%)	2 (0.01%)	2 (0.02%)	179 (0.15%)	2 (0.10%)
Other fracture ⁸	11 (1.58%)	29 (1.05%)	115 (0.77%)	74 (0.91%)	1983 (1.61%)	21 (1.04%)
Total fracture	11 (1.58%)	32 (1.16%)	124 (0.83%)	77 (0.95%)	2243 (1.83%)	22 (1.09%)
Deaths						
Cardiovascular deaths	2 (0.29%)	5 (0.18%)	43 (0.29%)	4 (0.05%)	201 (0.16%)	4 (0.20%)
Cancer deaths	1 (0.14%)	11 (0.40%)	39 (0.26%)	10 (0.12%)	311 (0.25%)	5 (0.25%)
Other known cause	2 (0.29%)	1 (0.04%)	12 (0.08%)	0 (0.00%)	109 (0.09%)	0 (0.00%)
Unknown cause	1 (0.14%)	0 (0.00%)	7 (0.05%)	1 (0.01%)	41 (0.03%)	1 (0.05%)
Not yet adjudicated	1 (0.14%)	0 (0.00%)	6 (0.04%)	2 (0.02%)	62 (0.05%)	1 (0.05%)
Total death	7 (1.01%)	17 (0.61%)	107 (0.72%)	17 (0.21%)	724 (0.59%)	11 (0.55%)

¹ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Total MI" includes clinical MI and evolving Q-wave MI.

⁴ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁵ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁶ Excludes four cases with borderline malignancy.

⁷ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁸ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

Table 2.14
Locally Verified Outcomes (Annualized Percentages) for HRT Participants Without and With Uterus

Data as of: August 31, 2002

Outcomes	Without Uterus		With Uterus	
Number randomized	10739		16608	
Mean follow-up (months)	65.2		67.2	
Cardiovascular				
CHD ¹	258	(0.44%)	310	(0.33%)
CHD death ²	70	(0.12%)	63	(0.07%)
Total MI ³	213	(0.36%)	266	(0.29%)
Clinical MI	205	(0.35%)	257	(0.28%)
Evolving Q-wave MI ⁴	8	(0.01%)	9	(0.01%)
Possible evolving Q-wave MI ⁴	36	(0.06%)	59	(0.06%)
Angina	418	(0.72%)	353	(0.38%)
CABG/PTCA	370	(0.63%)	395	(0.42%)
Carotid artery disease	70	(0.12%)	61	(0.07%)
Congestive heart failure	239	(0.41%)	201	(0.22%)
Stroke	221	(0.38%)	237	(0.25%)
Non-disabling stroke	127	(0.22%)	140	(0.15%)
Fatal/disabling stroke	49	(0.08%)	62	(0.07%)
Unknown status from stroke	45	(0.08%)	35	(0.04%)
PVD	63	(0.11%)	61	(0.07%)
DVT	81	(0.14%)	180	(0.19%)
Pulmonary embolism	50	(0.09%)	114	(0.12%)
CHD ¹ /Possible evolving Q-wave MI	293	(0.50%)	365	(0.39%)
Coronary disease ⁵	835	(1.43%)	857	(0.92%)
DVT/PE	109	(0.19%)	237	(0.25%)
Total cardiovascular disease	1198	(2.05%)	1345	(1.45%)
Cancer				
Breast cancer ⁶	204	(0.35%)	393	(0.42%)
Invasive breast cancer	161	(0.28%)	317	(0.34%)
Non-invasive breast cancer	44	(0.08%)	77	(0.08%)
Ovarian cancer	20	(0.03%)	40	(0.04%)
Endometrial cancer ⁷	0	N/A	50	(0.05%)
Colorectal cancer	98	(0.17%)	120	(0.13%)
Other cancer ⁸	294	(0.50%)	472	(0.51%)
Total cancer	601	(1.03%)	1044	(1.12%)
Fractures				
Hip fracture	63	(0.11%)	113	(0.12%)
Vertebral fracture	69	(0.12%)	118	(0.13%)
Other fracture ⁸	858	(1.47%)	1375	(1.48%)
Total fracture	956	(1.64%)	1553	(1.67%)
Deaths				
Cardiovascular deaths	128	(0.22%)	131	(0.14%)
Cancer deaths	160	(0.27%)	217	(0.23%)
Other known cause	42	(0.07%)	82	(0.09%)
Unknown cause	29	(0.05%)	22	(0.02%)
Not yet adjudicated	27	(0.05%)	45	(0.05%)
Total death	386	(0.66%)	497	(0.53%)

¹ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Total MI" includes clinical MI and evolving Q-wave MI.

⁴ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁵ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁶ Excludes four cases with borderline malignancy.

⁷ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁸ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

Table 2.15
Frequency (%)¹ of Various Subcategories of Stroke Diagnosis: HRT Participants

Data as of: August 31, 2002

	Without Uterus		With Uterus	
Number randomized	10739		16608	
<u>Stroke Diagnosis</u>				
Subarachoid hemorrhage	8	3.6%	11	4.6%
Intracerebral hemorrhage	26	11.8%	34	14.3%
Other intracranial hemorrhage	2	0.9%	2	0.8%
Occlusion of cerebral arteries with infarction	126	57.0%	135	57.0%
Acute cerebrovascular disease	42	19.0%	34	14.3%
Central nervous system complications	11	5.0%	8	3.4%
Report of cerebrovascular death only	6	2.7%	12	5.1%
Missing	0	0.0%	1	0.4%
Total	221	100%	237	100%

¹ Percentages are relative to the total number of stroke diagnoses.

Table 2.16
Frequency (%)¹ of Disability Levels Following Stroke – Glasgow Scale: HRT Participants

Data as of: August 31, 2002

	Without Uterus		With Uterus	
Number randomized	10739		16608	
<u>Glasgow scale</u>				
Good recovery	69	31.2%	76	32.1%
Moderately disabled	58	26.2%	64	27.0%
Severely disabled	21	9.5%	25	10.5%
Vegetative survival	0	0.0%	4	1.7%
Death or death within 1 month	28	12.7%	33	13.9%
Unable to categorize stroke	15	6.8%	14	5.9%
Not yet categorized	30	13.6%	21	8.9%
Total	221	100%	237	100%

¹ Percentages are relative to the total number of stroke diagnoses.

Table 2.17
Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Race/Ethnicity
for HRT Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	27347	3425	5408	12364	6150
Mean follow-up (months)	66.4	71.5	68.6	65.5	63.6
Hospitalizations					
Ever	10832 (7.15%)	955 (4.68%)	1710 (5.53%)	5027 (7.45%)	3140 (9.63%)
Two or more	5186 (3.42%)	402 (1.97%)	728 (2.35%)	2409 (3.57%)	1647 (5.05%)
Other					
Diabetes (treated)	1522 (1.06%)	206 (1.05%)	308 (1.05%)	690 (1.08%)	318 (1.04%)
Gallbladder disease ¹	1525 (1.21%)	210 (1.19%)	322 (1.22%)	716 (1.28%)	277 (1.05%)
Hysterectomy	496 (0.53%)	41 (0.34%)	91 (0.45%)	251 (0.60%)	113 (0.59%)
Glaucoma	2130 (1.47%)	180 (0.90%)	347 (1.15%)	1023 (1.58%)	580 (1.92%)
Osteoporosis	4224 (2.94%)	297 (1.48%)	623 (2.07%)	2034 (3.18%)	1270 (4.31%)
Osteoarthritis ²	3507 (3.76%)	434 (2.84%)	690 (3.23%)	1597 (3.98%)	786 (4.75%)
Rheumatoid arthritis	1176 (0.81%)	159 (0.81%)	263 (0.88%)	501 (0.78%)	253 (0.82%)
Intestinal polyps	2619 (1.86%)	261 (1.32%)	441 (1.49%)	1343 (2.14%)	574 (1.99%)
Lupus	200 (0.13%)	27 (0.13%)	43 (0.14%)	93 (0.14%)	37 (0.11%)
Kidney stones ²	466 (0.38%)	54 (0.35%)	89 (0.36%)	214 (0.39%)	109 (0.41%)
Cataracts ²	6178 (5.76%)	304 (1.93%)	839 (3.46%)	3319 (6.78%)	1716 (9.39%)
Pills for hypertension	5376 (5.00%)	569 (3.45%)	1011 (4.23%)	2454 (5.24%)	1342 (6.56%)

Outcomes	Race/Ethnicity					
	Am Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	130	527	2738	1537	22030	385
Mean follow-up (months)	64.1	63.0	65.5	63.6	66.9	62.7
Hospitalizations						
Ever	57 (8.20%)	136 (4.92%)	1114 (7.45%)	476 (5.84%)	8913 (7.25%)	136 (6.76%)
Two or more	30 (4.32%)	53 (1.92%)	557 (3.73%)	184 (2.26%)	4309 (3.51%)	53 (2.63%)
Other						
Diabetes (treated)	11 (1.84%)	33 (1.31%)	266 (2.03%)	136 (1.82%)	1057 (0.90%)	19 (1.02%)
Gallbladder disease ¹	9 (1.69%)	22 (0.87%)	132 (0.98%)	81 (1.33%)	1260 (1.23%)	21 (1.27%)
Hysterectomy	2 (0.68%)	2 (0.10%)	28 (0.45%)	24 (0.51%)	434 (0.55%)	6 (0.48%)
Glaucoma	10 (1.53%)	40 (1.50%)	273 (1.98%)	132 (1.68%)	1644 (1.39%)	31 (1.65%)
Osteoporosis	20 (3.04%)	92 (3.46%)	209 (1.45%)	207 (2.73%)	3633 (3.12%)	63 (3.31%)
Osteoarthritis ²	23 (4.88%)	67 (3.45%)	364 (4.04%)	247 (4.39%)	2742 (3.66%)	64 (4.95%)
Rheumatoid arthritis	8 (1.30%)	21 (0.79%)	199 (1.46%)	168 (2.17%)	757 (0.64%)	23 (1.21%)
Intestinal polyps	11 (1.72%)	38 (1.50%)	258 (1.85%)	128 (1.64%)	2163 (1.89%)	21 (1.13%)
Lupus	1 (0.14%)	3 (0.11%)	25 (0.17%)	13 (0.16%)	157 (0.13%)	1 (0.05%)
Kidney stones ²	5 (0.96%)	17 (0.75%)	47 (0.40%)	29 (0.45%)	363 (0.37%)	5 (0.30%)
Cataracts ²	30 (5.94%)	98 (4.92%)	555 (5.23%)	319 (5.09%)	5102 (5.90%)	74 (5.16%)
Pills for hypertension	33 (6.73%)	103 (5.32%)	504 (6.81%)	320 (5.24%)	4353 (4.82%)	63 (4.83%)

¹ "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

² These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

Table 2.18
Baseline Characteristics of HRT Participants Enrolled in WHIMS

Data as of: August 31, 2002

	HRT Participants	
	Without Uterus	With Uterus
Total HRT Participants	10739	16608
Eligible HRT Population	4999	7415
Enrolled in WHIMS	2970	4556
% Enrolled of Total HRT	27.7%	27.4%
% Enrolled of Eligible	59.4%	61.4%
<u>WHIMS Participants</u>	(N = 2970)	(N = 4556)
Age at Screening		
< 70	1424 (47.9%)	2293 (50.3%)
70-74	1062 (35.8%)	1540 (33.8%)
75+	484 (16.3%)	723 (15.9%)
Education		
Missing	8 (0.3%)	16 (0.4%)
0-8 years	68 (2.3%)	68 (1.5%)
Some high school	213 (7.2%)	231 (5.1%)
High school diploma/GED	706 (23.8%)	947 (20.8%)
School after high school	1246 (42.0%)	1775 (39.0%)
College degree or higher	729 (24.5%)	1519 (33.3%)
Ethnicity		
American Indian	16 (0.5%)	10 (0.2%)
Asian/Pacific Islander	37 (1.2%)	91 (2.0%)
Black	326 (11.0%)	216 (4.7%)
Hispanic	84 (2.8%)	105 (2.3%)
White	2457 (82.7%)	4065 (89.2%)
Unknown	50 (1.7%)	69 (1.5%)
Family Income		
Missing	182 (6.1%)	274 (6.0%)
< \$10,000	226 (7.6%)	197 (4.3%)
\$10,000 - \$19,999	649 (21.9%)	789 (17.3%)
\$20,000 - \$34,999	897 (30.2%)	1325 (29.1%)
\$35,000 - \$49,999	516 (17.4%)	931 (20.4%)
\$50,000 - \$74,999	324 (10.9%)	660 (14.5%)
\$75,000 +	176 (5.9%)	380 (8.3%)

3. DM Component

3.1 Recruitment

Age and race/ethnicity-specific DM recruitment data are presented in *Table 3.1*. The age-specific enrollment exceeded the design assumptions for ages 50-54, 55-59, and 60-69. For the age category 70-79, recruitment was lower than designed.

3.2 Adherence

Nutrient intake data for adherence monitoring are presented in *Table 3.2* and *Figure 3.1*. Studywide, the Food Frequency Questionnaire (FFQ) mean difference between Intervention and Control women is 10.9% energy from fat at AV-1 decreasing to 7.7% at AV-8. This report presents nutrient intake comparisons for each racial/ethnic group separately (*Table 3.3*). Because of sparse numbers, some of these results are highly variable. The C-I value in minority women is roughly 1-3 percentage points lower compared to white women. All C-I analyses are based on only those women providing a food frequency questionnaire at the designated visit. For example, missing data account for 11.5% of our sample at AV-1 and 15.2% at AV-3. The overall C-I percent energy from fat is approximately 2 to 3 percentage points lower than the design assumptions. Refer to *Section 3.7* for a discussion of the impact of the C-I on study power and of the adherence initiatives that are underway.

For fruit and vegetable intake, the mean difference between the arms of the trial remains consistently in excess of 1 more serving per day for Intervention vs. Control women. Compared to Control women, Intervention women consumed almost 1 more serving per day of grains at AV-1, decreasing to one-half servings from AV-4 to AV-7, with a recent decrease to one-third at AV-8. Generally, the C-I for fruit and vegetables intake, as well as grain intake, are similar across race/ethnicity groups.

Multivariate analyses were conducted to identify factors associated with C-I differences in percent energy from fat based on FFQs collected in the past year and controlling for visit year and clinic effect (*Table 3.4*). The only participant characteristics that are consistently associated with a lower C-I difference was being older than age 60-69 ($p < 0.05$) or being Black compared to White ($p < 0.05$). DM Participants randomized to HRT were also significantly more adherent than non-HRT participants. Separate analyses were conducted to examine session attendance, completion, and fat score provision variables in relation to C-I because these measures are highly correlated. For example, self-monitoring scores are almost always provided at sessions, and therefore session attendance (and completion) is closely associated with self-monitoring. Session attendance, completion, and self-monitoring are all significantly associated with much higher (i.e., better) C-I values.

Body weight data are presented in *Table 3.5*. The difference in body weight between Control and Intervention participants at AV-1 was almost 2 kg ($p < 0.01$). The body weight C-I has steadily decreased and there is no statistically significant difference at AV-8, although the mean intervention body weight is less than in control women. From a trend perspective, these results are consistent with changes in energy intake estimated with the FFQ. The body weight data by race/ethnicity show that American Indians on the Intervention have maintained the same mean weight for four years,

while the control arm has gained 4-5 kg, producing marginally significant differences at AV-3 through AV-6.

Tables 3.6-3.7 give reasons for stopping DM categorized by general type and stratified by age and race/ethnicity. Overall, the major reasons for stopping given by participants were family responsibilities (12.4%), demands of work (10.3%), and issues of interest in the study (9.8%). Issues specifically related to the DM intervention were seldom mentioned. The age and race/ethnicity stratified analyses have sparse numbers and may be confounded by other factors, and therefore should be interpreted cautiously. These data suggest that older participants were less likely to indicate that they were stopping due the demands of work, but were also less likely to stop the DM intervention because it was "Too far to the CC." Compared to the other race/ethnicity groups, Hispanic/Latino women were most likely to indicate that they were stopping intervention because of family demands, but least likely to stop intervention because of interest in the study. Black/African American women were most likely to stop DM because of demands of work and/or issues of interest in the study.

3.3 Blood Specimen and Bone Density Analyses

Tables 3.8-3.9 present the results of blinded blood specimen analyses from a small (4.3%) cohort of DM women selected randomly at baseline for these prospective analyses. This subsample incorporated oversampling of minorities. The results shown in *Table 3.8* are weighted to reflect the overall WHI distribution of race/ethnicity. *Table 3.9* presents analysis by race/ethnicity. Differences between baseline and AV-1 are mostly modest, with reductions of approximately 5% in LDL cholesterol and about 3% in total cholesterol for Intervention and Control women combined. There are no substantial changes in HDL-cholesterol or triglycerides in the combined groups. Blood specimen analyses are presented by race/ethnicity group and appear to be consistent with the dietary data. For example, LDL cholesterol reductions averaged 7% in Asian/Pacific Islander women and 5% in white women but are slightly lower among other groups (about 4% in Hispanic/Latinas and American Indian/Alaskan Native women and 3% in Blacks/African American). Note that baseline and AV-1 specimens were batched together for concurrent analyses by Medical Research Labs.

Tables 3.10-3.11 present blinded bone mineral density data from the DM bone density subsample overall and by race/ethnicity. Changes from baseline to AV-1, AV-3, and AV-6 are interesting with increases in mean bone mineral density in the whole body scan as well as the spine and hip scan. An increase in BMD was not expected from this intervention. There were, generally, similar trends by race/ethnicity. Possible reasons for this observation include use of calcium supplements and/or HRT, selection of health-conscious women, incomplete BMD data (e.g., 12.6% missing at AV-3), or measurement issues.

3.4 Adherence to Follow-up

Table 3.12 summarizes adherence to follow-up contacts by treatment arm and contact type. Follow-up participation has been roughly equivalent in the two arms. The acceptable adherence rates specified by the Steering Committee for collection of outcome data are 90% at AV-1, with a decline of no more than 1% per year, going no lower than 85%. WHI adherence rates are above those rates for all annual visits.

3.5 Vital Status

Table 3.13 presents data on the vital status and the participation status of participants in the DM trial. A detailed description of CCC and clinic activities to actively locate participants who do not complete their periodic visits is given in *Section 6 – Outcomes Processing*. For operational purposes, we define CT participants to have an “unknown” participation status if there is no outcomes information from the participant for 18 months and no other contacts for 6 months. Currently, about 3.7% of the DM participants are lost-to-follow-up or have stopped follow-up (an increase of 0.1% compared to the Spring 2002 report), and 2.6% of the participants are known to be deceased. Virtually all of the remaining participants have completed a *Form 33 – Medical History Update* in the last 18 months. The design assumed that 3% per year would be lost-to-follow-up or death. Currently, the average follow-up for DM participants is about 5.7 years, suggesting that approximately 15.9% could be expected to be dead or lost-to-follow-up. Our overall rates compare favorably to design assumptions.

3.6 Outcomes

Table 3.14 contains counts of the number of locally verified major WHI outcomes for DM participants by race/ethnicity and age. Approximately 4% of the self-reported outcomes have not yet been verified, so the numbers in this table can be seen as a lower bound to the actual number of outcomes that have occurred. Compared to the design assumptions, we have observed almost 110% of the expected number of breast cancers, 75% of the expected number of colorectal cancers, about 60% of the expected number of CHD events, and about 30% of the expected number hip fractures.

Table 3.15 contains counts of the number of self-reports for some outcomes that are not locally verified in WHI. As most of the locally verified outcomes are somewhat over reported (see *Section 6.3 – Outcomes Data Quality*), the number in this table should be taken as an upper bound to the number of events that have occurred in DM participants.

3.7 Issues

As noted above, the C-I difference is less than the design assumptions. The WHI investigators and staff have undertaken a number of activities addressing adherence. In summer 1999, the DM Intervention incorporated an Intensive Intervention Program (IIP) that consisted of interviews using motivational enhancement techniques. Nutritionists targeted “medium adherers,” defined as women who are attending some sessions but not meeting their fat gram goal or not self-monitoring (about 40% of intervention women). This protocol was completed on March 30, 2001. A preliminary evaluation of the IIP among intervention participants indicated that these contacts had a positive effect on adherence to fat intake goals among medium adherers. Specifically, when examining change (increases) in fat intake from AV-1 to most recent data collection, participants who received IIP contact had an increase in fat intake that was 0.75 percentage points less (i.e., had less slippage) than intervention women who did not receive IIP ($p < 0.05$).

The second major DM initiative was called the Targeted Message Campaign (TMC). The campaign began with a 2000 Fall/Winter Kickoff Newsletter to raise awareness and excitement. Starting in January 2001, participants received a mailing introducing five themes to help them rediscover their intrinsic motivation(s) for participating in WHI. This first mailing was followed by a motivational enhancement phone call that supports participants in the process of identifying their primary

motivation. Finally, based on information collected on the call, a second targeted mailing allowed a woman to select an action consistent with her readiness to enhance her intervention adherence. This campaign was completed at the end of 2001.

A Dietary Modification Working Group developed a third initiative called the Personalized Evaluation of Fat Intake (PEFI). This intervention uses tailored, food-based, feedback to facilitate dietary goal re-setting for participants. The dietary assessment is performed using a specially designed instrument that focuses on usual fat-intake over the past 4 weeks. After scanning, computerized algorithms provide printed, individualized feedback on estimated grams of fat consumed (by foods) and food-specific behavioral change suggestions. The dietary questionnaire was administered during Summer 2002 group sessions. The written feedback is provided and reinforced in Fall 2002 group sessions. CCs are conducting individual follow-up of group non-attenders by phone and mail.

Table 3.1
Dietary Modification Component Age – and Race/Ethnicity – Specific Recruitment

Data as of: August 31, 2002

	Total Randomized	% of Overall Goal	Distribution	Design Assumption
Age	48,835			
50-54	6961	149%	14%	10
55-59	11043	118%	23%	20
60-69	22713	108%	47%	45
70-79	8118	70%	17%	25
Race/Ethnicity	48,835			
American Indian	202		<1%	
Asian	1105		2%	
Black	5262		11%	
Hispanic	1845		4%	
White	39762		81%	
Unknown	659		1%	

Table 3.2
Nutrient Intake Monitoring

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	19541	38.8	5.0	29294	38.8	5.0	0.0	0.0	0.83
FFQ Year 1 ³	18098	25.2	7.5	26772	36.1	6.9	10.9	0.1	<.01
FFQ Year 2 ⁴	5923	26.3	7.6	8667	36.3	7.0	9.9	0.1	<.01
FFQ Year 3 ⁵	3241	27.7	7.9	4892	37.3	7.1	9.6	0.2	<.01
FFQ Year 4 ⁶	5025	28.5	8.1	7834	37.6	7.1	9.1	0.1	<.01
FFQ Year 5 ⁷	4908	28.9	8.2	7519	37.8	7.3	8.9	0.1	<.01
FFQ Year 6 ⁸	3741	29.4	8.2	5716	37.6	7.1	8.2	0.2	<.01
FFQ Year 7 ⁹	1521	30.0	8.0	2303	37.6	7.1	7.6	0.2	<.01
FFQ Year 8 ¹⁰	366	29.7	8.1	619	37.5	7.3	7.7	0.5	<.01
4DFR Baseline	892	32.8	6.4	1351	33.0	6.8	0.2	0.3	0.54
4DFR Year 1	805	21.7	7.3	1171	32.9	6.8	11.3	0.3	<.01
24 Hr Recall, Post-baseline	226	23.0	9.2	262	32.1	7.6	9.2	0.8	<.01
24 Hr Recall, Year 1	221	22.4	7.8	268	32.6	7.7	10.2	0.7	<.01
24 Hr Recall, Year 2	214	23.8	9.7	244	32.5	8.0	8.7	0.8	<.01
24 Hr Recall, Year 3	209	25.1	9.2	249	33.3	8.6	8.2	0.8	<.01
24 Hr Recall, Year 3 Cohort	787	24.8	8.5	1183	33.0	7.6	8.3	0.4	<.01
24 Hr Recall, Year 4	195	25.7	9.4	220	33.2	8.5	7.5	0.9	<.01
24 Hr Recall, Year 5	102	27.3	9.5	159	34.5	8.2	7.2	1.1	<.01
24 Hr Recall, Year 6	59	26.9	9.8	74	34.0	7.9	7.1	1.5	<.01
24 Hr Recall, Year 6 Cohort	309	26.5	8.7	511	33.5	7.5	7.0	0.6	<.01
24 Hr Recall, Year 7	17	27.7	11.5	23	35.4	9.0	7.7	3.2	0.03
Total Energy (kcal)									
FFQ Baseline	19541	1789.1	713.3	29294	1789.4	706.6	0.3	6.6	0.93
FFQ Year 1	18098	1473.9	534.4	26772	1584.3	641.5	110.4	5.8	<.01
FFQ Year 2	5923	1479.6	534.9	8667	1575.5	625.4	95.9	10.0	<.01
FFQ Year 3	3241	1476.7	539.0	4892	1571.9	644.3	95.2	13.7	<.01
FFQ Year 4	5025	1443.1	536.4	7834	1562.1	634.4	118.9	10.8	<.01
FFQ Year 5	4908	1465.5	541.1	7519	1560.7	640.2	95.2	11.1	<.01
FFQ Year 6	3741	1455.8	548.5	5716	1539.0	635.6	83.3	12.7	<.01
FFQ Year 7	1521	1455.0	528.0	2303	1545.4	632.7	90.4	19.6	<.01
FFQ Year 8	366	1425.5	512.1	619	1542.5	625.9	117.0	38.7	0.02
4DFR Baseline	892	1707.2	454.3	1351	1712.9	459.4	5.7	19.7	0.79
4DFR Year 1	805	1422.8	355.7	1171	1627.0	446.9	204.2	18.9	<.01
24 Hr Recall, Post-baseline	226	1519.8	418.2	262	1652.8	516.5	133.0	43.0	<.01
24 Hr Recall, Year 1	221	1482.1	417.8	268	1635.8	477.0	153.6	41.0	<.01
24 Hr Recall, Year 2	214	1436.4	430.0	244	1603.8	523.4	167.4	45.1	<.01
24 Hr Recall, Year 3	209	1443.3	427.8	249	1589.2	504.2	145.9	44.2	<.01
24 Hr Recall, Year 3 Cohort	787	1431.8	391.6	1183	1589.9	489.3	158.1	20.8	<.01
24 Hr Recall, Year 4	195	1447.7	398.9	220	1525.9	469.3	78.2	43.0	0.15
24 Hr Recall, Year 5	102	1460.3	473.3	159	1613.4	530.2	153.0	64.5	0.02
24 Hr Recall, Year 6	59	1375.5	411.3	74	1582.3	512.5	206.8	82.1	0.01
24 Hr Recall, Year 6 Cohort	309	1432.4	395.2	511	1547.5	482.5	115.2	32.5	<.01
24 Hr Recall, Year 7	17	1292.5	241.6	23	1514.0	477.0	221.5	126.5	0.18

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 4953 (27%) Intervention women had ≤20% energy from fat at year 1.

⁴ 1268 (21%) Intervention women had ≤20% energy from fat at year 2.

⁵ 566 (17%) Intervention women had ≤20% energy from fat at year 3.

⁶ 769 (15%) Intervention women had ≤20% energy from fat at year 4.

⁷ 685 (14%) Intervention women had ≤20% energy from fat at year 5.

⁸ 419 (11%) Intervention women had ≤20% energy from fat at year 6.

⁹ 146 (10%) Intervention women had ≤20% energy from fat at year 7.

¹⁰ 43 (12%) Intervention women had ≤20% energy from fat at year 8.

Table 3.2 (continued)
Nutrient Intake Monitoring

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Total Fat (g)									
FFQ Baseline	19541	77.9	35.3	29294	77.8	34.7	0.0	0.3	0.87
FFQ Year 1	18098	41.5	21.8	26772	64.5	31.7	23.0	0.3	<.01
FFQ Year 2	5923	43.5	22.3	8667	64.5	31.3	21.0	0.5	<.01
FFQ Year 3	3241	45.9	23.8	4892	66.0	32.5	20.2	0.7	<.01
FFQ Year 4	5025	46.2	23.9	7834	66.2	32.2	20.0	0.5	<.01
FFQ Year 5	4908	47.5	24.5	7519	66.6	32.9	19.1	0.5	<.01
FFQ Year 6	3741	47.8	24.0	5716	65.1	32.2	17.3	0.6	<.01
FFQ Year 7	1521	48.8	24.6	2303	65.5	32.3	16.8	1.0	<.01
FFQ Year 8	366	47.2	23.0	619	65.2	32.5	18.0	1.9	<.01
4DFR Baseline	892	63.0	23.6	1351	63.8	24.6	0.8	1.0	0.71
4DFR Year 1	805	34.1	14.5	1171	60.4	23.5	26.3	0.9	<.01
24 Hr Recall, Post-baseline	226	39.6	21.9	262	60.5	26.9	20.9	2.2	<.01
24 Hr Recall, Year 1	221	36.9	17.1	268	60.6	25.1	23.7	2.0	<.01
24 Hr Recall, Year 2	214	38.8	22.6	244	59.3	27.2	20.5	2.4	<.01
24 Hr Recall, Year 3	209	40.9	21.2	249	60.3	27.9	19.4	2.4	<.01
24 Hr Recall, Year 3 Cohort	787	39.8	18.7	1183	59.9	25.6	20.0	1.1	<.01
24 Hr Recall, Year 4	195	41.9	20.9	220	58.1	26.1	16.2	2.3	<.01
24 Hr Recall, Year 5	102	44.6	22.4	159	63.8	29.0	19.2	3.4	<.01
24 Hr Recall, Year 6	59	41.1	19.4	74	61.0	27.3	19.9	4.2	<.01
24 Hr Recall, Year 6 Cohort	309	42.6	20.3	511	59.3	26.3	16.7	1.7	<.01
24 Hr Recall, Year 7	17	41.9	23.1	23	59.5	26.2	17.6	8.0	0.02
Saturated Fat (g)									
FFQ Baseline	19541	27.4	13.4	29294	27.3	13.2	0.1	0.1	0.85
FFQ Year 1	18098	14.2	8.1	26772	22.5	11.9	8.4	0.1	<.01
FFQ Year 2	5923	14.8	8.2	8667	22.5	11.7	7.7	0.2	<.01
FFQ Year 3	3241	15.5	9.0	4892	22.9	12.2	7.4	0.2	<.01
FFQ Year 4	5025	15.7	8.9	7834	23.2	12.2	7.5	0.2	<.01
FFQ Year 5	4908	16.2	9.1	7519	23.3	12.5	7.1	0.2	<.01
FFQ Year 6	3741	16.2	8.8	5716	22.8	12.3	6.6	0.2	<.01
FFQ Year 7	1521	16.8	9.2	2303	23.1	12.5	6.3	0.4	<.01
FFQ Year 8	366	16.4	9.1	619	23.1	13.3	6.7	0.8	<.01
4DFR Baseline	892	20.6	8.9	1351	20.9	9.3	0.3	0.4	0.72
4DFR Year 1	805	10.6	5.2	1171	19.5	8.3	9.0	0.3	<.01
24 Hr Recall, Post-baseline	226	12.9	7.9	262	20.1	9.6	7.2	0.8	<.01
24 Hr Recall, Year 1	221	11.7	6.2	268	20.1	10.1	8.4	0.8	<.01
24 Hr Recall, Year 2	214	12.3	8.2	244	19.5	9.9	7.2	0.9	<.01
24 Hr Recall, Year 3	209	13.4	7.7	249	20.3	10.8	6.9	0.9	<.01
24 Hr Recall, Year 3 Cohort	787	12.4	6.8	1183	19.7	9.3	7.3	0.4	<.01
24 Hr Recall, Year 4	195	13.5	7.8	220	19.4	10.2	5.9	0.9	<.01
24 Hr Recall, Year 5	102	14.3	7.4	159	21.8	10.7	7.5	1.2	<.01
24 Hr Recall, Year 6	59	13.1	6.0	74	20.2	10.4	7.1	1.5	<.01
24 Hr Recall, Year 6 Cohort	309	13.6	7.4	511	19.7	9.9	6.2	0.7	<.01
24 Hr Recall, Year 7	17	13.0	9.1	23	20.4	10.2	7.4	3.1	0.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

Table 3.2 (continued)
Nutrient Intake Monitoring

Data as of: August 31, 2002

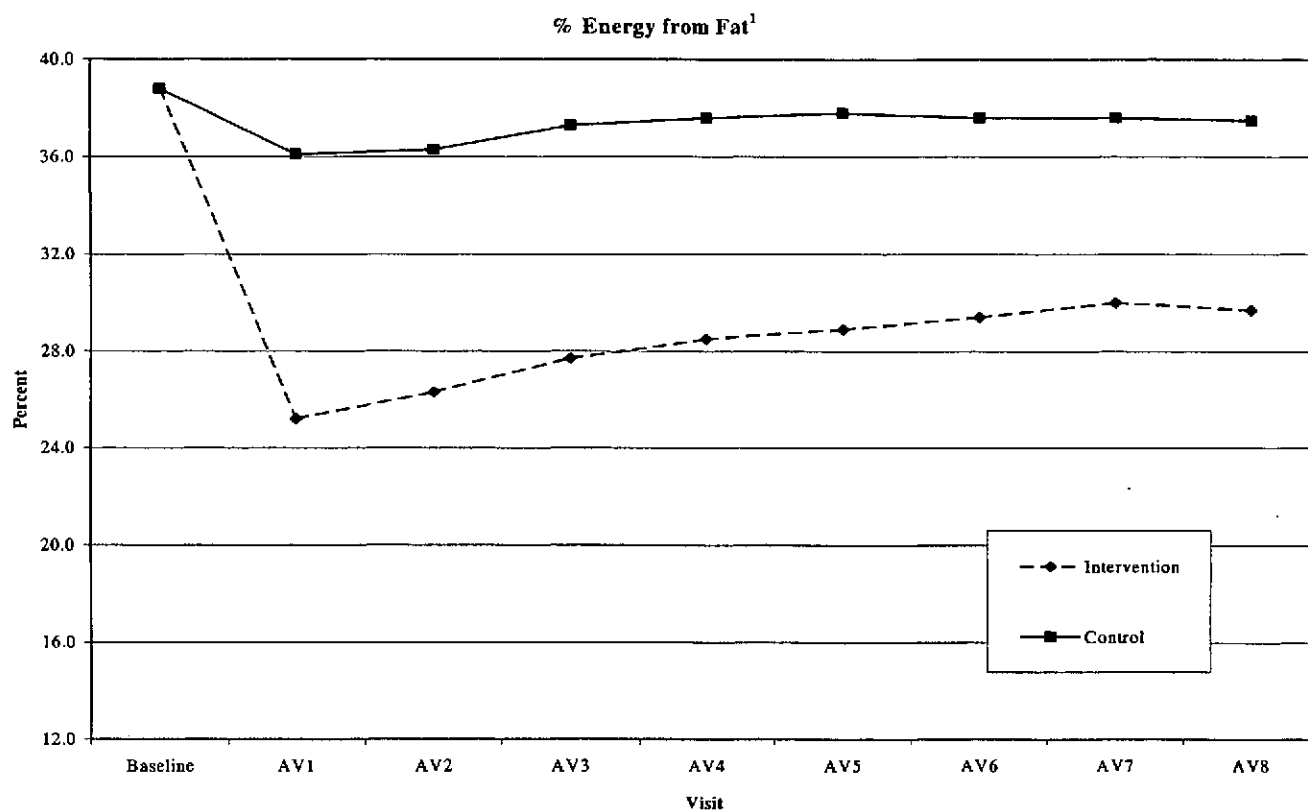
	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Polyunsaturated Fat (g)									
FFQ Baseline	19541	15.3	7.6	29294	15.3	7.6	0.0	0.1	0.79
FFQ Year 1	18098	7.9	4.4	26772	12.5	6.7	4.6	0.1	<.01
FFQ Year 2	5923	8.3	4.5	8667	12.4	6.5	4.1	0.1	<.01
FFQ Year 3	3241	8.8	4.7	4892	12.8	6.8	4.0	0.1	<.01
FFQ Year 4	5025	9.0	4.9	7834	12.8	6.7	3.8	0.1	<.01
FFQ Year 5	4908	9.2	5.0	7519	12.9	6.9	3.7	0.1	<.01
FFQ Year 6	3741	9.4	5.1	5716	12.6	6.5	3.2	0.1	<.01
FFQ Year 7	1521	9.4	5.1	2303	12.6	6.5	3.2	0.2	<.01
FFQ Year 8	366	9.0	4.4	619	12.3	6.1	3.3	0.4	<.01
4DFR Baseline	892	13.1	5.8	1351	13.5	6.1	0.3	0.3	0.40
4DFR Year 1	805	7.4	3.4	1171	12.7	6.2	5.3	0.2	<.01
24 Hr Recall, Post-baseline	226	8.3	5.0	262	12.6	7.3	4.3	0.6	<.01
24 Hr Recall, Year 1	221	7.8	4.4	268	12.4	6.3	4.6	0.5	<.01
24 Hr Recall, Year 2	214	8.3	5.7	244	12.5	7.6	4.2	0.6	<.01
24 Hr Recall, Year 3	209	8.5	5.5	249	12.2	6.6	3.8	0.6	<.01
24 Hr Recall, Year 3 Cohort	787	8.7	4.6	1183	12.2	6.9	3.6	0.3	<.01
24 Hr Recall, Year 4	195	8.8	5.1	220	11.7	7.0	2.9	0.6	<.01
24 Hr Recall, Year 5	102	9.4	6.7	159	12.6	8.3	3.1	1.0	<.01
24 Hr Recall, Year 6	59	8.7	5.3	74	13.0	6.9	4.3	1.1	<.01
24 Hr Recall, Year 6 Cohort	309	9.0	4.8	511	12.0	6.0	3.0	0.4	<.01
24 Hr Recall, Year 7	17	9.2	5.4	23	11.8	5.9	2.5	1.8	0.08
Fruits and Vegetables (servings)									
FFQ Baseline	19470	3.6	1.8	29216	3.6	1.8	0.0	0.0	0.69
FFQ Year 1	18017	5.0	2.3	26690	3.8	2.0	1.2	0.0	<.01
FFQ Year 2	5900	5.1	2.4	8635	3.9	2.0	1.2	0.0	<.01
FFQ Year 3	3235	5.2	2.5	4878	3.9	2.0	1.3	0.1	<.01
FFQ Year 4	5015	5.1	2.4	7820	3.8	2.0	1.3	0.0	<.01
FFQ Year 5	4886	5.1	2.5	7494	3.8	2.1	1.3	0.0	<.01
FFQ Year 6	3719	5.1	2.5	5693	3.8	2.0	1.3	0.0	<.01
FFQ Year 7	1510	5.0	2.4	2294	3.8	2.0	1.1	0.1	<.01
FFQ Year 8	364	5.1	2.4	618	3.8	2.0	1.3	0.1	<.01
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	19468	4.7	2.5	29214	4.8	2.5	0.0	0.0	0.42
FFQ Year 1	18013	5.1	2.7	26680	4.2	2.3	0.8	0.0	<.01
FFQ Year 2	5899	4.9	2.5	8629	4.1	2.2	0.7	0.0	<.01
FFQ Year 3	3234	4.6	2.5	4873	4.0	2.2	0.7	0.1	<.01
FFQ Year 4	5011	4.4	2.4	7808	3.9	2.2	0.5	0.0	<.01
FFQ Year 5	4882	4.3	2.3	7486	3.9	2.2	0.5	0.0	<.01
FFQ Year 6	3719	4.3	2.4	5690	3.8	2.1	0.5	0.0	<.01
FFQ Year 7	1510	4.2	2.3	2293	3.8	2.0	0.5	0.1	<.01
FFQ Year 8	364	4.0	2.1	618	3.7	2.0	0.3	0.1	0.03

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

Figure 3.1
Nutrient Intake

Data as of: August 31, 2002



(continues)

¹ Baseline % energy from fat values are about 3% higher in both groups due to the use of FFQ % energy from fat as an exclusionary criterion during screening.

Figure 3.1 (continued)
Nutrient Intake

Data as of: August 31, 2002

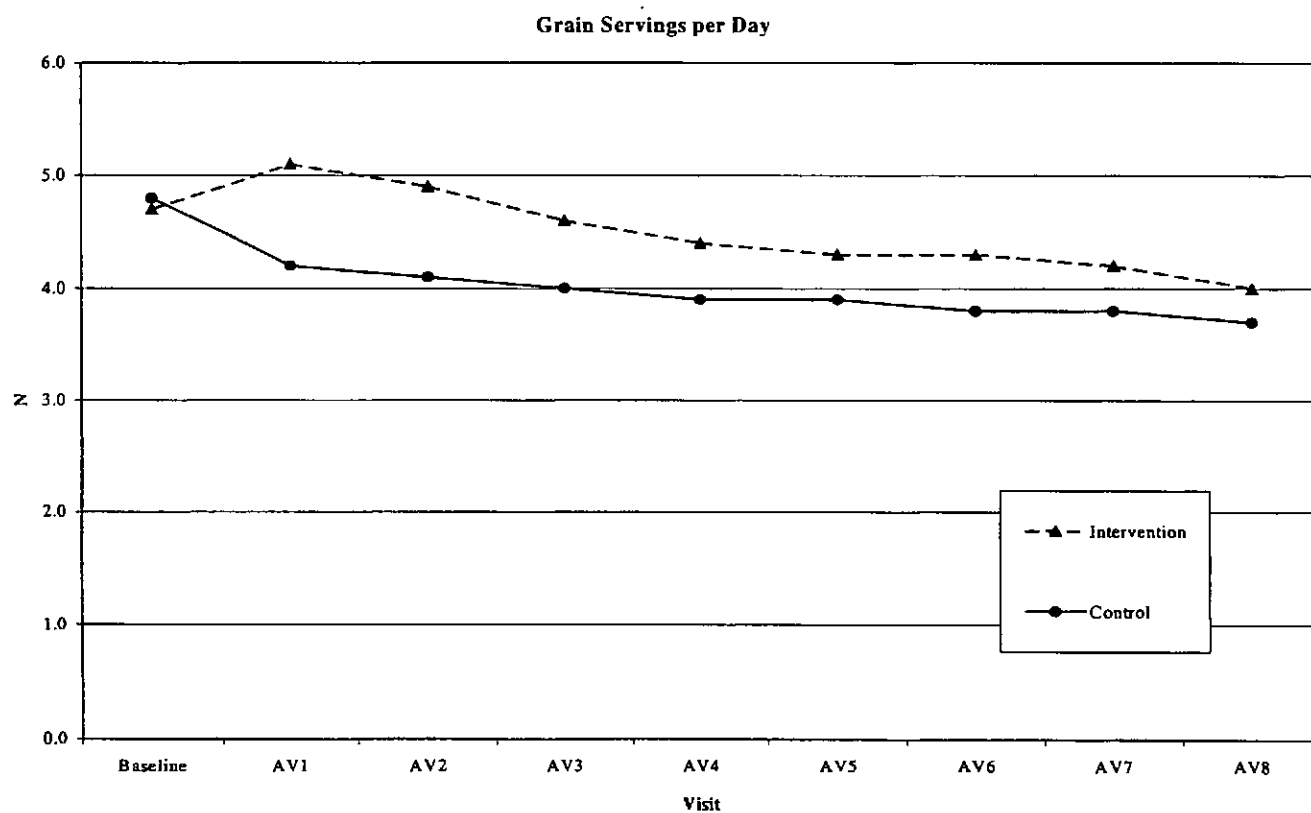
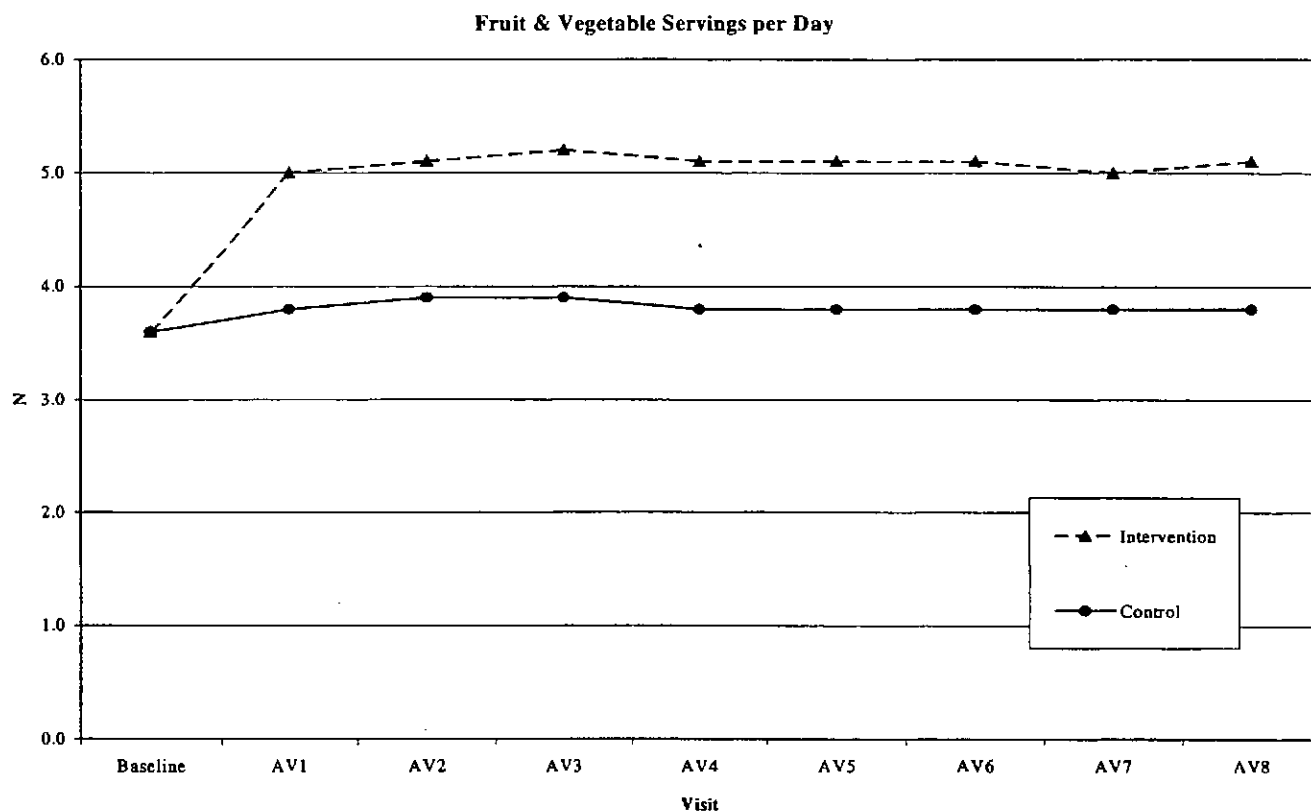


Table 3.3
Nutrient Intake Monitoring in American Indian/Alaskan Native Women¹

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ²	SE	p-value ³
% Energy from Fat									
FFQ Baseline	88	39.5	5.7	114	40.0	5.2	0.5	0.8	0.49
FFQ Year 1 ⁴	73	27.5	8.9	96	38.0	8.0	10.5	1.3	<.01
FFQ Year 2 ⁵	28	26.9	8.8	32	38.2	6.8	11.3	2.0	<.01
FFQ Year 3 ⁶	18	31.3	8.9	41	38.0	7.0	6.7	2.1	<.01
FFQ Year 4 ⁷	23	30.3	9.3	28	39.9	7.6	9.6	2.4	<.01
FFQ Year 5 ⁸	19	27.6	7.6	16	39.9	7.8	12.3	2.6	<.01
FFQ Year 6 ⁹	17	33.0	8.0	21	41.6	8.5	8.6	2.7	<.01
FFQ Year 7 ¹⁰	8	26.0	8.1	6	38.7	11.0	12.7	5.1	0.04
4DFR Baseline	24	34.0	6.7	44	33.4	7.8	0.6	1.9	0.73
4DFR Year 1	18	20.5	6.2	32	34.6	7.4	14.2	2.1	<.01
Total Energy (kcal)									
FFQ Baseline	88	1717.5	795.9	114	1771.7	718.2	54.3	106.8	0.42
FFQ Year 1	73	1631.3	689.6	96	1545.5	753.4	85.8	112.8	0.52
FFQ Year 2	28	1508.4	565.8	32	1554.0	706.9	45.6	166.9	0.95
FFQ Year 3	18	1520.0	614.4	41	1589.0	704.1	69.0	191.9	0.83
FFQ Year 4	23	1441.3	478.9	28	1821.1	932.9	379.7	214.8	0.09
FFQ Year 5	19	1673.2	661.5	16	1366.0	724.8	307.2	234.5	0.10
FFQ Year 6	17	1097.9	455.0	21	1734.5	464.2	636.6	150.1	<.01
FFQ Year 7	8	1719.4	334.4	6	1532.9	604.8	186.5	252.0	0.40
4DFR Baseline	24	1524.3	426.0	44	1672.0	606.8	147.7	139.7	0.47
4DFR Year 1	18	1283.9	418.7	32	1631.9	613.0	348.1	162.7	0.04
Total Fat (g)									
FFQ Baseline	88	76.5	40.3	114	79.3	35.6	2.8	5.4	0.34
FFQ Year 1	73	50.3	29.6	96	67.1	43.6	16.8	5.9	<.01
FFQ Year 2	28	45.8	29.0	32	68.5	40.0	22.7	9.1	<.01
FFQ Year 3	18	56.6	35.4	41	68.6	35.7	11.9	10.1	0.22
FFQ Year 4	23	48.9	21.7	28	81.3	44.5	32.4	10.2	<.01
FFQ Year 5	19	52.1	26.7	16	63.6	43.0	11.5	11.9	0.46
FFQ Year 6	17	39.4	17.5	21	80.0	24.7	40.5	7.1	<.01
FFQ Year 7	8	49.6	19.1	6	65.1	29.8	15.5	13.0	0.25
4DFR Baseline	24	57.4	17.5	44	63.8	30.8	6.4	6.8	0.83
4DFR Year 1	18	29.4	12.9	32	64.9	33.0	35.5	8.1	<.01

(continues)

¹ Insufficient sample size for FFQ Year 8.

² Absolute difference.

³ P-values based on testing in the natural log scale except for % Energy from fat.

⁴ 14 (19%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 1.

⁵ 6 (21%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 2.

⁶ 1 (5%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 3.

⁷ 5 (22%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 4.

⁸ 3 (16%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 5.

⁹ 2 (12%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 6.

¹⁰ 2 (25%) American Indian/Alaskan Native Intervention women had $\leq 20\%$ energy from fat at year 7.

Table 3.3 (continued)
Nutrient Intake Monitoring in American Indian/Alaskan Native Women¹

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ²	SE	p-value ³
Saturated Fat (g)									
FFQ Baseline	88	26.9	14.2	114	27.9	14.1	1.0	2.0	0.42
FFQ Year 1 ⁴	73	17.4	11.0	96	23.7	18.0	6.2	2.4	<.01
FFQ Year 2 ⁵	28	15.5	9.9	32	23.3	14.9	7.8	3.3	<.01
FFQ Year 3 ⁶	18	19.8	13.9	41	22.9	11.9	3.0	3.5	0.27
FFQ Year 4 ⁷	23	17.2	8.4	28	28.3	16.6	11.2	3.8	<.01
FFQ Year 5 ⁸	19	18.3	11.6	16	22.0	17.0	3.7	4.8	0.50
FFQ Year 6 ⁹	17	13.6	7.1	21	27.7	10.9	14.1	3.1	<.01
FFQ Year 7 ¹⁰	8	17.0	6.7	6	22.1	13.3	5.1	5.4	0.41
4DFR Baseline	24	19.1	6.9	44	21.4	12.3	2.4	2.7	0.87
4DFR Year 1	18	9.0	4.2	32	21.0	10.9	12.0	2.7	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	88	15.2	9.5	114	15.3	7.6	0.1	1.2	0.48
FFQ Year 1	73	9.4	6.3	96	12.7	8.5	3.3	1.2	<.01
FFQ Year 2	28	8.9	6.6	32	14.0	8.8	5.1	2.0	<.01
FFQ Year 3	18	10.2	5.8	41	14.0	7.9	3.8	2.1	0.10
FFQ Year 4	23	9.3	4.7	28	15.6	8.9	6.3	2.1	<.01
FFQ Year 5	19	9.7	3.9	16	11.8	8.2	2.0	2.1	0.64
FFQ Year 6	17	7.6	3.9	21	15.8	5.8	8.2	1.6	<.01
FFQ Year 7	8	9.0	3.9	6	13.2	5.4	4.2	2.5	0.12
4DFR Baseline	24	11.5	4.6	44	12.2	6.2	0.7	1.5	0.92
4DFR Year 1	18	6.9	3.8	32	13.6	9.6	6.7	2.4	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	88	3.5	1.9	114	3.0	1.6	0.4	0.2	0.23
FFQ Year 1	73	5.1	2.9	96	3.5	2.1	1.6	0.4	<.01
FFQ Year 2	28	5.2	3.3	32	3.3	1.6	1.9	0.7	0.05
FFQ Year 3	18	4.9	2.0	41	3.8	2.3	1.0	0.6	0.03
FFQ Year 4	23	5.1	3.1	28	4.0	2.1	1.1	0.7	0.25
FFQ Year 5	19	5.6	2.4	16	2.7	1.4	2.8	0.7	<.01
FFQ Year 6	17	4.7	3.2	21	3.7	2.3	1.0	0.9	0.42
FFQ Year 7	8	7.0	3.5	6	4.1	1.3	2.9	1.5	0.08
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	88	4.5	2.5	114	4.7	2.7	0.2	0.4	0.49
FFQ Year 1	73	5.5	3.4	96	4.2	2.3	1.3	0.4	0.02
FFQ Year 2	28	5.5	3.0	32	4.2	2.9	1.3	0.8	0.15
FFQ Year 3	18	4.2	2.6	41	4.2	2.5	0.0	0.7	0.76
FFQ Year 4	23	4.2	2.2	28	4.5	2.8	0.3	0.7	0.72
FFQ Year 5	19	4.6	2.4	16	3.8	2.2	0.8	0.8	0.26
FFQ Year 6	17	3.1	2.1	21	4.6	2.4	1.5	0.8	0.08
FFQ Year 7	8	5.2	2.7	6	3.4	1.8	1.7	1.3	0.23

(continues)

¹ Insufficient sample size for FFQ Year 8.

² Absolute difference.

³ P-values based on testing in the natural log scale except for % Energy from fat.

⁴ 14 (19%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 1.

⁵ 6 (21%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 2.

⁶ 1 (5%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 3.

⁷ 5 (22%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 4.

⁸ 3 (16%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 5.

⁹ 2 (12%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 6.

¹⁰ 2 (25%) American Indian/Alaskan Native Intervention women had ≤20% energy from fat at year 7.

Table 3.3 (continued)
Nutrient Intake Monitoring in Asian/Pacific Islander Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	431	37.7	4.4	674	38.4	4.7	0.7	0.3	0.02
FFQ Year 1 ³	409	25.8	7.3	629	36.1	6.6	10.3	0.4	<.01
FFQ Year 2 ⁴	147	27.2	7.4	213	36.1	6.9	8.9	0.8	<.01
FFQ Year 3 ⁵	107	28.1	7.5	152	36.3	6.4	8.2	0.9	<.01
FFQ Year 4 ⁶	106	29.6	8.3	188	37.4	6.7	7.8	0.9	<.01
FFQ Year 5 ⁷	118	28.6	8.0	189	37.1	7.2	8.5	0.9	<.01
FFQ Year 6 ⁸	63	28.9	7.4	111	38.2	6.3	9.3	1.1	<.01
FFQ Year 7 ⁹	11	26.7	8.5	18	38.2	6.9	11.5	2.9	<.01
FFQ Year 8 ¹⁰	2	31.6	8.2	4	36.9	9.4	5.3	7.9	0.54
4DFR Baseline	70	30.2	5.4	104	31.4	6.8	1.2	1.0	0.18
4DFR Year 1	68	21.5	7.6	88	31.6	5.8	10.1	1.1	<.01
Total Energy (kcal)									
FFQ Baseline	431	1699.9	722.7	674	1674.9	711.3	25.0	44.1	0.50
FFQ Year 1	409	1501.7	587.0	629	1523.7	635.3	22.0	39.2	0.94
FFQ Year 2	147	1512.0	636.7	213	1500.3	777.2	11.7	77.6	0.24
FFQ Year 3	107	1496.2	630.5	152	1414.8	582.8	81.5	76.1	0.28
FFQ Year 4	106	1475.7	616.6	188	1507.6	613.6	31.9	74.7	0.98
FFQ Year 5	118	1531.6	631.9	189	1515.2	834.4	16.4	89.5	0.24
FFQ Year 6	63	1458.7	521.7	111	1517.8	611.4	59.1	91.6	0.72
FFQ Year 7	11	1497.4	396.7	18	1352.1	443.6	145.3	163.4	0.26
FFQ Year 8	2	1539.9	473.9	4	882.7	301.8	657.2	305.5	0.16
4DFR Baseline	70	1683.3	400.1	104	1732.3	387.9	48.9	60.7	0.38
4DFR Year 1	68	1524.9	374.1	88	1619.6	397.2	94.7	62.5	0.12
Total Fat (g)									
FFQ Baseline	431	71.9	34.1	674	72.2	34.8	0.4	2.1	0.99
FFQ Year 1	409	43.5	23.5	629	62.3	31.4	18.9	1.8	<.01
FFQ Year 2	147	46.1	24.6	213	61.1	35.6	15.0	3.4	<.01
FFQ Year 3	107	47.3	28.0	152	57.7	28.0	10.3	3.5	<.01
FFQ Year 4	106	49.5	28.8	188	63.3	29.7	13.8	3.6	<.01
FFQ Year 5	118	50.1	29.5	189	63.3	39.8	13.1	4.3	<.01
FFQ Year 6	63	46.6	20.3	111	64.6	27.7	18.0	4.0	<.01
FFQ Year 7	11	46.4	26.2	18	59.3	28.7	12.9	10.6	0.15
FFQ Year 8	2	56.2	30.6	4	36.9	17.2	19.3	18.5	0.47
4DFR Baseline	70	57.1	19.1	104	61.8	23.4	4.7	3.4	0.24
4DFR Year 1	68	36.6	17.4	88	57.6	19.9	21.0	3.0	<.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 99 (24%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 1.

⁴ 24 (16%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 2.

⁵ 18 (17%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 3.

⁶ 12 (11%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 4.

⁷ 15 (13%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 5.

⁸ 5 (8%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 6.

⁹ 3 (27%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 7.

¹⁰ 0 (0%) Asian/Pacific Islander Intervention women had ≤20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Asian/Pacific Islander Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Saturated Fat (g)									
FFQ Baseline	431	22.8	12.0	674	22.9	12.0	0.1	0.7	0.94
FFQ Year 1 ³	409	13.5	8.0	629	19.5	10.8	6.0	0.6	<.01
FFQ Year 2 ⁴	147	14.3	8.5	213	19.2	11.9	5.0	1.1	<.01
FFQ Year 3 ⁵	107	14.8	10.1	152	18.1	9.8	3.3	1.3	<.01
FFQ Year 4 ⁶	106	15.4	10.1	188	19.9	9.6	4.5	1.2	<.01
FFQ Year 5 ⁷	118	15.7	10.0	189	19.9	13.7	4.2	1.5	<.01
FFQ Year 6 ⁸	63	14.3	7.2	111	20.2	9.5	5.9	1.4	<.01
FFQ Year 7 ⁹	11	14.6	9.8	18	19.3	11.2	4.7	4.1	0.15
FFQ Year 8 ¹⁰	2	16.8	9.8	4	11.0	5.0	5.8	5.6	0.51
4DFR Baseline	70	17.2	7.1	104	18.8	8.4	1.7	1.2	0.26
4DFR Year 1	68	10.5	5.5	88	17.7	7.2	7.2	1.0	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	431	15.6	7.4	674	15.7	7.8	0.0	0.5	0.54
FFQ Year 1	409	9.1	5.0	629	13.6	7.2	4.5	0.4	<.01
FFQ Year 2	147	9.8	5.5	213	13.0	8.0	3.2	0.8	<.01
FFQ Year 3	107	10.1	5.7	152	12.1	6.1	2.0	0.7	<.01
FFQ Year 4	106	10.8	6.2	188	13.4	6.5	2.6	0.8	<.01
FFQ Year 5	118	10.7	7.4	189	13.5	8.2	2.8	0.9	<.01
FFQ Year 6	63	10.1	5.2	111	14.0	6.0	3.9	0.9	<.01
FFQ Year 7	11	9.8	5.2	18	11.5	5.2	1.6	2.0	0.37
FFQ Year 8	2	11.5	5.4	4	6.3	3.1	5.2	3.3	0.27
4DFR Baseline	70	13.1	5.3	104	14.6	6.5	1.5	0.9	0.12
4DFR Year 1	68	8.8	4.4	88	12.9	5.9	4.1	0.9	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	429	3.4	1.7	674	3.3	1.9	0.1	0.1	0.26
FFQ Year 1	407	4.7	2.4	629	3.5	1.9	1.2	0.1	<.01
FFQ Year 2	146	4.8	2.7	213	3.4	1.9	1.4	0.2	<.01
FFQ Year 3	107	5.0	2.5	152	3.4	2.1	1.5	0.3	<.01
FFQ Year 4	105	4.7	2.4	188	3.2	1.9	1.5	0.3	<.01
FFQ Year 5	118	5.1	2.3	189	3.5	2.0	1.5	0.3	<.01
FFQ Year 6	63	5.0	2.4	111	3.6	2.0	1.4	0.3	<.01
FFQ Year 7	11	5.3	1.8	18	2.9	1.4	2.4	0.6	<.01
FFQ Year 8	2	7.0	0.6	4	2.0	1.0	5.0	0.8	0.01
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	429	5.0	2.6	674	4.8	2.3	0.2	0.1	0.43
FFQ Year 1	407	5.8	2.7	629	4.5	2.1	1.3	0.2	<.01
FFQ Year 2	146	5.4	2.7	213	4.3	2.4	1.1	0.3	<.01
FFQ Year 3	107	5.1	2.4	152	4.2	2.2	0.9	0.3	<.01
FFQ Year 4	105	5.1	2.4	188	4.4	2.2	0.6	0.3	<.01
FFQ Year 5	118	5.1	2.3	189	4.5	3.1	0.6	0.3	<.01
FFQ Year 6	63	5.0	2.4	111	4.3	2.2	0.7	0.4	0.06
FFQ Year 7	11	5.9	2.4	18	3.6	1.2	2.3	0.7	<.01
FFQ Year 8	2	5.5	0.5	4	2.5	1.2	2.9	0.9	0.06

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 99 (24%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 1.

⁴ 24 (16%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 2.

⁵ 18 (17%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 3.

⁶ 12 (11%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 4.

⁷ 15 (13%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 5.

⁸ 5 (8%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 6.

⁹ 3 (27%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 7.

¹⁰ 0 (0%) Asian/Pacific Islander Intervention women had <=20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Black/African American Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	2135	39.7	5.3	3127	39.9	5.2	0.1	0.1	0.41
FFQ Year 1 ³	1860	28.0	8.4	2628	36.9	7.4	8.8	0.2	<.01
FFQ Year 2 ⁴	612	29.4	8.0	829	36.4	7.3	7.0	0.4	<.01
FFQ Year 3 ⁵	351	29.4	7.9	514	38.2	7.2	8.8	0.5	<.01
FFQ Year 4 ⁶	483	30.7	8.3	766	37.6	7.4	6.9	0.4	<.01
FFQ Year 5 ⁷	481	31.2	8.5	715	37.5	7.6	6.3	0.5	<.01
FFQ Year 6 ⁸	427	30.9	8.1	651	37.3	7.6	6.5	0.5	<.01
FFQ Year 7 ⁹	103	31.7	7.5	178	37.1	6.5	5.4	0.9	<.01
FFQ Year 8 ¹⁰	17	33.2	8.5	28	36.2	7.3	3.1	2.4	0.22
4DFR Baseline	243	34.0	6.7	371	34.2	6.9	0.2	0.6	0.76
4DFR Year 1	219	23.5	7.9	307	34.2	7.0	10.8	0.7	<.01
Total Energy (kcal)									
FFQ Baseline	2135	1744.4	826.9	3127	1739.4	834.9	5.0	23.3	0.72
FFQ Year 1	1860	1382.7	633.4	2628	1492.6	774.7	109.9	21.8	<.01
FFQ Year 2	612	1392.3	717.6	829	1449.0	724.7	56.6	38.5	0.35
FFQ Year 3	351	1391.5	636.9	514	1537.1	791.3	145.5	50.7	0.02
FFQ Year 4	483	1341.1	623.0	766	1439.8	745.9	98.7	40.7	0.07
FFQ Year 5	481	1387.2	644.7	715	1368.9	688.9	18.2	39.6	0.59
FFQ Year 6	427	1306.3	561.9	651	1383.1	812.6	76.9	45.1	0.51
FFQ Year 7	103	1296.7	536.6	178	1349.1	727.8	52.4	82.2	0.99
FFQ Year 8	17	1338.9	852.7	28	1469.6	839.9	130.7	259.7	0.66
4DFR Baseline	243	1704.3	526.0	371	1651.0	478.3	53.4	41.1	0.32
4DFR Year 1	219	1345.6	341.6	307	1584.5	481.8	239.0	38.0	<.01
Total Fat (g)									
FFQ Baseline	2135	77.7	40.7	3127	77.8	41.3	0.1	1.2	0.92
FFQ Year 1	1860	43.6	26.8	2628	62.3	37.2	18.7	1.0	<.01
FFQ Year 2	612	46.4	32.5	829	60.1	36.0	13.7	1.8	<.01
FFQ Year 3	351	46.4	27.3	514	66.3	38.6	19.9	2.4	<.01
FFQ Year 4	483	46.1	26.7	766	61.1	35.8	15.0	1.9	<.01
FFQ Year 5	481	48.4	27.3	715	58.3	34.8	9.9	1.9	<.01
FFQ Year 6	427	45.4	24.9	651	58.6	40.5	13.2	2.2	<.01
FFQ Year 7	103	45.9	24.0	178	57.0	34.8	11.0	3.9	0.01
FFQ Year 8	17	50.3	36.8	28	60.7	42.0	10.4	12.3	0.39
4DFR Baseline	243	65.1	25.7	371	63.9	26.3	1.2	2.2	0.54
4DFR Year 1	219	34.9	14.7	307	61.5	25.7	26.6	1.9	<.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 323 (17%) Black/African American Intervention women had <=20% energy from fat at year 1.

⁴ 80 (13%) Black/African American Intervention women had <=20% energy from fat at year 2.

⁵ 46 (13%) Black/African American Intervention women had <=20% energy from fat at year 3.

⁶ 54 (11%) Black/African American Intervention women had <=20% energy from fat at year 4.

⁷ 38 (8%) Black/African American Intervention women had <=20% energy from fat at year 5.

⁸ 37 (9%) Black/African American Intervention women had <=20% energy from fat at year 6.

⁹ 4 (4%) Black/African American Intervention women had <=20% energy from fat at year 7.

¹⁰ 1 (6%) Black/African American Intervention women had <=20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Black/African American Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Saturated Fat (g)									
FFQ Baseline	2135	25.8	14.3	3127	25.9	14.7	0.1	0.4	0.91
FFQ Year 1 ³	1860	14.3	9.2	2628	20.5	12.8	6.2	0.3	<.01
FFQ Year 2 ⁴	612	15.3	11.8	829	19.8	12.3	4.5	0.6	<.01
FFQ Year 3 ⁵	351	15.1	9.6	514	21.8	13.4	6.7	0.8	<.01
FFQ Year 4 ⁶	483	14.8	9.2	766	20.1	12.5	5.3	0.7	<.01
FFQ Year 5 ⁷	481	15.6	9.3	715	19.0	12.2	3.4	0.7	<.01
FFQ Year 6 ⁸	427	14.6	8.4	651	19.2	14.1	4.6	0.8	<.01
FFQ Year 7 ⁹	103	14.9	8.9	178	19.0	12.3	4.1	1.4	<.01
FFQ Year 8 ¹⁰	17	16.6	13.6	28	19.7	14.3	3.0	4.3	0.46
4DFR Baseline	243	20.3	9.3	371	20.2	9.1	0.1	0.8	0.96
4DFR Year 1	219	10.6	5.2	307	18.7	8.2	8.1	0.6	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	2135	16.0	8.9	3127	16.0	8.9	0.0	0.3	0.98
FFQ Year 1	1860	8.7	5.6	2628	12.7	8.0	4.0	0.2	<.01
FFQ Year 2	612	9.1	6.2	829	12.1	7.5	2.9	0.4	<.01
FFQ Year 3	351	9.3	5.6	514	13.4	8.0	4.1	0.5	<.01
FFQ Year 4	483	9.5	5.7	766	12.4	7.6	3.0	0.4	<.01
FFQ Year 5	481	9.8	5.7	715	12.1	7.8	2.3	0.4	<.01
FFQ Year 6	427	9.3	5.6	651	12.0	8.2	2.7	0.5	<.01
FFQ Year 7	103	9.5	5.1	178	11.4	6.9	1.9	0.8	0.04
FFQ Year 8	17	10.2	7.9	28	12.4	8.6	2.2	2.6	0.32
4DFR Baseline	243	14.5	6.7	371	13.8	6.7	0.7	0.6	0.15
4DFR Year 1	219	7.6	3.2	307	13.7	6.9	6.1	0.5	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	2132	3.3	1.9	3123	3.2	1.9	0.0	0.1	0.73
FFQ Year 1	1854	4.5	2.6	2622	3.4	2.1	1.1	0.1	<.01
FFQ Year 2	611	4.5	2.6	824	3.5	2.2	1.0	0.1	<.01
FFQ Year 3	351	4.8	2.7	514	3.7	2.3	1.0	0.2	<.01
FFQ Year 4	483	4.8	2.7	766	3.4	2.2	1.3	0.1	<.01
FFQ Year 5	479	4.7	2.8	714	3.4	2.1	1.3	0.1	<.01
FFQ Year 6	427	4.6	2.6	649	3.5	2.1	1.1	0.1	<.01
FFQ Year 7	103	4.6	2.6	177	3.5	2.1	1.1	0.3	<.01
FFQ Year 8	17	4.8	2.6	28	3.3	2.0	1.6	0.7	0.13
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	2132	4.5	2.7	3122	4.4	2.8	0.1	0.1	0.32
FFQ Year 1	1853	4.4	2.8	2620	3.8	2.5	0.6	0.1	<.01
FFQ Year 2	611	4.2	2.6	823	3.7	2.4	0.4	0.1	<.01
FFQ Year 3	351	4.2	2.7	514	3.8	2.5	0.4	0.2	0.01
FFQ Year 4	483	4.0	2.5	764	3.6	2.4	0.4	0.1	<.01
FFQ Year 5	478	4.0	2.6	713	3.4	2.2	0.6	0.1	<.01
FFQ Year 6	427	3.7	2.2	648	3.3	2.2	0.4	0.1	<.01
FFQ Year 7	103	3.5	1.7	177	3.4	2.3	0.1	0.3	0.26
FFQ Year 8	17	3.2	1.5	28	3.8	2.6	0.6	0.7	0.75

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 323 (17%) Black/African American Intervention women had <=20% energy from fat at year 1.

⁴ 80 (13%) Black/African American Intervention women had <=20% energy from fat at year 2.

⁵ 46 (13%) Black/African American Intervention women had <=20% energy from fat at year 3.

⁶ 54 (11%) Black/African American Intervention women had <=20% energy from fat at year 4.

⁷ 38 (8%) Black/African American Intervention women had <=20% energy from fat at year 5.

⁸ 37 (9%) Black/African American Intervention women had <=20% energy from fat at year 6.

⁹ 4 (4%) Black/African American Intervention women had <=20% energy from fat at year 7.

¹⁰ 1 (6%) Black/African American Intervention women had <=20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Hispanic/Latino Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	751	39.3	5.1	1094	39.0	5.1	0.4	0.2	0.13
FFQ Year 1 ³	617	27.9	8.0	914	36.1	7.4	8.2	0.4	<.01
FFQ Year 2 ⁴	226	27.7	8.3	304	36.9	7.5	9.2	0.7	<.01
FFQ Year 3 ⁵	131	29.9	8.9	195	37.2	7.3	7.3	0.9	<.01
FFQ Year 4 ⁶	162	30.7	8.1	292	36.9	7.1	6.2	0.7	<.01
FFQ Year 5 ⁷	160	29.5	8.4	260	36.4	7.4	7.0	0.8	<.01
FFQ Year 6 ⁸	106	29.7	8.4	186	37.2	6.2	7.4	0.9	<.01
FFQ Year 7 ⁹	31	30.9	9.8	47	37.0	6.6	6.1	1.9	<.01
FFQ Year 8 ¹⁰	7	25.3	4.4	17	34.8	5.6	9.5	2.4	<.01
4DFR Baseline	96	32.4	5.7	134	32.4	6.5	0.1	0.8	0.95
4DFR Year 1	82	23.1	7.4	110	32.0	7.3	8.9	1.1	<.01
Total Energy (kcal)									
FFQ Baseline	751	1846.5	836.1	1094	1859.3	870.7	12.8	40.6	0.86
FFQ Year 1	617	1418.6	665.0	914	1569.9	862.5	151.2	41.1	<.01
FFQ Year 2	226	1411.2	614.8	304	1625.8	772.1	214.6	62.3	<.01
FFQ Year 3	131	1534.3	638.4	195	1576.7	710.7	42.4	77.1	0.80
FFQ Year 4	162	1382.2	652.6	292	1531.8	759.0	149.6	70.8	0.03
FFQ Year 5	160	1400.6	678.6	260	1566.3	878.8	165.7	81.2	0.08
FFQ Year 6	106	1333.9	718.3	186	1508.6	762.7	174.7	90.9	0.03
FFQ Year 7	31	1203.9	373.4	47	1419.4	571.3	215.4	116.3	0.12
FFQ Year 8	7	1583.6	817.8	17	1442.7	693.8	141.0	327.7	0.70
4DFR Baseline	96	1643.3	446.4	134	1748.5	460.0	105.2	60.8	0.06
4DFR Year 1	82	1399.8	412.1	110	1627.1	448.8	227.3	63.3	<.01
Total Fat (g)									
FFQ Baseline	751	81.6	41.0	1094	80.8	40.5	0.8	1.9	0.56
FFQ Year 1	617	44.5	27.2	914	64.3	41.2	19.8	1.9	<.01
FFQ Year 2	226	43.7	24.3	304	68.3	38.6	24.5	2.9	<.01
FFQ Year 3	131	52.3	31.8	195	66.1	34.8	13.8	3.8	<.01
FFQ Year 4	162	47.6	27.4	292	63.7	35.6	16.1	3.2	<.01
FFQ Year 5	160	47.1	30.7	260	65.4	42.9	18.3	3.9	<.01
FFQ Year 6	106	44.1	27.4	186	62.9	35.3	18.8	4.0	<.01
FFQ Year 7	31	40.9	17.0	47	58.3	25.9	17.4	5.3	<.01
FFQ Year 8	7	43.2	21.0	17	55.9	28.6	12.8	12.0	0.33
4DFR Baseline	96	59.6	20.1	134	64.1	25.6	4.5	3.1	0.22
4DFR Year 1	82	36.4	17.7	110	58.9	24.5	22.5	3.2	<.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 106 (17%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 1.

⁴ 45 (20%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 2.

⁵ 14 (11%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 3.

⁶ 16 (10%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 4.

⁷ 21 (13%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 5.

⁸ 12 (11%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 6.

⁹ 3 (10%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 7.

¹⁰ 0 (0%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Hispanic/Latino Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Saturated Fat (g)									
FFQ Baseline	751	27.8	14.9	1094	27.7	15.1	0.1	0.7	0.65
FFQ Year 1 ³	617	15.0	9.8	914	21.7	14.3	6.7	0.7	<.01
FFQ Year 2 ⁴	226	14.4	8.4	304	23.1	14.2	8.7	1.1	<.01
FFQ Year 3 ⁵	131	17.4	12.0	195	22.1	12.5	4.8	1.4	<.01
FFQ Year 4 ⁶	162	15.6	9.8	292	21.2	12.4	5.7	1.1	<.01
FFQ Year 5 ⁷	160	15.7	10.7	260	22.2	15.1	6.5	1.4	<.01
FFQ Year 6 ⁸	106	14.3	9.8	186	21.4	13.1	7.0	1.5	<.01
FFQ Year 7 ⁹	31	13.1	5.5	47	19.2	8.5	6.1	1.7	<.01
FFQ Year 8 ¹⁰	7	14.7	9.1	17	18.6	8.6	3.9	3.9	0.29
4DFR Baseline	96	19.8	7.6	134	20.9	10.0	1.1	1.2	0.57
4DFR Year 1	82	11.5	6.7	110	19.4	8.9	7.9	1.2	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	751	15.9	8.4	1094	15.7	8.2	0.2	0.4	0.48
FFQ Year 1	617	8.6	5.5	914	12.7	8.6	4.2	0.4	<.01
FFQ Year 2	226	8.7	5.3	304	13.4	8.2	4.7	0.6	<.01
FFQ Year 3	131	10.4	6.5	195	12.9	7.4	2.5	0.8	<.01
FFQ Year 4	162	9.3	5.5	292	12.5	7.2	3.2	0.6	<.01
FFQ Year 5	160	9.2	6.7	260	12.6	8.9	3.4	0.8	<.01
FFQ Year 6	106	8.9	5.6	186	12.1	6.9	3.2	0.8	<.01
FFQ Year 7	31	8.6	4.6	47	11.4	6.0	2.8	1.3	0.02
FFQ Year 8	7	8.1	4.0	17	10.4	6.4	2.4	2.6	0.44
4DFR Baseline	96	11.5	4.6	134	13.4	6.2	1.9	0.7	0.02
4DFR Year 1	82	7.8	4.1	110	12.0	6.3	4.2	0.8	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	748	3.0	1.9	1094	2.9	1.8	0.1	0.1	0.27
FFQ Year 1	614	4.2	2.3	914	3.1	1.9	1.0	0.1	<.01
FFQ Year 2	224	4.4	2.4	304	3.2	1.7	1.2	0.2	<.01
FFQ Year 3	130	4.6	2.9	195	3.4	2.0	1.3	0.3	<.01
FFQ Year 4	162	4.7	2.7	292	3.1	2.1	1.6	0.2	<.01
FFQ Year 5	159	4.5	2.4	260	3.3	2.2	1.1	0.2	<.01
FFQ Year 6	105	4.6	2.6	186	3.1	2.0	1.6	0.3	<.01
FFQ Year 7	31	4.1	3.0	47	3.2	2.1	0.9	0.6	0.11
FFQ Year 8	7	5.8	3.3	17	3.0	1.7	2.8	1.0	0.02
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	748	5.5	3.3	1094	5.7	3.5	0.2	0.2	0.54
FFQ Year 1	614	5.1	3.3	914	4.8	3.4	0.3	0.2	0.06
FFQ Year 2	224	5.0	3.5	304	4.9	3.1	0.0	0.3	0.48
FFQ Year 3	130	5.1	3.0	195	4.7	2.9	0.4	0.3	0.32
FFQ Year 4	162	4.3	2.9	292	4.6	2.9	0.3	0.3	0.16
FFQ Year 5	159	4.3	3.0	260	4.8	3.4	0.5	0.3	0.17
FFQ Year 6	105	4.6	3.5	186	4.7	3.3	0.1	0.4	0.55
FFQ Year 7	31	3.9	2.4	47	4.5	2.6	0.6	0.6	0.22
FFQ Year 8	7	5.4	3.8	17	5.1	3.8	0.3	1.7	0.72

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 106 (17%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 1.

⁴ 45 (20%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 2.

⁵ 14 (11%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 3.

⁶ 16 (10%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 4.

⁷ 21 (13%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 5.

⁸ 12 (11%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 6.

⁹ 3 (10%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 7.

¹⁰ 0 (0%) Hispanic/Latino Intervention women had $\leq 20\%$ energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in White Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	15871	38.7	5.0	23891	38.7	4.9	0.0	0.1	0.93
FFQ Year 1 ³	14899	24.6	7.3	22151	36.0	6.8	11.3	0.1	<.01
FFQ Year 2 ⁴	4831	25.8	7.5	7166	36.2	7.0	10.3	0.1	<.01
FFQ Year 3 ⁵	2588	27.3	7.8	3931	37.2	7.1	9.9	0.2	<.01
FFQ Year 4 ⁶	4180	28.1	8.0	6449	37.6	7.0	9.5	0.1	<.01
FFQ Year 5 ⁷	4074	28.7	8.1	6259	37.9	7.3	9.3	0.2	<.01
FFQ Year 6 ⁸	3092	29.2	8.1	4677	37.6	7.0	8.4	0.2	<.01
FFQ Year 7 ⁹	1358	29.8	8.0	2036	37.6	7.1	7.8	0.3	<.01
FFQ Year 8 ¹⁰	337	29.6	8.1	562	37.7	7.3	8.0	0.5	<.01
4DFR Baseline	442	32.6	6.5	669	32.6	6.7	0.1	0.4	0.88
4DFR Year 1	405	20.4	6.7	610	32.5	6.6	12.1	0.4	<.01
Total Energy (kcal)									
FFQ Baseline	15871	1795.1	687.8	23891	1797.1	677.4	2.0	7.0	0.62
FFQ Year 1	14899	1485.5	509.0	22151	1599.0	611.3	113.5	6.1	<.01
FFQ Year 2	4831	1493.0	497.0	7166	1590.4	597.6	97.4	10.4	<.01
FFQ Year 3	2588	1484.5	512.1	3931	1583.5	618.6	99.0	14.6	<.01
FFQ Year 4	4180	1457.4	515.8	6449	1579.5	610.2	122.2	11.4	<.01
FFQ Year 5	4074	1474.7	516.5	6259	1586.0	612.2	111.4	11.6	<.01
FFQ Year 6	3092	1480.2	536.6	4677	1561.9	599.4	81.8	13.3	<.01
FFQ Year 7	1358	1471.8	528.3	2036	1564.5	620.0	92.7	20.5	<.01
FFQ Year 8	337	1424.0	482.9	562	1560.3	612.0	136.4	39.1	<.01
4DFR Baseline	442	1744.2	422.9	669	1740.7	447.9	3.6	26.9	0.68
4DFR Year 1	405	1461.2	331.5	610	1652.6	428.1	191.4	25.2	<.01
Total Fat (g)									
FFQ Baseline	15871	77.8	34.1	23891	77.9	33.4	0.0	0.3	0.65
FFQ Year 1	14899	40.9	20.6	22151	64.8	30.5	23.9	0.3	<.01
FFQ Year 2	4831	43.0	20.2	7166	64.9	30.1	21.9	0.5	<.01
FFQ Year 3	2588	45.3	22.5	3931	66.3	31.5	21.0	0.7	<.01
FFQ Year 4	4180	46.0	23.2	6449	67.0	31.5	21.0	0.6	<.01
FFQ Year 5	4074	47.3	23.6	6259	67.8	31.9	20.4	0.6	<.01
FFQ Year 6	3092	48.3	23.8	4677	66.0	30.8	17.8	0.7	<.01
FFQ Year 7	1358	49.2	24.9	2036	66.4	32.0	17.2	1.0	<.01
FFQ Year 8	337	47.0	22.3	562	66.2	32.1	19.2	2.0	<.01
4DFR Baseline	442	64.1	23.9	669	64.0	23.5	0.2	1.5	0.81
4DFR Year 1	405	33.0	13.0	610	60.5	22.3	27.5	1.2	<.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 4373 (29%) White Intervention women had ≤20% energy from fat at year 1.

⁴ 1097 (23%) White Intervention women had ≤20% energy from fat at year 2.

⁵ 482 (19%) White Intervention women had ≤20% energy from fat at year 3.

⁶ 671 (16%) White Intervention women had ≤20% energy from fat at year 4.

⁷ 597 (15%) White Intervention women had ≤20% energy from fat at year 5.

⁸ 359 (12%) White Intervention women had ≤20% energy from fat at year 6.

⁹ 134 (10%) White Intervention women had ≤20% energy from fat at year 7.

¹⁰ 42 (12%) White Intervention women had ≤20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in White Women

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Saturated Fat (g)									
FFQ Baseline	15871	27.7	13.2	23891	27.6	12.8	0.1	0.1	0.95
FFQ Year 1 ³	14899	14.1	7.8	22151	22.9	11.6	8.8	0.1	<.01
FFQ Year 2 ⁴	4831	14.7	7.5	7166	22.9	11.4	8.1	0.2	<.01
FFQ Year 3 ⁵	2588	15.5	8.6	3931	23.4	12.0	7.8	0.3	<.01
FFQ Year 4 ⁶	4180	15.8	8.8	6449	23.7	12.1	7.9	0.2	<.01
FFQ Year 5 ⁷	4074	16.3	9.0	6259	24.0	12.2	7.7	0.2	<.01
FFQ Year 6 ⁸	3092	16.5	8.8	4677	23.4	12.0	6.8	0.3	<.01
FFQ Year 7 ⁹	1358	17.0	9.3	2036	23.5	12.5	6.5	0.4	<.01
FFQ Year 8 ¹⁰	337	16.4	8.9	562	23.6	13.4	7.2	0.8	<.01
4DFR Baseline	442	21.7	9.2	669	21.6	9.1	0.1	0.6	0.64
4DFR Year 1	405	10.4	4.7	610	20.2	8.3	9.8	0.5	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	15871	15.2	7.4	23891	15.2	7.3	0.0	0.1	0.48
FFQ Year 1	14899	7.7	4.1	22151	12.4	6.4	4.7	0.1	<.01
FFQ Year 2	4831	8.1	4.1	7166	12.3	6.2	4.2	0.1	<.01
FFQ Year 3	2588	8.6	4.4	3931	12.7	6.5	4.1	0.1	<.01
FFQ Year 4	4180	8.8	4.6	6449	12.8	6.5	4.0	0.1	<.01
FFQ Year 5	4074	9.1	4.8	6259	13.0	6.6	3.9	0.1	<.01
FFQ Year 6	3092	9.3	5.0	4677	12.6	6.2	3.2	0.1	<.01
FFQ Year 7	1358	9.4	5.1	2036	12.7	6.4	3.3	0.2	<.01
FFQ Year 8	337	8.9	4.2	562	12.5	5.9	3.5	0.4	<.01
4DFR Baseline	442	12.9	5.5	669	13.2	5.7	0.3	0.3	0.51
4DFR Year 1	405	7.1	3.1	610	12.4	5.6	5.3	0.3	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	15809	3.7	1.8	23818	3.7	1.8	0.0	0.0	0.17
FFQ Year 1	14830	5.2	2.3	22076	3.9	2.0	1.2	0.0	<.01
FFQ Year 2	4813	5.2	2.3	7139	4.0	2.0	1.2	0.0	<.01
FFQ Year 3	2583	5.3	2.4	3917	4.0	2.0	1.3	0.1	<.01
FFQ Year 4	4172	5.2	2.4	6435	3.9	2.0	1.3	0.0	<.01
FFQ Year 5	4055	5.2	2.4	6235	3.9	2.1	1.3	0.0	<.01
FFQ Year 6	3072	5.2	2.4	4656	3.9	2.0	1.3	0.1	<.01
FFQ Year 7	1347	5.0	2.4	2028	3.8	1.9	1.2	0.1	<.01
FFQ Year 8	335	5.1	2.4	561	3.8	2.0	1.2	0.1	<.01
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	15807	4.7	2.4	23817	4.8	2.4	0.0	0.0	0.21
FFQ Year 1	14827	5.1	2.6	22068	4.2	2.2	0.9	0.0	<.01
FFQ Year 2	4812	5.0	2.4	7134	4.1	2.1	0.8	0.0	<.01
FFQ Year 3	2582	4.6	2.5	3912	3.9	2.1	0.7	0.1	<.01
FFQ Year 4	4168	4.4	2.3	6425	3.9	2.1	0.6	0.0	<.01
FFQ Year 5	4052	4.4	2.2	6228	3.9	2.0	0.5	0.0	<.01
FFQ Year 6	3072	4.4	2.4	4654	3.8	2.0	0.6	0.1	<.01
FFQ Year 7	1347	4.3	2.3	2027	3.8	2.0	0.5	0.1	<.01
FFQ Year 8	335	4.0	2.1	561	3.7	1.9	0.3	0.1	0.10

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 4373 (29%) White Intervention women had ≤20% energy from fat at year 1.

⁴ 1097 (23%) White Intervention women had ≤20% energy from fat at year 2.

⁵ 482 (19%) White Intervention women had ≤20% energy from fat at year 3.

⁶ 671 (16%) White Intervention women had ≤20% energy from fat at year 4.

⁷ 597 (15%) White Intervention women had ≤20% energy from fat at year 5.

⁸ 359 (12%) White Intervention women had ≤20% energy from fat at year 6.

⁹ 134 (10%) White Intervention women had ≤20% energy from fat at year 7.

¹⁰ 42 (12%) White Intervention women had ≤20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Unknown Race/Ethnicity

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
% Energy from Fat									
FFQ Baseline	265	39.1	5.3	394	39.2	5.1	0.1	0.4	0.79
FFQ Year 1 ³	240	27.7	8.0	354	35.9	7.7	8.3	0.7	<.01
FFQ Year 2 ⁴	79	27.2	7.9	123	37.3	6.9	10.2	1.1	<.01
FFQ Year 3 ⁵	46	29.1	7.4	59	37.8	8.2	8.6	1.5	<.01
FFQ Year 4 ⁶	71	29.2	8.2	111	37.0	7.1	7.8	1.1	<.01
FFQ Year 5 ⁷	56	29.0	8.9	80	38.2	7.7	9.3	1.4	<.01
FFQ Year 6 ⁸	36	30.3	8.3	70	39.0	6.6	8.6	1.5	<.01
FFQ Year 7 ⁹	10	32.6	7.8	18	37.9	7.8	5.3	3.1	0.10
FFQ Year 8 ¹⁰	2	32.9	10.8	6	32.0	7.7	0.9	6.8	0.92
4DFR Baseline	17	32.2	5.5	29	32.8	5.6	0.6	1.7	0.71
4DFR Year 1	13	22.8	8.9	24	33.6	6.5	10.8	2.6	<.01
Total Energy (kcal)									
FFQ Baseline	265	1796.2	774.8	394	1726.3	769.8	70.0	61.3	0.23
FFQ Year 1	240	1505.5	628.2	354	1501.5	639.0	4.1	53.1	0.66
FFQ Year 2	79	1463.9	583.5	123	1571.6	674.2	107.8	92.3	0.33
FFQ Year 3	46	1463.7	598.3	59	1477.1	725.4	13.4	132.3	1.00
FFQ Year 4	71	1388.5	616.5	111	1497.3	660.1	108.8	97.8	0.31
FFQ Year 5	56	1445.1	562.6	80	1419.5	572.1	25.6	99.0	0.59
FFQ Year 6	36	1653.8	533.8	70	1511.4	629.2	142.4	122.8	0.13
FFQ Year 7	10	1330.4	618.6	18	1849.1	924.2	518.7	327.8	0.11
FFQ Year 8	2	1599.1	1010.1	6	1035.9	456.6	563.2	478.8	0.55
4DFR Baseline	17	1504.1	288.3	29	1693.4	404.8	189.3	112.0	0.10
4DFR Year 1	13	1334.5	469.5	24	1541.7	334.5	207.2	133.0	0.13
Total Fat (g)									
FFQ Baseline	265	79.0	39.4	394	75.9	38.4	3.1	3.1	0.31
FFQ Year 1	240	46.7	28.0	354	60.7	31.5	14.0	2.5	<.01
FFQ Year 2	79	44.9	29.0	123	66.7	35.1	21.8	4.7	<.01
FFQ Year 3	46	46.2	21.0	59	62.8	35.9	16.6	6.0	<.01
FFQ Year 4	71	46.2	30.4	111	63.0	33.3	16.8	4.9	<.01
FFQ Year 5	56	47.5	27.5	80	60.9	28.4	13.4	4.9	<.01
FFQ Year 6	36	55.7	25.1	70	66.2	33.8	10.5	6.4	0.08
FFQ Year 7	10	44.2	11.9	18	77.7	42.2	33.5	13.7	<.01
FFQ Year 8	2	52.4	17.8	6	39.5	26.2	12.9	20.4	0.30
4DFR Baseline	17	54.4	16.8	29	61.8	17.4	7.4	5.2	0.18
4DFR Year 1	13	33.7	19.1	24	57.9	17.3	24.2	6.2	<.01

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 38 (16%) Unknown Intervention women had <=20% energy from fat at year 1.

⁴ 16 (20%) Unknown Intervention women had <=20% energy from fat at year 2.

⁵ 5 (11%) Unknown Intervention women had <=20% energy from fat at year 3.

⁶ 11 (15%) Unknown Intervention women had <=20% energy from fat at year 4.

⁷ 11 (20%) Unknown Intervention women had <=20% energy from fat at year 5.

⁸ 4 (11%) Unknown Intervention women had <=20% energy from fat at year 6.

⁹ 0 (0%) Unknown Intervention women had <=20% energy from fat at year 7.

¹⁰ 0 (0%) Unknown Intervention women had <=20% energy from fat at year 8.

Table 3.3 (continued)
Nutrient Intake Monitoring in Unknown Race/Ethnicity

Data as of: August 31, 2002

	Intervention			Control			Difference		
	N	Mean	SD	N	Mean	SD	Mean ¹	SE	p-value ²
Saturated Fat (g)									
FFQ Baseline	265	27.2	14.6	394	26.3	14.2	0.9	1.1	0.47
FFQ Year 1 ³	240	15.4	9.4	354	20.9	11.7	5.5	0.9	<.01
FFQ Year 2 ⁴	79	15.3	10.7	123	23.2	12.6	7.9	1.7	<.01
FFQ Year 3 ⁵	46	15.3	7.9	59	20.9	13.0	5.6	2.2	0.01
FFQ Year 4 ⁶	71	15.2	10.3	111	21.8	12.3	6.6	1.8	<.01
FFQ Year 5 ⁷	56	15.6	9.2	80	20.8	10.5	5.2	1.7	<.01
FFQ Year 6 ⁸	36	18.2	9.7	70	22.3	12.4	4.1	2.4	0.04
FFQ Year 7 ⁹	10	15.7	4.7	18	28.3	16.5	12.6	5.4	0.01
FFQ Year 8 ¹⁰	2	16.6	7.8	6	13.1	8.9	3.5	7.2	0.48
4DFR Baseline	17	17.6	6.7	29	21.0	7.2	3.4	2.1	0.10
4DFR Year 1	13	11.3	8.7	24	18.9	5.7	7.6	2.4	<.01
Polyunsaturated Fat (g)									
FFQ Baseline	265	15.9	8.7	394	15.0	8.6	0.9	0.7	0.19
FFQ Year 1	240	9.0	6.0	354	11.9	6.8	2.8	0.5	<.01
FFQ Year 2	79	8.4	5.6	123	12.8	7.8	4.5	1.0	<.01
FFQ Year 3	46	9.0	4.1	59	13.1	7.9	4.1	1.3	<.01
FFQ Year 4	71	9.3	6.5	111	12.4	7.4	3.1	1.1	<.01
FFQ Year 5	56	9.5	5.7	80	12.0	6.2	2.4	1.0	0.02
FFQ Year 6	36	11.5	5.7	70	13.3	6.9	1.9	1.3	0.15
FFQ Year 7	10	7.7	2.2	18	14.5	8.9	6.8	2.9	<.01
FFQ Year 8	2	10.1	2.9	6	6.2	3.8	3.8	3.0	0.13
4DFR Baseline	17	11.7	3.7	29	12.5	4.4	0.8	1.3	0.59
4DFR Year 1	13	6.6	3.1	24	11.8	4.3	5.2	1.4	<.01
Fruits and Vegetables (servings)									
FFQ Baseline	264	3.7	2.0	393	3.4	2.0	0.2	0.2	0.04
FFQ Year 1	239	4.9	2.4	353	3.6	2.0	1.3	0.2	<.01
FFQ Year 2	78	5.0	2.2	123	3.9	2.3	1.1	0.3	<.01
FFQ Year 3	46	5.0	2.6	59	3.7	1.9	1.3	0.4	<.01
FFQ Year 4	70	5.1	2.7	111	4.0	2.1	1.1	0.4	0.02
FFQ Year 5	56	4.8	2.6	80	3.5	2.2	1.4	0.4	<.01
FFQ Year 6	35	5.7	2.4	70	4.1	2.1	1.6	0.5	<.01
FFQ Year 7	10	4.3	2.9	18	6.2	3.7	2.0	1.3	0.19
FFQ Year 8	2	4.4	3.1	6	5.1	2.9	0.7	2.4	0.88
Grain Servings (Not including desserts/pastries)									
FFQ Baseline	264	4.8	2.7	393	4.7	2.7	0.1	0.2	0.71
FFQ Year 1	239	5.0	3.0	353	4.2	2.4	0.8	0.2	<.01
FFQ Year 2	78	4.7	2.4	123	4.2	2.3	0.4	0.3	0.31
FFQ Year 3	46	4.7	3.0	59	4.2	2.8	0.5	0.6	0.41
FFQ Year 4	70	4.2	2.5	111	3.9	2.1	0.3	0.3	0.65
FFQ Year 5	56	4.6	2.3	80	3.8	2.3	0.8	0.4	0.04
FFQ Year 6	35	5.1	2.5	70	3.5	1.9	1.6	0.4	<.01
FFQ Year 7	10	4.5	3.3	18	4.1	2.3	0.3	1.1	0.87
FFQ Year 8	2	6.0	4.1	6	1.9	1.1	4.1	1.6	0.15

(continues)

¹ Absolute difference.

² P-values based on testing in the natural log scale except for % Energy from fat.

³ 38 (16%) Unknown Intervention women had ≤20% energy from fat at year 1.

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⁹ 0 (0%) Unknown Intervention women had ≤20% energy from fat at year 7.

¹⁰ 0 (0%) Unknown Intervention women had ≤20% energy from fat at year 8.

Table 3.4
Control - Intervention Difference in % Energy from Fat in WHI DM Participants
Study Subject Characteristics and Session Participation from FFQs Collected in the Last Year¹

Data as of: August 31, 2002

	Model Including Attendance (ΔR^2) for Inclusion				Model Including Completion (ΔR^2) for Inclusion				Model Including Fat Scores (ΔR^2) for Inclusion			
	N	C-I (%)	R ²		N	C-I (%)	R ²		N	C-I (%)	R ²	
Demographics			20.0%				20.0%				20.0%	
Age												
60-69	5922				5922				5922			
50-54 vs. 60-69	2011	0.27			2011	0.39			2011	0.45		
55-59 vs. 60-69	3116	0.21			3116	0.19			3116	0.11		
70-79 vs. 60-69	1993	-0.99 *			1993	-0.73			1993	-0.87 *		
Ethnicity												
White	10810				10810				10810			
American Indian vs. White	38	5.09 *			38	5.74 *			38	6.35 **		
Asian/Pacific Islander vs. White	285	-1.46			285	-1.51			285	-1.66		
Black vs. White	1318	-1.61 **			1318	-1.72 **			1318	-1.27 *		
Hispanic vs. White	425	-1.49			425	-1.36			425	-1.37		
Unknown vs. White	166	0.53			166	0.32			166	0.47		
Education												
Post H.S.	10354				10354				10354			
0-8 Years vs. Post H.S.	139	-0.40			139	-0.05			139	0.15		
Some H.S. or Diploma vs. Post H.S.	2549	-0.17			2549	0.03			2549	-0.16		
Family Income												
>75K	2317				2317				2317			
<20K vs. >75K	2242	0.10			2242	0.07			2242	0.10		
20-35K vs. >75K	2975	0.46			2975	0.43			2975	0.46		
35-50K vs. >75K	2790	0.39			2790	0.47			2790	0.28		
50-75K vs. >75K	2718	0.16			2718	0.09			2718	0.00		
HRT Randomized												
No	10916				10916				10916			
Yes vs. No	2126	0.34			2126	0.36			2126	0.46		
Visit			21.0%	(1.0%)			21.0%	(1.0%)			21.0%	(1.0%)
Visit Year												
AV-4	1823				1823				1823			
AV-3 vs. AV-4	69	-2.06			69	-2.04			69	-1.80		
AV-5 vs. AV-4	3928	-0.05			3928	-0.32			3928	-0.24		
AV-6 vs. AV-4	4179	-0.15			4179	-0.51			4179	-0.27		
AV-7 vs. AV-4	2081	-0.80 *			2081	-1.08 **			2081	-0.96 *		
AV-8 vs. AV-4	957	-0.07			957	-0.40			957	-0.33		
Clinic Effect			24.9%	(3.9%)			24.9%	(3.9%)			24.9%	(3.9%)
Intervention Participation												
# Sessions Attended in Previous 12 Months			29.3%	(4.3%)								
None	9576											
1 vs. None	631	4.13 **										
2 vs. None	916	4.87 **										
3 vs. None	1070	6.23 **										
4+ vs. None	849	7.56 **										
# Sessions Completed in Previous 12 Months							29.4%	(4.5%)				
None					8827							
1 vs. None					330	2.47 **						
2 vs. None					408	4.08 **						
3 vs. None					786	5.43 **						
4+ vs. None					2691	7.78 **						
# Fat Scores Provided in Previous 12 Months											30.1%	(5.2%)
None									9728			
1 vs. None									509	3.25 **		
2 vs. None									551	4.46 **		
3 vs. None									702	6.02 **		
4+ vs. None									1552	7.68 **		

¹ Model adjusted for clinic effects.

** P-value <0.05 from a two-sided test.

** P-value <0.01 from a two-sided test.

Table 3.5
Body Weight

Data as of: August 31, 2002

Body Weight (kg) ¹	Intervention			Control			Difference		
	N	Mean	S.D.	N	Mean	S.D.	Mean ²	S.E.	p-value
All Participants									
Baseline	19523	76.8	16.7	29271	76.7	16.5	-0.1	0.2	0.36
Year 1	18149	74.4	16.8	26681	76.3	16.8	1.9	0.2	<.01
Year 2	16706	75.3	17.2	25053	76.7	16.9	1.4	0.2	<.01
Year 3	16670	75.7	17.1	25388	76.8	16.8	1.1	0.2	<.01
Year 4	15747	76.0	17.1	24311	76.7	16.7	0.7	0.2	<.01
Year 5	12462	76.0	17.0	19244	76.7	16.8	0.7	0.2	<.01
Year 6	7846	76.1	16.7	12102	76.6	16.4	0.5	0.2	0.04
Year 7	3492	75.9	16.6	5352	75.9	16.0	0.1	0.4	0.88
Year 8	1040	74.9	16.1	1692	75.3	15.4	0.4	0.6	0.57
Participants Aged 70-79									
Baseline	3246	73.0	14.7	4870	72.9	14.5	-0.1	0.3	0.82
Year 1	3010	70.7	15.2	4486	72.6	15.4	1.9	0.4	<.01
Year 2	2787	71.0	15.0	4172	72.6	15.3	1.6	0.4	<.01
Year 3	2754	71.1	15.4	4197	72.2	14.8	1.1	0.4	<.01
Year 4	2550	71.0	15.1	3913	71.7	14.4	0.7	0.4	0.07
Year 5	1834	70.4	14.5	2846	71.2	14.4	0.8	0.4	0.06
Year 6	978	69.7	14.4	1541	70.5	13.9	0.7	0.6	0.20
Year 7	414	69.8	14.9	668	69.9	13.6	0.2	0.9	0.86
Year 8	107	68.6	13.8	192	69.7	15.6	1.2	1.8	0.50

¹ Shown for 30 ≤ weight (kg) ≤ 220.

² Control – Intervention.

Table 3.5 (continued)
Body Weight by Race/Ethnicity

Data as of: August 31, 2002

Body Weight (kg) ¹	Intervention			Control			Difference		
	N	Mean	S.D.	N	Mean	S.D.	Mean ²	S.E.	p-value
American Indian/ Alaskan Native									
Baseline	87	77.8	14.4	114	80.9	17.0	3.1	2.3	0.17
Year 1	74	75.6	15.0	93	81.3	16.9	5.7	2.5	0.02
Year 2	66	76.9	18.7	91	83.5	18.1	6.6	3.0	0.03
Year 3	67	75.5	15.5	95	83.6	17.5	8.1	2.7	<.01
Year 4	65	76.2	15.6	88	84.1	18.7	7.9	2.9	<.01
Year 5	57	77.4	15.4	65	85.0	17.4	7.6	3.0	0.01
Year 6	37	74.6	14.9	43	84.9	15.8	10.3	3.5	<.01
Year 7	14	76.1	16.8	16	78.0	12.9	1.9	5.4	0.73
Year 8	5	70.2	8.4	2	72.3	8.8	2.1	7.1	0.80
Asian/Pacific Islander									
Baseline	431	63.4	13.2	674	63.4	14.4	-0.1	0.9	0.93
Year 1	414	62.5	14.7	636	62.8	12.9	0.3	0.9	0.78
Year 2	392	62.7	14.1	615	63.0	12.4	0.3	0.8	0.73
Year 3	392	63.1	13.5	614	63.9	14.7	0.7	0.9	0.43
Year 4	366	63.2	12.6	608	63.8	13.8	0.5	0.9	0.54
Year 5	280	62.7	13.5	453	63.5	12.6	0.8	1.0	0.44
Year 6	141	61.7	12.5	240	62.2	13.3	0.6	1.4	0.67
Year 7	34	64.0	21.0	45	64.2	17.1	0.2	4.3	0.96
Year 8	9	62.6	7.8	6	59.1	7.9	-3.5	4.1	0.42
Black/African American									
Baseline	2133	85.3	18.2	3126	85.1	18.5	-0.1	0.5	0.79
Year 1	1891	84.3	19.3	2662	84.9	19.0	0.6	0.6	0.27
Year 2	1715	84.9	18.8	2503	85.2	19.0	0.4	0.6	0.51
Year 3	1698	85.3	19.4	2509	85.2	18.8	-0.1	0.6	0.90
Year 4	1578	85.4	19.1	2364	85.5	18.3	0.1	0.6	0.91
Year 5	1228	85.8	19.4	1845	85.8	19.1	0.0	0.7	0.98
Year 6	781	84.6	18.4	1182	85.2	18.4	0.6	0.8	0.49
Year 7	321	83.8	18.7	449	84.5	18.2	0.7	1.3	0.62
Year 8	50	80.9	14.8	88	82.1	15.9	1.2	2.8	0.67
Hispanic/Latino									
Baseline	750	75.2	16.0	1094	73.7	15.2	-1.5	0.7	0.05
Year 1	638	74.2	16.6	935	73.2	15.5	-1.0	0.8	0.22
Year 2	570	74.4	16.1	864	73.9	15.8	-0.4	0.9	0.63
Year 3	545	75.3	16.9	866	74.3	16.5	-1.0	0.9	0.28
Year 4	512	75.6	16.8	831	73.8	15.2	-1.7	0.9	0.06
Year 5	418	75.1	16.5	659	74.2	14.5	-0.9	1.0	0.34
Year 6	239	76.2	17.6	376	74.8	14.2	-1.4	1.3	0.29
Year 7	80	74.2	15.5	124	70.9	14.4	-3.2	2.1	0.13
Year 8	25	75.0	12.6	43	69.9	14.9	-5.1	3.6	0.14

¹ Shown for 30 ≤ weight (kg) ≤ 220.

² Control - Intervention.

Table 3.5 (continued)
Body Weight by Race/Ethnicity

Data as of: August 31, 2002

Body Weight (kg) ¹	Intervention			Control			Difference		
	N	Mean	S.D.	N	Mean	S.D.	Mean ²	S.E.	p-value
White									
Baseline	15857	76.1	16.1	23869	76.1	15.9	-0.0	0.2	0.87
Year 1	14893	73.5	15.9	22010	75.8	16.2	2.3	0.2	<.01
Year 2	13757	74.5	16.6	20656	76.2	16.3	1.6	0.2	<.01
Year 3	13762	74.9	16.5	20983	76.2	16.2	1.3	0.2	<.01
Year 4	13031	75.2	16.5	20104	76.2	16.2	1.0	0.2	<.01
Year 5	10344	75.3	16.3	16002	76.1	16.2	0.8	0.2	<.01
Year 6	6580	75.4	16.1	10134	75.9	15.8	0.6	0.3	0.02
Year 7	3019	75.2	16.0	4669	75.3	15.5	0.2	0.4	0.62
Year 8	944	74.7	16.2	1537	75.1	15.3	0.4	0.6	0.56
Unknown									
Baseline	265	78.3	18.4	394	76.4	16.8	-1.9	1.4	0.18
Year 1	239	77.6	20.4	345	77.0	18.0	-0.6	1.6	0.71
Year 2	206	76.2	18.7	324	77.3	18.5	1.1	1.7	0.52
Year 3	206	77.0	17.6	321	77.1	18.2	0.1	1.6	0.93
Year 4	195	76.4	18.2	316	76.6	16.3	0.2	1.6	0.90
Year 5	135	75.7	16.3	220	77.3	19.6	1.6	2.0	0.42
Year 6	68	78.4	18.6	127	76.5	19.3	-1.9	2.9	0.49
Year 7	24	82.3	17.6	49	76.6	16.4	-5.7	4.2	0.19
Year 8	7	81.0	17.8	16	77.5	17.9	-3.5	8.1	0.68

¹ Shown for 30 ≤ weight (kg) ≤ 220.

² Control - Intervention.

Table 3.6
Reasons for Stopping DM¹

Data as of: August 31, 2002

Reasons ²	(N = 2331)	
Personal/family		
Demands of work	241	10.3%
Family illness, emergency, or other family demands ³	288	12.4%
Financial problems	9	0.4%
Lack of cooperation/support from family/friends ⁴	39	1.7%
Living in nursing home	23	1.0%
Issues of interest in study ⁵	229	9.8%
Travel		
Too far to CC	113	4.8%
Moved out of area or refuses to be followed at another CC	17	0.7%
Other Travel Issues ⁶	63	2.7%
Visits & Procedures		
Doesn't like visits/calls	44	1.9%
Doesn't like required forms or safety procedures ⁷	44	1.9%
Problems with other procedures ⁸	9	0.4%
Worried about health effects of medical tests/procedures	3	0.1%
Wants test results ⁹	0	0.0%
Problems with the CC ¹⁰	32	1.4%

(continues)

¹ Does not include reasons reported by women who stopped and later restarted DM Intervention.

² Multiple reasons may be reported for a woman.

³ Combines "Family illness, emergency or other family demands", "Death in the family or of a close friend", and "Caregiver responsibilities demanding time, effort, lifestyle changes".

⁴ Combines "Lack of cooperation/support from family and/or friends" and "Family/friends request that she withdraw".

⁵ Combines "Conflicting priorities other than work or family", "Feels discouraged regarding participation overall", "Loss of interest, boredom", "Feels it is not an important study", and "In another study in conflict with WHI intervention".

⁶ Combines "Transportation problems (other than distance)", "Traffic", "Parking at CC", and "CC neighborhood/safety".

⁷ Combines "Doesn't like filling out forms (other than those required for safety)", and "Doesn't like required safety forms and/or procedures".

⁸ Combines "Doesn't like mammograms", "Cost of mammograms", "Doesn't like having blood drawn", "Doesn't like ECG", "Doesn't like gynecologic procedures" and "Doesn't like other procedures (other than those required for safety)".

⁹ Combines "Wants results of blood analyses", and "Wants results of bone mineral density measurement".

¹⁰ Combines "Problem with the CC", "Problem with CC staff person (other than DM Group Nutritionist)", and "Staff change/turnover".

Table 3.6 (continued)
Reasons for Stopping DM¹

Data as of: August 31, 2002

Reasons ²	(N = 2331)	
Symptoms		
GI Problems ³	2	< 0.1%
Hair/Skin Changes	1	< 0.1%
Weight loss/gain	5	0.2%
HRT Related Symptoms ⁴	4	0.2%
Other ⁵	7	0.3%
Health Conditions		
Disease and/or health conditions ⁶	81	3.5%
Communication difficulties ⁷	47	2.0%
Intervention		
Doesn't like randomized nature of intervention	11	0.5%
Expected some benefit from intervention	32	1.4%
Feels guilty/unhappy or like a failure for not meeting study goals	19	0.8%
Pill Issues ⁸	5	0.2%
CaD Issues ⁹	1	< 0.1%
HRT Issues ¹⁰	3	0.1%
Problem with DM group nutritionist or group members	31	1.3%
Doesn't like attending DM intervention classes	63	2.7%
Doesn't like self-monitoring	43	1.8%
Doesn't like budgeting fat grams	4	0.2%
Health concerns regarding long-term risk/benefits of low fat diet	17	0.7%
Unhappy that not losing weight	17	0.7%
Not in control of meal preparation	11	0.5%
Too difficult to meet or maintain dietary goals	41	1.8%
Doesn't like eating low fat diet	29	1.2%
Doesn't like eating 5 vegetables/fruits per day	2	< 0.1%
Doesn't like eating 6 grains per day	7	0.3%
Feels fat gram goal is unrealistic	6	0.3%
Eating pattern conflicts with personal health beliefs	26	1.1%
Other Health Issues		
Worried about costs if adverse effects occur	1	< 0.1%
Expected more health care	14	0.6%
Advised not to participate by health care provider ¹¹	21	0.9%
Study conflicts with other health issues ¹²	29	1.2%
Other		
Other reasons not listed above	459	19.7%
Refuses to give a reason	93	4.0%

¹ Does not include reasons reported by women who stopped and later restarted DM intervention.

² Multiple reasons may be reported for a woman.

³ Combines "Bloating/Gas", "Constipation", and "Other gastrointestinal problems".

⁴ Combines "Vaginal bleeding", "Breast tenderness", "Other breast changes", "Vaginal changes (e.g., dryness)", and "Hot flashes/night sweats".

⁵ Combines "Headaches", "Low energy/too tired", "Possible allergic reaction", and "Other symptoms not listed above".

⁶ Combines "Breast cancer", "Complex or atypical hyperplasia", "Endometrial cancer", "Deep vein thrombosis", "Pulmonary embolism", "Gallbladder disease", "Hypercalcemia", "Kidney failure/dialysis", "Renal calculi", "High triglycerides (> 1000 mg/dl)", "Malignant melanoma", "Meningioma", "Heart attack", "Stroke", "Arthritis", "Diabetes", "Depression", "Cholesterol (high or concern about levels)", "Osteoporosis", and "Other health conditions not listed above".

⁷ Combines "Communication problem", "Loss of vision and/or hearing", and "Cognitive/memory changes".

⁸ Combines "Doesn't like taking pills", "Doesn't like taste of pills", "Unable to swallow pills", and "Takes too many pills".

⁹ Combines "Wants to take her own calcium", "Feels diet is already sufficient in calcium/Vitamin D", "Taking more than the maximum allowable IU of Vit D", and "Taking Calcitriol".

¹⁰ Combines "Has made a personal decision to go on active HRT", "Has made a personal decision that she does not want to be on HRT", "Advised to go on active HRT by health care provider", "Advised to not be on active HRT by health care provider", "Has made a personal decision to go on SERM (e.g., Evista/raloxifene, tamoxifen)", "Advised to go on SERM (e.g., Evista/raloxifene, tamoxifen) by health care provider", and "Taking testosterone medications".

¹¹ Combines "Advised not to participate by health care provider" and "Advised not to participate by health care provider for other reason".

¹² Combines "Study conflicts with health care needs" and "Study conflicts with other health issues".

Table 3.7
Reasons for Stopping DM by Age at Screening and Race/Ethnicity¹

Data as of August 31, 2002

	Age at Screening					
	All	50 - 54	55 - 59	60 - 69	70 - 79	
	(N = 19,541)	(N = 2,783)	(N = 4,424)	(N = 9,086)	(N = 3,248)	
	N % ²	N % ²	N % ²	N % ²	N % ²	
Women Stopping Intervention	2331 11.9%	370 13.3%	528 11.9%	948 10.4%	485 14.9%	
REASONS FOR STOPPING³						
Family illness, emergency, or other family demands ³	288 12.4%	47 12.7%	71 13.4%	114 12.0%	56 11.5%	
Demands of work	241 10.3%	76 20.5%	71 13.4%	78 8.2%	16 3.3%	
Issues of interest in study ⁶	229 9.8%	35 9.5%	58 11.0%	92 9.7%	44 9.1%	
Too far to CC	113 4.8%	25 6.8%	33 6.3%	41 4.3%	14 2.9%	
Other ("Other reasons not listed above")	459 19.7%	77 20.8%	129 24.4%	180 19.0%	73 15.1%	

	Race/Ethnicity					
	American Indian/Alaskan	Asian/Pacific Islander	Black/African American	Hispanic/Latino	White	Unknown
	(N = 88)	(N = 431)	(N = 2,135)	(N = 751)	(N = 15,871)	(N = 265)
	N % ⁷	N % ⁷	N % ⁷	N % ⁷	N % ⁷	N % ⁷
Women Stopping Intervention	21 23.9%	52 12.1%	323 15.1%	163 21.7%	1725 10.9%	47 17.7%
REASONS FOR STOPPING³						
Family illness, emergency, or other family demands ³	2 9.5%	3 5.8%	34 10.5%	25 15.3%	218 12.6%	6 12.8%
Demands of work	1 4.8%	5 9.6%	47 14.6%	17 10.4%	167 9.7%	4 8.5%
Issues of interest in study ⁶	3 14.3%	5 9.6%	36 11.1%	7 4.3%	175 10.1%	3 6.4%
Too far to CC	2 9.5%	2 3.8%	6 1.9%	6 3.7%	96 5.6%	1 2.1%
Other ("Other reasons not listed above")	5 23.8%	8 15.4%	50 15.5%	49 30.1%	339 19.7%	8 17.0%

¹ Does not include reasons reported by women who stopped and later restarted DM intervention.

² Percentages are of DM intervention participants in the same age category.

³ Multiple reasons may be reported for a woman.

⁴ Percentages are of DM intervention participants in the same age category who stopped DM intervention.

⁵ Combines "Family illness, emergency or other family demands", "Death in the family or of a close friend", and "Caregiver responsibilities demanding time, effort, lifestyle changes".

⁶ Combines "Conflicting priorities other than work or family", "Feels discouraged regarding participation overall", "Loss of interest, boredom", "Feels it is not an important study", and "In another study in conflict with WHI intervention".

⁷ Percentages are of DM intervention participants in the same race/ethnicity category.

⁸ Percentages are of DM intervention participants in the same race/ethnicity category who stopped DM intervention.

Table 3.8
Blood Specimen Analysis: DM Participants

Data as of: August 31, 2002

	N	Mean ¹	S.D. ¹
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	2731	0.08	0.08
AV-1	2501	0.08	0.07
AV-3	2129	0.07	0.07
AV-1 – Baseline	2426	0.00	0.06
AV-3 – Baseline	2059	-0.01	0.07
Beta-Carotene (µg/ml)			
Baseline	2731	0.30	0.28
AV-1	2501	0.30	0.29
AV-3	2129	0.29	0.29
AV-1 – Baseline	2426	0.00	0.22
AV-3 – Baseline	2059	0.00	0.26
Alpha-tocopherol (µg/ml)			
Baseline	2731	16.28	7.30
AV-1	2501	16.96	7.52
AV-3	2129	18.16	7.74
AV-1 – Baseline	2426	0.76	5.49
AV-3 – Baseline	2059	1.95	6.73
Gamma-tocopherol (µg/ml)			
Baseline	2731	2.21	1.42
AV-1	2500	1.85	1.31
AV-3	2129	1.69	1.32
AV-1 – Baseline	2425	-0.36	0.92
AV-3 – Baseline	2059	-0.55	1.13
Beta-Cryptoxanthine (µg/ml)			
Baseline	2731	0.09	0.07
AV-1	2500	0.09	0.07
AV-3	2129	0.10	0.08
AV-1 – Baseline	2425	0.00	0.06
AV-3 – Baseline	2059	0.01	0.07
Lycopene (µg/ml)			
Baseline	2731	0.41	0.19
AV-1	2501	0.41	0.19
AV-3	2129	0.38	0.20
AV-1 – Baseline	2426	-0.01	0.16
AV-3 – Baseline	2059	-0.03	0.20
Lutein and Zeaxanthin (µg/ml)			
Baseline	2731	0.21	0.10
AV-1	2501	0.22	0.10
AV-3	2129	0.20	0.10
AV-1 – Baseline	2426	0.00	0.07
AV-3 – Baseline	2059	-0.02	0.08
Retinol (µg/ml)			
Baseline	2731	0.61	0.15
AV-1	2501	0.62	0.15
AV-3	2129	0.61	0.15
AV-1 – Baseline	2426	0.00	0.10
AV-3 – Baseline	2059	0.00	0.13

(continues)

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

Table 3.8 (continued)
Blood Specimen Analysis: DM Participants

Data as of: August 31, 2002

	N	Mean ¹	S.D. ¹
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	2640	130.69	32.41
AV-1	2399	130.70	32.64
AV-3	2033	132.25	33.27
AV-1 – Baseline	2276	-0.23	22.36
AV-3 – Baseline	1910	0.96	28.18
Factor VII C (%) ²			
Baseline	2595	129.82	30.74
AV-1	2368	127.30	30.37
AV-3	2025	131.06	33.88
AV-1 – Baseline	2211	-2.82	22.49
AV-3 – Baseline	1865	0.85	28.35
Fibrinogen (mg/dl)			
Baseline	2630	299.80	60.77
AV-1	2392	297.57	60.62
AV-3	2034	289.37	59.12
AV-1 – Baseline	2264	-2.56	49.77
AV-3 – Baseline	1903	-10.72	52.91
Hormones/Other			
Glucose (mg/dl)			
Baseline	2729	100.17	26.76
AV-1	2493	98.81	26.23
AV-3	2155	99.36	26.86
AV-1 – Baseline	2418	-1.33	18.98
AV-3 – Baseline	2083	-1.00	21.12
Insulin (μIU/ml)			
Baseline	2661	11.69	8.77
AV-1	2431	11.30	10.33
AV-3	2066	12.79	10.10
AV-1 – Baseline	2320	-0.31	8.54
AV-3 – Baseline	1950	1.08	8.42

(continues)

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

² Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.8 (continued)
Blood Specimen Analysis: DM Participants

Data as of: August 31, 2002

	N	Mean ¹	S.D. ¹
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	2730	157.45	86.55
AV-1	2499	159.31	86.45
AV-3	2155	160.15	90.01
AV-1 – Baseline	2424	2.51	54.98
AV-3 – Baseline	2083	2.06	74.72
Total Cholesterol (mg/dl)			
Baseline	2730	224.13	38.13
AV-1	2499	217.41	37.32
AV-3	2155	215.56	35.67
AV-1 – Baseline	2424	-6.61	26.66
AV-3 – Baseline	2083	-8.33	32.09
LDL-C (mg/dl)			
Baseline	2680	133.82	35.18
AV-1	2454	126.49	34.05
AV-3	2121	125.45	33.69
AV-1 – Baseline	2360	-6.91	23.78
AV-3 – Baseline	2022	-7.69	29.33
HDL-C (mg/dl)			
Baseline	2722	59.05	15.68
AV-1	2497	59.28	15.30
AV-3	2155	58.82	15.68
AV-1 – Baseline	2416	-0.08	8.79
AV-3 – Baseline	2077	-0.40	9.95
HDL-2 (mg/dl)			
Baseline	2662	18.29	8.17
AV-1	2456	18.84	8.36
AV-3	2127	16.45	6.64
AV-1 – Baseline	2329	0.31	4.97
AV-3 – Baseline	2009	-1.90	5.63
HDL-3 (mg/dl)			
Baseline	2664	40.86	9.05
AV-1	2457	40.47	8.58
AV-3	2127	42.24	9.80
AV-1 – Baseline	2332	-0.51	5.55
AV-3 – Baseline	2011	1.42	6.98
Lp(a) (mg/dl)			
Baseline	2693	25.96	26.14
AV-1	2466	25.11	25.93
AV-3	2092	22.79	23.17
AV-1 – Baseline	2366	-0.66	10.22
AV-3 – Baseline	2002	-2.77	13.55

¹ Means and standard deviations are weighted by ethnicity using the ethnicity distribution of participants randomized to CT.

Table 3.9
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	74	0.05	0.04
AV-1	58	0.06	0.05
AV-3	44	0.05	0.03
AV-1 – Baseline	57	0.01	0.04
AV-3 – Baseline	43	-0.01	0.03
Beta-Carotene (µg/ml)			
Baseline	74	0.25	0.24
AV-1	58	0.27	0.31
AV-3	44	0.21	0.14
AV-1 – Baseline	57	0.00	0.20
AV-3 – Baseline	43	-0.05	0.19
Alpha-tocopherol (µg/ml)			
Baseline	74	18.18	10.41
AV-1	58	18.10	9.60
AV-3	44	16.36	6.42
AV-1 – Baseline	57	1.00	5.58
AV-3 – Baseline	43	-1.70	9.23
Gamma-tocopherol (µg/ml)			
Baseline	74	2.20	1.27
AV-1	58	1.80	1.22
AV-3	44	1.88	1.14
AV-1 – Baseline	57	-0.41	0.84
AV-3 – Baseline	43	-0.33	1.04
Beta-Cryptoxanthine (µg/ml)			
Baseline	74	0.07	0.04
AV-1	58	0.07	0.04
AV-3	44	0.08	0.04
AV-1 – Baseline	57	0.01	0.04
AV-3 – Baseline	43	0.02	0.04
Lycopene (µg/ml)			
Baseline	74	0.36	0.17
AV-1	58	0.35	0.16
AV-3	44	0.32	0.18
AV-1 – Baseline	57	0.00	0.13
AV-3 – Baseline	43	-0.05	0.19
Lutein and Zeaxanthin (µg/ml)			
Baseline	74	0.20	0.13
AV-1	58	0.20	0.10
AV-3	44	0.17	0.08
AV-1 – Baseline	57	0.00	0.06
AV-3 – Baseline	43	-0.01	0.05
Retinol (µg/ml)			
Baseline	74	0.61	0.15
AV-1	58	0.60	0.16
AV-3	44	0.56	0.13
AV-1 – Baseline	57	-0.01	0.08
AV-3 – Baseline	43	-0.04	0.13

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	71	136.94	31.58
AV-1	56	138.29	30.70
AV-3	45	137.31	32.47
AV-1 – Baseline	54	0.72	18.41
AV-3 – Baseline	43	-1.21	26.72
Factor VII C (%) ¹			
Baseline	71	131.42	29.79
AV-1	56	127.55	26.77
AV-3	45	133.64	34.30
AV-1 – Baseline	54	-2.04	14.64
AV-3 – Baseline	43	2.51	23.28
Fibrinogen (mg/dl)			
Baseline	71	305.41	66.58
AV-1	56	312.86	75.90
AV-3	45	298.40	62.33
AV-1 – Baseline	54	4.89	54.99
AV-3 – Baseline	43	-10.95	41.25
Hormones/Other			
Glucose (mg/dl)			
Baseline	74	105.54	33.02
AV-1	58	102.17	21.11
AV-3	46	106.35	28.25
AV-1 – Baseline	57	-3.11	17.66
AV-3 – Baseline	45	0.02	37.99
Insulin (μIU/ml)			
Baseline	69	13.31	7.90
AV-1	56	12.09	6.16
AV-3	42	14.90	9.80
AV-1 – Baseline	52	-1.10	4.70
AV-3 – Baseline	39	2.48	8.12

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: American Indian/Alaskan Native Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	73	183.51	91.72
AV-1	57	170.98	88.64
AV-3	46	174.30	98.36
AV-1 – Baseline	55	-1.87	52.17
AV-3 – Baseline	44	-14.73	73.94
Total Cholesterol (mg/dl)			
Baseline	73	218.42	34.36
AV-1	57	210.86	36.96
AV-3	46	204.35	38.88
AV-1 – Baseline	55	-7.84	23.63
AV-3 – Baseline	44	-13.61	29.59
LDL-C (mg/dl)			
Baseline	71	127.08	33.42
AV-1	54	123.00	33.59
AV-3	44	117.11	38.03
AV-1 – Baseline	52	-5.42	20.42
AV-3 – Baseline	42	-10.79	27.20
HDL-C (mg/dl)			
Baseline	73	55.62	15.88
AV-1	57	56.05	15.58
AV-3	46	54.59	13.84
AV-1 – Baseline	55	-0.07	7.51
AV-3 – Baseline	44	0.68	6.65
HDL-2 (mg/dl)			
Baseline	70	16.94	8.07
AV-1	56	17.41	7.86
AV-3	45	15.51	5.32
AV-1 – Baseline	52	0.27	4.41
AV-3 – Baseline	41	-1.07	3.67
HDL-3 (mg/dl)			
Baseline	71	38.83	8.31
AV-1	56	38.21	8.59
AV-3	45	39.71	8.60
AV-1 – Baseline	53	-0.25	5.01
AV-3 – Baseline	42	1.90	5.49
Lp(a) (mg/dl)			
Baseline	71	21.48	20.85
AV-1	56	20.38	19.84
AV-3	44	17.41	16.56
AV-1 – Baseline	54	0.69	9.69
AV-3 – Baseline	41	-4.56	12.13

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	194	0.10	0.10
AV-1	176	0.10	0.10
AV-3	159	0.09	0.09
AV-1 – Baseline	174	0.00	0.10
AV-3 – Baseline	157	-0.02	0.09
Beta-Carotene (µg/ml)			
Baseline	194	0.44	0.42
AV-1	176	0.48	0.53
AV-3	159	0.46	0.59
AV-1 – Baseline	174	0.05	0.40
AV-3 – Baseline	157	0.02	0.47
Alpha-tocopherol (µg/ml)			
Baseline	194	19.35	9.96
AV-1	176	19.48	11.01
AV-3	159	22.11	11.59
AV-1 – Baseline	174	0.34	6.81
AV-3 – Baseline	157	3.14	9.71
Gamma-tocopherol (µg/ml)			
Baseline	194	1.68	1.18
AV-1	176	1.30	0.98
AV-3	159	1.16	0.89
AV-1 – Baseline	174	-0.38	0.85
AV-3 – Baseline	157	-0.58	0.90
Beta-Cryptoxanthine (µg/ml)			
Baseline	194	0.18	0.17
AV-1	176	0.19	0.18
AV-3	159	0.21	0.22
AV-1 – Baseline	174	0.01	0.14
AV-3 – Baseline	157	0.03	0.18
Lycopene (µg/ml)			
Baseline	194	0.38	0.21
AV-1	176	0.37	0.19
AV-3	159	0.33	0.22
AV-1 – Baseline	174	-0.02	0.18
AV-3 – Baseline	157	-0.05	0.22
Lutein and Zeaxanthin (µg/ml)			
Baseline	194	0.27	0.12
AV-1	176	0.28	0.12
AV-3	159	0.25	0.12
AV-1 – Baseline	174	0.01	0.09
AV-3 – Baseline	157	-0.02	0.09
Retinol (µg/ml)			
Baseline	194	0.61	0.14
AV-1	176	0.62	0.15
AV-3	159	0.61	0.14
AV-1 – Baseline	174	0.01	0.09
AV-3 – Baseline	157	0.01	0.12

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	188	130.96	29.85
AV-1	167	130.84	29.26
AV-3	150	135.85	31.95
AV-1 – Baseline	161	-0.96	20.48
AV-3 – Baseline	145	3.99	27.42
Factor VII C (%) ¹			
Baseline	188	126.67	24.61
AV-1	167	126.11	26.33
AV-3	150	132.81	28.93
AV-1 – Baseline	161	-1.03	18.59
AV-3 – Baseline	145	5.53	24.09
Fibrinogen (mg/dl)			
Baseline	189	290.03	57.67
AV-1	167	284.84	57.04
AV-3	151	277.07	58.12
AV-1 – Baseline	162	-6.69	53.11
AV-3 – Baseline	147	-10.56	53.92
Hormones/Other			
Glucose (mg/dl)			
Baseline	194	99.77	18.15
AV-1	176	100.55	23.78
AV-3	161	101.75	21.77
AV-1 – Baseline	174	0.29	19.27
AV-3 – Baseline	159	1.81	14.56
Insulin (μIU/ml)			
Baseline	188	10.24	5.58
AV-1	168	10.02	5.92
AV-3	154	11.66	6.16
AV-1 – Baseline	164	-0.28	3.78
AV-3 – Baseline	148	1.21	5.49

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: Asian/Pacific Islander Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	193	171.96	92.30
AV-1	176	172.70	94.01
AV-3	161	191.74	214.54
AV-1 – Baseline	173	0.05	60.11
AV-3 – Baseline	158	18.96	200.05
Total Cholesterol (mg/dl)			
Baseline	193	219.75	35.95
AV-1	176	213.29	33.31
AV-3	161	209.53	35.43
AV-1 – Baseline	173	-7.59	24.36
AV-3 – Baseline	158	-7.81	28.78
LDL-C (mg/dl)			
Baseline	186	127.87	34.91
AV-1	170	120.72	30.18
AV-3	155	116.52	31.49
AV-1 – Baseline	164	-8.60	25.08
AV-3 – Baseline	149	-8.34	26.91
HDL-C (mg/dl)			
Baseline	193	58.23	13.48
AV-1	176	59.91	14.05
AV-3	161	58.24	14.10
AV-1 – Baseline	173	1.27	8.38
AV-3 – Baseline	158	-0.65	9.74
HDL-2 (mg/dl)			
Baseline	189	18.05	7.21
AV-1	174	19.51	7.32
AV-3	159	16.14	5.48
AV-1 – Baseline	168	1.10	4.53
AV-3 – Baseline	152	-2.36	5.18
HDL-3 (mg/dl)			
Baseline	189	40.39	8.00
AV-1	174	40.50	8.34
AV-3	159	42.06	9.35
AV-1 – Baseline	168	0.17	5.36
AV-3 – Baseline	152	1.50	7.40
Lp(a) (mg/dl)			
Baseline	190	18.31	16.20
AV-1	175	16.41	14.04
AV-3	157	13.97	12.26
AV-1 – Baseline	170	-2.14	12.79
AV-3 – Baseline	151	-3.95	9.96

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	778	0.06	0.08
AV-1	696	0.07	0.07
AV-3	557	0.05	0.06
AV-1 – Baseline	674	0.00	0.06
AV-3 – Baseline	537	-0.01	0.05
Beta-Carotene (µg/ml)			
Baseline	778	0.31	0.34
AV-1	696	0.32	0.30
AV-3	557	0.31	0.34
AV-1 – Baseline	674	0.00	0.22
AV-3 – Baseline	537	0.01	0.25
Alpha-tocopherol (µg/ml)			
Baseline	778	13.95	6.04
AV-1	696	14.55	6.12
AV-3	557	15.18	6.62
AV-1 – Baseline	674	0.49	4.71
AV-3 – Baseline	537	1.31	5.78
Gamma-tocopherol (µg/ml)			
Baseline	778	2.54	1.35
AV-1	696	2.27	1.31
AV-3	557	2.11	1.30
AV-1 – Baseline	674	-0.20	0.91
AV-3 – Baseline	537	-0.42	1.05
Beta-Cryptoxanthine (µg/ml)			
Baseline	778	0.09	0.06
AV-1	696	0.09	0.06
AV-3	557	0.09	0.07
AV-1 – Baseline	674	0.00	0.06
AV-3 – Baseline	537	0.01	0.06
Lycopene (µg/ml)			
Baseline	778	0.40	0.21
AV-1	696	0.38	0.20
AV-3	557	0.36	0.21
AV-1 – Baseline	674	-0.01	0.19
AV-3 – Baseline	537	-0.03	0.22
Lutein and Zeaxanthin (µg/ml)			
Baseline	778	0.23	0.11
AV-1	696	0.24	0.11
AV-3	557	0.22	0.10
AV-1 – Baseline	674	0.01	0.08
AV-3 – Baseline	537	-0.01	0.09
Retinol (µg/ml)			
Baseline	778	0.55	0.15
AV-1	696	0.55	0.14
AV-3	557	0.56	0.16
AV-1 – Baseline	674	0.01	0.09
AV-3 – Baseline	537	0.01	0.12

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	750	114.89	27.06
AV-1	677	115.59	27.52
AV-3	534	119.17	29.25
AV-1 – Baseline	635	0.95	20.65
AV-3 – Baseline	498	3.93	25.52
Factor VII C (%) ¹			
Baseline	730	118.33	30.11
AV-1	665	116.40	26.76
AV-3	532	119.80	30.26
AV-1 – Baseline	609	-1.90	21.05
AV-3 – Baseline	479	0.68	27.63
Fibrinogen (mg/dl)			
Baseline	748	321.11	66.58
AV-1	677	319.59	66.77
AV-3	533	310.26	66.67
AV-1 – Baseline	635	-3.57	49.22
AV-3 – Baseline	496	-15.24	58.52
Hormones/Other			
Glucose (mg/dl)			
Baseline	778	106.88	37.04
AV-1	693	106.99	38.21
AV-3	568	105.63	34.86
AV-1 – Baseline	671	0.67	26.78
AV-3 – Baseline	547	-0.97	28.29
Insulin (μIU/ml)			
Baseline	766	14.32	17.77
AV-1	686	13.94	10.91
AV-3	549	15.72	18.62
AV-1 – Baseline	658	-0.23	6.17
AV-3 – Baseline	523	0.64	14.44

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: Black/African American Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	778	119.73	53.08
AV-1	696	118.90	48.12
AV-3	568	119.93	51.54
AV-1 – Baseline	674	0.63	36.49
AV-3 – Baseline	547	0.93	42.12
Total Cholesterol (mg/dl)			
Baseline	778	220.25	41.98
AV-1	696	216.28	41.42
AV-3	568	210.66	39.57
AV-1 – Baseline	674	-3.45	25.91
AV-3 – Baseline	547	-9.46	30.43
LDL-C (mg/dl)			
Baseline	777	137.81	39.42
AV-1	695	132.76	39.29
AV-3	568	128.01	37.13
AV-1 – Baseline	672	-4.55	24.25
AV-3 – Baseline	546	-9.63	29.48
HDL-C (mg/dl)			
Baseline	777	58.50	15.06
AV-1	696	59.79	15.02
AV-3	568	58.67	14.37
AV-1 – Baseline	673	0.97	8.15
AV-3 – Baseline	546	0.00	9.15
HDL-2 (mg/dl)			
Baseline	766	18.30	7.83
AV-1	689	19.38	8.63
AV-3	562	16.30	5.78
AV-1 – Baseline	657	0.79	4.96
AV-3 – Baseline	536	-1.96	5.45
HDL-3 (mg/dl)			
Baseline	766	40.18	8.64
AV-1	689	40.35	8.02
AV-3	562	42.41	9.51
AV-1 – Baseline	657	0.11	5.17
AV-3 – Baseline	536	1.99	6.46
Lp(a) (mg/dl)			
Baseline	766	38.57	27.55
AV-1	691	37.91	28.00
AV-3	552	34.13	24.40
AV-1 – Baseline	660	-0.06	11.97
AV-3 – Baseline	526	-3.43	18.56

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	304	0.09	0.10
AV-1	268	0.09	0.07
AV-3	218	0.07	0.08
AV-1 – Baseline	261	0.00	0.10
AV-3 – Baseline	212	-0.02	0.11
Beta-Carotene (µg/ml)			
Baseline	304	0.30	0.41
AV-1	268	0.28	0.27
AV-3	218	0.25	0.26
AV-1 – Baseline	261	-0.01	0.35
AV-3 – Baseline	212	-0.07	0.38
Alpha-tocopherol (µg/ml)			
Baseline	304	15.99	7.06
AV-1	268	17.01	7.71
AV-3	218	17.21	7.45
AV-1 – Baseline	261	1.26	5.94
AV-3 – Baseline	212	0.95	6.62
Gamma-tocopherol (µg/ml)			
Baseline	304	2.12	1.35
AV-1	268	1.89	1.40
AV-3	218	1.86	1.38
AV-1 – Baseline	261	-0.25	0.94
AV-3 – Baseline	212	-0.35	1.06
Beta-Cryptoxanthine (µg/ml)			
Baseline	304	0.11	0.10
AV-1	268	0.11	0.09
AV-3	218	0.11	0.09
AV-1 – Baseline	261	-0.01	0.09
AV-3 – Baseline	212	0.00	0.09
Lycopene (µg/ml)			
Baseline	304	0.43	0.21
AV-1	268	0.41	0.19
AV-3	218	0.39	0.20
AV-1 – Baseline	261	-0.02	0.16
AV-3 – Baseline	212	-0.05	0.20
Lutein and Zeaxanthin (µg/ml)			
Baseline	304	0.20	0.10
AV-1	268	0.20	0.10
AV-3	218	0.19	0.08
AV-1 – Baseline	261	0.00	0.08
AV-3 – Baseline	212	-0.01	0.07
Retinol (µg/ml)			
Baseline	304	0.55	0.13
AV-1	268	0.57	0.13
AV-3	218	0.57	0.14
AV-1 – Baseline	261	0.02	0.09
AV-3 – Baseline	212	0.00	0.10

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	292	123.52	27.45
AV-1	254	124.28	28.84
AV-3	214	128.82	32.44
AV-1 – Baseline	241	2.02	21.59
AV-3 – Baseline	204	4.72	26.97
Factor VII C (%) ¹			
Baseline	285	123.49	28.28
AV-1	244	121.88	27.43
AV-3	212	127.29	31.84
AV-1 – Baseline	229	0.34	21.10
AV-3 – Baseline	197	3.26	27.76
Fibrinogen (mg/dl)			
Baseline	291	305.49	65.72
AV-1	253	309.02	70.72
AV-3	214	293.64	61.06
AV-1 – Baseline	240	-0.18	55.83
AV-3 – Baseline	203	-12.57	51.93
Hormones/Other			
Glucose (mg/dl)			
Baseline	303	101.84	32.88
AV-1	267	105.04	35.37
AV-3	222	107.11	37.99
AV-1 – Baseline	259	1.56	20.97
AV-3 – Baseline	215	2.50	19.05
Insulin (μIU/ml)			
Baseline	295	13.48	8.60
AV-1	264	13.29	11.77
AV-3	212	14.06	8.24
AV-1 – Baseline	252	-0.41	8.83
AV-3 – Baseline	201	0.79	6.66

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: Hispanic/Latino Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	304	162.20	74.64
AV-1	268	165.55	76.95
AV-3	222	177.91	104.86
AV-1 – Baseline	261	2.52	54.45
AV-3 – Baseline	216	11.35	79.87
Total Cholesterol (mg/dl)			
Baseline	304	217.42	34.74
AV-1	268	211.75	35.63
AV-3	222	212.96	35.07
AV-1 – Baseline	261	-4.50	25.14
AV-3 – Baseline	216	-4.80	29.44
LDL-C (mg/dl)			
Baseline	299	130.02	32.07
AV-1	263	124.25	33.22
AV-3	214	123.62	32.10
AV-1 – Baseline	254	-5.89	22.66
AV-3 – Baseline	205	-6.30	26.80
HDL-C (mg/dl)			
Baseline	304	55.16	13.69
AV-1	268	55.39	12.67
AV-3	222	55.46	14.16
AV-1 – Baseline	261	1.38	7.92
AV-3 – Baseline	216	0.53	8.87
HDL-2 (mg/dl)			
Baseline	299	16.27	6.53
AV-1	265	16.84	6.84
AV-3	220	15.25	5.64
AV-1 – Baseline	256	0.79	4.83
AV-3 – Baseline	210	-1.02	5.30
HDL-3 (mg/dl)			
Baseline	299	38.53	8.03
AV-1	265	38.54	7.60
AV-3	220	40.10	9.05
AV-1 – Baseline	256	0.67	5.16
AV-3 – Baseline	210	1.50	6.25
Lp(a) (mg/dl)			
Baseline	303	20.75	22.48
AV-1	264	19.30	19.99
AV-3	216	17.76	19.56
AV-1 – Baseline	257	-1.04	7.88
AV-3 – Baseline	210	-2.15	11.05

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	1327	0.08	0.08
AV-1	1255	0.08	0.07
AV-3	1113	0.07	0.07
AV-1 – Baseline	1212	0.00	0.06
AV-3 – Baseline	1073	-0.01	0.07
Beta-Carotene (µg/ml)			
Baseline	1327	0.29	0.26
AV-1	1255	0.30	0.27
AV-3	1113	0.28	0.26
AV-1 – Baseline	1212	0.01	0.21
AV-3 – Baseline	1073	0.00	0.25
Alpha-tocopherol (µg/ml)			
Baseline	1327	16.46	7.23
AV-1	1255	17.16	7.43
AV-3	1113	18.48	7.61
AV-1 – Baseline	1212	0.79	5.50
AV-3 – Baseline	1073	2.09	6.68
Gamma-tocopherol (µg/ml)			
Baseline	1327	2.19	1.43
AV-1	1254	1.82	1.31
AV-3	1113	1.64	1.32
AV-1 – Baseline	1211	-0.39	0.93
AV-3 – Baseline	1073	-0.58	1.15
Beta-Cryptoxanthine (µg/ml)			
Baseline	1327	0.08	0.06
AV-1	1254	0.09	0.07
AV-3	1113	0.09	0.07
AV-1 – Baseline	1211	0.00	0.05
AV-3 – Baseline	1073	0.01	0.06
Lycopene (µg/ml)			
Baseline	1327	0.41	0.19
AV-1	1255	0.41	0.19
AV-3	1113	0.39	0.20
AV-1 – Baseline	1212	-0.01	0.16
AV-3 – Baseline	1073	-0.03	0.20
Lutein and Zeaxanthin (µg/ml)			
Baseline	1327	0.21	0.10
AV-1	1255	0.21	0.10
AV-3	1113	0.19	0.10
AV-1 – Baseline	1212	0.00	0.07
AV-3 – Baseline	1073	-0.02	0.08
Retinol (µg/ml)			
Baseline	1327	0.63	0.15
AV-1	1255	0.63	0.15
AV-3	1113	0.62	0.15
AV-1 – Baseline	1212	0.00	0.10
AV-3 – Baseline	1073	-0.01	0.13

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	1285	133.03	32.74
AV-1	1199	132.97	32.99
AV-3	1055	133.94	33.48
AV-1 – Baseline	1139	-0.47	22.67
AV-3 – Baseline	986	0.31	28.46
Factor VII C (%) ¹			
Baseline	1267	131.72	30.77
AV-1	1191	129.05	30.81
AV-3	1051	132.63	34.30
AV-1 – Baseline	1113	-3.18	22.90
AV-3 – Baseline	967	0.57	28.55
Fibrinogen (mg/dl)			
Baseline	1277	297.02	59.14
AV-1	1193	294.43	58.41
AV-3	1056	286.92	57.44
AV-1 – Baseline	1127	-2.46	49.42
AV-3 – Baseline	980	-9.98	52.33
Hormones/Other			
Glucose (mg/dl)			
Baseline	1326	99.21	24.82
AV-1	1251	97.36	23.57
AV-3	1120	97.99	24.79
AV-1 – Baseline	1209	-1.79	17.66
AV-3 – Baseline	1080	-1.35	19.99
Insulin (μIU/ml)			
Baseline	1289	11.31	6.90
AV-1	1209	10.90	10.28
AV-3	1072	12.37	8.61
AV-1 – Baseline	1146	-0.32	8.94
AV-3 – Baseline	1003	1.11	7.53

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: White Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	1329	161.16	88.95
AV-1	1255	163.56	89.10
AV-3	1120	163.10	84.58
AV-1 – Baseline	1214	2.93	56.73
AV-3 – Baseline	1081	1.35	69.94
Total Cholesterol (mg/dl)			
Baseline	1329	225.13	37.82
AV-1	1255	217.95	36.96
AV-3	1120	216.56	35.07
AV-1 – Baseline	1214	-7.11	26.89
AV-3 – Baseline	1081	-8.39	32.53
LDL-C (mg/dl)			
Baseline	1296	133.76	34.74
AV-1	1225	125.95	33.38
AV-3	1102	125.55	33.29
AV-1 – Baseline	1173	-7.27	23.73
AV-3 – Baseline	1044	-7.51	29.51
HDL-C (mg/dl)			
Baseline	1322	59.37	15.86
AV-1	1253	59.41	15.46
AV-3	1120	59.06	15.93
AV-1 – Baseline	1207	-0.33	8.91
AV-3 – Baseline	1076	-0.50	10.13
HDL-2 (mg/dl)			
Baseline	1285	18.40	8.27
AV-1	1225	18.86	8.40
AV-3	1103	16.54	6.82
AV-1 – Baseline	1149	0.20	4.97
AV-3 – Baseline	1033	-1.93	5.69
HDL-3 (mg/dl)			
Baseline	1286	41.11	9.18
AV-1	1226	40.60	8.70
AV-3	1103	42.36	9.88
AV-1 – Baseline	1151	-0.68	5.61
AV-3 – Baseline	1034	1.33	7.07
Lp(a) (mg/dl)			
Baseline	1309	24.94	25.94
AV-1	1234	24.15	25.81
AV-3	1086	21.97	23.08
AV-1 – Baseline	1179	-0.68	10.00
AV-3 – Baseline	1038	-2.66	12.82

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Unknown Women

Data as of: August 31, 2002

	N	Mean	S.D.
Micronutrients			
Alpha-Carotene (µg/ml)			
Baseline	54	0.08	0.08
AV-1	48	0.08	0.08
AV-3	38	0.08	0.09
AV-1 – Baseline	48	0.00	0.06
AV-3 – Baseline	37	0.00	0.06
Beta-Carotene (µg/ml)			
Baseline	54	0.27	0.22
AV-1	48	0.27	0.21
AV-3	38	0.29	0.26
AV-1 – Baseline	48	0.01	0.13
AV-3 – Baseline	37	0.04	0.24
Alpha-tocopherol (µg/ml)			
Baseline	54	17.31	9.14
AV-1	48	17.12	9.40
AV-3	38	17.84	8.97
AV-1 – Baseline	48	-0.32	6.54
AV-3 – Baseline	37	0.17	6.12
Gamma-tocopherol (µg/ml)			
Baseline	54	2.14	1.16
AV-1	48	2.01	1.05
AV-3	38	2.08	1.39
AV-1 – Baseline	48	-0.11	0.76
AV-3 – Baseline	37	0.03	0.91
Beta-Cryptoxanthine (µg/ml)			
Baseline	54	0.11	0.11
AV-1	48	0.10	0.06
AV-3	38	0.10	0.08
AV-1 – Baseline	48	-0.01	0.08
AV-3 – Baseline	37	0.00	0.07
Lycopene (µg/ml)			
Baseline	54	0.41	0.20
AV-1	48	0.40	0.20
AV-3	38	0.33	0.16
AV-1 – Baseline	48	-0.01	0.18
AV-3 – Baseline	37	-0.06	0.19
Lutein and Zeaxanthin (µg/ml)			
Baseline	54	0.22	0.12
AV-1	48	0.23	0.16
AV-3	38	0.22	0.11
AV-1 – Baseline	48	0.01	0.10
AV-3 – Baseline	37	-0.01	0.08
Retinol (µg/ml)			
Baseline	54	0.60	0.19
AV-1	48	0.59	0.15
AV-3	38	0.59	0.11
AV-1 – Baseline	48	0.00	0.11
AV-3 – Baseline	37	0.00	0.14

(continues)

Table 3.9 (continued)
Blood Specimen Analysis: Unknown Women

Data as of: August 31, 2002

	N	Mean	S.D.
Clotting Factors			
Factor VII Activity, Antigen (%)			
Baseline	54	122.80	29.36
AV-1	46	117.07	27.58
AV-3	35	127.14	29.11
AV-1 – Baseline	46	-2.28	24.54
AV-3 – Baseline	34	1.71	39.35
Factor VII C (%) ¹			
Baseline	54	124.19	29.15
AV-1	45	120.33	24.54
AV-3	35	126.20	30.24
AV-1 – Baseline	45	0.24	21.75
AV-3 – Baseline	34	1.47	36.76
Fibrinogen (mg/dl)			
Baseline	54	303.07	65.04
AV-1	46	299.48	64.12
AV-3	35	277.51	55.42
AV-1 – Baseline	46	-8.85	39.70
AV-3 – Baseline	34	-22.29	39.13
Hormones/Other			
Glucose (mg/dl)			
Baseline	54	98.13	24.54
AV-1	48	100.52	25.50
AV-3	38	105.21	35.68
AV-1 – Baseline	48	0.63	11.85
AV-3 – Baseline	37	7.62	29.80
Insulin (μIU/ml)			
Baseline	54	10.05	5.84
AV-1	48	10.77	5.60
AV-3	37	12.60	6.78
AV-1 – Baseline	48	0.44	3.29
AV-3 – Baseline	36	3.19	4.98

(continues)

¹ Factor VII C values greater than 300% are considered biologically implausible and are set to missing.

Table 3.9 (continued)
Blood Specimen Analysis: Unknown Women

Data as of: August 31, 2002

	N	Mean	S.D.
Lipoproteins			
Triglyceride (mg/dl)			
Baseline	53	164.81	100.03
AV-1	47	156.70	77.06
AV-3	38	163.24	72.13
AV-1 – Baseline	47	-5.06	60.23
AV-3 – Baseline	37	-2.05	67.13
Total Cholesterol (mg/dl)			
Baseline	53	227.85	36.95
AV-1	47	228.19	34.97
AV-3	38	223.03	34.50
AV-1 – Baseline	47	-2.96	26.93
AV-3 – Baseline	37	-2.65	31.98
LDL-C (mg/dl)			
Baseline	51	135.41	35.38
AV-1	47	135.53	34.62
AV-3	38	129.97	33.15
AV-1 – Baseline	45	-1.62	24.69
AV-3 – Baseline	36	-2.83	31.09
HDL-C (mg/dl)			
Baseline	53	59.77	16.73
AV-1	47	61.23	15.74
AV-3	38	60.34	17.70
AV-1 – Baseline	47	0.81	9.88
AV-3 – Baseline	37	0.19	9.79
HDL-2 (mg/dl)			
Baseline	53	19.72	10.47
AV-1	47	20.62	10.35
AV-3	38	17.97	7.99
AV-1 – Baseline	47	0.38	6.46
AV-3 – Baseline	37	-2.16	7.02
HDL-3 (mg/dl)			
Baseline	53	40.06	7.72
AV-1	47	40.62	7.03
AV-3	38	42.37	10.51
AV-1 – Baseline	47	0.43	6.08
AV-3 – Baseline	37	2.35	6.72
Lp(a) (mg/dl)			
Baseline	54	23.89	29.23
AV-1	46	21.20	20.78
AV-3	37	21.03	20.21
AV-1 – Baseline	46	-0.57	9.08
AV-3 – Baseline	36	-3.78	29.11

Table 3.10
Bone Mineral Density¹ Analysis: DM Participants

Data as of: August 31, 2002

	N	Mean	S.D.
Whole Body Scan			
Baseline	3594	1.03	0.11
AV1	3261	1.03	0.11
AV3	3077	1.04	0.11
AV6	2286	1.05	0.12
AV1 % Change from baseline BMD ²	3220	0.17	2.49
AV3 % Change from baseline BMD ³	3038	1.27	3.58
AV6 % Change from baseline BMD ⁴	2253	2.34	5.30
Spine Scan			
Baseline	3515	0.99	0.17
AV1	3182	1.00	0.17
AV3	3006	1.01	0.17
AV6	2233	1.02	0.18
AV1 % Change from baseline BMD ²	3157	0.73	3.83
AV3 % Change from baseline BMD ³	2982	2.12	5.20
AV6 % Change from baseline BMD ⁴	2216	3.48	6.75
Hip Scan			
Baseline	3620	0.87	0.14
AV1	3275	0.87	0.14
AV3	3099	0.88	0.14
AV6	2329	0.88	0.14
AV1 % Change from baseline BMD ²	3254	-0.04	2.76
AV3 % Change from baseline BMD ³	3071	0.98	4.17
AV6 % Change from baseline BMD ⁴	2303	0.74	5.21

¹ Measured in (g/cm²).

² AV1 % Change from baseline BMD is defined as ((AV1-Baseline)/Baseline)x100.

³ AV3 % Change from baseline BMD is defined as ((AV3-Baseline)/Baseline)x100.

⁴ AV6 % Change from baseline BMD is defined as ((AV6-Baseline)/Baseline)x100.

Table 3.11
Bone Mineral Density¹ Analysis: DM Participants by Race/Ethnicity

Data as of: August 31, 2002

	Black/African American			Hispanic/Latino			White		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Whole Body Scan									
Baseline	581	1.07	0.11	195	1.05	0.11	2761	1.01	0.10
AV1	512	1.08	0.11	152	1.05	0.11	2554	1.01	0.10
AV3	495	1.10	0.12	152	1.05	0.12	2388	1.02	0.11
AV6	332	1.08	0.12	144	1.10	0.14	1769	1.05	0.12
AV1 % Change from baseline BMD ²	506	0.98	2.96	151	-0.33	2.24	2521	0.04	2.36
AV3 % Change from baseline BMD ³	490	1.97	2.89	151	0.65	4.45	2356	1.16	3.63
AV6 % Change from baseline BMD ⁴	329	0.48	3.16	144	4.57	7.51	1740	2.49	5.31
Spine Scan									
Baseline	575	1.07	0.18	190	0.98	0.16	2693	0.97	0.16
AV1	506	1.08	0.18	148	0.98	0.16	2485	0.98	0.16
AV3	491	1.09	0.19	148	0.96	0.15	2325	0.99	0.17
AV6	314	1.09	0.19	141	0.98	0.15	1737	1.01	0.17
AV1 % Change from baseline BMD ²	500	0.79	4.31	147	0.15	4.36	2468	0.74	3.67
AV3 % Change from baseline BMD ³	486	2.09	5.14	147	0.09	5.90	2308	2.28	5.14
AV6 % Change from baseline BMD ⁴	311	2.62	6.83	141	1.04	6.86	1724	3.83	6.68
Hip Scan									
Baseline	584	0.97	0.15	195	0.88	0.14	2784	0.85	0.13
AV1	514	0.98	0.15	152	0.88	0.14	2566	0.85	0.13
AV3	497	0.99	0.15	152	0.88	0.15	2408	0.86	0.13
AV6	340	0.96	0.15	145	0.89	0.14	1803	0.87	0.13
AV1 % Change from baseline BMD ²	510	0.84	2.86	151	-0.62	2.94	2551	-0.18	2.66
AV3 % Change from baseline BMD ³	493	1.40	3.82	150	0.80	5.76	2387	0.91	4.10
AV6 % Change from baseline BMD ⁴	337	-1.05	4.87	143	2.09	6.02	1783	0.95	5.10

¹ Measured in (g/cm²).

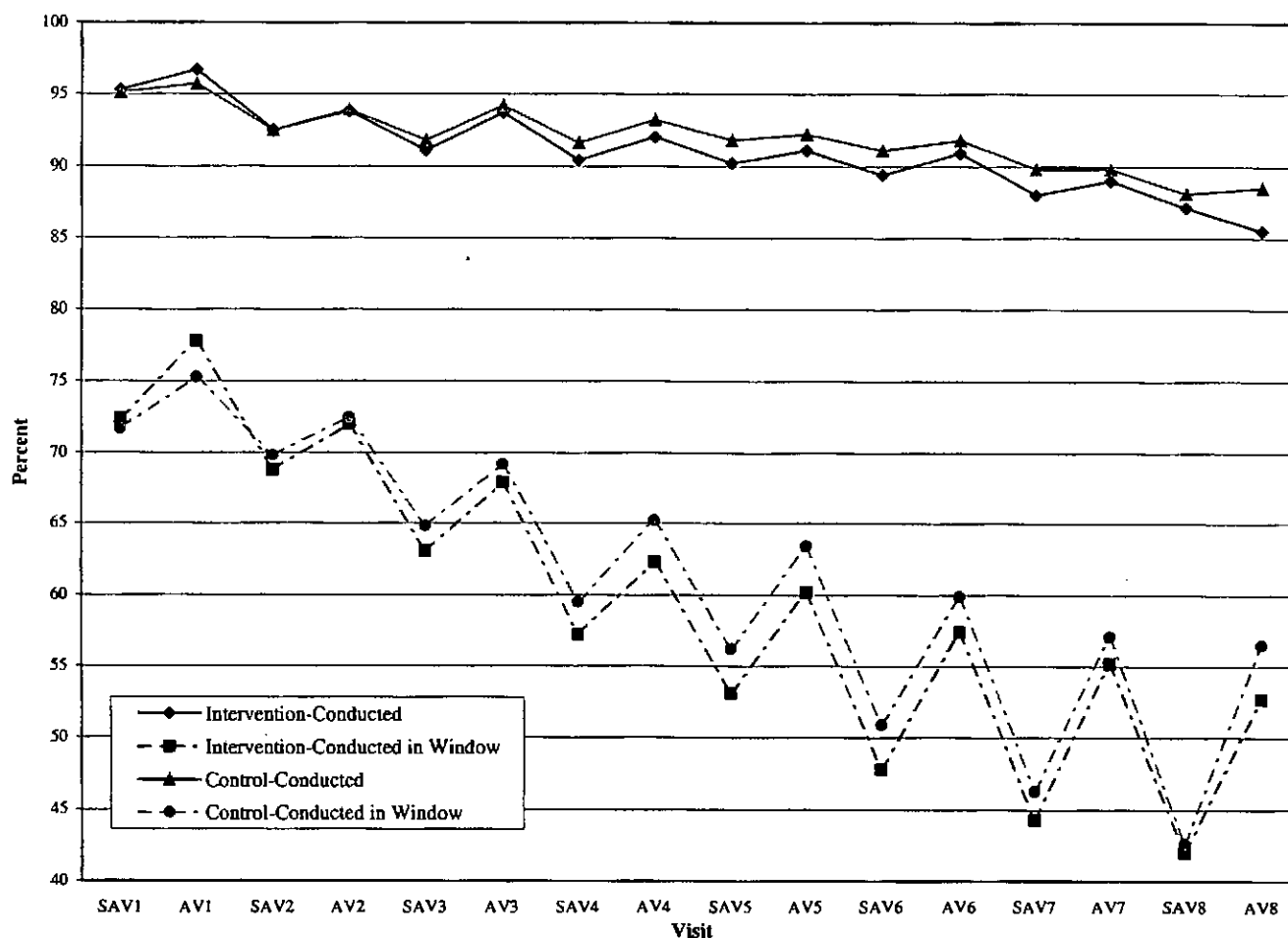
² AV1 % Change from baseline BMD is defined as ((AV1-Baseline)/Baseline)x100.

³ AV3 % Change from baseline BMD is defined as ((AV3-Baseline)/Baseline)x100.

⁴ AV6 % Change from baseline BMD is defined as ((AV6-Baseline)/Baseline)x100.

Table 3.12
Adherence to Follow-up Contacts

Data as of: August 31, 2002



Contact		Due N	Conducted N	%	Conducted in Window N	%
Semi-Annual Contact 3	Intervention	19541	17801	91.1	12306	63.0
	Control	29294	26878	91.8	18989	64.8
Annual Visit 3	Intervention	19541	18314	93.7	13262	67.9
	Control	29294	27598	94.2	20262	69.2
Semi-Annual Contact 4	Intervention	19541	17673	90.4	11170	57.2
	Control	29294	26836	91.6	17430	59.5
Annual Visit 4	Intervention	19538	17972	92.0	12166	62.3
	Control	29289	27284	93.2	19108	65.2
Semi-Annual Contact 5	Intervention	18099	16321	90.2	9614	53.1
	Control	27154	24928	91.8	15266	56.2
Annual Visit 5	Intervention	15678	14285	91.1	9442	60.2
	Control	23494	21663	92.2	14898	63.4
Semi-Annual Visit 6	Intervention	12708	11361	89.4	6073	47.8
	Control	19045	17359	91.1	9689	50.9
Annual Visit 6	Intervention	9530	8662	90.9	5472	57.4
	Control	14314	13144	91.8	8579	59.9
Semi-Annual Visit 7	Intervention	6659	5857	88.0	2948	44.3
	Control	9951	8937	89.8	4611	46.3
Annual Visit 7	Intervention	4372	3891	89.0	2413	55.2
	Control	6531	5864	89.8	3730	57.1
Semi-Annual Visit 8	Intervention	2690	2342	87.1	1129	42.0
	Control	4017	3539	88.1	1710	42.6
Annual Visit 8	Intervention	1322	1130	85.5	697	52.7
	Control	1998	1768	88.5	1128	56.5

Table 3.13
Lost-to-Follow-up and Vital Status: DM Participants

Data as of: August 31, 2002

Vital Status/Participation	DM Participants (N = 48,835)	
	N	%
Deceased	1282	2.6
Alive: Current Participation ¹	44857	91.9
Alive: Recent Participation ²	838	1.7
Alive: Past/Unknown Participation ³	40	0.1
Stopped Follow-Up ⁴	1076	2.2
Lost to Follow-Up ⁵	742	1.5

¹ Participants who have filled in a Form 33 within the last 9 months.

² Participants who last filled in a Form 33 between 9 and 18 months ago.

³ Participants without a Form 33 within the last 18 months, who have been located (as indicated on Form 23) within the last 6 months.

⁴ Participants with codes 5 (no follow-up) or 8 (absolutely no follow-up) on Form 7.

⁵ Participants not in any of the above categories.

Table 3.14
Locally Verified Outcomes (Annualized Percentages) by Age for Dietary Modification

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	48835	6961	11043	22713	8118
Mean follow-up (months)	67.8	74.1	70.1	65.7	65.0
Cancer					
Breast cancer ¹	1385 (0.50%)	153 (0.36%)	315 (0.49%)	669 (0.54%)	248 (0.56%)
Invasive breast cancer	1105 (0.40%)	108 (0.25%)	255 (0.40%)	542 (0.44%)	200 (0.45%)
Non-invasive breast cancer	286 (0.10%)	45 (0.10%)	61 (0.09%)	131 (0.11%)	49 (0.11%)
Ovarian cancer	129 (0.05%)	18 (0.04%)	24 (0.04%)	55 (0.04%)	32 (0.07%)
Endometrial cancer ²	184 (0.12%)	22 (0.09%)	42 (0.11%)	83 (0.12%)	37 (0.15%)
Colorectal cancer	347 (0.13%)	21 (0.05%)	54 (0.08%)	180 (0.14%)	92 (0.21%)
Other cancer ³	1279 (0.46%)	116 (0.27%)	202 (0.31%)	637 (0.51%)	324 (0.74%)
Total cancer	3234 (1.17%)	323 (0.75%)	615 (0.95%)	1583 (1.27%)	713 (1.62%)
Cardiovascular					
CHD ⁴	821 (0.30%)	45 (0.10%)	97 (0.15%)	385 (0.31%)	294 (0.67%)
CHD death ⁵	168 (0.06%)	7 (0.02%)	17 (0.03%)	74 (0.06%)	70 (0.16%)
Total MI ⁶	713 (0.26%)	39 (0.09%)	85 (0.13%)	339 (0.27%)	250 (0.57%)
Clinical MI	679 (0.25%)	32 (0.07%)	81 (0.13%)	324 (0.26%)	242 (0.55%)
Evolving Q-wave MI ⁷	36 (0.01%)	7 (0.02%)	4 (0.01%)	17 (0.01%)	8 (0.02%)
Possible evolving Q-wave MI ⁷	136 (0.05%)	19 (0.04%)	21 (0.03%)	62 (0.05%)	34 (0.08%)
Angina	1094 (0.40%)	62 (0.14%)	144 (0.22%)	572 (0.46%)	316 (0.72%)
CABG/PTCA	1117 (0.40%)	45 (0.10%)	140 (0.22%)	583 (0.47%)	349 (0.79%)
Carotid artery disease	168 (0.06%)	4 (0.01%)	20 (0.03%)	84 (0.07%)	60 (0.14%)
Congestive heart failure	633 (0.23%)	28 (0.07%)	68 (0.11%)	287 (0.23%)	250 (0.57%)
Stroke	630 (0.23%)	30 (0.07%)	55 (0.09%)	293 (0.24%)	252 (0.57%)
PVD	153 (0.06%)	6 (0.01%)	18 (0.03%)	73 (0.06%)	56 (0.13%)
CHD ⁴ /Possible evolving Q-wave MI	953 (0.35%)	64 (0.15%)	118 (0.18%)	443 (0.36%)	328 (0.75%)
Coronary disease ⁸	2434 (0.88%)	140 (0.33%)	306 (0.47%)	1212 (0.97%)	776 (1.76%)
Total cardiovascular disease	3198 (1.16%)	174 (0.40%)	378 (0.59%)	1594 (1.28%)	1052 (2.39%)
Fractures					
Hip fracture	251 (0.09%)	8 (0.02%)	19 (0.03%)	105 (0.08%)	119 (0.27%)
Vertebral fracture	298 (0.11%)	12 (0.03%)	33 (0.05%)	127 (0.10%)	126 (0.29%)
Other fracture ³	3574 (1.30%)	454 (1.06%)	717 (1.11%)	1664 (1.34%)	739 (1.68%)
Total fracture	3991 (1.45%)	470 (1.09%)	761 (1.18%)	1841 (1.48%)	919 (2.09%)
Deaths					
Cardiovascular deaths	352 (0.13%)	14 (0.03%)	27 (0.04%)	154 (0.12%)	157 (0.36%)
Cancer deaths	579 (0.21%)	36 (0.08%)	68 (0.11%)	287 (0.23%)	188 (0.43%)
Other known cause	192 (0.07%)	13 (0.03%)	21 (0.03%)	82 (0.07%)	76 (0.17%)
Unknown cause	53 (0.02%)	3 (0.01%)	8 (0.01%)	29 (0.02%)	13 (0.03%)
Not yet adjudicated	106 (0.04%)	5 (0.01%)	14 (0.02%)	51 (0.04%)	36 (0.08%)
Total death	1282 (0.46%)	71 (0.17%)	138 (0.21%)	603 (0.48%)	470 (1.07%)

¹ Excludes five cases with borderline malignancy.

² Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

³ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

⁴ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

⁵ "CHD death" includes definite and possible CHD death.

⁶ "Total MI" includes clinical MI and evolving Q-wave MI.

⁷ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁸ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

Table 3.14 (continued)
Locally Verified Outcomes (Annualized Percentages) by Race/Ethnicity for Dietary Modification

Data as of: August 31, 2002

Outcome	Race/Ethnicity					
	American Indian/Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/Latino	White	Unknown
Number randomized	202	1105	5262	1845	39762	659
Mean follow-up (months)	66.3	64.2	66.0	63.6	68.4	63.7
Cancer						
Breast cancer ¹	2 (0.18%)	31 (0.52%)	89 (0.31%)	35 (0.36%)	1211 (0.53%)	17 (0.49%)
Invasive breast cancer	2 (0.18%)	23 (0.39%)	67 (0.23%)	29 (0.30%)	971 (0.43%)	13 (0.37%)
Non-invasive breast cancer	0 (0.00%)	8 (0.14%)	23 (0.08%)	6 (0.06%)	245 (0.11%)	4 (0.11%)
Ovarian cancer	1 (0.09%)	2 (0.03%)	12 (0.04%)	2 (0.02%)	109 (0.05%)	3 (0.09%)
Endometrial cancer ²	0 (0.00%)	1 (0.03%)	11 (0.08%)	7 (0.13%)	162 (0.12%)	3 (0.15%)
Colorectal cancer	4 (0.36%)	5 (0.08%)	40 (0.14%)	14 (0.14%)	278 (0.12%)	6 (0.17%)
Other cancer ³	4 (0.36%)	18 (0.30%)	96 (0.33%)	27 (0.28%)	1118 (0.49%)	16 (0.46%)
Total cancer	11 (0.99%)	57 (0.96%)	241 (0.83%)	81 (0.83%)	2803 (1.24%)	41 (1.17%)
Cardiovascular						
CHD ⁴	1 (0.09%)	8 (0.14%)	78 (0.27%)	14 (0.14%)	713 (0.31%)	7 (0.20%)
CHD death ⁵	0 (0.00%)	1 (0.02%)	20 (0.07%)	1 (0.01%)	144 (0.06%)	2 (0.06%)
Total MI ⁶	1 (0.09%)	8 (0.14%)	68 (0.23%)	14 (0.14%)	615 (0.27%)	7 (0.20%)
Clinical MI	1 (0.09%)	7 (0.12%)	64 (0.22%)	14 (0.14%)	587 (0.26%)	6 (0.17%)
Evolving Q-wave MI ⁷	0 (0.00%)	1 (0.02%)	4 (0.01%)	0 (0.00%)	30 (0.01%)	1 (0.03%)
Possible evolving Q-wave MI ⁷	2 (0.18%)	3 (0.05%)	20 (0.07%)	3 (0.03%)	107 (0.05%)	1 (0.03%)
Angina	2 (0.18%)	13 (0.22%)	150 (0.52%)	30 (0.31%)	882 (0.39%)	17 (0.49%)
CABG/PTCA	1 (0.09%)	9 (0.15%)	108 (0.37%)	22 (0.22%)	967 (0.43%)	10 (0.29%)
Carotid artery disease	2 (0.18%)	1 (0.02%)	15 (0.05%)	1 (0.01%)	147 (0.06%)	2 (0.06%)
Congestive heart failure	0 (0.00%)	3 (0.05%)	118 (0.41%)	14 (0.14%)	488 (0.22%)	10 (0.29%)
Stroke	3 (0.27%)	14 (0.24%)	75 (0.26%)	14 (0.14%)	514 (0.23%)	10 (0.29%)
PVD	1 (0.09%)	1 (0.02%)	29 (0.10%)	1 (0.01%)	118 (0.05%)	3 (0.09%)
CHD ⁴ /Possible evolving Q-wave MI	3 (0.27%)	11 (0.19%)	98 (0.34%)	17 (0.17%)	816 (0.36%)	8 (0.23%)
Coronary disease ⁸	5 (0.45%)	25 (0.42%)	330 (1.14%)	59 (0.60%)	1983 (0.88%)	32 (0.92%)
Total cardiovascular disease	11 (0.99%)	40 (0.68%)	418 (1.44%)	73 (0.75%)	2612 (1.15%)	44 (1.26%)
Fractures						
Hip fracture	0 (0.00%)	1 (0.02%)	7 (0.02%)	4 (0.04%)	236 (0.10%)	3 (0.09%)
Vertebral fracture	0 (0.00%)	7 (0.12%)	3 (0.01%)	6 (0.06%)	279 (0.12%)	3 (0.09%)
Other fracture ³	14 (1.25%)	53 (0.90%)	201 (0.69%)	86 (0.88%)	3181 (1.40%)	39 (1.12%)
Total fracture	14 (1.25%)	60 (1.01%)	209 (0.72%)	94 (0.96%)	3569 (1.58%)	45 (1.29%)
Deaths						
Cardiovascular deaths	1 (0.09%)	4 (0.07%)	48 (0.17%)	5 (0.05%)	290 (0.13%)	4 (0.11%)
Cancer deaths	1 (0.09%)	8 (0.14%)	52 (0.18%)	13 (0.13%)	496 (0.22%)	9 (0.26%)
Other known cause	5 (0.45%)	0 (0.00%)	28 (0.10%)	4 (0.04%)	153 (0.07%)	2 (0.06%)
Unknown cause	0 (0.00%)	0 (0.00%)	7 (0.02%)	1 (0.01%)	45 (0.02%)	0 (0.00%)
Not yet adjudicated	1 (0.09%)	3 (0.05%)	12 (0.04%)	5 (0.05%)	85 (0.04%)	0 (0.00%)
Total death	8 (0.72%)	15 (0.25%)	147 (0.51%)	28 (0.29%)	1069 (0.47%)	15 (0.43%)

¹ Excludes five cases with borderline malignancy.

² Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

³ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

⁴ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

⁵ "CHD death" includes definite and possible CHD death.

⁶ "Total MI" includes clinical MI and evolving Q-wave MI.

⁷ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁸ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

Table 3.15
Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Race/Ethnicity
for DM Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	48835	6961	11043	22713	8118
Mean follow-up (months)	67.8	74.1	70.1	65.7	65.0
Hospitalizations					
Ever	18750 (6.80%)	2001 (4.66%)	3507 (5.44%)	9106 (7.32%)	4136 (9.41%)
Two or more	8717 (3.16%)	784 (1.82%)	1465 (2.27%)	4228 (3.40%)	2240 (5.09%)
Other					
DVT ¹	365 (0.14%)	22 (0.05%)	58 (0.09%)	168 (0.14%)	117 (0.28%)
Pulmonary embolism	226 (0.08%)	11 (0.03%)	40 (0.06%)	113 (0.09%)	62 (0.14%)
Diabetes (treated)	2438 (0.92%)	335 (0.80%)	555 (0.89%)	1129 (0.95%)	419 (1.01%)
Gallbladder disease ²	2777 (1.20%)	425 (1.11%)	659 (1.20%)	1297 (1.27%)	396 (1.12%)
Hysterectomy	1122 (0.72%)	166 (0.68%)	256 (0.65%)	530 (0.76%)	170 (0.71%)
Glaucoma	3567 (1.34%)	355 (0.84%)	712 (1.13%)	1745 (1.46%)	755 (1.86%)
Osteoporosis	7341 (2.82%)	735 (1.75%)	1336 (2.14%)	3670 (3.15%)	1600 (4.07%)
Osteoarthritis ³	6975 (4.14%)	998 (3.17%)	1594 (3.67%)	3236 (4.51%)	1147 (5.26%)
Rheumatoid arthritis	2023 (0.76%)	283 (0.68%)	460 (0.74%)	934 (0.78%)	346 (0.83%)
Intestinal polyps	5150 (2.01%)	620 (1.49%)	1132 (1.85%)	2570 (2.24%)	828 (2.11%)
Lupus	336 (0.12%)	55 (0.13%)	81 (0.13%)	159 (0.13%)	41 (0.09%)
Kidney stones ³	812 (0.37%)	108 (0.34%)	183 (0.37%)	389 (0.39%)	132 (0.38%)
Cataracts ³	10656 (5.41%)	634 (1.95%)	1730 (3.49%)	5942 (6.59%)	2350 (9.47%)
Pills for hypertension	8767 (4.55%)	1163 (3.36%)	1932 (3.97%)	4102 (4.92%)	1570 (6.02%)

Outcomes	Race/Ethnicity					
	Am Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	202	1105	5262	1845	39762	659
Mean follow-up (months)	66.3	64.2	66.0	63.6	68.4	63.7
Hospitalizations						
Ever	72 (6.45%)	268 (4.53%)	2012 (6.95%)	589 (6.02%)	15580 (6.88%)	229 (6.55%)
Two or more	41 (3.67%)	90 (1.52%)	955 (3.30%)	239 (2.44%)	7283 (3.21%)	109 (3.12%)
Other						
DVT ¹	0 (0.00%)	0 (0.00%)	32 (0.11%)	5 (0.05%)	322 (0.15%)	6 (0.18%)
Pulmonary embolism	2 (0.18%)	1 (0.02%)	19 (0.07%)	2 (0.02%)	198 (0.09%)	4 (0.12%)
Diabetes (treated)	15 (1.44%)	70 (1.25%)	463 (1.81%)	137 (1.49%)	1717 (0.78%)	36 (1.09%)
Gallbladder disease ²	10 (1.26%)	41 (0.77%)	218 (0.84%)	113 (1.53%)	2358 (1.25%)	37 (1.24%)
Hysterectomy	4 (0.75%)	23 (0.61%)	68 (0.53%)	34 (0.65%)	984 (0.74%)	9 (0.45%)
Glaucoma	17 (1.59%)	66 (1.16%)	510 (1.89%)	135 (1.42%)	2799 (1.28%)	40 (1.21%)
Osteoporosis	33 (3.11%)	182 (3.26%)	419 (1.50%)	271 (2.98%)	6339 (2.97%)	97 (3.00%)
Osteoarthritis ³	35 (5.48%)	154 (3.63%)	712 (4.14%)	293 (4.45%)	5679 (4.12%)	102 (4.80%)
Rheumatoid arthritis	17 (1.70%)	36 (0.63%)	372 (1.38%)	163 (1.75%)	1400 (0.64%)	35 (1.06%)
Intestinal polyps	28 (2.71%)	109 (2.01%)	566 (2.09%)	165 (1.77%)	4204 (2.00%)	78 (2.43%)
Lupus	3 (0.27%)	3 (0.05%)	51 (0.18%)	10 (0.10%)	265 (0.12%)	4 (0.12%)
Kidney stones ³	6 (0.71%)	14 (0.30%)	81 (0.36%)	39 (0.50%)	659 (0.37%)	13 (0.47%)
Cataracts ³	45 (5.84%)	211 (4.89%)	1032 (4.96%)	359 (4.81%)	8856 (5.49%)	153 (6.07%)
Pills for hypertension	33 (4.56%)	187 (4.73%)	947 (6.53%)	367 (5.04%)	7122 (4.34%)	111 (4.71%)

¹ Inpatient DVT only.

² "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

³ These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

4. CaD Component

4.1 Recruitment

Table 4.1 presents the final sample size for number of women randomized in the Calcium and Vitamin D component of the WHI Clinical Trial. A total of 36,282 women have been randomized which is 80.6% of the overall goal of 45,000. The age distribution of the CaD trial participants is somewhat younger than anticipated in the design assumptions for the trial. Seventeen percent of women randomized are aged 70-79 years compared with the design assumption of 25%.

4.2 Adherence

Table 4.2 presents rates of follow-up, stopping intervention and pill collection, and adherence to pill taking by visit schedule for all CaD participants. The adherence summary for all CaD participants, defined as those women known to be consuming 80% or more of the prescribed dose, has remained steady since the last report (see *Figure 4.1*) at 56%-64%. At AV-4, which is nearly complete, 96% of visits due have been conducted, 2% of women have stopped taking the CaD study medication, and 83% completed the pill collection procedure. AV-5 and AV-6 adherence have improved slightly over the most recent time interval (*Figure 4.1*). The adherence summary remains low primarily because about 20-37% of women on study medication take less than 80% of their CaD pills.

Table 4.3 summarizes interval and cumulative drop-out rates in comparison to the original design assumptions. The original power calculations for CaD assumed a 6% drop-out rate in year 1 and a 3% per year drop-out rate thereafter. An independent lost-to-follow-up rate of 3% per year was also incorporated, resulting in approximately 8.8% stopping intervention in year 1 and 5.9% in subsequent years. Drop-out rates in this report now account for re-starting CaD, which results in lower rates than seen in earlier reports. At every annual visit, the observed drop-out rates are lower than design assumptions. Interval drop-out rates at AV-3 and beyond range from 2.8-5.0%, which compares favorably to the 5.9% design assumption. At AV-4, the cumulative drop-out rate was 12.7% (design assumption was 19.2%). By AV-6 and AV-7, observed rates are below the design assumption by >10%.

Table 4.4 summarizes the frequency of reported reasons for stopping CaD. The majority of women stopping study supplements do so of their own accord. Only 7.9% have indicated that they were advised by their physician to discontinue these supplements. 809 women (9.1%) reported health problems or diseases, 2,260 women (25.4%) reported symptoms not known to be related to the intervention, and 501 women (5.6%) reported that the study conflicts with other health issues. "Other pill issues" was the most frequently reported intervention-related reason (11.1%) followed by not liking the randomized nature of the intervention (4.1%). Miscellaneous reasons grouped together as "other reasons not listed above" were reported by 22.1% of women. Four common reasons for stopping CaD are shown first by age, and then by race/ethnicity, in *Table 4.5*. No strong associations by race/ethnicity are present, though "being advised by one's health care provider not to participate" and "study conflicts with other health issues" were slightly more common among white women. These reasons were reported with similar frequency by women in the various age groups.

We also monitor the number of women who have begun alternative anti-osteoporosis therapies within the CaD trial. As of August 31, 2002, 2,030 (5.6%) women were taking alendronate, 265 (0.7%) were taking calcitonin, and 649 (1.8%) were taking raloxifene.

4.3 Bone Mineral Density

Table 4.6 presents the mean bone mineral density levels at AV-1, AV-3, and AV-6 and percent change in BMD during these intervals among women randomized at the three BMD measurement sites (Pittsburgh, Arizona, Birmingham). At the three skeletal sites examined (hip, spine, and whole body), BMD has increased between AV-1 and AV-3 from 1.3-1.6%, with the greatest change occurring at the spine. The percent changes between AV-6 and AV-1 were approximately 2 times as large as those observed at AV-3 for the spine and whole body but only slightly larger at the hip. *Table 4.7* presents the mean bone mineral density levels and percent change according to race/ethnicity. At AV-3 the rates of change relative to AV-1 were generally in the range of 1-2% gains for all skeletal sites.

4.4 Vital Status

Table 4.8 presents data on the vital status and the participation status of participants in the CaD trial. A detailed description of CCC and clinic activities to actively locate participants who do not complete their periodic visits is given in *Section 6 – Outcomes Processing*. For operational purposes, we define CT participants to have an “unknown” participation status if there is no outcomes information from the participant for 18 months and no other contacts for 6 months. Currently, 1.9% of the participants are lost-to-follow-up or have stopped follow-up, and 2.2% of the participants are known to be deceased. Virtually all of the remaining participants have completed a *Form 33 – Medical History Update* in the last 18 months. The design assumed that 3% per year would be lost-to-follow-up or death. Currently, the average follow-up for CaD participants is about 4.6 years, suggesting that approximately 13.1% could be expected to be dead or lost-to-follow-up. Our overall rates compare favorably to design assumptions.

4.5 Outcomes

Table 4.9 contains counts of the number of locally verified major WHI outcomes for CaD participants. In this table only outcomes that took place after randomization in the CaD trial are included. Approximately 4% of the self-reported outcomes have not yet been verified, so the numbers in this table should thus be seen as a lower bound to the actual number of outcomes that have taken place. Currently, with 165 cases of hip fracture locally verified, we have observed only about 35% of the number of hip fractures that were projected by the assumptions underlying the power calculations. The number of observed colorectal cancer cases (208 cases) is approximately 75%, the number of invasive breast cancer cases (661 cases) is approximately 110%, and the number of CHD cases is about 70% of what was expected (535 cases).

Table 4.10 contains counts of the number of self-reports for some outcomes that are not locally verified in WHI. As most of the self-reported outcomes are somewhat over reported (see *Section 6.3 – Outcomes Data Quality*), the number in this table should be taken as an upper bound to the number of events that have occurred in CaD participants.

4.6 Issues

During this period of follow-up, our focus remains primarily on maximizing adherence (if applicable) and retention in all components of the WHI Clinical Trial. Work continues on identifying and implementing strategies to improve adherence to CaD study medication. The CaD committee has overseen the development of a handbook, which is currently being printed for distribution at annual visits in the clinic. In addition, the CaD committee is organizing the development of brief articles on special CaD-relevant topics for publication in the WHI Matters newsletter.

A key issue during this last period was communicating with CaD participants about the E+P findings. When the E+P findings were published on July 9, 2002, CaD participants received the HRT update and a special letter informing them about the E+P findings and emphasizing that all other components of the WHI program are continuing as planned. Following publication of the E+P findings on July 9, 2002, a one-page update entitled "Your Important Role" was developed for mailing to CaD participants to encourage their continued participation.

Table 4.1
Calcium and Vitamin D Component Age – and Race/Ethnicity – Specific Recruitment

Data as of: August 31, 2002

	Total Randomized	% of Overall Goal	Distribution	Design Assumption
Age	36,282			
50-54	5157	118%	14%	10
55-59	8265	94%	23%	20
60-69	16520	84%	46%	45
70-79	6340	58%	17%	25
Race/Ethnicity	36,282			
American Indian	149		<1%	
Asian	721		2%	
Black	3315		9%	
Hispanic	1502		4%	
White	30155		83%	
Unknown	440		1%	

Table 4.2
CaD Adherence Summary
All CaD Participants

Data as of: August 31, 2002

	Due	Conducted		Conducted in Window		Stopped CaD		Missed Pill Collection		Total with Collections		Medication Rate ¹ <50%		Medication Rate ¹ 50%-80%		Medication Rate ¹ 80% +		Adherence Summary ²	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Semi-Annual Contact - 2	33047	32217	97	26177	79	1252	4	202	1	32824	99	5742	17	6712	20	20370	62		62
Annual Visit - 2	33047	32262	98	25858	78	1146	3	517	2	33069	98	5691	17	6235	19	21143	64		64
Annual Visit - 3	36243	35233	97	26515	73	873	2	543	2	32071	98	4684	15	5133	16	22254	69		62
Annual Visit - 4	36216	34690	96	24577	68	682	2	684	2	30046	98	3542	12	4382	15	22122	74		62
Annual Visit - 5	28784	27206	95	18736	65	523	2	739	3	22416	97	2423	11	2991	13	17002	76		60
Annual Visit - 6	16558	15553	94	10252	62	206	1	478	4	12181	96	1231	10	1594	13	9356	77		58
Annual Visit - 7	7297	6762	93	4362	60	97	1	257	5	5118	95	504	10	620	12	3994	78		56
Annual Visit - 8	1966	1793	91	1170	60	32	2	104	7	1322	93	114	9	146	11	1062	80		56

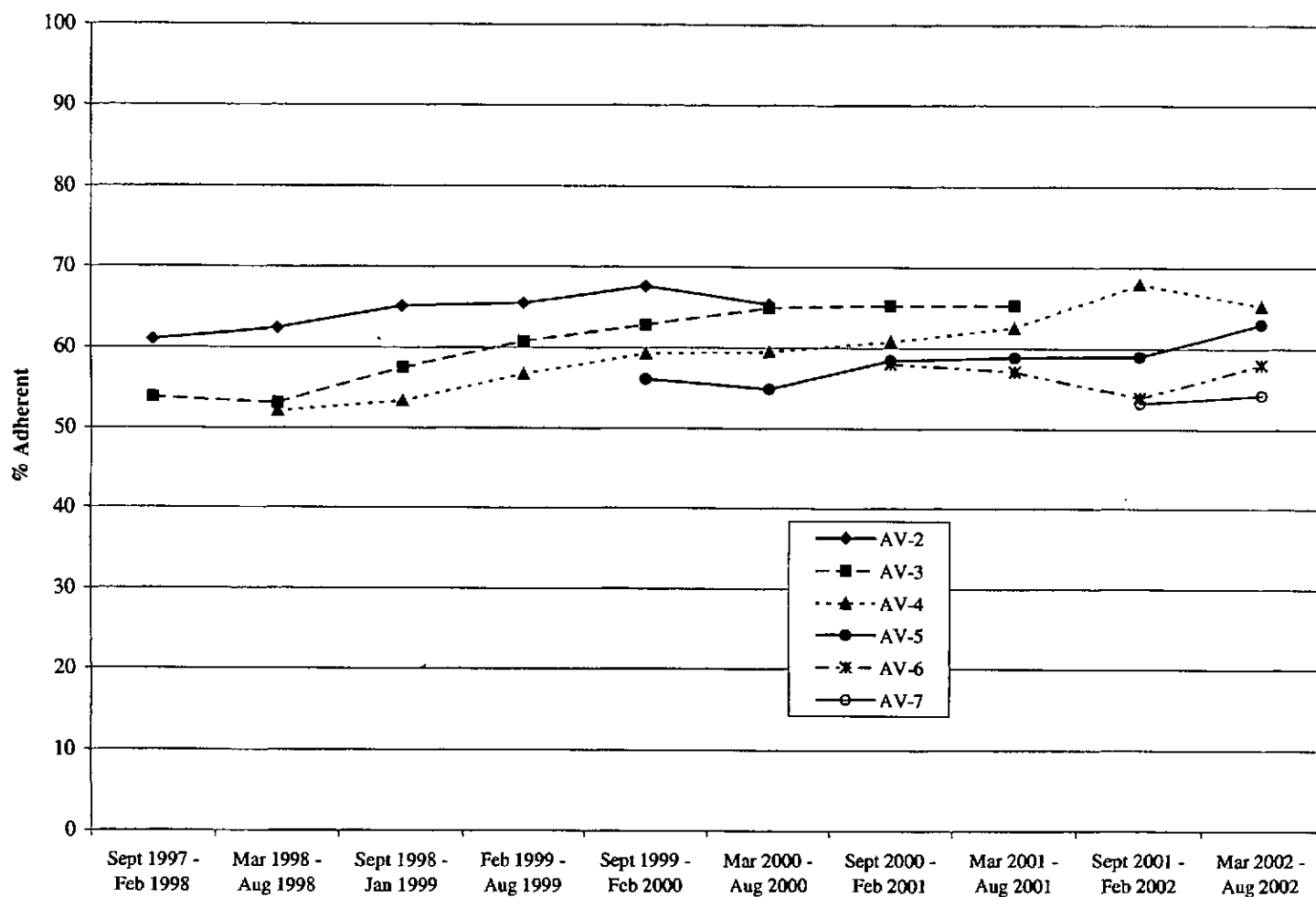
¹ Medication rate calculated as the number of pills taken divided by the number of days since bottle(s) were dispensed.

² Adherence summary calculated as the number of women consuming ≥80% of pills divided by the number due for a visit.

Note: Deceased women are excluded from all medication adherence calculations, but are included in the number "Due."

Figure 4.1
CaD Adherence Summary
% Participants Due for a Visit Who Took at Least 80% of Study Pills¹

Data as of: August 31, 2002



¹ Adherence calculations changed as of the September 2001 – February 2002 interval.

Table 4.3
CaD Drop-Out Rates by Follow-Up Time

Data as of: August 31, 2002

	Design		Observed			
	Int	Cum	Stopped ¹	Dead/ Lost ²	Int ³	Cum ⁴
Drop-Outs⁵						
AV-2	8.8	8.8	7.2	0.3	7.4	7.4
AV-3	5.9	14.2	2.4	0.6	3.0	10.2
AV-4	5.9	19.2	1.9	0.9	2.8	12.7
AV-5	5.9	24.0	1.8	1.3	3.1	15.4
AV-6	5.9	28.5	1.3	1.7	3.0	17.9
AV-7	5.9	32.7	1.4	2.2	3.6	20.8
AV-8	5.9	36.7	1.7	3.3	5.0	24.8

¹ Estimated rate of stopping CaD in the interval.

² Death or lost to follow-up rate in the interval.

³ Combined rate of stopping and death or lost to follow-up in the interval.

⁴ Estimated cumulative rate of stopping and death or lost to follow-up.

⁵ Drop-out rates derived from Form 7 by date. Cumulative rates calculated as life-table estimates.

Table 4.4
Reasons for Stopping CaD¹

Data as of: August 31, 2002

Reasons ²	(N = 8896)	
Personal/family		
Demands of work	194	2.2%
Family illness, emergency or other family demands ³	337	3.8%
Financial problems	14	0.2%
Lack of cooperation/support from family/friends ⁴	63	0.7%
Living in nursing home	30	0.3%
Issues of interest in study ⁵	292	3.3%
Travel		
Too far to CC	222	2.5%
Moved out of area or refuses to be followed at another CC	85	1.0%
Other travel issues ⁶	90	1.0%
Visits & Procedures		
Doesn't like visits, calls	81	0.9%
Doesn't like required forms or safety procedures ⁷	78	0.9%
Problems with other procedures ⁸	34	0.4%
Worried about health effects of medical tests/procedures	30	0.3%
Wants results of blood analyses	4	<0.1%
Wants results of bone mineral density	2	<0.1%
Problems with CC ⁹	54	0.6%

(continues)

¹ Does not include reasons reported by women who stopped and later restarted CaD.

² Multiple reasons may be reported for a woman.

³ Combines "Family illness, emergency or other family demands", "Death in the family or of a close friend", and "Caregiver responsibilities demanding time, effort, lifestyle changes".

⁴ Combines "Lack of cooperation/support from family and/or friends" and "Family/friends request that she withdraw".

⁵ Combines "Conflicting priorities other than work or family", "Feels discouraged regarding participation overall", "Loss of interest, boredom", "Feels it is not an important study", and "In another study in conflict with WHI intervention".

⁶ Combines "Transportation problems (other than distance)", "Traffic", "Parking at CC", and "CC neighborhood/safety".

⁷ Combines "Doesn't like filling out forms (other than those required for safety)", and "Doesn't like required safety forms and/or procedures".

⁸ Combines "Doesn't like mammograms", "Cost of mammograms", "Doesn't like having blood drawn", "Doesn't like ECG", "Doesn't like gynecologic procedures" and "Doesn't like other procedures (other than those required for safety)".

⁹ Combines "Problem with the CC", "Problem with CC staff person (other than DM Group Nutritionist)", and "Staff change/turnover".

Table 4.4 (continued)
Reasons for Stopping CaD¹

Data as of: August 31, 2002

Reasons ²	(N = 8896)	
Symptoms		
Bloating/gas	168	1.9%
Constipation	195	2.2%
Other gastrointestinal problems	230	2.6%
HRT Related Symptoms ³	42	0.5%
Other ⁴	2260	25.4%
Health Conditions		
Hypercalcemia	154	1.7%
Renal calculi	152	1.7%
Osteoporosis	66	0.7%
Other Diseases/Health Conditions ⁵	809	9.1%
Communication difficulties ⁶	78	0.9%
Intervention		
Doesn't like randomized nature of intervention	367	4.1%
Expected some benefit from intervention	56	0.6%
Feels guilty, unhappy, or like a failure for not meeting study goals of intervention	20	0.2%
Takes too many pills	265	3.0%
Other pill issues ⁷	985	11.1%
HRT Issues ⁸	129	1.5%
DM Issues ⁹	17	0.2%
Wants to take her own calcium	316	3.6%
Feels diet is already sufficient in calcium/Vit D	32	0.4%
Taking more than the max allowable IU of Vit D	34	0.4%
Taking Calcitrol	19	0.2%
Other Health Issues		
Worried about cost if adverse effects occur	8	0.1%
Expected more health care	23	0.3%
Advised not to participate by health care provider ¹⁰	706	7.9%
Study conflicts with other health issues ¹¹	501	5.6%
Other		
Other reasons not listed above	1964	22.1%
Refuses to give a reason	143	1.6%

¹ Does not include reasons reported by women who stopped and later restarted CaD.

² Multiple reasons may be reported for a woman.

³ Combines "Vaginal bleeding", "Breast tenderness", "Other breast changes", "Vaginal changes (e.g., dryness)", and "Hot flashes/night sweats".

⁴ Combines "Experiencing health problems or symptoms not due to intervention", "Reports other health problems or symptoms from the WHI intervention", "Reports health problems or symptoms from the WHI intervention", "Hair/skin changes", "Headaches", "Weight loss/gain", "Low energy/too tired", "Possible allergic reaction", and "Other symptoms not listed above".

⁵ Combines "Removed from intervention due to WHI symptom management", "Removed from intervention due to adverse health event", "Breast cancer", "Complex or atypical hyperplasia", "Endometrial cancer", "Deep vein thrombosis", "Pulmonary embolism", "Gallbladder disease", "Kidney failure/dialysis", "High triglycerides (> 1000 mg/dl)", "Malignant melanoma", "Meningioma", "Heart attack", "Stroke", "Arthritis", "Diabetes", "Depression", "Cholesterol (high or concern about levels)", and "Other health conditions not listed above".

⁶ Combines "Communication problem", "Loss of vision and/or hearing", and "Cognitive/memory changes".

⁷ Combines "Doesn't like taking pills", "Doesn't like taste of pills", and "Unable to swallow pills".

⁸ Combines "Has made a personal decision to go on active HRT", "Has made a personal decision that she does not want to be on HRT", "Advised to go on active HRT by health care provider", "Advised to not be on active HRT by health care provider", "Has made a personal decision to go on SERM (e.g., Evista/raloxifene, tamoxifen)", "Advised to go on SERM (e.g., Evista/raloxifene, tamoxifen) by health care provider", and "Taking testosterone medications".

⁹ Combines "Doesn't like DM requirements", "Problem with DM Group Nutritionist or group members", "Doesn't like DM eating pattern", "Doesn't like attending DM intervention classes", "Doesn't like self-monitoring", "Doesn't like budgeting fat grams", "Has concerns regarding long-term risks/benefits of low fat diet", "Unhappy that not losing weight", "Not in control of meal preparation", "Too difficult to meet or maintain dietary goals", "Doesn't like eating low fat diet", "Doesn't like eating 5 vegetables/fruits per day", "Doesn't like eating 6 grains per day", "Feels fat gram goal is unrealistic", and "Eating pattern conflicts with personal health beliefs".

¹⁰ Combines "Advised not to participate by health care provider" and "Advised not to participate by health care provider for other reason".

¹¹ Combines "Study conflicts with health care needs" and "Study conflicts with other health issues".

Table 4.5
Reasons for Stopping CaD by Age at Screening and Race/Ethnicity¹

Data as of August 31, 2002

	Age at Screening									
	All		50 - 54		55 - 59		60 - 69		70 - 79	
	N	% ²	N	% ²	N	% ²	N	% ²	N	% ²
		(N = 36,282)		(N = 5,157)		(N = 8,265)		(N = 16,520)		(N = 6,340)
Women Stopping CaD	8896	24.5%	1407	27.3%	1980	24.0%	3777	22.9%	1732	27.3%
REASONS FOR STOPPING³	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴	N	% ⁴
Doesn't like randomized nature of intervention	367	4.1%	59	4.2%	83	4.2%	164	4.3%	61	3.5%
Other pill issues ⁵	985	11.1%	155	11.0%	229	11.6%	420	11.1%	181	10.5%
Advised not to participate by health care provider ⁶	706	7.9%	74	5.3%	150	7.6%	331	8.8%	151	8.7%
Study conflicts with other health issues ⁷	501	5.6%	63	4.5%	96	4.8%	222	5.9%	120	6.9%

	Race/Ethnicity											
	American Indian/ Alaskan Native		Asian/Pacific Islander		Black/African American		Hispanic/Latino		White		Unknown	
	N	% ⁸	N	% ⁸	N	% ⁸	N	% ⁸	N	% ⁸	N	% ⁸
Women Stopping CaD	42	28.2%	174	24.1%	939	28.3%	434	28.9%	7184	23.8%	123	28.0%
REASONS FOR STOPPING ³	N	% ⁹	N	% ⁹	N	% ⁹	N	% ⁹	N	% ⁹	N	% ⁹
Doesn't like randomized nature of intervention	0	0.0%	3	1.7%	33	3.5%	9	2.1%	317	4.4%	5	4.1%
Other pill issues ⁵	6	14.3%	20	11.5%	96	10.2%	53	12.2%	800	11.1%	10	8.1%
Advised not to participate by health care provider ⁶	2	4.8%	6	3.4%	60	6.4%	31	7.1%	598	8.3%	9	7.3%
Study conflicts with other health issues ⁷	1	2.4%	6	3.4%	41	4.4%	18	4.1%	428	6.0%	7	5.7%

¹ Does not include reasons reported by women who stopped and later restarted CaD.

² Percentages are of CaD participants in the same age category.

³ Multiple reasons may be reported for a woman.

⁴ Percentages are of CaD participants in the same age category who stopped CaD. Multiple reasons may be reported for a woman.

Combines "Doesn't like taking pills" "Doesn't like taste of pills", and "Unable to swallow pills".

^d Combines "Advised not to participate by health care provider" and "Advised not to participate for other reason".

Combines "Study conflicts with health care needs" and "Study conflicts with other health issues":

^a Percentages are of CaD participants in the same race/ethnicity category. Combines Study conflicts with health care needs and Study conflicts

Percentages are of CaD participants in the same race/ethnicity category who stopped CaD.

Table 4.6
Bone Mineral Density¹ Analysis: CaD Participants

Data as of: August 31, 2002

	N	Mean	S.D.
Whole Body Scan			
AV1	2426	1.02	0.10
AV3	2263	1.03	0.11
AV6	1475	1.05	0.12
AV3 % Change from AV1 BMD ²	2190	1.42	3.36
AV6 % Change from AV1 BMD ³	1422	2.62	5.18
Spine Scan			
AV1	2350	0.99	0.16
AV3	2211	1.01	0.17
AV6	1447	1.02	0.17
AV3 % Change from AV1 BMD ²	2141	1.58	4.21
AV6 % Change from AV1 BMD ³	1396	3.07	5.88
Hip Scan			
AV1	2431	0.86	0.14
AV3	2285	0.88	0.14
AV6	1506	0.88	0.14
AV3 % Change from AV1 BMD ²	2211	1.28	3.55
AV6 % Change from AV1 BMD ³	1447	1.13	4.84

¹ Measured in (g/cm²).

² Percent Change from BMD is defined as ((AV3-AV1)/AV1)x100.

³ Percent Change from BMD is defined as ((AV6-AV1)/AV1)x100.

Table 4.7
Bone Mineral Density¹ Analysis: CaD Participants by Race/Ethnicity

Data as of: August 31, 2002

	Black/African American			Hispanic/Latino			White		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Whole Body Scan									
AV1	279	1.08	0.11	123	1.04	0.12	1986	1.01	0.10
AV3	265	1.10	0.12	116	1.05	0.12	1846	1.02	0.11
AV6	157	1.08	0.12	89	1.11	0.16	1202	1.04	0.12
AV3 % Change from AV1 BMD ²	261	1.21	3.02	104	2.20	4.36	1791	1.41	3.34
AV6 % Change from AV1 BMD ³	154	0.27	3.61	73	5.76	8.42	1171	2.74	4.96
Spine Scan									
AV1	274	1.07	0.18	120	0.98	0.17	1918	0.98	0.16
AV3	261	1.08	0.19	114	0.97	0.15	1800	1.00	0.17
AV6	146	1.09	0.18	88	1.00	0.16	1186	1.02	0.17
AV3 % Change from AV1 BMD ²	257	1.16	4.40	101	0.39	3.99	1749	1.75	4.17
AV6 % Change from AV1 BMD ³	143	1.98	6.13	72	1.84	5.89	1157	3.28	5.84
Hip Scan									
AV1	279	0.98	0.14	123	0.87	0.14	1991	0.85	0.13
AV3	265	0.99	0.15	116	0.88	0.13	1868	0.86	0.13
AV6	161	0.97	0.14	90	0.90	0.14	1228	0.86	0.13
AV3 % Change from AV1 BMD ²	261	0.82	3.18	103	1.68	4.67	1813	1.32	3.52
AV6 % Change from AV1 BMD ³	157	-1.10	4.29	73	3.38	5.27	1193	1.31	4.77

¹ Measured in (g/cm³).

² Percent Change from BMD is defined as ((AV3-AV1)/AV1)x100.

³ Percent Change from BMD is defined as ((AV6-AV1)/AV1)x100.

Table 4.8
Lost-to-Follow-up and Vital Status: CaD Participants

Data as of: August 31, 2002

Vital Status/Participation	CaD Participants (N=36,282)	
	N	%
Deceased	803	2.2
Alive: Current Participation ¹	34278	94.5
Alive: Recent Participation ²	486	1.3
Alive: Past/Unknown Participation ³	16	0.0
Stopped Follow-Up ⁴	394	1.1
Lost to Follow-Up ⁵	305	0.8

¹ Participants who have filled in a Form 33 within the last 9 months.

² Participants who last filled in a Form 33 between 9 and 18 months ago.

³ Participants without a Form 33 within the last 18 months, who have been located (as indicated on Form 23) within the last 6 months.

⁴ Participants with codes 5 (no follow-up) or 8 (absolutely no follow-up) on Form 7.

⁵ Participants not in any of the above categories.

Table 4.9
Locally Verified Outcomes (Annualized Percentages) by Age for Calcium and Vitamin D

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number of participants	36282	5157	8265	16520	6340
Mean follow-up (months)	55.1	60.7	57.3	53.4	52.4
Fractures					
Hip fracture	165 (0.10%)	4 (0.02%)	12 (0.03%)	66 (0.09%)	83 (0.30%)
Vertebral fracture	188 (0.11%)	5 (0.02%)	20 (0.05%)	80 (0.11%)	83 (0.30%)
Other fracture ¹	2295 (1.38%)	300 (1.15%)	455 (1.15%)	1042 (1.42%)	498 (1.80%)
Total fracture	2567 (1.54%)	306 (1.17%)	483 (1.22%)	1152 (1.57%)	626 (2.26%)
Cancer					
Colorectal cancer	208 (0.12%)	13 (0.05%)	32 (0.08%)	99 (0.13%)	64 (0.23%)
Breast cancer ²	834 (0.50%)	94 (0.36%)	198 (0.50%)	398 (0.54%)	144 (0.52%)
Invasive breast cancer	661 (0.40%)	71 (0.27%)	158 (0.40%)	316 (0.43%)	116 (0.42%)
Non-invasive breast cancer	175 (0.10%)	23 (0.09%)	40 (0.10%)	84 (0.11%)	28 (0.10%)
Ovarian cancer	79 (0.05%)	10 (0.04%)	19 (0.05%)	32 (0.04%)	18 (0.07%)
Endometrial cancer ³	112 (0.11%)	14 (0.09%)	26 (0.11%)	51 (0.12%)	21 (0.13%)
Other cancer ¹	797 (0.48%)	74 (0.28%)	133 (0.34%)	382 (0.52%)	208 (0.75%)
Total cancer	1987 (1.19%)	203 (0.78%)	398 (1.01%)	943 (1.28%)	443 (1.60%)
Cardiovascular					
CHD ⁴	535 (0.32%)	32 (0.12%)	52 (0.13%)	251 (0.34%)	200 (0.72%)
CHD death ⁵	115 (0.07%)	7 (0.03%)	12 (0.03%)	46 (0.06%)	50 (0.18%)
Total MI ⁶	457 (0.27%)	27 (0.10%)	42 (0.11%)	223 (0.30%)	165 (0.60%)
Clinical MI	423 (0.25%)	23 (0.09%)	39 (0.10%)	209 (0.28%)	152 (0.55%)
Evolving Q-wave MI ⁷	36 (0.02%)	4 (0.02%)	3 (0.01%)	16 (0.02%)	13 (0.05%)
Possible evolving Q-wave MI ⁷	111 (0.07%)	15 (0.06%)	20 (0.05%)	44 (0.06%)	32 (0.12%)
Angina	697 (0.42%)	31 (0.12%)	96 (0.24%)	348 (0.47%)	222 (0.80%)
CABG/PTCA	733 (0.44%)	32 (0.12%)	87 (0.22%)	370 (0.50%)	244 (0.88%)
Carotid artery disease	108 (0.06%)	3 (0.01%)	11 (0.03%)	58 (0.08%)	36 (0.13%)
Congestive heart failure	408 (0.24%)	15 (0.06%)	43 (0.11%)	193 (0.26%)	157 (0.57%)
Stroke	399 (0.24%)	15 (0.06%)	39 (0.10%)	180 (0.24%)	165 (0.60%)
PVD	103 (0.06%)	5 (0.02%)	13 (0.03%)	48 (0.07%)	37 (0.13%)
CHD ⁴ /Possible evolving Q-wave MI	641 (0.38%)	47 (0.18%)	72 (0.18%)	292 (0.40%)	230 (0.83%)
Coronary disease ⁸	1600 (0.96%)	87 (0.33%)	202 (0.51%)	764 (1.04%)	547 (1.98%)
Total cardiovascular disease	2092 (1.25%)	106 (0.41%)	254 (0.64%)	1010 (1.37%)	722 (2.61%)
Deaths					
Cardiovascular deaths	216 (0.13%)	11 (0.04%)	19 (0.05%)	86 (0.12%)	100 (0.36%)
Cancer deaths	364 (0.22%)	29 (0.11%)	44 (0.11%)	171 (0.23%)	120 (0.43%)
Other known cause	107 (0.06%)	6 (0.02%)	14 (0.04%)	48 (0.07%)	39 (0.14%)
Unknown cause	37 (0.02%)	3 (0.01%)	5 (0.01%)	19 (0.03%)	10 (0.04%)
Not yet adjudicated	79 (0.05%)	3 (0.01%)	8 (0.02%)	40 (0.05%)	28 (0.10%)
Total death	803 (0.48%)	52 (0.20%)	90 (0.23%)	364 (0.50%)	297 (1.07%)

¹ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

² Excludes five cases with borderline malignancy.

³ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁴ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

⁵ "CHD death" includes definite and possible CHD death.

⁶ "Total MI" includes clinical MI and evolving Q-wave MI.

⁷ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁸ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

Table 4.9 (continued)
Locally Verified Outcomes (Annualized Percentages) by Race/Ethnicity for Calcium and Vitamin D

Data as of: August 31, 2002

Outcome	Race/Ethnicity					
	American Indian/Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number of participants	149	721	3315	1502	30155	440
Mean follow-up (months)	54.9	51.4	53.7	53.5	55.5	51.5
Fractures						
Hip fracture	0 (0.00%)	3 (0.10%)	4 (0.03%)	2 (0.03%)	156 (0.11%)	0 (0.00%)
Vertebral fracture	0 (0.00%)	3 (0.10%)	2 (0.01%)	5 (0.07%)	174 (0.12%)	4 (0.21%)
Other fracture ¹	11 (1.61%)	28 (0.91%)	113 (0.76%)	56 (0.84%)	2067 (1.48%)	20 (1.06%)
Total fracture	11 (1.61%)	32 (1.04%)	118 (0.80%)	63 (0.94%)	2320 (1.66%)	23 (1.22%)
Cancer						
Colorectal cancer	2 (0.29%)	4 (0.13%)	21 (0.14%)	7 (0.10%)	172 (0.12%)	2 (0.11%)
Breast cancer ²	1 (0.15%)	18 (0.58%)	47 (0.32%)	26 (0.39%)	735 (0.53%)	7 (0.37%)
Invasive breast cancer	1 (0.15%)	12 (0.39%)	33 (0.22%)	23 (0.34%)	585 (0.42%)	7 (0.37%)
Non-invasive breast cancer	0 (0.00%)	6 (0.19%)	14 (0.09%)	3 (0.04%)	152 (0.11%)	0 (0.00%)
Ovarian cancer	0 (0.00%)	2 (0.06%)	7 (0.05%)	0 (0.00%)	69 (0.05%)	1 (0.05%)
Endometrial cancer ³	1 (0.35%)	0 (0.00%)	2 (0.03%)	2 (0.05%)	106 (0.13%)	1 (0.09%)
Other cancer ¹	3 (0.44%)	15 (0.49%)	48 (0.32%)	16 (0.24%)	708 (0.51%)	7 (0.37%)
Total cancer	7 (1.03%)	39 (1.26%)	124 (0.84%)	48 (0.72%)	1751 (1.25%)	18 (0.95%)
Cardiovascular						
CHD ⁴	1 (0.15%)	2 (0.06%)	45 (0.30%)	11 (0.16%)	468 (0.34%)	8 (0.42%)
CHD death ⁵	1 (0.15%)	1 (0.03%)	17 (0.11%)	2 (0.03%)	92 (0.07%)	2 (0.11%)
Total MI ⁶	1 (0.15%)	2 (0.06%)	32 (0.22%)	10 (0.15%)	405 (0.29%)	7 (0.37%)
Clinical MI	1 (0.15%)	2 (0.06%)	29 (0.20%)	10 (0.15%)	375 (0.27%)	6 (0.32%)
Evolving Q-wave MI ⁷	0 (0.00%)	0 (0.00%)	3 (0.02%)	0 (0.00%)	32 (0.02%)	1 (0.05%)
Possible evolving Q-wave MI ⁷	0 (0.00%)	3 (0.10%)	17 (0.11%)	3 (0.04%)	88 (0.06%)	0 (0.00%)
Angina	1 (0.15%)	8 (0.26%)	72 (0.49%)	26 (0.39%)	582 (0.42%)	8 (0.42%)
CABG/PTCA	1 (0.15%)	5 (0.16%)	62 (0.42%)	23 (0.34%)	632 (0.45%)	10 (0.53%)
Carotid artery disease	1 (0.15%)	1 (0.03%)	5 (0.03%)	0 (0.00%)	101 (0.07%)	0 (0.00%)
Congestive heart failure	1 (0.15%)	3 (0.10%)	62 (0.42%)	11 (0.16%)	326 (0.23%)	5 (0.26%)
Stroke	3 (0.44%)	10 (0.32%)	42 (0.28%)	10 (0.15%)	328 (0.24%)	6 (0.32%)
PVD	1 (0.15%)	1 (0.03%)	16 (0.11%)	0 (0.00%)	84 (0.06%)	1 (0.05%)
CHD ⁴ /Possible evolving Q-wave MI	1 (0.15%)	5 (0.16%)	61 (0.41%)	14 (0.21%)	552 (0.40%)	8 (0.42%)
Coronary disease ⁸	2 (0.29%)	15 (0.49%)	178 (1.20%)	46 (0.69%)	1339 (0.96%)	20 (1.06%)
Total cardiovascular disease	6 (0.88%)	27 (0.87%)	230 (1.55%)	56 (0.84%)	1746 (1.25%)	27 (1.43%)
Deaths						
Cardiovascular deaths	1 (0.15%)	4 (0.13%)	34 (0.23%)	4 (0.06%)	171 (0.12%)	2 (0.11%)
Cancer deaths	0 (0.00%)	11 (0.36%)	32 (0.22%)	6 (0.09%)	312 (0.22%)	3 (0.16%)
Other known cause	2 (0.29%)	0 (0.00%)	13 (0.09%)	0 (0.00%)	91 (0.07%)	1 (0.05%)
Unknown cause	1 (0.15%)	0 (0.00%)	5 (0.03%)	0 (0.00%)	31 (0.02%)	0 (0.00%)
Not yet adjudicated	0 (0.00%)	1 (0.03%)	3 (0.02%)	2 (0.03%)	72 (0.05%)	1 (0.05%)
Total death	4 (0.59%)	16 (0.52%)	87 (0.59%)	12 (0.18%)	677 (0.49%)	7 (0.37%)

¹ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

² Excludes five cases with borderline malignancy.

³ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁴ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

⁵ "CHD death" includes definite and possible CHD death.

⁶ "Total MI" includes clinical MI and evolving Q-wave MI.

⁷ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁸ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

Table 4.10
Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Race/Ethnicity
for CaD Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	36282	5157	8265	16520	6340
Mean follow-up (months)	55.1	60.7	57.3	53.4	52.4
Hospitalizations					
Ever	12115 (7.27%)	1257 (4.82%)	2279 (5.77%)	5773 (7.86%)	2806 (10.14%)
Two or more	5089 (3.05%)	450 (1.72%)	862 (2.18%)	2398 (3.26%)	1379 (4.98%)
Other					
DVT ¹	253 (0.16%)	14 (0.05%)	45 (0.12%)	108 (0.15%)	86 (0.32%)
Pulmonary embolism	144 (0.09%)	8 (0.03%)	29 (0.07%)	71 (0.10%)	36 (0.13%)
Diabetes (treated)	1717 (1.07%)	252 (0.99%)	401 (1.06%)	768 (1.09%)	296 (1.13%)
Gallbladder disease ²	1669 (1.19%)	256 (1.11%)	426 (1.25%)	758 (1.24%)	229 (1.01%)
Hysterectomy	653 (0.67%)	92 (0.61%)	154 (0.63%)	310 (0.72%)	97 (0.62%)
Glaucoma	2331 (1.45%)	240 (0.93%)	462 (1.20%)	1117 (1.58%)	512 (1.98%)
Osteoporosis	4745 (2.99%)	444 (1.73%)	867 (2.26%)	2313 (3.32%)	1121 (4.45%)
Osteoarthritis ³	4578 (4.42%)	661 (3.44%)	1067 (3.97%)	2077 (4.79%)	773 (5.48%)
Rheumatoid arthritis	1212 (0.76%)	187 (0.74%)	298 (0.78%)	514 (0.73%)	213 (0.81%)
Intestinal polyps	3195 (2.05%)	384 (1.52%)	700 (1.86%)	1564 (2.30%)	547 (2.21%)
Lupus	211 (0.13%)	38 (0.15%)	51 (0.13%)	85 (0.12%)	37 (0.13%)
Kidney stones ³	433 (0.32%)	59 (0.29%)	105 (0.33%)	194 (0.32%)	75 (0.33%)
Cataracts ³	7499 (6.26%)	462 (2.33%)	1251 (4.10%)	4061 (7.59%)	1725 (10.93%)
Pills for hypertension	6442 (5.40%)	838 (3.93%)	1424 (4.68%)	2951 (5.84%)	1229 (7.21%)

Outcomes	Race/Ethnicity					
	American Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	149	721	3315	1502	30155	440
Mean follow-up (months)	54.9	51.4	53.7	53.5	55.5	51.5
Hospitalizations						
Ever	49 (7.19%)	158 (5.12%)	1133 (7.64%)	414 (6.19%)	10215 (7.32%)	146 (7.74%)
Two or more	28 (4.11%)	53 (1.72%)	485 (3.27%)	151 (2.26%)	4312 (3.09%)	60 (3.18%)
Other						
DVT ¹	2 (0.30%)	0 (0.00%)	18 (0.12%)	4 (0.06%)	227 (0.17%)	2 (0.11%)
Pulmonary embolism	3 (0.44%)	0 (0.00%)	10 (0.07%)	2 (0.03%)	126 (0.09%)	3 (0.16%)
Diabetes (treated)	9 (1.43%)	46 (1.59%)	279 (2.11%)	120 (1.91%)	1239 (0.92%)	24 (1.36%)
Gallbladder disease ²	8 (1.55%)	27 (0.96%)	107 (0.80%)	78 (1.51%)	1427 (1.22%)	22 (1.39%)
Hysterectomy	2 (0.69%)	10 (0.50%)	29 (0.45%)	20 (0.54%)	587 (0.69%)	5 (0.47%)
Glaucoma	12 (1.84%)	36 (1.21%)	303 (2.18%)	114 (1.76%)	1846 (1.37%)	20 (1.12%)
Osteoporosis	17 (2.62%)	96 (3.22%)	246 (1.72%)	191 (3.04%)	4138 (3.11%)	57 (3.24%)
Osteoarthritis ³	27 (6.27%)	85 (3.81%)	407 (4.52%)	229 (5.03%)	3766 (4.37%)	64 (5.23%)
Rheumatoid arthritis	11 (1.82%)	20 (0.68%)	207 (1.51%)	107 (1.67%)	848 (0.63%)	19 (1.07%)
Intestinal polyps	18 (2.86%)	56 (1.97%)	308 (2.22%)	107 (1.66%)	2672 (2.05%)	34 (1.96%)
Lupus	3 (0.45%)	1 (0.03%)	26 (0.18%)	5 (0.08%)	174 (0.13%)	2 (0.11%)
Kidney stones ³	3 (0.55%)	9 (0.35%)	31 (0.26%)	22 (0.41%)	362 (0.32%)	6 (0.39%)
Cataracts ³	38 (7.63%)	120 (5.34%)	615 (5.75%)	304 (5.97%)	6340 (6.35%)	82 (5.89%)
Pills for hypertension	26 (6.03%)	120 (5.66%)	634 (8.21%)	296 (5.73%)	5294 (5.15%)	72 (5.99%)

¹ Inpatient DVT only.

² "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

³ These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

5. Observational Study

5.1 Recruitment

Recruitment into the OS component, completed in December of 1998, reached 93,717, approximately 94% of the expected sample size. After removing duplicate enrollments and a few enrollments with insufficient data, the final analytic cohort was established with 93,676 participants. *Table 5.1* documents the age distribution and the racial/ethnic composition of this cohort.

5.2 Overview of Follow-up

OS follow-up is conducted by annual mailed self-administered questionnaires except for year 3, when participants attend a clinic follow-up visit. Participants at the 3 bone density sites also attend a clinic visit at year 6 for a bone density scan. For all other years, the CCC mails the *Medical History Update* and the *OS Exposure Update* questionnaires approximately 2 months prior to the anniversary of the participants' enrollment. Participants mail their completed questionnaires to their local CC for data entry and outcomes processing. Non-respondents receive up to two additional mailings from the CCC. For odd numbered follow-up years, CCs attempt to complete follow-up of non-responders by local contacts, usually telephone reminders or interviews.

The year 3 clinic visit was incorporated to assess change in physical measures, blood analytes, diet, and use of medications and supplements. These visits began in the first VCCs in Fall 1997.

5.3 Completeness of Annual Mail Follow-up

Table 5.2 shows completeness of OS mail follow-up by follow-up year, type of contact, and clinic group. These rates include participants for whom the full sequence of mailings are complete and there has been at least two months for CC follow-up of non-responders.

The overall response of 95.7% for year 1 data collection, which includes mailings plus CC follow-up of non-responders, slightly exceeds the 95% goal for completion of *Form 48 – OS Exposure Update*, but falls short of the optimal goal (98%) for completion of *Form 33 – Medical History Update*. For years 2, 4, 5, and 6 the rates of 94.2% (Y2), 93.6% (Y4), 94.8% (Y5), and 94.5% (Y6) exceed the 94% (Y2), 92% (Y4), 91% (Y5), and 90% (Y6) goals for the *Exposure Update*. These rates fall slightly short of the optimal goals (98% at Y1 with a ½% annual decline to 95.5% by Y6) for the *Medical History Update*.

5.4 Completeness of Year 3 Clinic Visit

Table 5.3 shows completeness of activities conducted at the year 3 clinic visit for all participants and at the year 6 visit for bone density participants. Of those participants due for the year 3 visit through 8/31/02, 96.0% overall completed *Form 33 – Medical History Updates* and 82.6% provided *Form 100 – Blood Samples*. Of those participants due for the year 6 visit, 87.1% completed *Form 33 – Medical History Updates* and 78.5% completed *Form 87 – Bone Densitometry*.

5.5 Bone Mineral Density

Bone scans are given to all enrolled WHI participants in three Clinical Centers: Birmingham, Pittsburgh, and Tucson. The choice of three centers was based on reducing the variability

associated with multiple sites and operators while achieving adequate sample size. The selection of these three clinical centers was based both on their previous experience in bone densitometry and the expected enrollment of minorities which will allow us to address hypotheses regarding racial/ethnic differences. Bone scans are given at baseline and years 1, 3, 6, and 9 in these centers.

Table 5.4 (overall) and *Table 5.5* (by race and ethnicity) show the OS component-specific BMD means and standard deviations for baseline AV-3 along with % change from baseline for the three types of scans available: whole body, spine, and hip. Baseline and % change is also given using only those women who have an AV-3 bone scan, as nearly 3,000 of the women with a baseline do not have an AV-3 measure. The current data suggest overall a small increase in bone density over three years in this group of women. In general, we would have expected a small decrease in BMD over time. As with the corresponding DM results, this increase could be related to some selection of health conscious women who may be taking hormone replacement therapy or calcium supplements of their own, or could be due to measurement issues.

5.6 Vital Status

Table 5.6 presents data on the vital status and the participation status of participants in the OS. A detailed description of CC and CCC activities to actively locate participants who do not complete their periodic visits is given in *Section 6 – Outcomes Processing*. For operational purposes, we define OS participants to be lost-to-follow-up if there is no outcomes information from the participant for 24 months. Currently 2.2% of the participants are lost-to-follow-up, and an additional 1.5% of the participants have stopped follow-up. 3.2% of the OS participants are deceased. Compared to six months ago, the percentage of participants who were lost-to-follow-up or stopped follow-up increased by 0.5%. Over the same period, participation levels have remained stable, as 90.0% of the participants are considered current, 0.3% more than six months ago.

5.7 Outcomes

Table 5.7 contains counts of the number of locally verified major WHI outcomes for OS participants by age and race/ethnicity. As approximately 5% of the self-reported outcomes have not yet been verified, the numbers in this table can be seen as a lower bound to the actual number of outcomes that took place. Compared to the incidence rates used in the CT design, we have about 125% of the expected number of breast cancers, 65% of the expected number of colorectal cancers, about 50% of the expected number of CHD events, and about 30% of the expected number hip fractures.

Table 5.8 contains counts of the number of self-reports for some outcomes that are not locally verified in WHI. As most of the locally verified outcomes are somewhat over-reported (see *Section 6.3 – Outcomes Data Quality*), the number in this table should be taken as an upper bound to the number of events that have occurred among OS participants.

Tables 5.9 and 5.10, contain counts of outcomes relative to AV-3. These tables count the *first* event of a particular type, thus a participant who reports, say, an Angina at AV-1 and another one at AV-4 gets only counted in the “Before AV-3” category. These tables may be useful for investigators who want to propose ancillary studies or papers.

Table 5.1
Observational Study Age and Race/Ethnicity Specific Recruitment

Data as of: August 31, 2002

	Total Enrolled	Distribution
Age	93,676	
50-54	12386	13%
55-59	17321	18%
60-69	41196	44%
70-79	22773	24%
Race/Ethnicity	93,676	
American Indian	421	<1%
Asian	2671	3%
Black	7635	8%
Hispanic	3609	4%
White	78016	83%
Unknown	1324	1%

Table 5.2
Response Rates to OS Follow-up Procedures

Data as of: August 31, 2002

	# Due ¹	Mailings Initiated ²		Response to Mailings		Response to CC follow-up		Total Responses	
		N	%	N	% ³	N	% ⁴	N	% ⁵
Year 1	93,466	93,280	99.8%	86,656	92.9%	2,829	42.8%	89,485	95.7%
VCC	41,637	41,603	99.9%	38,421	92.4%	1,689	53.1%	40,110	96.3%
NCC	51,829	51,677	99.7%	48,235	93.4%	1,140	33.2%	49,375	95.3%
Year 2	93,032	91,394	98.2%	86,317	94.4%	N/A		87,615	94.2%
VCC	41,453	40,707	98.2%	38,479	94.5%	N/A		39,100	94.3%
NCC	51,579	50,687	98.3%	47,838	94.4%	N/A		48,515	94.1%
Year 4	64,796	63,549	98.1%	59,360	93.4%	N/A		60,663	93.6%
VCC	30,333	29,698	97.9%	27,620	93.0%	N/A		28,171	92.9%
NCC	34,463	33,851	98.2%	31,740	93.8%	N/A		32,492	94.3%
Year 5	41,705	40,958	98.2%	38,615	94.3%	936	39.9%	39,551	94.8%
VCC	20,151	19,851	98.5%	18,553	93.5%	460	35.4%	19,013	94.4%
NCC	21,554	21,107	97.9%	20,062	95.0%	476	45.6%	20,538	95.3%
Year 6⁶	11,038	10,799	97.8%	10,242	94.8%	N/A		10,434	94.5%
VCC	5,959	5,835	97.9%	5,480	93.9%	N/A		5,573	93.5%
NCC	5,079	4,964	97.7%	4,762	95.9%	N/A		4,861	95.7%

¹ Excludes women who are deceased.

² Mailings are not sent to women who have requested no follow-up, who are deceased, who have a non-deliverable address at the time of mailing, or who have a Form 33 completed within the previous 3 months.

³ Percent response of those initiated.

⁴ Percent response from OS participants not responding to mailings. CC follow-up not required in even numbered follow-up years.

⁵ Percent response of those due.

⁶ Does not include bone density sites.

Table 5.3
OS Annual Visit 3 Task Completeness

Data as of: August 31, 2002

	Task	# Due¹	# Done²	% Done
Year 3	Form 33 - Medical History Update	92,136	88,419	96.0%
	Form 38 - Daily Life	92,136	81,938	88.9%
	Form 44 - Current Medications	92,136	78,839	85.6%
	Form 45 - Current Supplements	92,136	78,738	85.5%
	Form 60 - Food Frequency Quest	92,136	82,096	89.1%
	Form 80 - Physical Measures	92,136	77,006	83.6%
	Form 100 - Blood Collection	92,136	76,117	82.6%
	Form 143 - Follow-up	92,136	81,590	88.6%
Year 6³	Form 33 - Medical History Update	2,663	2,320	87.1%
	Form 80 - Physical Measures	2,663	2,097	78.7%
	Form 87 - Bone Densitometry	2,663	2,090	78.5%
	Form 146 - Follow-up	2,663	2,240	84.1%

¹ Includes all Year 3/6 contacts due through 5/31/02. Excludes women who are deceased.

² Tasks completed within the -6/+15 month window for Year 3 and -2/+10 month window for Year 6.

³ Includes bone density sites only.

Table 5.4
Bone Mineral Density¹ Analysis: OS Participants

Data as of: August 31, 2002

	N	Mean	S.D.
Whole Body Scan			
Baseline	6390	1.01	0.11
Baseline (for pts. with an AV3 scan)	5075	1.01	0.11
Baseline (for pts. with an AV6 scan)	3248	1.01	0.11
AV3	5134	1.02	0.11
AV6	3273	1.03	0.12
AV3 % Change from baseline BMD ²	5068	0.92	3.63
AV6 % Change from baseline BMD ³	3240	1.88	5.45
Spine Scan			
Baseline	6265	0.98	0.17
Baseline (for pts. with an AV3 scan)	4995	0.97	0.17
Baseline (for pts. with an AV6 scan)	3155	0.98	0.17
AV3	5033	0.99	0.17
AV6	3167	1.01	0.18
AV3 % Change from baseline BMD ²	4987	1.67	5.14
AV6 % Change from baseline BMD ³	3147	3.73	6.87
Hip Scan			
Baseline	6418	0.84	0.14
Baseline (for pts. with an AV3 scan)	5145	0.84	0.14
Baseline (for pts. with an AV6 scan)	3296	0.84	0.14
AV3	5185	0.85	0.14
AV6	3308	0.84	0.14
AV3 % Change from baseline BMD ²	5113	0.49	4.35
AV6 % Change from baseline BMD ³	3262	0.22	5.30

¹ Measured in (g/cm²).

² AV3 % Change from baseline BMD is defined as ((AV3-Baseline)/Baseline)x100.

³ AV6 % Change from baseline BMD is defined as ((AV6-Baseline)/Baseline)x100.

Table 5.5
Bone Mineral Density¹ Analysis: OS Participants by Race/Ethnicity

Data as of: August 31, 2002

	American Indian/ Alaskan Native		Asian/Pacific Islander		Black/African American		Hispanic/Latino		White		Unknown	
	N	Mean S.D.	N	Mean S.D.	N	Mean S.D.	N	Mean S.D.	N	Mean S.D.	N	Mean S.D.
Whole Body Scan												
Baseline	108	1.01 0.12	25	1.02 0.09	824	1.04 0.11	462	1.01 0.11	4925	1.00 0.10	46	1.01 0.12
Baseline (for ppts. with an AV3 scan)	77	1.02 0.12	22	1.03 0.09	568	1.05 0.11	323	1.01 0.10	4049	1.01 0.10	36	1.00 0.11
Baseline (for ppts. with an AV6 scan)	24	1.07 0.13	11	1.02 0.08	343	1.04 0.11	144	1.04 0.10	2709	1.01 0.10	17	1.00 0.14
AV3	81	1.03 0.13	22	1.03 0.11	576	1.06 0.12	338	1.03 0.11	4080	1.01 0.11	37	1.01 0.10
AV6	24	1.08 0.14	11	1.03 0.12	346	1.05 0.12	144	1.08 0.14	2731	1.03 0.12	17	0.99 0.14
AV3 % Change from baseline BMD ²	77	0.70 4.45	22	-0.03 5.44	568	1.52 3.35	322	1.51 4.43	4043	0.80 3.56	36	0.42 2.92
AV6 % Change from baseline BMD ³	24	0.87 4.91	11	1.22 5.12	343	0.29 3.70	143	3.75 6.72	2702	2.01 5.52	17	-0.89 5.45
Spine Scan												
Baseline	109	0.99 0.17	25	0.95 0.12	815	1.04 0.18	454	0.95 0.16	4817	0.97 0.17	45	0.99 0.19
Baseline (for ppts. with an AV3 scan)	77	0.99 0.15	22	0.96 0.12	571	1.04 0.17	315	0.95 0.16	3976	0.97 0.17	34	0.95 0.18
Baseline (for ppts. with an AV6 scan)	24	1.06 0.18	10	0.94 0.10	326	1.04 0.18	142	0.98 0.17	2636	0.97 0.16	17	0.97 0.26
AV3	81	1.00 0.16	22	0.96 0.12	574	1.05 0.19	328	0.95 0.16	3993	0.98 0.17	35	0.95 0.17
AV6	24	1.09 0.15	10	0.95 0.10	326	1.07 0.19	142	0.99 0.18	2648	1.01 0.18	17	1.01 0.27
AV3 % Change from baseline BMD ²	77	0.19 5.80	22	0.22 4.62	571	1.16 5.53	314	0.30 5.42	3969	1.90 5.02	34	0.84 5.17
AV6 % Change from baseline BMD ³	24	3.62 7.06	10	1.61 4.39	326	2.40 6.00	141	0.79 6.85	2629	4.06 6.92	17	4.43 7.75
Hip Scan												
Baseline	109	0.87 0.15	25	0.82 0.10	827	0.93 0.15	463	0.83 0.13	4948	0.83 0.13	46	0.85 0.14
Baseline (for ppts. with an AV3 scan)	78	0.88 0.15	22	0.82 0.10	581	0.93 0.15	324	0.83 0.12	4104	0.83 0.13	36	0.83 0.12
Baseline (for ppts. with an AV6 scan)	24	0.95 0.17	11	0.79 0.09	347	0.93 0.15	144	0.85 0.12	2752	0.83 0.13	18	0.82 0.17
AV3	82	0.88 0.15	22	0.82 0.09	587	0.94 0.15	338	0.85 0.13	4119	0.83 0.13	37	0.82 0.13
AV6	24	0.94 0.15	11	0.81 0.09	349	0.91 0.15	144	0.87 0.12	2762	0.83 0.13	18	0.82 0.17
AV3 % Change from baseline BMD ²	77	-0.34 4.95	22	0.81 4.42	581	0.37 4.01	322	1.70 5.07	4075	0.43 4.30	36	-0.81 4.76
AV6 % Change from baseline BMD ³	24	-0.38 6.41	11	3.06 6.01	345	-1.61 4.76	143	1.91 5.89	2721	0.36 5.26	18	-0.49 6.87

¹ Measured in (g/cm³).

² AV3 % Change from baseline BMD is defined as ((AV3-Baseline)/Baseline)x100.

³ AV6 % Change from baseline BMD is defined as ((AV6-Baseline)/Baseline)x100.

Table 5.6
Lost-to-Follow-up and Vital Status: OS Participants

Data as of: August 31, 2002

Vital Status/Participation	OS Participants (N=93,676)	
	N	%
Deceased	2981	3.2
Alive: Current Participation ¹	84308	90.0
Alive: Recent Participation ²	2691	2.9
Alive: Past/Unknown Participation ³	260	0.3
Stopped Follow-Up ⁴	1393	1.5
Lost to Follow-Up ⁵	2043	2.2

¹ Participants who have filled in a Form 33 within the last 15 months.

² Participants who last filled in a Form 33 between 15 and 24 months ago.

³ Participants without a Form 33 within the last 24 months, who have been located (as indicated on Form 23) within the last 6 months.

⁴ Participants with codes 5 (no follow-up) or 8 (absolutely no follow-up) on Form 7.

⁵ Participants not in any of the above categories.

Table 5.7
Locally Verified Outcomes (Annualized Percentages) by Age for OS Participants

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number enrolled	93676	12386	17321	41196	22773
Mean follow-up (months)	60.8	64.5	63.2	59.8	58.6
Cardiovascular					
CHD ¹	1297 (0.27%)	40 (0.06%)	110 (0.12%)	532 (0.26%)	615 (0.55%)
CHD death ²	329 (0.07%)	5 (0.01%)	19 (0.02%)	111 (0.05%)	194 (0.17%)
Clinical MI	1069 (0.23%)	36 (0.05%)	97 (0.11%)	452 (0.22%)	484 (0.44%)
Angina	1982 (0.42%)	88 (0.13%)	199 (0.22%)	911 (0.44%)	784 (0.71%)
CABG/PTCA	1872 (0.39%)	64 (0.10%)	186 (0.20%)	870 (0.42%)	752 (0.68%)
Carotid artery disease	409 (0.09%)	23 (0.03%)	29 (0.03%)	157 (0.08%)	200 (0.18%)
Congestive heart failure	1263 (0.27%)	41 (0.06%)	101 (0.11%)	497 (0.24%)	624 (0.56%)
Stroke	1061 (0.22%)	29 (0.04%)	84 (0.09%)	408 (0.20%)	540 (0.49%)
PVD	297 (0.06%)	11 (0.02%)	29 (0.03%)	114 (0.06%)	143 (0.13%)
Coronary disease ³	4058 (0.86%)	161 (0.24%)	385 (0.42%)	1750 (0.85%)	1762 (1.58%)
Total cardiovascular disease	5498 (1.16%)	216 (0.32%)	498 (0.55%)	2293 (1.12%)	2491 (2.24%)
Cancer					
Breast cancer ⁴	2570 (0.54%)	258 (0.39%)	460 (0.50%)	1183 (0.58%)	669 (0.60%)
Invasive breast cancer	2138 (0.45%)	217 (0.33%)	379 (0.42%)	972 (0.47%)	570 (0.51%)
Non-invasive breast cancer	454 (0.10%)	45 (0.07%)	87 (0.10%)	220 (0.11%)	102 (0.09%)
Ovarian cancer	226 (0.05%)	20 (0.03%)	38 (0.04%)	101 (0.05%)	67 (0.06%)
Endometrial cancer ⁵	329 (0.12%)	28 (0.07%)	44 (0.08%)	157 (0.13%)	100 (0.16%)
Colorectal cancer	554 (0.12%)	31 (0.05%)	64 (0.07%)	251 (0.12%)	208 (0.19%)
Other cancer ⁶	2374 (0.50%)	164 (0.25%)	290 (0.32%)	1084 (0.53%)	836 (0.75%)
Total cancer	5878 (1.24%)	490 (0.74%)	872 (0.96%)	2696 (1.31%)	1820 (1.64%)
Fractures					
Hip fracture	540 (0.11%)	12 (0.02%)	46 (0.05%)	173 (0.08%)	309 (0.28%)
Vertebral fracture ⁷	66 (0.18%)	4 (0.07%)	5 (0.07%)	24 (0.15%)	33 (0.38%)
Other fracture ^{6,7}	487 (1.33%)	63 (1.17%)	81 (1.18%)	192 (1.23%)	151 (1.72%)
Total fracture⁸	1061 N/A	78 N/A	129 N/A	378 N/A	476 N/A
Deaths					
Cardiovascular deaths	747 (0.16%)	18 (0.03%)	45 (0.05%)	252 (0.12%)	432 (0.39%)
Cancer deaths	1254 (0.26%)	71 (0.11%)	137 (0.15%)	543 (0.26%)	503 (0.45%)
Other known cause	476 (0.10%)	23 (0.03%)	55 (0.06%)	179 (0.09%)	219 (0.20%)
Unknown cause	200 (0.04%)	8 (0.01%)	16 (0.02%)	75 (0.04%)	101 (0.09%)
Not yet adjudicated	304 (0.06%)	10 (0.02%)	25 (0.03%)	129 (0.06%)	140 (0.13%)
Total death	2981 (0.63%)	130 (0.20%)	278 (0.30%)	1178 (0.57%)	1395 (1.25%)

¹ "CHD" includes clinical MI and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Coronary disease" includes clinical MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁴ Excludes seven cases with borderline malignancy.

⁵ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁶ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

⁷ For the OS, only women from three bone density clinics are used to compute the annual rates for vertebral and other fractures.

⁸ Hip fractures are adjudicated at all clinics, while other fractures for OS participants are adjudicated only at a few clinics. A combined annualized percentage cannot be computed.

Table 5.7 (continued)
Locally Verified Outcomes (Annualized Percentages) by Race/Ethnicity for OS Participants

Data as of: August 31, 2002

Outcomes	Ethnicity					
	American Indian/Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number enrolled	421	2671	7635	3609	78016	1324
Mean follow-up (months)	56.7	58.7	56.5	53.2	61.7	58.0
Cardiovascular						
CHD ¹	7 (0.35%)	27 (0.21%)	111 (0.31%)	23 (0.14%)	1107 (0.28%)	22 (0.34%)
CHD death ²	2 (0.10%)	8 (0.06%)	42 (0.12%)	2 (0.01%)	269 (0.07%)	6 (0.09%)
Clinical MI	6 (0.30%)	22 (0.17%)	81 (0.23%)	22 (0.14%)	921 (0.23%)	17 (0.27%)
Angina	12 (0.60%)	39 (0.30%)	170 (0.47%)	49 (0.31%)	1693 (0.42%)	19 (0.30%)
CABG/PTCA	9 (0.45%)	37 (0.28%)	117 (0.33%)	47 (0.29%)	1636 (0.41%)	26 (0.41%)
Carotid artery disease	3 (0.15%)	6 (0.05%)	24 (0.07%)	10 (0.06%)	359 (0.09%)	7 (0.11%)
Congestive heart failure	9 (0.45%)	19 (0.15%)	139 (0.39%)	26 (0.16%)	1054 (0.26%)	16 (0.25%)
Stroke	7 (0.35%)	33 (0.25%)	107 (0.30%)	19 (0.12%)	880 (0.22%)	15 (0.23%)
PVD	2 (0.10%)	4 (0.03%)	32 (0.09%)	4 (0.02%)	250 (0.06%)	5 (0.08%)
Coronary disease ³	22 (1.11%)	72 (0.55%)	366 (1.02%)	92 (0.57%)	3459 (0.86%)	47 (0.73%)
Total cardiovascular disease	29 (1.46%)	109 (0.83%)	509 (1.42%)	120 (0.75%)	4662 (1.16%)	69 (1.08%)
Cancer						
Breast cancer ⁴	6 (0.30%)	46 (0.35%)	157 (0.44%)	65 (0.41%)	2274 (0.57%)	22 (0.34%)
Invasive breast cancer	4 (0.20%)	35 (0.27%)	127 (0.35%)	51 (0.32%)	1902 (0.47%)	19 (0.30%)
Non-invasive breast cancer	2 (0.10%)	11 (0.08%)	31 (0.09%)	14 (0.09%)	392 (0.10%)	4 (0.06%)
Ovarian cancer	0 (0.00%)	4 (0.03%)	11 (0.03%)	7 (0.04%)	203 (0.05%)	1 (0.02%)
Endometrial cancer ⁵	0 (0.00%)	6 (0.07%)	8 (0.05%)	6 (0.07%)	303 (0.13%)	6 (0.16%)
Colorectal cancer	1 (0.05%)	8 (0.06%)	64 (0.18%)	12 (0.07%)	464 (0.12%)	5 (0.08%)
Other cancer ⁶	10 (0.50%)	39 (0.30%)	158 (0.44%)	44 (0.27%)	2086 (0.52%)	37 (0.58%)
Total cancer	17 (0.85%)	99 (0.76%)	384 (1.07%)	133 (0.83%)	5176 (1.29%)	69 (1.08%)
Fractures						
Hip fracture	3 (0.15%)	7 (0.05%)	13 (0.04%)	6 (0.04%)	504 (0.13%)	7 (0.11%)
Vertebral fracture ⁷	1 (0.21%)	0 (0.00%)	1 (0.02%)	2 (0.08%)	62 (0.22%)	0 (0.00%)
Other fracture ^{6,7}	7 (1.45%)	2 (1.34%)	27 (0.58%)	21 (0.87%)	425 (1.48%)	5 (2.18%)
Total fracture⁸	10 N/A	9 N/A	40 N/A	28 N/A	962 N/A	12 N/A
Deaths						
Cardiovascular deaths	6 (0.30%)	20 (0.15%)	87 (0.24%)	10 (0.06%)	613 (0.15%)	11 (0.17%)
Cancer deaths	5 (0.25%)	22 (0.17%)	104 (0.29%)	26 (0.16%)	1079 (0.27%)	18 (0.28%)
Other known cause	8 (0.40%)	9 (0.07%)	41 (0.11%)	26 (0.16%)	385 (0.10%)	7 (0.11%)
Unknown cause	2 (0.10%)	4 (0.03%)	34 (0.09%)	7 (0.04%)	151 (0.04%)	2 (0.03%)
Not yet adjudicated	3 (0.15%)	7 (0.05%)	39 (0.11%)	12 (0.07%)	240 (0.06%)	3 (0.05%)
Total death	24 (1.21%)	62 (0.47%)	305 (0.85%)	81 (0.51%)	2468 (0.62%)	41 (0.64%)

¹ "CHD" includes clinical MI and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Coronary disease" includes clinical MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁴ Excludes seven cases with borderline malignancy.

⁵ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁶ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

⁷ For the OS, only women from three bone density clinics are used to compute the annual rates for vertebral and other fractures.

⁸ Hip fractures are adjudicated at all clinics, while other fractures for OS participants are adjudicated only at a few clinics. A combined annualized percentage cannot be computed.

Table 5.8
Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Race/Ethnicity
for OS Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Total	Age				
		50-54	55-59	60-69	70-79	
Number randomized	93676	12386	17321	41196	22773	
Mean follow-up (months)	60.8	64.5	63.2	59.8	58.6	
Hospitalizations						
Ever	32187 (6.79%)	2983 (4.48%)	4618 (5.06%)	14386 (7.01%)	10200 (9.17%)	
Two or more	13681 (2.88%)	1065 (1.60%)	1652 (1.81%)	6059 (2.95%)	4905 (4.41%)	
Other						
DVT ¹	469 (0.10%)	40 (0.06%)	52 (0.06%)	210 (0.11%)	167 (0.16%)	
Pulmonary embolism	295 (0.06%)	29 (0.04%)	38 (0.04%)	126 (0.06%)	102 (0.09%)	
Diabetes (treated)	3174 (0.70%)	387 (0.60%)	574 (0.65%)	1444 (0.73%)	769 (0.72%)	
Gallbladder disease ²	3903 (0.98%)	607 (1.03%)	778 (0.99%)	1735 (1.01%)	783 (0.86%)	
Hysterectomy	2133 (0.77%)	303 (0.76%)	416 (0.73%)	990 (0.83%)	424 (0.68%)	
Glaucoma	5182 (1.15%)	509 (0.78%)	758 (0.85%)	2403 (1.23%)	1512 (1.48%)	
Osteoporosis	15091 (3.48%)	1438 (2.24%)	2305 (2.65%)	6982 (3.73%)	4366 (4.54%)	
Osteoarthritis ³	10903 (3.95%)	1335 (2.78%)	1913 (3.19%)	4921 (4.29%)	2734 (5.09%)	
Rheumatoid arthritis	3126 (0.70%)	437 (0.68%)	601 (0.69%)	1267 (0.65%)	821 (0.79%)	
Intestinal polyps	8434 (1.96%)	961 (1.52%)	1551 (1.81%)	3929 (2.13%)	1993 (2.08%)	
Lupus	702 (0.15%)	109 (0.16%)	140 (0.15%)	307 (0.15%)	146 (0.13%)	
Kidney stones ³	1436 (0.38%)	190 (0.38%)	261 (0.37%)	611 (0.37%)	374 (0.42%)	
Cataracts ³	18043 (5.67%)	930 (1.84%)	2324 (3.36%)	9445 (6.66%)	5344 (9.43%)	
Pills for hypertension	14526 (4.29%)	1626 (2.94%)	2518 (3.53%)	6309 (4.42%)	4073 (5.84%)	

Outcomes	Race/Ethnicity					
	American Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	421	2671	7635	3609	78016	1324
Mean follow-up (months)	56.7	58.7	56.5	53.2	61.7	58.0
Hospitalizations						
Ever	166 (8.35%)	570 (4.37%)	2522 (7.02%)	906 (5.66%)	27616 (6.89%)	407 (6.36%)
Two or more	79 (3.97%)	206 (1.58%)	1068 (2.97%)	313 (1.96%)	11834 (2.95%)	181 (2.83%)
Other						
DVT ¹	3 (0.16%)	4 (0.03%)	38 (0.11%)	8 (0.05%)	413 (0.11%)	3 (0.05%)
Pulmonary embolism	1 (0.05%)	3 (0.02%)	23 (0.06%)	2 (0.01%)	264 (0.07%)	2 (0.03%)
Diabetes (treated)	35 (2.06%)	116 (0.94%)	513 (1.62%)	209 (1.40%)	2261 (0.58%)	40 (0.65%)
Gallbladder disease ²	25 (1.59%)	55 (0.46%)	256 (0.80%)	156 (1.24%)	3359 (1.00%)	52 (0.97%)
Hysterectomy	4 (0.41%)	35 (0.41%)	93 (0.57%)	78 (0.90%)	1885 (0.79%)	38 (1.02%)
Glaucoma	32 (1.76%)	164 (1.32%)	623 (1.89%)	178 (1.17%)	4110 (1.07%)	75 (1.22%)
Osteoporosis	67 (3.69%)	452 (3.79%)	667 (1.95%)	495 (3.37%)	13179 (3.60%)	231 (3.94%)
Osteoarthritis ³	44 (3.97%)	321 (3.49%)	904 (4.34%)	498 (4.73%)	8967 (3.89%)	169 (4.33%)
Rheumatoid arthritis	24 (1.32%)	67 (0.54%)	466 (1.43%)	266 (1.79%)	2243 (0.59%)	60 (1.00%)
Intestinal polyps	30 (1.64%)	205 (1.75%)	662 (2.01%)	249 (1.66%)	7175 (1.98%)	113 (1.96%)
Lupus	7 (0.36%)	12 (0.09%)	69 (0.19%)	37 (0.23%)	566 (0.14%)	11 (0.17%)
Kidney stones ³	12 (0.77%)	24 (0.23%)	167 (0.58%)	85 (0.65%)	1124 (0.36%)	24 (0.47%)
Cataracts ³	62 (4.66%)	470 (5.43%)	1301 (5.22%)	571 (4.78%)	15371 (5.75%)	268 (6.21%)
Pills for hypertension	67 (5.29%)	398 (4.33%)	1201 (6.83%)	611 (5.09%)	12030 (4.09%)	219 (4.89%)

¹ Inpatient DVT only.

² "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

³ These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

Table 5.9
First Reported Locally Verified Outcomes Before and After AV-3¹ for OS Participants

Data as of: August 31, 2002

Outcome	Number of Events	
	Before AV-3	After AV-3
Cardiovascular		
CHD ²	747	550
CHD death ³	166	163
Clinical MI	630	439
Angina	1340	642
CABG/PTCA	1151	720
Carotid artery disease	250	159
Congestive heart failure	707	556
Stroke	565	496
PVD	196	101
Coronary disease ⁴	2556	1502
Total cardiovascular disease	3407	2091
Cancer		
Breast cancer ⁵	1581	989
Invasive breast cancer	1287	851
Non-invasive breast cancer	309	145
Ovarian cancer	150	76
Endometrial cancer	202	127
Colorectal cancer	339	215
Other cancer ⁶	1409	965
Total cancer	3615	2263
Fractures		
Hip fracture ⁷	289	251
Vertebral fracture ⁷	34	32
Other fracture ^{6,7}	275	212
Total fracture⁷	588	473
Deaths		
Cardiovascular deaths	357	390
Cancer deaths	588	666
Deaths: other known cause	215	261
Deaths: unknown cause	62	138
Deaths: not yet adjudicated	38	266
Total death	1260	1721

¹ AV-3 date is the blood draw date for participants with an AV-3 blood draw and the OS enrollment date plus 3 years for participants without an AV-3 blood draw. All participants have completed at least 3 years of follow-up.

² "CHD" includes clinical MI and CHD death.

³ "CHD death" includes definite and possible CHD death.

⁴ "Coronary disease" includes clinical MI, Evolving Q-wave MI, Possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁵ Excludes seven cases with borderline malignancy.

⁶ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

⁷ Hip fractures are adjudicated at all clinics, while other fractures are adjudicated only at a few clinics.

Table 5.10
Counts of Participants with Self-Reported Outcomes Before and After AV-3¹
for OS Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Number of Events	
	Before AV-3	After AV-3
Ever hospitalized	19141	13046
DVT ²	226	243
Pulmonary embolism	130	165
Diabetes (treated)	1739	1435
Gallbladder disease ³	2133	1770
Hysterectomy	1245	888
Glaucoma	2750	2432
Osteoporosis	8693	6398
Osteoarthritis ⁴	6330	4573
Rheumatoid arthritis	1722	1404
Intestinal polyps	4393	4041
Lupus	347	355
Kidney stones ⁴	644	792
Cataracts ⁴	9138	8905
Pills for hypertension	8137	6389

¹ AV-3 date is the blood draw date for participants with an AV-3 blood draw and the OS enrollment date plus 3 years for participants without an AV-3 blood draw. All participants have completed at least 3 years of follow-up.

² Inpatient DVT only.

³ "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

⁴ These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

6. Outcomes Processing

6.1 Overview

Most outcomes are initially ascertained by self-report on *Form 33 – Medical History Update*. CT participants complete this form every six months; OS participants complete this form every year. Those participants who report an outcome requiring documentation and adjudication are asked to complete a more detailed form (*Form 33D*) that collects the information needed to request the associated medical records.

After these forms are completed and entered into the database, the CCs identify adjudication cases based on the *Form 33D* information. CCs then request hospital and related records. Once the cases are documented, clinic staff sends the charts having potential cardiovascular, cancer, and fracture outcomes to the local physician adjudicator for evaluation and classification. Key cardiovascular outcomes are further adjudicated by a central committee process. The investigators at UCSF (Steve Cummings, PI) subcontract to the CCC to adjudicate all hip fractures. Staff at the CCC code and adjudicate all cancers of major interest in the study (breast, colon, rectum, ovary, and endometrium) using standardized SEER guidelines. Outcomes for selected other diseases, such as diabetes, gallbladder disease, and hysterectomy, are collected as self-reports only.

The monitoring analysis is conducted on outcomes as classified by the local adjudicator. Currently, about 94% of the self-reports have been adjudicated. We do *not* report on the self-reports for which the adjudication process is not yet finished. We feel that we have now reached the stage in the study where the fraction of the self-reports that are not yet adjudicated is sufficiently small that omitting unadjudicated self-reports does not distort the larger picture.

6.2 Terminology

When a particular outcome, say MI, is investigated, all participants can be divided into five groups:

1. Those who have no self-report of an MI and have no locally confirmed MI.
2. Those who have a self-report of an MI and a locally confirmed MI. We refer to these participants' cases as *confirmed (with self-report)*.
3. Those who have no self-report of an MI but do have a locally confirmed MI usually as a result of an investigation of a self-report of another outcome. We refer to these participants' cases as *confirmed (without self-report)*.
4. Those who have a self-report of an MI but do not have a locally confirmed MI, and for whom all relevant adjudication cases are closed. We refer to these participants' self-reports as *denied*.
5. Those who have a self-report of an MI, but do not have a locally confirmed MI, while some of the relevant adjudication cases are still open. We refer to these participants' self-reports as *open*.

The *confirmed cases* are the cases of participants in categories 2 and 3; the *self-reports* are the cases of participants in categories 2, 4, and 5; the *closed self-reports* are the cases of participants in categories 2 and 4. For some analyses we divide the *denied* self-reports into three groups:

- 4a. The reports of the participants for which the self-reported outcome was denied, but for whom a related outcome (e.g., an angina based on an MI self-report) was found. We refer to those participants' self-reports as *denied - related outcome found*. For the outcome tables, we consider all cardiovascular outcomes to be related, all cancer outcomes to be related, and all fracture outcomes to be related.
- 4b. The reports of the participants for which the self-reported outcome was denied after review of the relevant documentation. We refer to those participants' self-reports as *denied - no (related) outcome found*.
- 4c. The reports of the participants for which the self-report was *denied* for *administrative reasons*. Self-reports can only be denied if they satisfy one of several narrowly defined rules. Usually this means that no documentation was obtained after several attempts over a one-year period.

6.3 Outcomes Data Quality

Tables 6.1-6.2 – Timeliness and Completeness of Local Adjudications display the distribution of time required to locally adjudicate a self-reported outcome by month on *Form 33* for the CT and the OS, respectively. This table is based on the day on which the form was received by the clinic, which may not be the same as the day on which the form was entered in the database. Overall 96% of self-reported outcomes in the CT and 95% of the self-reported outcomes in the OS requiring adjudication have been closed. In particular, 56% of the outcomes in the CT and 58% of the outcomes in the OS have been closed within 90 days of self-report and 75% (CT) and 78% (OS) within 180 days. (Note: the fact that the percentages for the OS appear better is because most of the outcomes in 1996 and earlier, when outcomes processing was considerably slower, are CT outcomes.)

Since 1997, the percentage of forms that were adjudicated within 90 days has increased from about 40% to about 75%, and the percentage of forms that were adjudicated within 180 days has increased from about 60% to over 90%. At the same time, the percentage of forms that are more than a year old that have not yet been adjudicated has been reduced to 0.3%. Currently, 33 of the 40 clinics have twelve or fewer outstanding *Forms 33D* that are more than a year old.

Figures 6.1-6.2 – Timeliness per Period of Self-Report display Kaplan-Meier curves for the time period from reporting an outcome on *Form 33D* until the adjudication case is closed per year of self-report separately for the CT and OS. Both figures clearly show that improvements in the processing of outcomes have happened throughout the study. The CCC continues to work closely with the Outcomes-PMC to develop reports and other tools that will facilitate timely outcomes processing by the CCs.

Tables 6.3-6.4 – Agreement of Local Adjudications with Self-Reports show condition types that the participant can indicate on *Form 33* or *Form 33D* and the fraction of time that the local adjudicator agrees with that self-report. Because of the complications of the adjudication

process, it is not straightforward to define an appropriate estimate of the accuracy of individual self-reports. For example, for most outcome types, second occurrences do not need to be adjudicated, but if the participant reports a second occurrence before the first is confirmed, an adjudication case will be opened. This case will be closed without a locally confirmed outcome when the first self-report is confirmed. To circumvent this and similar problems, the unit in *Tables 6.3* and *6.4* is defined to be a *participant* rather than an outcome event. For some participants whose self-report is denied, related outcomes may be found. We also note that on *Form 33* and *Form 33D* participants report a "stroke or transient ischemic attack (TIA)," while for monitoring purposes only the outcome "stroke" is used. Thus, the number of confirmed cases in *Tables 6.3* and *6.4*, which include TIA, is substantially larger than that in some of the outcomes tables in other sections of this report.

A self-reported outcome may be denied for the following reasons: (i) the outcome did take place, but could not be verified because insufficient evidence was available to the WHI adjudicator; (ii) the outcome did not take place, but a related outcome (which may or may not be of interest to WHI) occurred; (iii) the outcome took place before enrollment in WHI; and (iv) the current self-report was a duplicate report of a previous self-report.

The accuracy of self-reports varies considerably by outcome. For many outcomes the agreement rates for the CT are a few percentage points higher than for the OS. The accuracy of cancer and fracture self-reports may be higher than that for cardiovascular disease because more cardiovascular self-reports result in a related outcome. If those related outcomes are included with the confirmed self-reports, cardiovascular outcomes have a 76% agreement rate between self-reports and locally confirmed outcomes (83% if we exclude angina, which is probably the softest cardiovascular outcome), cancer outcomes have an agreement rate of 87% (93% for the primary cancers), and fracture outcomes have an agreement rate of 80% for the CT and OS combined.

Note that the accuracy of self-reports for *other fractures (other cancers)* reflects the percentage of people who reported an *other fracture (other cancer)* for whom any of the fractures (cancers) in the other category was found, even if the participant indicated the wrong skeletal site (cancer site).

The current rules regarding which cases are centrally adjudicated are:

- Clinical MI, angina, CHF, CABG/PTCA, self reports of MI that are denied locally: all cases that occurred before January 1, 2001, all cases for HRT participants, and 10% of the cases that occurred after January 1, 2001 for other participants are centrally adjudicated. Note that many of the self-reports of MI that are denied locally are already centrally adjudicated because another outcome, such as CHF or angina, was found.
- Stroke, PE, DVT, self reports of stroke that are denied locally: all cases for HRT participants are centrally adjudicated.
- Primary cancer, hip fracture, self reports of primary cancer and hip fracture that are denied locally: all cases are centrally adjudicated.

- Death: all cases for CT participants, all cases for OS participants that occurred before January 1, 2001, 10% of all cases for OS participants that occurred after January 1, 2001 are centrally adjudicated.

Tables 6.5-6.6 – Agreement of Central Adjudications with Local Adjudications have been modified to reflect these changes. In particular, we added a column for which cases are called forward for central adjudication. These tables show that there is good agreement between local and central adjudications for all outcomes. Often angina and congestive heart failure occur in conjunction with an MI. Disagreement on angina or CHF, when there is agreement about the MI is not considered very serious. Some self-reports are locally adjudicated as one type of outcome, while they are centrally adjudicated as another outcome. Data regarding such cross-classification is not shown.

We note that, thanks to the effort of the central adjudicators and the CCC cancer coders the fraction of outcomes that were called forward for central adjudication that have been centrally adjudicated has increased considerably. Except for stroke, now about 85% of the cardiovascular outcomes has been adjudicated (was 80%) and over 90% of the cancer outcomes has been centrally adjudicated (was also 80%).

Tables 6.5 and 6.6 show how many outcomes were identified by local adjudicators, but denied central. *Tables 6.7 and 6.8 – Source of Central Confirmed Outcomes* shows outcomes that were identified by the central adjudicators, but not by the local adjudicators. Approximately 16%(CT)-18%(OS) of the MIs that were identified by central adjudicators were not found by local adjudicators. All of these MIs were identified on cases that were called forward for “related” events, such as angina, CHF, and CABG/PTCA. Currently, few cases have been reviewed for self-reports that were denied locally and did not have a related outcome. Most of the cases of endometrial cancer that were identified based on a locally confirmed other outcome, were identified because of a locally confirmed case of cancer of the uterus; most of the cases of hip fracture that were identified based on a locally confirmed other outcome, were identified because of a locally confirmed case of fractures of the upper leg. Cancer of the uterus and upper leg fractures are reviewed centrally specifically for this reason.

Tables 6.9-6.10 – Agreement of Locally and Centrally Adjudicated Cause of Death. We note that in general there is good agreement between the local and central assessment of the cause of death. For most causes the agreement is about 80-90%. Notable exceptions are the “other” and “unknown” categories of all types: central adjudication seems to be able to determine the cause of death more frequently than local adjudication. In this table arteriosclerotic death includes both definite and possible CHD death, as early on in the study these two categories were a combined cause of death.

6.4 Outcomes Data Summary

Table 6.11 – Locally Verified Outcomes (Annualized Percentages) by Age and Ethnicity for CT contains the number of locally verified outcomes for the major WHI outcomes categories. Since about 5% of the self-reports still need to be adjudicated, the numbers in these tables give a lower bound on the number of outcomes that currently have occurred.

Currently, for the CT we observe approximately 100% of the invasive breast cancer, 75% of the colorectal cancer and 35% of the hip fracture, and 65% of the CHD cases of what was assumed

for the power calculations. Note that DVT and PE, which are only adjudicated for HRT participants, are not included in this table.

Table 6.12 – Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Ethnicity for CT Participants contains counts of the number of self-reports for some of the WHI outcomes that are not adjudicated. As for many of the confirmed outcomes, the participants over report (see *Tables 6.3-6.4*). The numbers in these tables should be seen as upper bounds to the number of outcomes that have currently occurred. Not surprisingly, for many of the outcomes the rates differ considerably by minority status and by age at baseline.

Similar tables for the HRT, DM, CaD, and the OS components are in the chapters about these components. Currently, the rate of fractures in the OS and CT is very similar. The rate of cardiovascular events is slightly higher and the rate of cancers is slightly lower in the CT than in the OS.

Table 6.13 – Locally Confirmed Other Cancers and *Table 6.14 – Locally Confirmed Other Fractures* split out the other cancers and other fractures for the locally verified outcomes by event type and by study. Since for OS participants other fractures are only locally verified at the three bone mineral density clinics, we provide the number of self-reported fractures for these participants. In the CT, approximately 80% of self-reported fractures are confirmed, though the location of the fracture is misreported in approximately 25-30% of cases.

6.5 ECG Data

Electrocardiograms (ECGs) are given to all CT participants at baseline and in years 3, 6, and 9. The ECGs are sent to EPICARE (Pentti Rauthaharju, PI), which subcontracts to the CCC. EPICARE provides the CCC with a comprehensive analysis of each individual ECG, as well as with a serial analysis of the follow-up ECGs of a participant relative to that participant's baseline ECG. This serial analysis is intended to identify silent MIs: MIs that are detected by this ECG analysis, but were not reported by the participant (and locally confirmed, if closed). As of August 31, 2002, the CCC had received serial analysis on 57,978 CT participants whose year 3 ECGs and/or their year 6 ECGs had been analyzed by EPICARE.

Table 6.15 – Cross-tabulation of ECG Codes Suggesting an MI and Locally Confirmed and Self-Reported MI for All CT Participants shows the relation between MIs that have been identified prior to the follow-up ECG and incident MIs as identified by the ECG analysis. A total of 45 evolving Q-wave MIs have been identified. We note that 18 of these MIs were also identified by the regular outcomes reporting process. The remaining 27 evolving Q-wave MIs are thus the "definite silent MIs." *Table 6.15* also gives the number of possible silent MIs.

6.6 Vital Status

Table 6.16 – Cause of Death: CT and OS Participants (Annualized Percentages) presents the cause of death for CT and OS participants. To reduce the time that it takes before cause of death information is available on WHI participants who have passed away, clinics are encouraged to report a "temporary" cause of death for those participants for whom some, but not all, documentation related to the death has been collected. The goal is that a temporary cause is entered in the database as soon as possible, preferably within eight weeks. The cause based on the complete documentation should be entered as soon as all documents are collected.

Cases for which reported unsuccessful requests for documentation have been made over a one-year period can be closed out with incomplete documentation.

During the summer of 2001, we have completed the first NDI search. Results of this investigation are detailed in *Table 6.17*. The NDI search identified 26 women as dead, whose death had not otherwise been ascertained by WHI. The death of an additional 10 participants was also identified by WHI, but their death was not yet adjudicated. For these participants we used the cause of death based on the NDI provided ICD code, in *Table 6.16*.

As of the August 31, 2002 database, there were 1,929 deaths in the CT and 2,981 in the OS. Of the 1,929 CT deaths, there were 1,617 (84%) for which a final adjudication (or NDI report) was available, and an additional 1,146 (8%) for which a temporary adjudication was available. For the OS there is cause of death information on 90% of all deaths.

Table 6.18 – Lost-to-follow-up and Vital Status by Clinic: CT Participants displays information about the follow-up and vital status by clinic. Since 1999, clinics are regularly provided with a list of participants for whom there is no *Form 33* within the last 18 months and who are not known to be deceased. Clinics are asked to make every effort to try to locate these participants and to encourage further study participation. Some participants had information in the database that indicated that she never wanted to be contacted again by WHI. If this were the case, clinics were to verify whether this participation status was correct. If indeed a participant has expressed this opinion, she is not to be contacted again. For these participants, we will still be able to obtain limited vital status information from National Death Index (NDI) searches.

About 2.8% of the CT participants are deceased, we do not know the vital status of about 1.5% of the CT participants, and 2.2% of the participants request no further follow-up. In addition, we lack recent outcomes information on an additional 0.1% of the participants. The study design assumed that 3% per year of the participants would be lost-to-follow-up or death. As the average follow-up of participants is now 5.7 years, we note that the follow-up is much better than what was assumed in the design.

There is considerable clinic-to-clinic variation in the vital status data. The percentage of participants who are lost-to-follow-up ranges from 0 to 10.6% per clinic. The percentage of participants who stopped follow-up ranges from less than 0.1 to 6.8%.

Table 6.19 – Lost-to-Follow-up and Vital Status by Clinic: OS Participants contains the same information as *Table 6.18* but about the OS. For OS, the participants are considered lost-to-follow-up if we have not received a *Form 33* within the last 24 months. Approximately 3.7% of the OS participants are either lost-to-follow-up or have stopped follow-up.

Table 6.1
Timeliness and Completeness of Local Adjudications – CT Participants¹

Data as of: August 31, 2002

Forms with conditions ²		Number and % of forms with conditions locally adjudicated by days from Form 33 encounter date to completion of local adjudication							
Date of Form 33 encounter		≤ 90		≤ 180		Closed		Open	
	N	N	%	N	%	N	%	N	%
<= June 30 1996	3947	269	7%	778	20%	3937	100%	10	<1%
1996 July-December	1382	307	22%	716	52%	1382	100%	0	0%
1997 January-June	2179	764	35%	1328	61%	2173	100%	6	<1%
1997 July-December	2548	980	38%	1517	60%	2547	100%	1	<1%
1998 January-June	3576	1664	47%	2782	78%	3575	100%	1	<1%
1998 July-December	4160	2361	57%	3336	80%	4158	100%	2	<1%
1999 January-June	4604	2831	61%	3806	83%	4601	100%	3	<1%
1999 July-December	4472	2870	64%	3695	83%	4470	100%	2	<1%
2000 January-June	4714	3103	66%	3963	84%	4702	100%	12	<1%
2000 July-December	4409	2986	68%	3814	87%	4398	100%	11	<1%
2001 January- June	5207	3661	70%	4563	88%	5174	99%	33	1%
2001 July	838	571	68%	748	89%	825	98%	13	2%
2001 August	835	566	68%	744	89%	814	97%	21	3%
2001 September	713	513	72%	654	92%	702	98%	11	2%
2001 October	943	614	65%	862	91%	919	97%	24	3%
2001 November	794	515	65%	727	92%	765	96%	29	4%
2001 December	640	470	73%	583	91%	619	97%	21	3%
2002 January	941	714	76%	874	93%	901	96%	40	4%
2002 February	836	656	78%	762	91%	768	92%	68	8%
2002 March	890	687	77%	823	92%	823	92%	67	8%
2002 April	936	719	77%	809	86%	809	86%	127	14%
2002 May	900	714	79%	742	82%	742	82%	158	18%
2002 June	763	523	69%	523	69%	523	69%	240	31%
2002 July	1051	472	45%	472	45%	472	45%	579	55%
2002 August	760	87	11%	87	11%	87	11%	673	89%
Total	53038	29617	56%	39708	75%	50886	96%	2152	4%

¹ This table is based on the day Form 33 was received by the clinic, not on the day the form was entered in the database.

² Conditions are self-reported events that require additional documentation.

Table 6.2
Timeliness and Completeness of Local Adjudications – OS Participants¹

Data as of: August 31, 2002

Forms with conditions ²		Number and % of forms with conditions locally adjudicated by days from Form 33 encounter date to completion of local adjudication							
Date of Form 33 encounter		≤ 90		≤ 180		Closed		Open	
	N	N	%	N	%	N	%	N	%
<= June 30 1996	238	84	35%	127	53%	238	100%	0	0%
1996 July-December	1311	307	23%	701	53%	1308	100%	3	<1%
1997 January-June	2154	844	39%	1402	65%	2154	100%	0	0%
1997 July-December	2296	709	31%	1357	59%	2296	100%	0	0%
1998 January-June	2834	1268	45%	2037	72%	2833	100%	1	<1%
1998 July-December	3806	2005	53%	2901	76%	3805	100%	1	<1%
1999 January-June	4753	2845	60%	3926	83%	4751	100%	2	<1%
1999 July-December	4222	2529	60%	3417	81%	4221	100%	1	<1%
2000 January-June	5929	3781	64%	4891	82%	5917	100%	12	<1%
2000 July-December	4316	2837	66%	3639	84%	4294	99%	22	1%
2001 January- June	5378	3587	67%	4612	86%	5303	99%	75	1%
2001 July	911	650	71%	799	88%	891	98%	20	2%
2001 August	1017	662	65%	869	85%	995	98%	22	2%
2001 September	696	502	72%	629	90%	679	98%	17	2%
2001 October	780	468	60%	695	89%	760	97%	20	3%
2001 November	658	412	63%	595	90%	626	95%	32	5%
2001 December	641	455	71%	583	91%	621	97%	20	3%
2002 January	886	652	74%	814	92%	840	95%	46	5%
2002 February	817	621	76%	752	92%	763	93%	54	7%
2002 March	823	597	73%	730	89%	730	89%	93	11%
2002 April	1121	795	71%	956	85%	956	85%	165	15%
2002 May	1129	860	76%	931	82%	931	82%	198	18%
2002 June	982	656	67%	656	67%	656	67%	326	33%
2002 July	952	443	47%	443	47%	443	47%	509	53%
2002 August	778	74	10%	74	10%	74	10%	704	90%
Total	49428	28643	58%	38536	78%	47085	95%	2343	5%

¹ This table is based on the day *Form 33* was received by the clinic, not on the day the form was entered in the database.

² Conditions are self-reported events that require additional documentation.

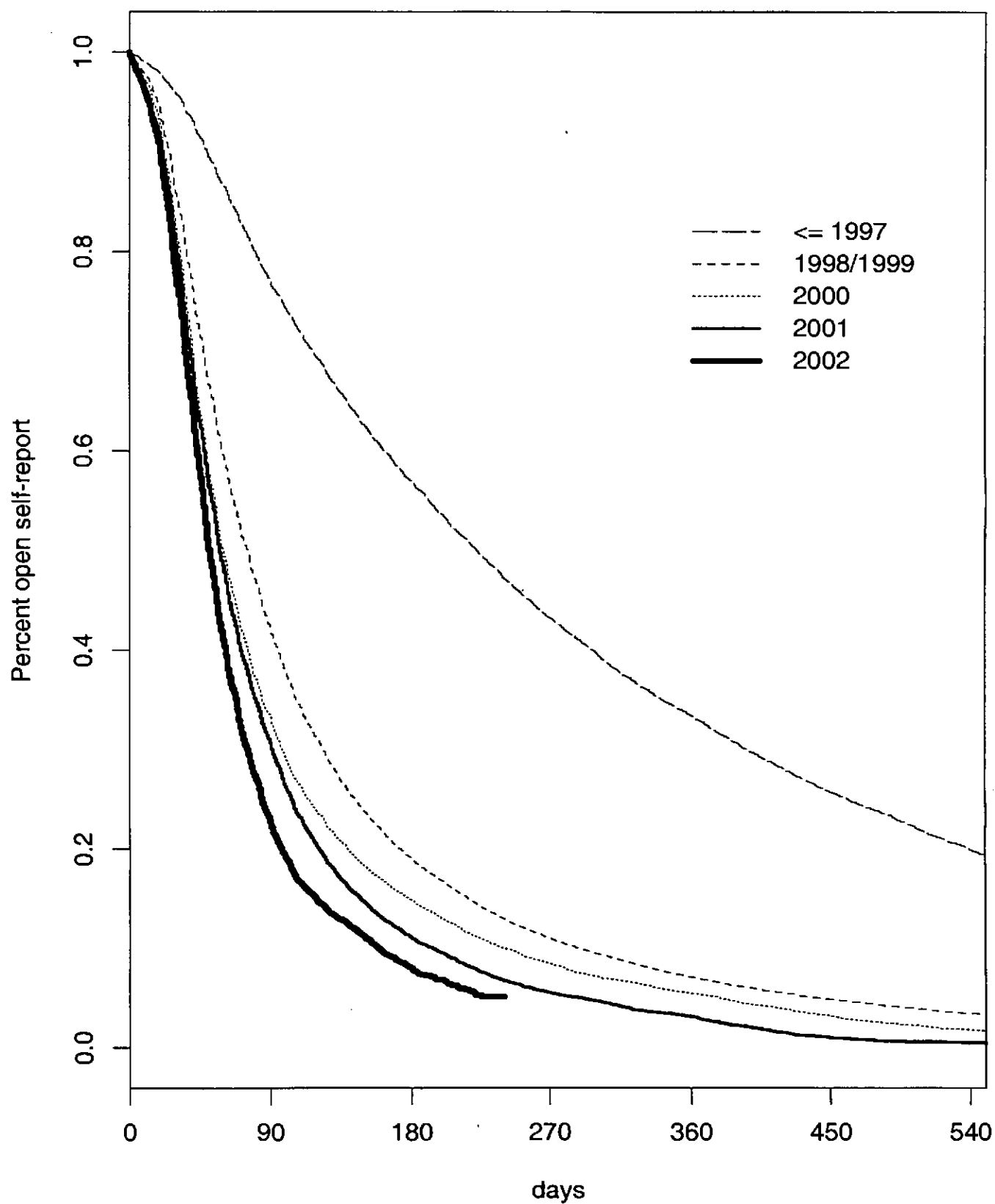
Figure 6.1 Clinical Trial Timeliness per Period of Self-Report

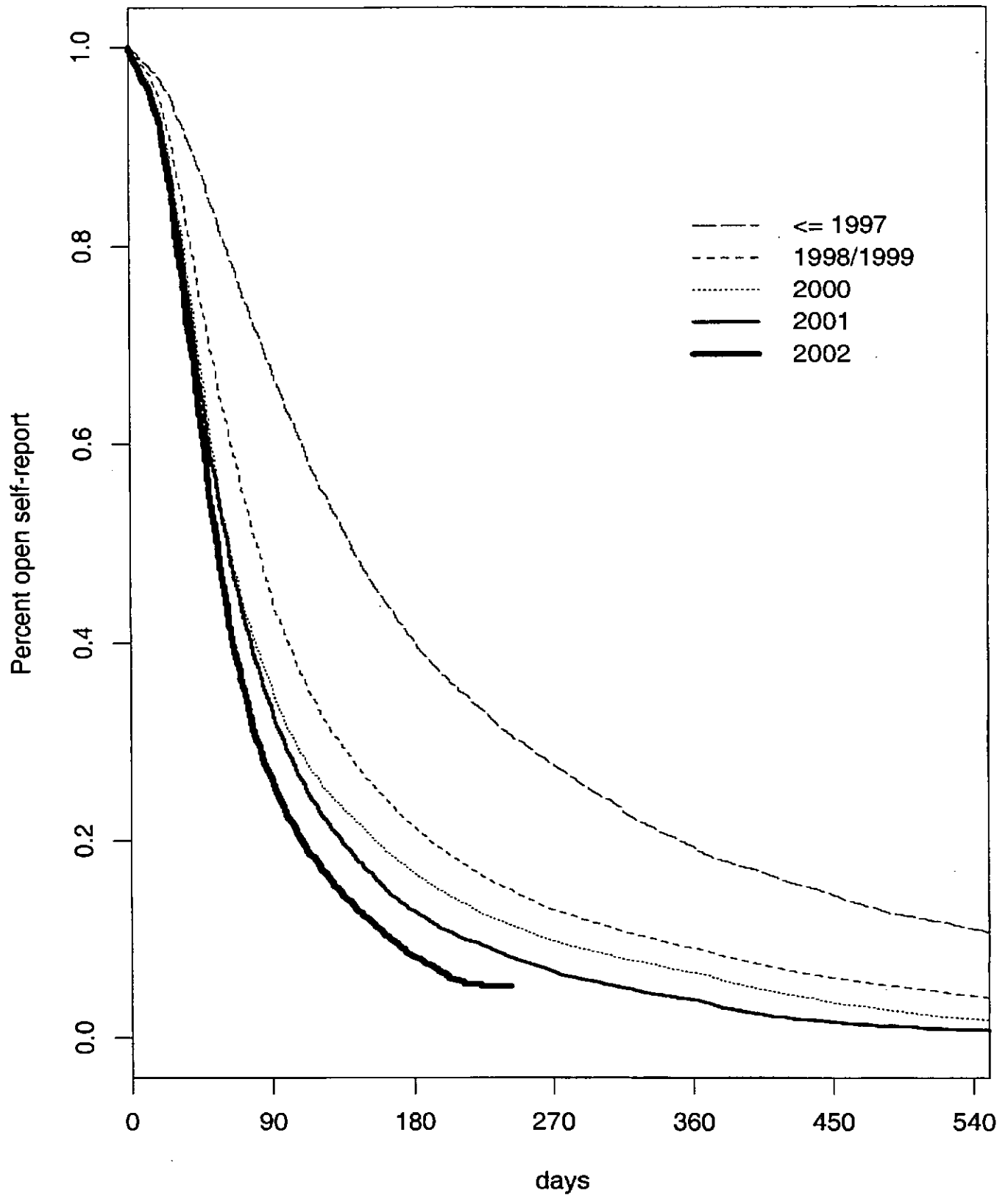
Figure 6.2 Observational Study Timeliness per Period of Self-Report

Table 6.3
Agreement of the Local Adjudications with Self-Reports — CT Participants

Data as of: August 31, 2002

	Participants with a self-report	Closed N %	Confirmed N % ¹	Denied – related outcome found N % ¹	Denied – no outcome found N % ¹	Administrative denials N % ¹
Cardiovascular						
Clinical MI	954	896	638 (71%)	139 (16%)	108 (12%)	11 (1%)
Angina ²	1886	1774	845 (48%)	79 (4%)	815 (46%)	35 (2%)
Congestive heart failure	620	589	428 (73%)	36 (6%)	116 (20%)	9 (2%)
CABG/PTCA	2074	1961	1566 (80%)	159 (8%)	212 (11%)	24 (1%)
Carotid artery disease ³	280	264	218 (83%)	26 (10%)	16 (6%)	4 (2%)
Stroke/TIA ⁴	1560	1451	1113 (77%)	66 (5%)	246 (17%)	26 (2%)
PVD	200	186	110 (59%)	26 (14%)	46 (25%)	4 (2%)
DVT ⁵	315	289	204 (71%)	38 (13%)	40 (14%)	7 (2%)
Pulmonary embolism ⁵	151	140	119 (85%)	7 (5%)	14 (10%)	0 (0%)
Cancers						
Breast cancer	1946	1826	1759 (96%)	1 (<1%)	57 (3%)	9 (<1%)
Ovarian cancer	187	175	128 (73%)	36 (21%)	8 (5%)	3 (2%)
Endometrial cancer	233	220	171 (78%)	25 (11%)	22 (10%)	2 (1%)
Colorectal cancer	523	501	438 (87%)	30 (6%)	32 (6%)	1 (<1%)
Other cancer ⁶	2170	2029	1537 (76%)	113 (6%)	341 (17%)	38 (2%)
Fractures						
Hip fracture	424	389	317 (81%)	29 (7%)	38 (10%)	5 (1%)
Vertebral fracture	728	679	364 (54%)	25 (4%)	269 (40%)	21 (3%)
Other fracture	6348	6099	4968 (81%)	56 (1%)	907 (15%)	168 (3%)

¹ Percentages between parentheses are relative to "closed."

² Angina that is self-reported after a confirmed MI is not adjudicated. In particular, 212 such self-reports of angina are excluded from this table.

³ Carotid artery disease that is self-reported after a confirmed stroke is not adjudicated. In particular, 4 such self-reports of carotid artery disease are excluded from this table.

⁴ Stroke and TIA have a combined self-report. Only stroke is monitored. There were 341 participants who reported stroke/TIA for whom only TIA was confirmed.

⁵ HRT participants only.

⁶ Excludes non-melanoma skin cancer.

Table 6.4
Agreement of the Local Adjudications with Self-Reports — OS Participants

Data as of: August 31, 2002

	Participants with a self-report	Closed N %	Confirmed N % ¹	Denied – related outcome found N % ¹	Denied – no outcome found N % ¹	Administrative denials N % ¹
Cardiovascular						
Clinical MI	910	843 93%	560 (66%)	149 (18%)	116 (14%)	18 (2%)
Angina ²	2168	2055 95%	924 (45%)	125 (6%)	963 (47%)	43 (2%)
Congestive heart failure	763	704 92%	521 (74%)	47 (7%)	122 (17%)	14 (2%)
CABG/PTCA	2343	2209 94%	1687 (76%)	212 (10%)	270 (12%)	40 (2%)
Carotid artery disease ³	342	327 96%	263 (80%)	33 (10%)	26 (8%)	5 (2%)
Stroke/TIA ⁴	1841	1712 93%	1253 (73%)	75 (4%)	341 (20%)	43 (3%)
PVD	284	264 93%	155 (59%)	33 (13%)	70 (27%)	6 (2%)
Cancers						
Breast cancer	2820	2623 93%	2392 (91%)	18 (1%)	174 (7%)	39 (1%)
Ovarian cancer	248	231 93%	158 (68%)	37 (16%)	34 (15%)	2 (1%)
Endometrial cancer	312	289 93%	224 (78%)	40 (14%)	20 (7%)	5 (2%)
Colorectal	596	562 94%	472 (84%)	34 (6%)	45 (8%)	11 (2%)
Other cancer ⁵	2925	2691 92%	1876 (70%)	180 (7%)	558 (21%)	77 (3%)
Fractures						
Hip fracture	606	563 93%	439 (78%)	3 (1%)	107 (19%)	14 (2%)
Vertebral fracture	95	86 91%	53 (62%)	6 (7%)	21 (24%)	6 (7%)
Other fracture	701	670 96%	491 (73%)	13 (2%)	137 (20%)	29 (4%)

¹ Percentages between parentheses are relative to "closed."

² Angina that is self-reported after a confirmed MI, is not adjudicated. In particular, 191 such self-reports of angina are excluded from this table.

³ Carotid artery disease that is self-reported after a confirmed stroke is not adjudicated. In particular, 5 such self-reports of carotid artery disease are excluded from this table.

⁴ Stroke and TIA have a combined self-report. Only stroke is monitored. There were 422 participants who reported stroke/TIA for whom only TIA was confirmed.

⁵ Excludes non-melanoma skin cancer.

Table 6.5
Agreement of Central Adjudications with Local Adjudications — CT Participants

Data as of: August 31, 2002

	Locally confirmed N	Called forward for central adjudication N % ¹	Centrally adjudicated N % ²	In agreement N % ³
Cardiovascular				
Clinical MI	1016	809 80%	714 88%	606 85%
Angina ⁴	1740	1438 83%	1301 90%	975 75%
Congestive heart failure	945	738 78%	621 84%	467 75%
CABG/PTCA	1688	1345 80%	1189 88%	1148 97%
DVT ⁵	261	261 100%	224 86%	196 88%
Pulmonary embolism ⁵	162	162 100%	126 78%	120 95%
Stroke	908	431 47%	83 19%	80 96%
Cancers				
Breast cancer	1781	1781 100%	1638 92%	1633 100%
Invasive	1412	1412 100%	1292 92%	1262 98%
Non-invasive	369	369 100%	346 94%	297 86%
Ovarian cancer	157	157 100%	138 88%	111 80%
Endometrial cancer	219	219 100%	201 92%	193 96%
Colorectal cancer	489	489 100%	434 89%	424 98%
Fractures				
Hip fracture	391	389 99%	353 91%	335 95%

¹ Percentage is relative to locally confirmed cases.

² Percentage is relative to cases called forward for central adjudication.

³ Percentage is relative to centrally adjudicated cases.

⁴ Participants with a confirmed MI no longer require adjudication of angina.

⁵ HRT only.

Table 6.6
Agreement of Central Adjudications with Local Adjudications — OS Participants

Data as of: August 31, 2002

	Locally confirmed N	Called forward for central adjudication N % ¹	Centrally adjudicated N % ²	In agreement N % ³
Cardiovascular				
Clinical MI	1069	697 65%	630 90%	514 82%
Angina ⁴	1982	1411 71%	1300 92%	999 77%
Congestive heart failure	1263	774 61%	685 89%	543 79%
CABG/PTCA	1872	1246 67%	1149 92%	1098 96%
Cancers				
Breast cancer	2468	2468 100%	2322 94%	2274 98%
Invasive	2036	2036 100%	1912 94%	1822 95%
Non-Invasive	432	432 100%	410 95%	326 80%
Ovarian cancer	202	202 100%	178 88%	145 81%
Endometrial cancer	316	316 100%	262 83%	241 92%
Colorectal cancer	528	528 100%	451 85%	425 94%
Fractures				
Hip fracture	540	540 100%	445 82%	432 97%

¹ Percentage is relative to locally confirmed cases.

² Percentage is relative to cases called forward for central adjudication.

³ Percentage is relative to centrally adjudicated cases.

⁴ Participants with a confirmed MI no longer require adjudication of angina.

Table 6.7
Source of Outcomes Identified by Central Adjudications – CT Participants

Data as of: August 31, 2002

	Centrally confirmed N	Reason for central investigation				Denied self-reports reviewed by CCC N		
		Locally confirmed same outcome N %	Locally confirmed other outcome N %	Self-report but no outcome found N %				
Cardiovascular								
Clinical MI	702	590	84%	112	16%	0	0%	29
Angina	1178	940	80%	232	20%	6	1%	N/A
Congestive heart failure	540	454	84%	85	16%	1	<1%	N/A
CABG/PTCA	1183	1133	96%	49	4%	1	<1%	N/A
DVT	205	194	95%	7	3%	4	2%	38
Pulmonary embolism	126	120	95%	3	2%	3	2%	12
Stroke	80	78	98%	0	0%	2	3%	4
Cancers								
Breast cancer	1644	1638	100%	3	<1%	3	<1%	61
Ovarian cancer	120	111	93%	6	5%	3	3%	25
Endometrial cancer	208	192	92%	14	7%	2	1%	26
Colorectal cancer	429	423	99%	1	<1%	5	1%	45
Fractures								
Hip fracture	347	335	97%	7	2%	5	1%	32

Table 6.8
Source of Outcomes Identified by Central Adjudications – OS Participants

Data as of: August 31, 2002

	Centrally confirmed N	Reason for central investigation						Denied self-reports reviewed by CCC N
		Locally confirmed same outcome N %		Locally confirmed other outcome N %		Self-report but no outcome found N %		
Cardiovascular								
Clinical MI	612	502	82%	110	18%	0	0%	13
Angina	1206	983	82%	218	18%	5	<1%	N/A
Congestive heart failure	609	536	88%	72	12%	1	<1%	N/A
CABG/PTCA	1125	1082	96%	43	4%	0	0%	N/A
Cancers								
Breast cancer	2286	2277	100%	1	<1%	8	<1%	118
Ovarian cancer	155	145	94%	8	5%	2	1%	40
Endometrial cancer	271	240	89%	29	11%	2	1%	22
Colorectal cancer	433	425	98%	4	1%	4	1%	69
Fractures								
Hip fracture	436	432	99%	1	0%	3	1%	43

Table 6.9
Agreement of Locally and Centrally Adjudicated Cause of Death for All CT Participants

Data as of: August 31, 2002

	Closed Local ¹	Closed Central N %	Confirmed Cause N % ²	Related Cause N % ²	Unrelated Cause N % ²
Final adjudicated death	1617	1316 81%	1089 (83%)	108 (8%)	119 (9%)
Cardiovascular					
Atherosclerotic cardiac ³	261	209 80%	177 (85%)	15 (7%)	17 (8%)
Cerebrovascular	117	88 75%	77 (88%)	3 (3%)	8 (9%)
Pulmonary embolism	10	6 60%	4 (67%)	1 (17%)	1 (17%)
Other cardiovascular	94	75 80%	37 (49%)	26 (35%)	12 (16%)
Unknown cardiovascular	26	22 85%	1 (5%)	13 (59%)	8 (36%)
Total cardiovascular deaths	508	400 79%	296 (74%)	58 (15%)	46 (12%)
Cancer					
Breast cancer	25	23 92%	22 (96%)	0 (0%)	1 (4%)
Ovarian cancer	63	51 81%	44 (86%)	6 (12%)	1 (2%)
Endometrial cancer	6	6 100%	5 (83%)	1 (17%)	0 (0%)
Colorectal cancer	79	63 80%	58 (92%)	2 (3%)	3 (5%)
Other cancer	576	500 87%	473 (95%)	14 (3%)	13 (3%)
Unknown cancer site	38	29 76%	17 (59%)	12 (41%)	0 (0%)
Total cancer deaths	787	672 85%	619 (92%)	35 (5%)	18 (3%)
Accident/injury					
Homicide	5	4 80%	3 (75%)	1 (25%)	0 (0%)
Accident	41	36 88%	31 (86%)	3 (8%)	2 (6%)
Suicide	7	6 86%	6 (100%)	0 (0%)	0 (0%)
Other injury	3	3 100%	0 (0%)	2 (67%)	1 (33%)
Total accidental deaths	56	49 88%	40 (82%)	6 (12%)	3 (6%)
Other					
Other known cause	209	149 71%	112 (75%)	4 (3%)	33 (22%)
Unknown cause	57	46 81%	22 (48%)	5 (11%)	19 (41%)
Total deaths - other causes	266	195 73%	134 (69%)	9 (5%)	52 (27%)

¹ Excludes temporary adjudications.

² Percentages are relative to closed central.

³ "Atherosclerotic cardiac" combines definite and possible CHD death.

Table 6.10
Agreement of Locally and Centrally Adjudicated Cause of Death for All OS Participants

Data as of: August 31, 2002

	Closed Local ¹	Closed Central N	Closed Central %	Confirmed Cause N	Confirmed Cause % ²	Related Cause N	Related Cause % ²	Unrelated Cause N	Unrelated Cause % ²
Final adjudicated death	2417	1605	66%	1304	(81%)	139	(9%)	162	(10%)
Cardiovascular									
Atherosclerotic cardiac ³	317	221	70%	173	(78%)	19	(9%)	29	(13%)
Cerebrovascular	172	103	60%	92	(89%)	5	(5%)	6	(6%)
Pulmonary embolism	19	12	63%	8	(67%)	0	(0%)	4	(33%)
Other cardiovascular	155	109	70%	47	(43%)	46	(42%)	16	(15%)
Unknown cardiovascular	34	21	62%	1	(5%)	14	(67%)	6	(29%)
Total cardiovascular deaths	697	466	67%	321	(69%)	84	(18%)	61	(13%)
Cancer									
Breast cancer	155	97	63%	91	(94%)	3	(3%)	3	(3%)
Ovarian cancer	79	51	65%	48	(94%)	1	(2%)	2	(4%)
Endometrial cancer	22	11	50%	7	(64%)	4	(36%)	0	(0%)
Colorectal cancer	93	67	72%	63	(94%)	2	(3%)	2	(3%)
Other cancer	768	530	69%	491	(93%)	19	(4%)	20	(4%)
Unknown cancer site	66	44	67%	32	(73%)	11	(25%)	1	(2%)
Total cancer deaths	1183	800	68%	732	(92%)	40	(5%)	28	(4%)
Accident/Injury									
Homicide	4	4	100%	4	(100%)	0	(0%)	0	(0%)
Accident	57	41	72%	36	(88%)	2	(5%)	3	(7%)
Suicide	17	15	88%	12	(80%)	1	(7%)	2	(13%)
Other injury	3	2	67%	2	(100%)	0	(0%)	0	(0%)
Total accidental deaths	81	62	77%	54	(87%)	3	(5%)	5	(8%)
Other									
Other known cause	361	223	62%	174	(78%)	4	(2%)	45	(20%)
Unknown cause	95	54	57%	23	(43%)	8	(15%)	23	(43%)
Total deaths - other causes	456	277	61%	197	(71%)	12	(4%)	68	(25%)

¹ Excludes temporary adjudications.

² Percentages are relative to closed central.

³ "Atherosclerotic cardiac" combines definite and possible CHD death.

Table 6.11
Locally Verified Outcomes (Annualized Percentages) by Age for CT Participants

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	68132	9190	14664	31391	12887
Mean follow-up (months)	67.2	73.3	69.6	65.4	64.3
Cardiovascular					
CHD ¹	1241 (0.33%)	72 (0.13%)	132 (0.16%)	558 (0.33%)	479 (0.69%)
CHD death ²	271 (0.07%)	13 (0.02%)	26 (0.03%)	108 (0.06%)	124 (0.18%)
Total MI ³	1062 (0.28%)	62 (0.11%)	112 (0.13%)	486 (0.28%)	402 (0.58%)
Clinical MI	1016 (0.27%)	55 (0.10%)	108 (0.13%)	465 (0.27%)	388 (0.56%)
Evolving Q-wave MI ⁴	48 (0.01%)	7 (0.01%)	4 (<0.01%)	23 (0.01%)	14 (0.02%)
Possible evolving Q-wave MI ⁴	210 (0.06%)	27 (0.05%)	30 (0.04%)	86 (0.05%)	67 (0.10%)
Angina	1659 (0.43%)	83 (0.15%)	213 (0.25%)	817 (0.48%)	546 (0.79%)
CABG/PTCA	1688 (0.44%)	69 (0.12%)	197 (0.23%)	845 (0.49%)	577 (0.84%)
Carotid artery disease	270 (0.07%)	6 (0.01%)	32 (0.04%)	136 (0.08%)	96 (0.14%)
Congestive heart failure	945 (0.25%)	45 (0.08%)	101 (0.12%)	405 (0.24%)	394 (0.57%)
Stroke	941 (0.25%)	34 (0.06%)	83 (0.10%)	430 (0.25%)	394 (0.57%)
PVD	243 (0.06%)	11 (0.02%)	27 (0.03%)	117 (0.07%)	88 (0.13%)
CHD ¹ /Possible evolving Q-wave MI	1444 (0.38%)	99 (0.18%)	162 (0.19%)	640 (0.37%)	543 (0.79%)
Coronary disease ⁵	3672 (0.96%)	209 (0.37%)	440 (0.52%)	1736 (1.01%)	1287 (1.86%)
Total cardiovascular disease	4831 (1.27%)	251 (0.45%)	547 (0.64%)	2307 (1.35%)	1726 (2.50%)
Cancer					
Breast cancer ⁶	1784 (0.47%)	187 (0.33%)	376 (0.44%)	861 (0.50%)	360 (0.52%)
Invasive breast cancer	1416 (0.37%)	137 (0.24%)	303 (0.36%)	685 (0.40%)	291 (0.42%)
Non-invasive breast cancer	375 (0.10%)	50 (0.09%)	74 (0.09%)	181 (0.11%)	70 (0.10%)
Ovary cancer	173 (0.05%)	19 (0.03%)	33 (0.04%)	80 (0.05%)	41 (0.06%)
Endometrial cancer ⁷	220 (0.10%)	23 (0.07%)	48 (0.09%)	101 (0.10%)	48 (0.12%)
Colorectal cancer	493 (0.13%)	26 (0.05%)	69 (0.08%)	253 (0.15%)	145 (0.21%)
Other cancer ⁸	1810 (0.47%)	149 (0.27%)	280 (0.33%)	880 (0.51%)	501 (0.73%)
Total cancer	4359 (1.14%)	397 (0.71%)	781 (0.92%)	2116 (1.24%)	1065 (1.54%)
Fractures					
Hip fracture	391 (0.10%)	11 (0.02%)	21 (0.02%)	148 (0.09%)	211 (0.31%)
Vertebral fracture	440 (0.12%)	16 (0.03%)	48 (0.06%)	184 (0.11%)	192 (0.28%)
Other fracture ⁸	5179 (1.36%)	623 (1.11%)	945 (1.11%)	2414 (1.41%)	1197 (1.73%)
Total fracture	5815 (1.52%)	643 (1.15%)	1002 (1.18%)	2665 (1.56%)	1505 (2.18%)
Deaths					
Cardiovascular deaths	543 (0.14%)	21 (0.04%)	44 (0.05%)	222 (0.13%)	256 (0.37%)
Cancer deaths	842 (0.22%)	49 (0.09%)	95 (0.11%)	414 (0.24%)	284 (0.41%)
Other known cause	282 (0.07%)	19 (0.03%)	30 (0.04%)	118 (0.07%)	115 (0.17%)
Unknown cause	96 (0.03%)	7 (0.01%)	13 (0.02%)	45 (0.03%)	31 (0.04%)
Not yet adjudicated	166 (0.04%)	6 (0.01%)	18 (0.02%)	80 (0.05%)	62 (0.09%)
Total death	1929 (0.51%)	102 (0.18%)	200 (0.24%)	879 (0.51%)	748 (1.08%)

¹ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Total MI" includes clinical MI and evolving Q-wave MI.

⁴ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁵ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁶ Excludes nine cases with borderline malignancy.

⁷ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁸ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

Table 6.11 (continued)
Locally Verified Outcomes (Annualized Percentages) by Race/Ethnicity for CT Participants

Data as of: August 31, 2002

Outcome	Race/Ethnicity					
	American Indian/Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	292	1519	6983	2875	55525	938
Mean follow-up (months)	65.0	63.8	65.7	63.4	67.7	63.2
Cardiovascular						
CHD ¹	3 (0.19%)	14 (0.17%)	115 (0.30%)	26 (0.17%)	1064 (0.34%)	19 (0.38%)
CHD death ²	2 (0.13%)	4 (0.05%)	39 (0.10%)	4 (0.03%)	218 (0.07%)	4 (0.08%)
Total MI ³	2 (0.13%)	13 (0.16%)	91 (0.24%)	23 (0.15%)	916 (0.29%)	17 (0.34%)
Clinical MI	2 (0.13%)	12 (0.15%)	87 (0.23%)	23 (0.15%)	877 (0.28%)	15 (0.30%)
Evolving Q-wave MI ⁴	0 (0.00%)	1 (0.01%)	4 (0.01%)	0 (0.00%)	41 (0.01%)	2 (0.04%)
Possible evolving Q-wave MI ⁴	2 (0.13%)	4 (0.05%)	28 (0.07%)	6 (0.04%)	168 (0.05%)	2 (0.04%)
Angina	5 (0.32%)	23 (0.28%)	200 (0.52%)	53 (0.35%)	1356 (0.43%)	22 (0.45%)
CABG/PTCA	5 (0.32%)	14 (0.17%)	158 (0.41%)	43 (0.28%)	1450 (0.46%)	18 (0.36%)
Carotid artery disease	3 (0.19%)	2 (0.02%)	19 (0.05%)	1 (0.01%)	243 (0.08%)	2 (0.04%)
Congestive heart failure	3 (0.19%)	8 (0.10%)	160 (0.42%)	21 (0.14%)	739 (0.24%)	14 (0.28%)
Stroke	5 (0.32%)	20 (0.25%)	110 (0.29%)	26 (0.17%)	768 (0.25%)	12 (0.24%)
PVD	3 (0.19%)	1 (0.01%)	36 (0.09%)	3 (0.02%)	197 (0.06%)	3 (0.06%)
CHD ¹ /Possible evolving Q-wave MI	5 (0.32%)	18 (0.22%)	142 (0.37%)	32 (0.21%)	1226 (0.39%)	21 (0.42%)
Coronary disease ⁵	12 (0.76%)	44 (0.54%)	452 (1.18%)	103 (0.68%)	3011 (0.96%)	50 (1.01%)
Total cardiovascular disease	20 (1.26%)	66 (0.82%)	582 (1.52%)	128 (0.84%)	3971 (1.27%)	64 (1.30%)
Cancer						
Breast cancer ⁶	2 (0.13%)	43 (0.53%)	124 (0.32%)	46 (0.30%)	1551 (0.49%)	18 (0.36%)
Invasive breast cancer	2 (0.13%)	32 (0.40%)	94 (0.25%)	38 (0.25%)	1236 (0.39%)	14 (0.28%)
Non-invasive breast cancer	0 (0.00%)	11 (0.14%)	31 (0.08%)	8 (0.05%)	321 (0.10%)	4 (0.08%)
Ovary cancer	1 (0.06%)	2 (0.02%)	15 (0.04%)	2 (0.01%)	149 (0.05%)	4 (0.08%)
Endometrial cancer ⁷	1 (0.14%)	1 (0.02%)	11 (0.07%)	7 (0.08%)	197 (0.10%)	3 (0.10%)
Colorectal cancer	4 (0.25%)	10 (0.12%)	54 (0.14%)	20 (0.13%)	398 (0.13%)	7 (0.14%)
Other cancer ⁸	8 (0.51%)	29 (0.36%)	135 (0.35%)	45 (0.30%)	1572 (0.50%)	21 (0.42%)
Total cancer	16 (1.01%)	85 (1.05%)	329 (0.86%)	115 (0.76%)	3765 (1.20%)	49 (0.99%)
Fractures						
Hip fracture	0 (0.00%)	3 (0.04%)	13 (0.03%)	6 (0.04%)	365 (0.12%)	4 (0.08%)
Vertebral fracture	0 (0.00%)	9 (0.11%)	5 (0.01%)	6 (0.04%)	416 (0.13%)	4 (0.08%)
Other fracture ⁸	21 (1.33%)	78 (0.97%)	269 (0.70%)	137 (0.90%)	4623 (1.48%)	51 (1.03%)
Total fracture	21 (1.33%)	88 (1.09%)	285 (0.75%)	146 (0.96%)	5218 (1.67%)	57 (1.15%)
Deaths						
Cardiovascular deaths	3 (0.19%)	8 (0.10%)	80 (0.21%)	8 (0.05%)	438 (0.14%)	6 (0.12%)
Cancer deaths	2 (0.13%)	18 (0.22%)	77 (0.20%)	20 (0.13%)	714 (0.23%)	11 (0.22%)
Other known cause	5 (0.32%)	1 (0.01%)	34 (0.09%)	4 (0.03%)	236 (0.08%)	2 (0.04%)
Unknown cause	1 (0.06%)	0 (0.00%)	13 (0.03%)	1 (0.01%)	80 (0.03%)	1 (0.02%)
Not yet adjudicated	1 (0.06%)	3 (0.04%)	17 (0.04%)	7 (0.05%)	137 (0.04%)	1 (0.02%)
Total death	12 (0.76%)	30 (0.37%)	221 (0.58%)	40 (0.26%)	1605 (0.51%)	21 (0.42%)

¹ "CHD" includes clinical MI, evolving Q-wave MI, and CHD death.

² "CHD death" includes definite and possible CHD death.

³ "Total MI" includes clinical MI and evolving Q-wave MI.

⁴ Only women with a follow-up ECG are used to compute the annual rates for (possible) evolving Q-wave MIs.

⁵ "Coronary disease" includes clinical MI, evolving Q-wave MI, possible evolving Q-wave MI, CHD death, angina, congestive heart failure, and CABG/PTCA.

⁶ Excludes nine cases with borderline malignancy.

⁷ Only women without a baseline hysterectomy are used to compute the annual rates of endometrial cancer.

⁸ Only one report of "other cancer" or "other fracture" is counted per woman; however, the first other cancer or other fracture of each type is adjudicated. Excludes non-melanoma skin cancer and fractures indicated as pathological.

Table 6.12
Counts (Annualized Percentages) of Participants with Self-Reported Outcomes by Age and Race/Ethnicity
for CT Participants who did not report a prevalent condition at baseline

Data as of: August 31, 2002

Outcome	Total	Age			
		50-54	55-59	60-69	70-79
Number randomized	68132	9190	14664	31391	12887
Mean follow-up (months)	67.2	73.3	69.6	65.4	64.3
Hospitalizations					
Ever	26388 (6.92%)	2620 (4.67%)	4652 (5.47%)	12558 (7.34%)	6558 (9.49%)
Two or more	12342 (3.24%)	1057 (1.88%)	1940 (2.28%)	5846 (3.42%)	3499 (5.06%)
Other					
DVT ¹	561 (0.15%)	33 (0.06%)	84 (0.10%)	250 (0.15%)	194 (0.29%)
Pulmonary embolism	323 (0.09%)	16 (0.03%)	52 (0.06%)	156 (0.09%)	99 (0.14%)
Diabetes (treated)	3415 (0.94%)	469 (0.86%)	722 (0.88%)	1568 (0.96%)	656 (1.00%)
Gallbladder disease ²	3796 (1.19%)	552 (1.11%)	874 (1.20%)	1769 (1.25%)	601 (1.08%)
Hysterectomy	1492 (0.67%)	193 (0.60%)	322 (0.61%)	719 (0.73%)	258 (0.66%)
Glaucoma	5054 (1.38%)	467 (0.85%)	939 (1.13%)	2462 (1.50%)	1186 (1.86%)
Osteoporosis	10445 (2.90%)	939 (1.71%)	1771 (2.15%)	5130 (3.19%)	2605 (4.22%)
Osteoarthritis ³	9385 (5.57%)	1269 (3.07%)	2049 (3.55%)	4319 (4.34%)	1748 (5.06%)
Rheumatoid arthritis	2816 (0.77%)	389 (0.71%)	640 (0.78%)	1251 (0.76%)	536 (0.82%)
Intestinal polyps	6962 (1.96%)	778 (1.43%)	1423 (1.76%)	3498 (2.21%)	1263 (2.06%)
Lupus	486 (0.13%)	77 (0.14%)	115 (0.14%)	225 (0.13%)	69 (0.10%)
Kidney stones ³	1140 (0.53%)	147 (0.35%)	240 (0.36%)	535 (0.39%)	218 (0.39%)
Cataracts ³	15013 (7.62%)	824 (1.93%)	2266 (3.45%)	8250 (6.65%)	3673 (9.45%)
Pills for hypertension	12534 (4.67%)	1532 (3.38%)	2592 (4.00%)	5799 (4.98%)	2611 (6.21%)

Outcomes	Race/Ethnicity					
	Am Indian/ Alaskan Native	Asian/Pacific Islander	Black/African American	Hispanic/ Latino	White	Unknown
Number randomized	292	1519	6983	2875	55525	938
Mean follow-up (months)	65.0	63.8	65.7	63.4	67.7	63.2
Hospitalizations						
Ever	113 (7.14%)	382 (4.73%)	2735 (7.15%)	891 (5.86%)	21938 (7.00%)	329 (6.66%)
Two or more	62 (3.92%)	137 (1.70%)	1311 (3.43%)	361 (2.38%)	10324 (3.29%)	147 (2.97%)
Other						
DVT ¹	2 (0.13%)	1 (0.01%)	50 (0.13%)	9 (0.06%)	493 (0.16%)	6 (0.12%)
Pulmonary embolism	4 (0.25%)	2 (0.02%)	26 (0.07%)	3 (0.02%)	283 (0.09%)	5 (0.10%)
Diabetes (treated)	21 (1.47%)	94 (1.24%)	626 (1.85%)	228 (1.61%)	2396 (0.79%)	50 (1.08%)
Gallbladder disease ²	16 (1.38%)	60 (0.82%)	299 (0.87%)	168 (1.45%)	3197 (1.23%)	56 (1.33%)
Hysterectomy	5 (0.70%)	25 (0.48%)	88 (0.53%)	49 (0.58%)	1313 (0.69%)	12 (0.42%)
Glaucoma	24 (1.60%)	97 (1.25%)	670 (1.88%)	227 (1.54%)	3972 (1.31%)	64 (1.38%)
Osteoporosis	47 (3.13%)	260 (3.39%)	559 (1.52%)	409 (2.89%)	9027 (3.06%)	143 (3.11%)
Osteoarthritis ³	51 (0.12%)	211 (0.37%)	936 (0.94%)	467 (1.35%)	7570 (5.49%)	150 (7.06%)
Rheumatoid arthritis	22 (1.55%)	55 (0.71%)	502 (1.41%)	264 (1.82%)	1921 (0.64%)	52 (1.11%)
Intestinal polyps	35 (2.41%)	140 (1.89%)	727 (2.04%)	245 (1.69%)	5724 (1.97%)	91 (2.00%)
Lupus	4 (0.26%)	6 (0.07%)	68 (0.18%)	19 (0.13%)	384 (0.12%)	5 (0.10%)
Kidney stones ³	9 (0.02%)	28 (0.04%)	112 (0.08%)	56 (0.10%)	918 (0.52%)	17 (0.61%)
Cataracts ³	65 (0.15%)	292 (0.44%)	1383 (1.12%)	565 (1.45%)	12500 (7.75%)	208 (8.25%)
Pills for hypertension	56 (5.42%)	271 (4.93%)	1258 (6.58%)	569 (5.01%)	10225 (4.48%)	155 (4.74%)

¹ Inpatient DVT only.

² "Gallbladder disease" includes self-reports of both hospitalized and non-hospitalized events.

³ These outcomes have not been self-reported on all versions of Form 33. The annualized percentages are corrected for the different amounts of follow-up.

Table 6.13
Locally Confirmed Other Cancers (Annualized Percentages): CT and OS Participants

Data as of: August 31, 2002

	CT		OS	
Number of participants	68132		93676	
Mean follow-up time (months)	67.2		60.8	
Ppts with other cancer	1810	(0.47%)	2374	(0.50%)
Accessory sinus	0	(0.00%)	0	(0.00%)
Adrenal gland	2	<(0.01%)	4	<(0.01%)
Anus	8	<(0.01%)	9	<(0.01%)
Biliary tract, parts of (other/unspecified)	26	(0.01%)	17	<(0.01%)
Bladder	104	(0.03%)	132	(0.03%)
Bones/joints/articular cartilage (limbs)	4	<(0.01%)	4	<(0.01%)
Bones/joints/articular cartilage (other)	2	<(0.01%)	2	<(0.01%)
Brain	51	(0.01%)	60	(0.01%)
Cervix	39	(0.01%)	31	(0.01%)
Connective/subcutaneous/soft tissues	7	<(0.01%)	12	<(0.01%)
Endocrine glands, related structures	2	<(0.01%)	1	<(0.01%)
Esophagus	16	<(0.01%)	24	(0.01%)
Eye and adnexa	3	<(0.01%)	3	<(0.01%)
Genital organs	18	<(0.01%)	9	<(0.01%)
Kidney	81	(0.02%)	105	(0.02%)
Larynx	9	<(0.01%)	7	<(0.01%)
Leukemia	78	(0.02%)	86	(0.02%)
Liver	22	(0.01%)	21	<(0.01%)
Lung	349	(0.09%)	421	(0.09%)
Lymph nodes	8	<(0.01%)	4	<(0.01%)
Lymphoma,Hodgkins	10	<(0.01%)	9	<(0.01%)
Lymphoma,Non-Hodgkins	152	(0.04%)	206	(0.04%)
Melanoma of the skin	227	(0.06%)	312	(0.07%)
Multiple myeloma	72	(0.02%)	58	(0.01%)
Oral (mouth)	11	<(0.01%)	11	<(0.01%)
Palate	3	<(0.01%)	4	<(0.01%)
Pancreas	88	(0.02%)	106	(0.02%)
Parotid gland (Stensen's duct)	3	<(0.01%)	14	<(0.01%)
Peripheral nerves and autonomic nervous system	0	(0.00%)	3	<(0.01%)
Pyriform sinus	0	(0.00%)	1	<(0.01%)
Respiratory system, intrathoracic, other	5	<(0.01%)	8	<(0.01%)
Salivary glands, major (other/unspecified)	2	<(0.01%)	5	<(0.01%)
Stomach	19	<(0.01%)	30	(0.01%)
Thyroid	56	(0.01%)	67	(0.01%)
Tongue, part of (other/unspecified)	15	<(0.01%)	13	<(0.01%)
Urinary organs (other/unspecified)	5	<(0.01%)	12	<(0.01%)
Uterus, not otherwise specified	23	(0.01%)	45	(0.01%)
Other/unknown site of cancer	215	(0.06%)	287	(0.06%)
Other/unknown cancers reported on death form	102	(0.03%)	258	(0.05%)

Table 6.14
Locally Confirmed Other Fractures (Annualized Percentages): CT and OS Participants

Data as of: August 31, 2002

	CT	OS ¹
<u>Locally confirmed</u>		
Number of participants	68132	6365
Mean follow-up time (months)	67.2	69.1
Ppts with other fractures	5179 (1.36%)	487 (1.33%)
Ankle	915 (0.24%)	80 (0.22%)
Carpal bone(s) in wrist	130 (0.03%)	8 (0.02%)
Clavicle or collar bone	84 (0.02%)	8 (0.02%)
Elbow, not otherwise specified	11 (<0.01%)	0 (0.00%)
Humerus, shaft/unspecified	56 (0.01%)	5 (0.01%)
Humerus, upper end	541 (0.14%)	44 (0.12%)
Humerus, lower end	68 (0.02%)	6 (0.02%)
Metacarpal bone(s)	185 (0.05%)	13 (0.04%)
Patella	234 (0.06%)	23 (0.06%)
Pelvis	189 (0.05%)	27 (0.07%)
Radius or ulna	1443 (0.38%)	150 (0.41%)
Sacrum and coccyx	58 (0.02%)	8 (0.02%)
Scapula	23 (0.01%)	4 (0.01%)
Shaft of femur	68 (0.02%)	5 (0.01%)
Tarsal/metatarsal bones	898 (0.24%)	94 (0.26%)
Tibia and fibula	443 (0.12%)	27 (0.07%)
Tibial plateau	103 (0.03%)	7 (0.02%)
Upper radius/ulna	274 (0.07%)	27 (0.07%)
Unknown other fracture	2 (<0.01%)	2 (0.01%)
<u>Self-Reports</u>		
Number of participants		93676
Mean follow-up time (months)		60.8
Elbow		430 (0.09%)
Foot		1564 (0.33%)
Hand		286 (0.06%)
Knee		524 (0.11%)
Lower Arm		2239 (0.47%)
Lower Leg		1751 (0.37%)
Pelvis		381 (0.08%)
Tailbone		114 (0.02%)
Upper Arm		910 (0.19%)
Upper Leg		216 (0.05%)
Vertebra		967 (0.20%)
Other Fracture		1920 (0.40%)

¹ Other fractures for OS Participants are only confirmed in the three bone density clinics.

Table 6.15
Cross-tabulation of ECG Codes Suggesting an Incident MI and
Locally Confirmed and Self-Reported MI for All CT Participants

Data as of: August 31, 2002

	No Locally Confirmed MI or Open Self-Report of MI	Locally Confirmed MI ¹	Total
All CT Participants			
No significant Q or ST-T evolution ²	55101	287	55388
Borderline Q-wave change ³	1695	38	1733
Ischemic ST-T evolution ⁴	1020	37	1057
Possible evolving Q-wave MI ⁵	135 ⁶	19	154
Evolving Q-wave MI ⁷	27 ⁸	18	45
Total	57978	399	58377
HRT Participants			
No significant Q or ST-T evolution ²	22002	135	22137
Borderline Q-wave change ³	726	16	742
Ischemic ST-T evolution ⁴	467	15	482
Possible evolving Q-wave MI ⁵	63 ⁶	8	71
Evolving Q-wave MI ⁷	9 ⁸	11	20
Total	23267	185	23452
DM Participants			
No significant Q or ST-T evolution ²	39570	191	39761
Borderline Q-wave change ³	1175	26	1201
Ischemic ST-T evolution ⁴	695	25	720
Possible evolving Q-wave MI ⁵	83 ⁶	16	99
Evolving Q-wave MI ⁷	20 ⁸	9	29
Total	41543	267	41810
CaD Participants			
No significant Q or ST-T evolution ²	31204	94	31298
Borderline Q-wave change ³	985	14	999
Ischemic ST-T evolution ⁴	543	13	556
Possible evolving Q-wave MI ⁵	78 ⁶	7	85
Evolving Q-wave MI ⁷	18 ⁸	8	26
Total	32828	136	32964

¹ Includes only locally confirmed MIs that took place before the latest follow-up ECG.

² Novacode Incident MI code I 5.0.

³ Novacode Incident MI code I 5.7.

⁴ Novacode Incident MI code I 5.5, I 5.6.1, and I 5.6.2.

⁵ Novacode Incident MI code I 5.3 and I 5.4.

⁶ Cases in this cell are possible evolving Q-wave MIs.

⁷ Novacode Incident MI code I 5.1 and I 5.2.

⁸ Cases in this cell are definite evolving Q-wave MIs.

Table 6.16
Cause of Death (Annualized Percentages): CT and OS Participants

Data as of: August 31, 2002

	CT		OS	
Number Randomized	68132		93676	
Mean Follow-up Time (months)	67.2		60.8	
Total death	1929	(0.51%)	2981	(0.63%)
Adjudicated death	1763	(0.46%)	2677	(0.56%)
Final adjudicated death	1617	(0.42%)	2417	(0.51%)
Temporary adjudicated death	146	(0.04%)	259	(0.05%)
Identified by NDI search	0	(0.00%)	1	<0.01%
Cardiovascular				
Atherosclerotic cardiac	271	(0.07%)	329	(0.07%)
CHD deaths adjudicated before 10/99	86	(0.02%)	82	(0.02%)
Definite CHD deaths adjudicated after 10/99	105	(0.03%)	126	(0.03%)
Possible CHD deaths adjudicated after 10/99	80	(0.02%)	121	(0.03%)
Cerebrovascular	127	(0.03%)	184	(0.04%)
Pulmonary embolism	12	<0.01%	21	<0.01%
Other cardiovascular	104	(0.03%)	171	(0.04%)
Unknown cardiovascular	29	(0.01%)	42	(0.01%)
Total cardiovascular deaths	543	(0.14%)	747	(0.16%)
Cancer				
Breast cancer	31	(0.01%)	165	(0.03%)
Ovarian cancer	66	(0.02%)	85	(0.02%)
Endometrial cancer	7	<0.01%	24	(0.01%)
Colorectal cancer	84	(0.02%)	97	(0.02%)
Other cancer	609	(0.16%)	811	(0.17%)
Unknown cancer site	45	(0.01%)	72	(0.02%)
Total cancer deaths	842	(0.22%)	1254	(0.26%)
Accident/injury				
Homicide	5	<0.01%	5	<0.01%
Accident	45	(0.01%)	59	(0.01%)
Suicide	7	<0.01%	17	<0.01%
Other injury	4	<0.01%	4	<0.01%
Total accidental deaths	61	(0.02%)	85	(0.02%)
Other				
Other known cause	221	(0.06%)	391	(0.08%)
Unknown cause	96	(0.03%)	200	(0.04%)
Total deaths – other causes	317	(0.08%)	591	(0.12%)

Table 6.17
Results of NDI Search¹

	Known dead ²		Lost to follow-up ³		Known alive ⁴	
	N	%	N	%	N	%
Submitted to NDI	1252		2249		500	
NDI returned matches	1235	98.6	731	32.5	149	29.8
Matches satisfying WHI criteria	1224	97.8	53	2.4	0	0.0
Reported dead to WHI after 8/31/2000	N/A		27	1.2 ⁵	N/A	
Only identified using NDI	N/A		26	1.2 ⁶	N/A	

¹ Analysis has not been updated from that of August 31, 2001.

² Participants having a Form 120 or Form 124 with date of death before 1/1/2000.

³ Participants who were lost-to-follow-up or no-follow-up by 8/31/2000, for whom contact was before 1/1/2000.

⁴ Randomly selected participants with whom there was clinic contact after 1/1/2000.

⁵ 1 of these participants was a CT participant, 26 were OS participants.

⁶ 8 of these participants were CT participants, 18 were OS participants.

Table 6.18
Lost-to-Follow-up and Vital Status by Clinic: CT Participants

Data as of: August 31, 2002

Clinic	Deceased		Alive: Current Participation ¹		Alive: Recent Participation ²		Alive: Past/Unknown Participation ³		Stopped Follow-up ⁴		Lost to Follow-up ⁵		Total N
	N	%	N	%	N	%	N	%	N	%	N	%	
Atlanta	50	2.9	1621	94.2	13	0.8	1	0.1	28	1.6	7	0.4	1720
Birmingham	62	3.4	1701	92.8	23	1.3	1	0.1	34	1.9	11	0.6	1832
Bowman	42	2.8	1364	89.3	35	2.3	0	0.0	57	3.7	29	1.9	1527
Brigham	54	2.3	2199	95.5	27	1.2	3	0.1	1	0.0	19	0.8	2303
Buffalo	50	3.1	1526	95.1	6	0.4	0	0.0	20	1.2	3	0.2	1605
Chapel Hill	41	2.7	1467	95.3	1	0.1	0	0.0	30	1.9	0	0.0	1539
Chicago	53	3.3	1495	92.1	8	0.5	0	0.0	45	2.8	23	1.4	1624
Chi-Rush	43	3.2	1197	90.3	16	1.2	4	0.3	32	2.4	34	2.6	1326
Cincinnati	29	2.1	1275	91.7	28	2.0	1	0.1	48	3.5	10	0.7	1391
Columbus	48	3.1	1458	94.1	4	0.3	0	0.0	29	1.9	10	0.6	1549
Detroit	19	1.4	1184	86.0	52	3.8	1	0.1	88	6.4	33	2.4	1377
GWU-DC	36	2.4	1426	94.3	26	1.7	2	0.1	15	1.0	7	0.5	1512
Gainesville	59	2.8	1933	93.2	20	1.0	0	0.0	50	2.4	11	0.5	2073
Honolulu	30	2.1	1275	90.6	39	2.8	0	0.0	41	2.9	22	1.6	1407
Houston	27	2.1	1128	88.8	37	2.9	2	0.2	60	4.7	16	1.3	1270
Iowa City	75	3.1	2319	95.3	4	0.2	0	0.0	17	0.7	18	0.7	2433
Irvine	34	2.1	1478	91.1	19	1.2	0	0.0	45	2.8	47	2.9	1623
L.A.	42	2.5	1572	93.8	16	1.0	2	0.1	34	2.0	10	0.6	1676
La Jolla	69	3.2	1839	85.1	77	3.6	10	0.5	25	1.2	140	6.5	2160
Madison	31	2.0	1500	96.4	4	0.3	0	0.0	18	1.2	3	0.2	1556
Medlantic	52	3.5	1340	89.6	39	2.6	1	0.1	42	2.8	21	1.4	1495
Memphis	74	4.2	1543	88.6	44	2.5	3	0.2	45	2.6	33	1.9	1742
Miami	30	2.0	1189	80.2	56	3.8	1	0.1	50	3.4	157	10.6	1483
Milwaukee	42	2.5	1546	93.6	12	0.7	0	0.0	45	2.7	6	0.4	1651
Minneapolis	59	3.0	1889	95.0	20	1.0	0	0.0	19	1.0	2	0.1	1989
NY-City	50	2.7	1734	92.2	43	2.3	9	0.5	19	1.0	26	1.4	1881
Nevada	55	3.7	1403	94.6	6	0.4	1	0.1	14	0.9	4	0.3	1483
Newark	64	2.6	2137	87.2	108	4.4	2	0.1	112	4.6	28	1.1	2451
Oakland	39	2.5	1493	95.2	10	0.6	0	0.0	18	1.1	8	0.5	1568
Pawtucket	70	2.6	2460	93.0	27	1.0	1	0.0	53	2.0	33	1.2	2644
Pittsburgh	58	3.5	1578	95.1	6	0.4	0	0.0	17	1.0	0	0.0	1659
Portland	48	2.9	1485	90.9	31	1.9	0	0.0	40	2.4	30	1.8	1634
San Antonio	21	1.5	1240	89.5	3	0.2	0	0.0	94	6.8	28	2.0	1386
Seattle	58	3.2	1605	88.9	87	4.8	5	0.3	28	1.6	22	1.2	1805
Stanford	40	2.3	1656	94.4	12	0.7	2	0.1	33	1.9	12	0.7	1755
Stonybrook	36	2.7	1282	94.6	12	0.9	0	0.0	25	1.8	0	0.0	1355
Torrance	25	2.5	872	86.6	41	4.1	1	0.1	34	3.4	34	3.4	1007
Tucson	98	4.7	1831	87.8	18	0.9	1	0.0	51	2.4	87	4.2	2086
U.C. Davis	74	3.8	1765	91.8	32	1.7	1	0.1	24	1.2	27	1.4	1923
Worcester	42	2.6	1546	94.7	27	1.7	0	0.0	9	0.6	8	0.5	1632
Total	1929	2.8	62551	91.8	1089	1.6	55	0.1	1489	2.2	1019	1.5	68132

¹ Participants who have filled in a Form 33 within the last 9 months.

² Participants who last filled in a Form 33 between 9 and 18 months ago.

³ Participants without a Form 33 within the last 18 months, who have been located (as indicated on Form 23) within the last 6 months.

⁴ Participants with codes 5 (no follow-up) or 8 (absolutely no follow-up) on Form 7.

⁵ Participants not in any of the above categories.

Table 6.19
Lost-to-Follow-up and Vital Status by Clinic: OS Participants

Data as of: August 31, 2002

Clinic	Deceased		Alive: Current Participation ¹		Alive: Recent Participation ²		Alive: Past/Unknown Participation ³		Stopped Follow-up ⁴		Lost to Follow-up ⁵		Total N
	N	%	N	%	N	%	N	%	N	%	N	%	
Atlanta	64	2.6	2277	92.4	98	4.0	1	0.0	7	0.3	16	0.6	2463
Birmingham	103	4.1	2223	87.9	93	3.7	0	0.0	63	2.5	47	1.9	2529
Bowman	61	2.7	1932	86.8	90	4.0	0	0.0	33	1.5	111	5.0	2227
Brigham	46	1.6	2822	95.8	55	1.9	1	0.0	1	0.0	21	0.7	2946
Buffalo	108	4.8	2091	93.0	31	1.4	0	0.0	14	0.6	4	0.2	2248
Chapel Hill	55	2.6	1981	95.1	30	1.4	0	0.0	12	0.6	5	0.2	2083
Chicago	62	3.3	1727	91.4	44	2.3	4	0.2	26	1.4	26	1.4	1889
Chi-Rush	73	3.6	1713	83.6	150	7.3	5	0.2	36	1.8	72	3.5	2049
Cincinnati	71	3.2	1971	87.6	71	3.2	8	0.4	50	2.2	78	3.5	2249
Columbus	54	2.4	2122	95.6	27	1.2	1	0.0	11	0.5	4	0.2	2219
Detroit	43	2.0	1822	86.3	75	3.6	58	2.7	64	3.0	50	2.4	2112
GWU-DC	73	3.2	2134	95.0	31	1.4	2	0.1	5	0.2	2	0.1	2247
Gainesville	93	3.3	2534	90.8	86	3.1	1	0.0	58	2.1	20	0.7	2792
Honolulu	49	2.3	1851	87.6	117	5.5	2	0.1	62	2.9	32	1.5	2113
Houston	85	4.0	1921	90.2	33	1.5	7	0.3	73	3.4	11	0.5	2130
Iowa City	77	2.5	2954	94.7	28	0.9	0	0.0	31	1.0	30	1.0	3120
Irvine	66	3.0	2071	92.9	10	0.4	0	0.0	45	2.0	38	1.7	2230
L.A.	58	2.6	2073	94.4	14	0.6	2	0.1	28	1.3	20	0.9	2195
La Jolla	126	3.6	2842	82.1	188	5.4	25	0.7	17	0.5	265	7.7	3463
Madison	68	3.4	1888	95.3	13	0.7	0	0.0	9	0.5	3	0.2	1981
Medlantic	70	3.2	1958	89.3	97	4.4	7	0.3	30	1.4	31	1.4	2193
Memphis	81	3.2	2095	83.3	149	5.9	5	0.2	76	3.0	110	4.4	2516
Miami	45	3.3	1041	75.8	65	4.7	0	0.0	34	2.5	189	13.8	1374
Milwaukee	60	2.7	2038	90.7	59	2.6	1	0.0	27	1.2	61	2.7	2246
Minneapolis	71	2.6	2530	92.8	58	2.1	0	0.0	26	1.0	42	1.5	2727
NY-City	95	3.3	2554	88.0	153	5.3	11	0.4	21	0.7	69	2.4	2903
Nevada	121	5.6	2003	92.1	30	1.4	0	0.0	17	0.8	3	0.1	2174
Newark	79	2.3	2919	86.5	141	4.2	2	0.1	58	1.7	174	5.2	3373
Oakland	81	3.9	1906	92.8	37	1.8	0	0.0	25	1.2	4	0.2	2053
Pawtucket	105	2.9	3274	91.2	73	2.0	72	2.0	38	1.1	26	0.7	3588
Pittsburgh	86	4.5	1705	88.9	41	2.1	2	0.1	56	2.9	27	1.4	1917
Portland	54	2.4	2008	90.0	92	4.1	3	0.1	39	1.7	36	1.6	2232
San Antonio	52	2.7	1729	89.0	25	1.3	0	0.0	113	5.8	23	1.2	1942
Seattle	74	4.4	1462	87.9	59	3.5	28	1.7	19	1.1	21	1.3	1663
Stanford	95	3.6	2476	92.8	36	1.3	3	0.1	51	1.9	8	0.3	2669
Stonybrook	47	2.3	1878	92.6	48	2.4	2	0.1	14	0.7	39	1.9	2028
Torrance	53	3.5	1280	85.2	41	2.7	1	0.1	27	1.8	101	6.7	1503
Tucson	129	4.6	2362	84.9	55	2.0	1	0.0	37	1.3	198	7.1	2782
U.C. Davis	89	3.9	2086	91.9	53	2.3	2	0.1	30	1.3	9	0.4	2269
Worcester	59	2.6	2055	91.8	95	4.2	3	0.1	10	0.4	17	0.8	2239
Total	2981	3.2	84308	90.0	2691	2.9	260	0.3	1393	1.5	2043	2.2	93676

¹ Participants who have filled in a Form 33 within the last 15 months.

² Participants who last filled in a Form 33 between 15 and 24 months ago.

³ Participants without a Form 33 within the last 24 months, who have been located (as indicated on Form 23) within the last 6 months.

⁴ Participants with codes 5 (no follow-up) or 8 (absolutely no follow-up) on Form 7.

⁵ Participants not in any of the above categories.

7. Laboratory Studies

7.1 Overview

Blood samples are collected on all CT participants at baseline and year 1 and on a 6% subsample of participants at years 3, 6, and 9. Blood samples are collected on all OS participants at baseline and Year 3. All blood samples are obtained in the fasting state (at least 12 hours), maintained at 4°C until plasma or serum is separated. In addition, urine samples are collected on both CT and OS participants at the three Bone Density sites at baseline, year 1 and year 9 for CT, and baseline and year 3 for OS participants. Plasma, serum, RBCs, buffy coat, and urine aliquots are frozen at -70°C and sent on dry ice to the central repository (McKesson Biological Services, Rockville, MD) where storage at -70°C is maintained.

7.2 Status of Analyses

Core Analytes

The analyses of the twenty core analytes are done by Medical Research Laboratories, Highland Heights, Kentucky (MRL). MRL has completed the analyses of the CT 6% subsample core analytes for baseline, Year 1, and Year 3 samples. Analysis of Year 6 bloods will begin later this year. See *Sections 2 and 3* in this report for presentation of the laboratory results for HRT and DM.

MRL has also completed the analysis of the 1% OS Measurement Precision Study (OS-MPS) participants. See *Section 5.3* in the February 1, 1999 to August 25, 1999 Semi-Annual Progress Report for the results.

DNA Extraction

DNA extraction for WHI is done by BioServe Biotechnologies, Laurel, MD. For each buffy coat sample, BioServe prepares up to four daughter aliquots containing 3 micrograms DNA each and divides the remaining DNA into parent aliquots containing up to 200 micrograms DNA each, depending on the quantity of DNA extracted. BioServe sends the extracted DNA aliquots to McKesson for storage and/or distribution to DNA testing laboratories.

To date, BioServe has completed the DNA extraction of over 1,700 samples, including all of the samples for the CVD Biomarker Case Control Study of CHD, Stroke, and VTE in the HRT Clinical Trial and for ancillary study #83, Paul Ridker, Thrombotic, Inflammatory, and Genetic Markers for Coronary Heart Disease in Postmenopausal Women: A WHI Umbrella Study.

CVD Biomarker Case-Control Study of CHD, Stroke, and VTE in the HRT Clinical Trial

This study is divided into two phases, with phase I including all locally adjudicated cases of CHD, stroke, and VTE occurring within two years of randomization and phase II including similar types of cases occurring more than two years after randomization. The University of Leiden was contracted to perform the DNA testing for the study. All phase I and phase II DNA samples were sent to Leiden, and results from all but two polymorphisms have been received, with these final results expected in November. The University of Vermont was contracted to perform the thrombosis analyses for the study. The phase I and phase II samples were sent to Vermont in October 2001, and completion of the phase I thrombosis analyses Vermont is expected by the end of 2002 and completion of phase II analyses is expected in mid-2003.

MRL has completed the phase I and phase II lipid analyses for the study.

Hormones

Esoterix (Calabasas Hills, CA; formerly Endocrine Sciences) has completed hormone analyses on baseline and year 1 samples for 120 of the 300 participants included in the approved paper "Correlates of endogenous sex hormone concentrations in WHI". Samples from the remaining 180 participants will be sent in monthly batches of 30 participants by the end of the year.

In addition, serum samples were sent to Esoterix to conduct a pilot study of the correlation between the standard Esoterix assay for total estradiol, which uses 1.0 ml of serum, and the alternative Vitros IRA assay, which uses only 0.1 ml of serum. At the same time, aliquots of serum from the samples were sent to two other labs for an IGF validation study.

Ancillary Studies

Analyses of blood samples for ancillary study (AS) #83, Paul Ridker, Thrombotic, Inflammatory, and Genetic Markers for Coronary Heart Disease in Postmenopausal Women: A WHI Umbrella Study, were completed last year. The analyses of the lipid core analytes was also completed at the AS laboratory. Samples for core analytes will be sent to MRL for analyses at a later time.

Analyses of bloods for AS #110, Kathryn Rexrode, Sex Steroid Hormones and Risk of Coronary Heart Disease: A nested Case Control Study were partially completed this fall. The analyses of samples for AS #129, Howard Strickler, Association of Diabetes and Insulin-like Growth Factor-I with Risks of Colorectal, Breast and Endometrial Cancers are on hold pending the results of the estradiol assay pilot study being conducted by Esoterix.

Currently, WHI has made available 1.8 ml baseline and 1.8 ml Year 3 serum, citrate plasma, and EDTA plasma samples for use by OS ancillary studies. Through August 30, 2002, WHI has approved 19 ASs using WHI blood specimens, with 7 funded and the other 12 pending funding. Six ASs were reviewed for the Spring 2002 OS blood competition, and review of 7 additional AS requesting blood specimens is planned for the Fall 2002 OS blood competition due in September. Table 1 gives a summary of the volume of OS blood samples committed to OS ancillary studies by disease type as of Aug. 30, 2002. To date, no more baseline serum is available for current CHD and hip fracture cases, and very limited baseline citrate and EDTA plasma is available for stroke cases (see volumes indicated in Table 7.1).

Table 7.1
OS Blood Committed to Ancillary Studies (AS)

Outcomes	# of AS	Cases reported as of 8/02	Max # of cases committed ¹	Volume committed (baseline/year 3)			
				Serum (ml)	Citrate plasma (ml)	EDTA plasma (ml)	DNA (µg)
CHD	3	1,297	2,015	1.8 ²	1.0	0.8	9
Stroke	1	1,061	1,100		1.5	1.5	3
Hypertension	1	14,526	800			0.8	3
Type 2 diabetes	1	3,174	2,150			0.25	3
Hip fracture	1	540	400	1.7 ²			3
Breast cancer	5	2,570	5,400	1.3 – 1.7 ²			9
Colorectal cancer	3	554	1,984	0.5			12
Endometrial cancer	3	329	891	0.5			9
Leukemia	1	78	59				3
Ovarian cancer	3	226	546	1.5 ² /1.0			6
Pancreatic cancer	1	88	93			0.6	3
Eye disease	1	See note 3	1,700	1.1			

¹ Not all volume committed to all cases

² No more baseline sample available for these cases

³ Determined by local ancillary study screening

8. Clinical Center Performance Monitoring

8.1 Performance Monitoring

A four step plan is used 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. CCC staff train, monitor, and communicate with CC staff on an ongoing basis.

8.2 PMC Committee Activity

The Performance Monitoring Committee (PMC) provides a facilitating and monitoring role for CCs. In July 1998, the PMC separated its monitoring activities into two separate groups, with one group addressing outcomes and one group addressing adherence/retention and other issues. Membership of the Adherence and Retention PMC (A&R PMC) includes: Sally Shumaker, CFC PI, chair; Shari Ludlum and Linda Pottern, Project Office; Gerardo Heiss, Chapel Hill Clinical Center PI; Betty Caan, Oakland Clinical Center PI (began in April, replacing Judy Hsia, George Washington Clinical Center PI in March 2002), Michelle Naughton, Steve Rapp, Sara Wilcox, CFC; and Barb Cochrane, Julie Hunt, Andrea LaCroix, Bernedine Lund, and Lesley Tinker, CCC. Membership of the Outcomes PMC (O-PMC) includes Anne McTiernan, CCC, chair; David Curb, Honolulu Clinical Center PI; Marian Limacher, Gainesville Clinical Center PI; Ronald Prineas, CFC; Jacques Rossouw, Project Office; and Charles Kooperberg, Bernedine Lund, and Lori Proulx-Burns, CCC.

Since March 1, 2002, the A&R PMC held six conference calls, reviewing 5-6 Clinical Centers on each call. Information reviewed about each Clinical Center includes: 1) cumulative and recent measures of participant intervention and follow-up status; 2) HRT and CaD adherence measures; 3) DM C-I and DM intervention measures; and 4) cumulative and recent measures of completion of required tasks. Each performance measure is compared to study goals, study-wide averages, and performance in the last 3-12 month period. At the request of the PMC, many of the CCs submitted copies of their Biannual Technical Reports and/or informational memos about their recent performance in the materials they sent to the PMC for review on the conference calls. The A&R PMC held separate targeted conference calls with two CCs.

Specific issues the PMC-A&R addressed since March 1, 2002:

- In March, at the request of the Adherence and Retention Working Group, the PMC-A&R reviewed the CC priorities for task completion, and agreed that the priorities established in 1993-4 should not be changed. Instead, the PMC suggested that the priorities be redistributed to the CCs.
- In May, the Committee reviewed tables showing the percent of HRT and CaD participants who had restarted taking study pills after they had previously stopped.
- In June, the PMC discussed the issue of participants not wanting to come into the CC for a visit, and agreed to investigate how CCs address getting distant participants into the CCs, and which sites use remote sites for those participants.
- In August, the Committee discussed possible strategies for helping CCs prioritize and carry out local implementation of the Estrogen plus Progestin update (including stopping study pills and unblinding).

In the same period, the O-PMC held six conference calls, reviewing 5-7 Clinical Centers on each call. A summary of each CC included: 1) recent and cumulative data on collection of required outcomes forms, outcomes packet assembly, and local adjudication; 2) a graph showing the timeliness of outcomes processing over time; 3) CC responsiveness to CCC queries for more information on cancer and CVD cases; and 4) a summary of number of staff and local adjudicators. In the letters to CCs, specific goals were listed for CCs. In addition, the O-PMC held separate targeted conference calls with four CCs to discuss issues with outcomes processing in more detail and to provide direction and interim goals for improving performance. Four CCs receiving the follow-up calls had made substantial progress on decreasing their backlog of outcomes cases.

In February, the Executive Committee asked for an outcomes catch-up plan similar to the recruitment catch-up plan the CCs used during recruitment. Using a backlog defined as the number of cases that were in process for more than two months, the following two reports were developed:

- A CC-specific catch-up 'worksheet' for the CCs to use as a tool to calculate the CC's average monthly and daily outcomes processing workload. The worksheet shows the number of cases the CC needs to process to eliminate the CC's backlog and/or to maintain the current workload. In May, CCs were sent a copy of the worksheet with data for their own CC filled in (data as of February 28, 2002). CCs are able to update their copy of the worksheet using data from their own CC-run reports on an on-going basis to monitor their status as close-out approaches. CCs with satellite sites are able to update the worksheet for each site.
- A one-page summary report titled "Outcomes Collection and Processing Backlog" showing the number of *Form 33/Form 33D - Medical History Update/(Detail)* completed, current outcomes processing workload, backlog, and the additional cases the CC would need to process each month to decrease the backlog by May 31, 2003. This date was selected to give time for CCs to evaluate their outcomes processing procedures and to eliminate any backlog they may have before CT and OS close-out begins. The final column in the report shows the percent increase in workload the CC needs to accomplish to eliminate the backlog by May 2003.
- As an additional aid to CCs, a current report showing timeliness of outcomes processing was enhanced to show data for the preceding last 12 months, allowing CCs to see more recent progress of outcomes case processing.

Plans over the next six months include having CCC Outcomes Liaisons attend 3-4 QA Visits to assist CCs having particular difficulty in processing outcomes efficiently.

The PMC report showing data as of August 30, 2002, is in *Tables 8.1-8.5*. Changes were made to the HRT table, dropping the adherence summary for the E-plus-P trial and including the adherence for only the E-Alone trial participants. The CCs also receive these tables quarterly.

Table 8.1
Performance Monitoring Committee Report
 Data as of 8/31/02

DM

	Adjusted C-I ¹				Task Completeness Form 60 - FFQ ⁴		% Stopped ⁵	
	Average ²		Sep 01 - Aug 02 ³		Dec 01 - May 02		Cum Aug 02	
	%	Quartile	%	Quartile	%	Quartile	%	Quartile
Nevada	12.9	1	10.6	1	96.2	1	6.5	2
Oakland	11.6	1	10.5	1	94.9	1	4.4	1
Iowa City	11.0	1	8.0	2	96.9	1	4.7	1
Madison	10.9	1	9.0	1	94.9	1	4.3	1
Columbus	10.8	1	8.5	1	95.4	1	6.5	2
Stanford	10.7	1	8.5	1	92.9	2	5.7	1
Milwaukee	10.7	1	9.4	1	94.4	1	5.2	1
Pittsburgh	10.5	1	8.3	1	96.0	1	4.7	1
Seattle	10.4	1	8.1	2	85.6	3	8.0	2
Minneapolis	10.3	1	7.4	2	93.2	2	6.5	2
GWU-DC	10.2	2	8.1	2	89.0	3	6.2	1
Irvine	9.8	2	7.3	2	92.2	2	6.6	2
Chicago	9.7	2	8.7	1	91.3	2	9.9	3
Portland	9.4	2	6.6	3	87.0	3	8.2	2
Gainesville	9.3	2	8.4	1	89.1	3	6.6	2
Worcester	9.2	2	7.6	2	95.5	1	5.9	1
Torrance	9.2	2	7.2	2	77.0	4	11.5	4
Chapel Hill	9.1	2	8.1	2	93.5	2	4.7	1
UC Davis	8.9	2	6.9	3	87.3	3	8.8	3
LA	8.9	2	6.7	3	89.7	3	8.6	3
Brigham	8.7	3	6.4	4	91.1	2	6.3	2
Buffalo	8.7	3	6.3	4	93.8	1	7.1	2
Pawtucket	8.7	3	7.0	3	92.4	2	8.3	3
Tucson	8.6	3	7.7	2	90.0	3	11.4	4
Memphis	8.6	3	7.0	3	86.3	3	11.2	4
Newark	8.4	3	6.9	3	75.3	4	11.5	4
Stony Brook	8.4	3	8.2	1	84.2	4	7.4	2
Houston	8.4	3	6.4	4	90.1	3	9.1	3
Bowman	8.3	3	6.2	4	78.8	4	10.0	3
Chi-Rush	8.2	3	7.3	2	94.0	1	13.1	4
Atlanta	8.1	4	6.5	3	87.8	3	5.5	1
Cincinnati	8.0	4	6.3	4	90.9	2	8.7	3
Honolulu	8.0	4	6.9	3	90.6	2	9.4	3
LaJolla	7.7	4	6.5	3	85.1	4	12.1	4
NYC	7.6	4	6.5	3	79.6	4	9.9	3
Detroit	7.1	4	5.2	4	72.7	4	12.8	4
Birmingham	6.7	4	6.0	4	85.1	4	9.9	3
San Antonio	6.1	4	4.8	4	82.3	4	14.8	4
Medlantic	5.7	4	4.1	4	92.5	2	11.3	4
Miami	5.0	4	4.2	4	68.3	4	21.5	4
CC Average	9.0		7.2		88.6		8.6	
Ave F/U 5.7 yr	Design Assumption 11.8				Goal ≥ 90%		Design Assumption 15.8	

¹ Adjusted C-I defined as (C-I of collected FFQs) x (FFQ completion rate)

² Based on FFQs collected after randomization through AV7.

³ Based on FFQs collected in the last 12 months

⁴ From WHIP 1445-Task Completeness; complete if encounter date on Form 60 is -6/+12 months from visit target date, using 6 month period ending 3 months before the data as of date; excludes deaths

⁵ From WHIP0751- DM Intervention & F/U Status, includes stopped intervention, stopped F/U, lost-to-F/U, and deaths

Table 8.2
Performance Monitoring Committee Report
 Data as of 8/31/02

HT

	E-Along Adherence Summary > 80%				Task Completeness Dec 01 – May 02				% Stopped ⁵	
	Average ¹ % Quartile		Sep 01 - Aug 02 ² % Quartile		Form 10 ³ % Quartile		Form 85 ⁴ % Quartile		Cum Aug 02 % Quartile	
Oakland	78.9	1	75.9	1	98.4	2	92.5	1	11.3	1
Iowa City	70.2	1	62.2	1	98.3	2	95.7	1	13.0	1
LA	69.5	1	50.0	3	95.2	3	91.5	2	15.2	1
Minneapolis	67.7	1	64.5	1	98.2	2	94.6	1	13.5	1
Pittsburgh	67.7	1	58.8	1	95.4	3	93.6	1	19.5	2
Cincinnati	65.6	1	62.3	1	98.7	1	94.7	1	22.0	3
Stanford	64.7	1	59.0	1	98.6	1	75.4	4	15.3	1
Portland	63.4	1	56.0	1	95.4	3	84.2	3	18.5	2
Nevada	62.9	1	59.8	1	99.5	1	91.6	2	22.2	3
Milwaukee	62.4	1	55.8	1	97.2	2	94.2	1	16.1	1
Chapel Hill	62.2	2	51.6	2	98.9	1	95.6	1	16.3	2
Gainesville	61.4	2	52.1	2	98.9	1	93.2	1	23.9	3
Brigham	60.7	2	59.2	1	99.5	1	90.9	2	14.5	1
Columbus	60.7	2	54.4	2	98.7	1	92.4	2	21.5	2
Pawtucket	59.9	2	54.7	2	99.0	1	91.4	2	21.8	3
Worcester	58.3	2	55.1	2	93.9	4	95.9	1	16.0	1
Birmingham	56.4	2	47.1	3	95.6	3	87.5	3	24.6	4
Honolulu	56.3	2	54.4	2	95.2	3	91.5	2	15.3	1
Madison	55.8	2	52.0	2	96.3	2	94.9	1	19.6	2
GWU-DC	55.0	2	48.1	3	96.1	3	88.8	3	12.9	1
Seattle	54.7	3	50.7	2	94.3	3	69.4	4	22.6	3
Chicago	53.5	3	54.2	2	99.7	1	91.5	2	20.3	2
Bowman	52.1	3	47.6	3	93.1	4	81.8	4	22.7	3
Newark	51.8	3	41.7	4	90.1	4	89.1	3	19.0	2
Buffalo	51.7	3	45.5	4	98.9	1	91.3	2	21.3	2
UC Davis	51.5	3	46.8	3	94.7	3	89.0	3	23.5	3
Irvine	51.1	3	47.0	3	93.9	4	83.1	4	23.0	3
Stony Brook	51.1	3	46.3	4	97.2	2	91.1	2	16.7	2
LaJolla	51.0	3	48.3	3	89.5	4	77.7	4	24.0	3
Chi-Rush	50.2	3	47.4	3	96.9	2	91.5	2	26.0	4
Torrance	50.0	4	50.9	2	97.6	2	84.1	3	22.5	3
NYC	49.4	4	45.9	4	96.1	3	80.3	4	19.6	2
Memphis	49.0	4	48.2	3	94.2	4	81.4	4	29.4	4
Tucson	47.2	4	43.5	4	92.3	4	86.1	3	29.7	4
Atlanta	46.3	4	45.5	4	97.7	2	88.6	3	27.3	4
San Antonio	45.1	4	46.4	3	97.1	2	84.5	3	29.3	4
Detroit	45.1	4	38.2	4	86.4	4	73.0	4	26.1	4
Medlantic	42.4	4	40.4	4	96.3	3	87.5	3	27.6	4
Houston	39.9	4	30.0	4	88.4	4	77.8	4	32.1	4
Miami	28.7	4	26.9	4	87.5	4	74.1	4	35.6	4
CC Average	55.9		50.8		96.0		88.0		20.9	
Ave F/U 5.5 yr	-		-		Goal ≥ 90%		Goal ≥ 90%		Design Assump. 30.9	

¹ Adherence from randomization through 1) 12 months before data as of date 2) last adherence collection within the last 12 months before the data as of date, or 3) death; women off intervention are considered non-adherent

² Adherence in previous 12 months; excludes deaths; women off intervention are considered non-adherent

³ From WHIP 1445-Task Completeness, complete if encounter date on Form 10 - HRT Management and Safety is -3/+3 months from target date

⁴ From WHIP 1445-Task Completeness, complete if mammogram date on Form 85 - Mammogram date is -12/+6 months from AV target date

⁵ From WHIP CCC750-HRT Intervention & F/U Status; includes E-Along stopped intervention (excludes E-plus-P stop intervention), stopped F/U, lost-to-F/U, and deaths

Table 8.3
Performance Monitoring Committee Report
 Data as of 8/31/02

CaD

	Adherence Summary ≥ 80%				Task Completeness Form 17 ³		% Stopped ⁴	
	Average ¹ %	Quartile	Sep 01 - Aug 02 ² %	Quartile	Dec 01 - May 02 %	Quartile	Cum Aug 02 %	Quartile
Oakland	80.8	1	83.1	1	99.2	1	10.4	1
Iowa City	71.7	1	71.8	1	98.3	2	15.7	1
Stanford	71.5	1	72.5	1	98.7	1	20.6	2
Minneapolis	68.8	1	69.2	1	96.8	3	17.1	1
Nevada	67.6	1	70.2	1	99.5	1	19.1	1
Columbus	67.2	1	66.1	1	99.3	1	23.3	2
Gainesville	64.8	1	63.7	1	98.2	2	26.9	3
Portland	63.6	1	64.1	1	96.1	3	22.7	2
Brigham	63.1	1	62.9	2	99.1	1	23.9	2
Pittsburgh	62.6	1	59.6	3	97.0	2	25.4	2
Chi-Rush	62.5	2	62.3	2	98.6	2	27.6	3
Pawtucket	62.0	2	65.7	1	99.4	1	24.1	2
Chapel Hill	61.7	2	62.1	2	98.2	2	15.3	1
Milwaukee	60.6	2	62.1	2	98.7	1	19.1	1
Honolulu	60.2	2	61.6	2	94.4	3	28.5	4
Worcester	60.1	2	61.3	2	95.8	3	17.0	1
Madison	59.5	2	57.3	3	97.8	2	19.6	1
Cincinnati	59.3	2	66.4	1	99.0	1	26.6	3
GWU-DC	58.9	2	55.6	3	96.3	3	23.7	2
LA	58.8	2	57.7	3	96.2	3	26.9	3
Torrance	57.9	3	60.0	2	92.3	4	25.6	3
Buffalo	57.0	3	62.5	2	98.6	1	20.2	1
UC Davis	56.8	3	59.9	3	94.7	3	26.0	3
Bowman	56.5	3	60.1	2	93.3	4	24.8	2
Birmingham	56.3	3	60.3	2	96.2	3	20.4	1
Seattle	56.3	3	57.1	3	93.9	4	26.7	3
Stony Brook	55.8	3	53.3	4	98.2	2	29.3	4
LaJolla	55.2	3	55.1	4	89.4	4	23.7	2
Atlanta	53.8	3	57.8	3	98.4	2	26.7	3
Tucson	52.8	3	59.5	3	93.3	4	33.5	4
Chicago	52.6	4	55.2	3	99.3	1	29.3	4
Irvine	52.1	4	51.0	4	95.5	3	28.0	4
San Antonio	51.7	4	55.4	3	97.8	2	27.5	3
NYC	49.7	4	53.9	4	96.3	3	29.5	4
Memphis	48.2	4	51.6	4	94.3	4	34.1	4
Detroit	46.9	4	48.2	4	89.8	4	31.5	4
Houston	46.8	4	45.5	4	87.5	4	32.0	4
Newark	46.2	4	50.6	4	90.8	4	26.6	3
Medlantic	43.3	4	48.0	4	97.5	2	24.3	2
Miami	31.2	4	36.9	4	87.0	4	44.2	4
CC Average	58.3		60.0		96.3		24.5	
Ave F/U 4.6 yr	-		-		Goal ≥ 90%		Design Assump. 22.0	

¹ Adherence from randomization through 1) 12 months before data as of date 2) last adherence collection within the last 12 months before the data as of date, or 3) death; women off intervention are considered non-adherent

² Adherence in previous 12 months; excludes deaths; women off intervention are considered non-adherent

³ From WHIP 1445-Task Completeness, complete if encounter date on Form 17 - CaD Management and Safety is -3/+3 months from target date

⁴ From WHIP CCC750-CaD Intervention & F/U Status; includes stopped intervention, stopped F/U, lost-to-F/U, and deaths

Table 8.4
Performance Monitoring Committee Report
 (Data as of 8/31/02)

OS

	Task Completeness - Year 3 ¹ May 00-Oct 01 ²				% Stopped ³	
	Form 100		Form 143		Cum Aug 02	
	%	Quartile	%	Quartile	%	Quartile
Iowa City	-	-	-	-	4.4	1
UC Davis	-	-	-	-	5.6	2
Buffalo	-	-	-	-	5.6	2
Chicago	-	-	-	-	6.1	2
Irvine	-	-	-	-	6.7	3
Seattle	-	-	-	-	6.9	3
Bowman	-	-	-	-	9.2	4
Pittsburgh	-	-	-	-	9.9	4
Gainesville	95.4	1	99.1	1	6.2	2
Madison	95.2	1	100.0	1	4.0	1
Nevada	93.3	1	96.0	1	6.5	3
Brigham	91.7	1	96.8	1	2.3	1
Worcester	91.5	1	92.3	2	3.8	1
Oakland	89.6	1	98.7	1	5.4	2
Stanford	89.5	1	94.6	2	5.8	2
Columbus	89.1	1	95.5	1	3.2	1
Pawtucket	89.1	1	95.1	1	4.7	1
GWU-DC	88.5	1	94.3	2	3.6	1
NYC	88.1	2	91.1	2	6.4	3
Milwaukee	86.7	2	89.5	2	6.6	3
Cincinnati	86.3	2	93.0	2	9.1	4
Atlanta	85.9	2	93.1	2	3.6	1
Medlantic	85.2	2	87.4	3	6.0	2
Portland	84.9	2	94.8	1	5.9	2
Minneapolis	84.4	2	95.1	1	5.2	2
Birmingham	84.2	2	85.7	3	8.4	3
Honolulu	83.8	2	86.5	3	6.9	3
Chapel Hill	83.1	2	94.7	1	3.5	1
LaJolla	83.0	3	86.6	3	11.9	4
Stony Brook	82.9	3	91.6	2	5.0	1
LA	80.8	3	87.5	2	5.0	1
Chi-Rush	79.4	3	90.1	2	8.9	3
Torrance	77.8	3	86.1	3	12.2	4
San Antonio	75.8	3	86.6	3	9.7	4
Newark	73.1	3	74.2	3	10.0	4
Tucson	71.5	3	78.9	3	13.2	4
Memphis	69.7	3	76.1	3	10.7	4
Detroit	66.3	3	72.1	3	7.4	3
Houston	59.9	4	70.4	4	8.2	3
Miami	24.0	4	32.0	4	19.5	4
CC Average	83.6		89.5		6.9	
Ave F/U 5.1 yr	Goal ≥ 90%		Goal ≥ 90.9%		-	

¹ From WHIP1445-Task Completeness; complete if encounter date is -3/+15 months from AV3 target date.

Six CCs have no OS Year 3 visits due in the time period.

² 6-month period ending 10 months before data as of date to allow for 10 month lag in completeness

³ From WHIP CCC752 Intervention & F/U Status; includes stopped F/U, lost-to-F/U, and deaths

Table 8.5
Performance Monitoring Committee Report
 Data as of 8/31/02

Outcomes

	Task Completeness						Outcomes Processing							
	CT Form 33 ¹		OS Form 33 ²		Form 33D ³		Sept 01 – Aug 02							
	Dec 01- May 02		May 01 - Oct 01		Jun 01- Aug 02		Cases Assembled ≤ 12 weeks ⁴		Cases Adjudicated ≤ 14 days ⁵		Cases Open > 16 weeks ⁶		Cases Closed ≤ 16 weeks ⁷	
	%	Quartile	%	Quartile	%	Quartile	%	Quartile	%	Quartile	%	Quartile	%	Quartile
Buffalo	97.9	1	95.1	2	98.4	1	95.2	1	99.7	1	29.7	4	92.1	1
Iowa City	97.4	1	96.1	2	91.6	4	91.6	2	78.2	3	13.5	1	86.9	2
Nevada	98.1	1	99.0	1	99.4	1	92.4	2	86.6	3	8.1	1	86.6	2
Oakland	96.4	1	98.3	1	93.8	3	95.1	1	85.2	3	16.0	2	83.3	3
Chapel Hill	97.4	1	98.8	1	98.5	1	98.0	1	91.9	2	0.0	1	98.1	1
Madison	97.3	1	98.8	1	96.6	2	94.7	1	65.1	4	10.3	1	87.7	2
Stanford	96.2	1	96.9	1	97.4	2	89.8	3	85.8	3	23.2	3	84.7	2
Atlanta	95.5	2	97.5	1	98.8	1	93.8	1	82.9	3	33.1	4	84.2	2
Columbus	96.8	1	98.7	1	95.9	2	90.9	2	68.9	4	27.6	3	78.4	3
Milwaukee	95.8	2	94.6	2	95.3	3	91.3	2	56.5	4	25.9	3	66.7	4
Brigham	96.8	1	96.3	2	99.4	1	93.3	2	72.1	4	14.7	2	87.7	2
Gainesville	95.1	2	97.2	1	96.9	2	89.7	3	98.6	1	17.4	2	87.7	2
Stony Brook	95.1	2	94.4	2	92.1	4	83.2	3	93.8	2	19.2	2	78.1	3
Minneapolis	95.5	2	95.6	2	94.8	3	95.5	1	78.1	3	10.8	1	90.8	1
GWU-DC	94.9	2	99.3	1	95.8	3	83.6	3	99.8	1	12.4	1	77.1	3
Pawtucket	95.1	2	95.0	2	96.0	2	89.3	3	34.2	4	25.3	3	69.9	3
Worcester	95.3	2	96.6	1	97.0	2	97.3	1	87.5	3	16.9	2	92.5	1
Pittsburgh	97.4	1	88.9	4	99.8	1	89.3	3	100.0	1	19.4	2	89.4	1
Chicago	94.4	2	93.5	3	93.1	4	90.9	2	98.7	1	27.9	3	73.1	3
Cincinnati	92.2	3	92.5	3	97.9	1	85.4	3	98.9	1	10.2	1	53.1	4
Birmingham	95.1	2	92.1	3	93.0	4	60.2	4	98.6	1	40.4	4	45.6	4
LA	94.2	3	96.5	2	97.1	2	67.9	4	97.5	1	46.6	4	46.9	4
Irvine	91.6	3	93.7	3	88.6	4	83.2	4	88.8	2	25.0	3	70.3	3
Portland	92.1	3	95.2	2	87.6	4	92.1	2	93.3	2	21.4	2	88.9	1
Seattle	90.1	4	89.7	3	94.6	3	92.5	2	89.7	2	24.0	3	83.2	3
Chi-Rush	91.4	3	89.0	4	95.9	3	94.5	1	96.5	2	10.9	1	90.2	1
NYC	92.2	3	93.7	3	98.8	1	92.4	2	85.8	3	47.1	4	83.5	2
UC Davis	92.6	3	96.4	2	98.6	1	81.0	4	100.0	1	31.6	4	84.3	2
Medlantic	91.3	3	92.4	3	97.0	2	89.1	3	84.9	3	28.8	3	86.4	2
Memphis	90.6	3	89.7	4	95.7	3	99.1	1	95.2	2	8.4	1	94.3	1
Bowman	90.1	3	89.3	4	92.7	4	80.1	4	86.0	3	33.6	4	46.9	4
San Antonio	89.7	4	92.8	3	89.4	4	96.9	1	90.6	2	10.8	1	87.9	1
Tucson	88.3	4	88.8	4	96.9	2	93.2	2	93.6	2	22.2	2	90.3	1
Newark	86.4	4	87.8	4	95.9	3	90.4	3	63.4	4	21.2	2	69.9	3
Honolulu	88.0	4	92.1	3	91.7	4	81.3	4	71.6	4	23.0	3	55.4	4
Houston	86.0	4	93.9	3	94.6	3	57.2	4	58.4	4	29.4	4	40.2	4
Detroit	84.5	4	86.9	4	93.4	3	70.1	4	98.4	1	27.4	3	61.8	4
Torrance	83.2	4	86.4	4	97.0	2	81.9	4	96.8	2	13.8	2	74.9	3
LaJolla	83.1	4	86.1	4	43.9	4	88.0	3	68.8	4	54.3	4	59.3	4
Miami	76.4	4	76.1	4	97.9	1	69.7	4	58.6	4	38.5	4	55.4	4
CC Ave	92.6		93.5		94.0		88.2		84.4		26.3		77.0	
Goals	≥ 95.7%		≥ 96.0%		≥ 96.8%		≥ 80%		≥ 80%		< 20%		≥ 80%	

¹ From WHIP 1445-Task Completeness; complete if encounter date is -3/+3 months from target date

² From WHIP 1445-Task Completeness; complete if encounter date is -2/+10 months from AV1, 4+ target date, -2/+9 from AV2, and -3/+15 for AV3

³ From WHIP 2030-Timeliness of Outcomes Processing; includes both CT and OS

⁴ From WHIP 1263-Timeliness of Outcomes Packet Assembly; percent of assembled cases that were assembled (assigned) within 12 weeks

⁵ From WHIP 1264-Timeliness of Local Adjudications; percent of adjudicated cases that were adjudicated within 14 days

⁶ From WHIP 2030-Timeliness of Outcomes Processing; percent of open cases that were open more than 16 weeks

⁷ From WHIP 2030-Timeliness of Outcomes Processing; percent of closed cases that were closed within 16 weeks

9. Other 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 9.1 – Publications presents current and proposed publications that have been approved by the Publications and Presentations Committee.

Table 9.2 – 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.

These tables represent the current information available to the relevant committees. Updates are clearly needed. Status reports for papers or ancillary studies may be sent to the CCC, attention Sundara Murphy. The CCC requests one reprint from each published manuscript for study archives.

Table 9.1
Publications

MS ID	Title	Authors	Data Focus	Stage	Reference
1	Informed Consent in the Women's Health Initiative Clinical Trial and Observational Study	McTiernan, Rossouw, Manson, Franz, Taylor, Carleton, Johnson, Nevitt	Gen.	11	Journal of Women's Health 4(5):519-29, 1995
4	The Women's Health Initiative: Overview of the Nutrition Component	Tinker, Burrows, Henry, Patterson, Van Horn, Rupp	Gen.	11	Nutrition and Women's Health, pp. 510-542, 1996.
5	Women Health Initiative: Why Now? What is it? What's New?	Matthews, Shumaker, Bowen, Langer, Hunt, Kaplan, Klesges, Ritenbaugh	Gen.	11	American Psychologist. 52(2):101-116, 1997 Feb.
6	Low-fat Diet Practices of Older Women: "Prevalence and Implication for Dietary Assessment"	Patterson, Kristal, Coates, Ritenbaugh, Van Horn, Caggiula, Snetelaar, Tyavsky	Gen.	11	Journal of the American Dietetic Association. 96(7):670-9, 1996 Jul.
7	The Evolution of the Women's Health Initiative: Perspectives from the NIH	Rossouw, Finnegan, Harlan, Pinn, Clifford, McGowan	Gen.	11	Journal of the American Medical Women's Association. 50(2):50-5, 1995 Mar-Apr
8	Design of the WHI Clinical Trial and Observational Study	Prentice, Rossouw, Furberg, Johnson, Henderson, Cummings, Manson, Freedman, Oberman, Kuller, Anderson	Gen.	11	Controlled Clinical Trials 19:61-109, 1998
9	Approaches to Monitoring the Results of Long-term Disease Prevention Trials: Examples from the Women's Health Initiative	Freedman, Anderson, Kipnis, Prentice, Wang, Rossouw, Wittes, DeMets	CT	11	Controlled Clinical Trials. 17(6):509-25, 1996 Dec.
11	The Role of Randomized Controlled Trials in Assessing the Benefits and Risks of Long-term Hormone Replacement Therapy: Example of the Women's Health Initiative	Prentice, Rossouw, Johnson, Freedman, McTiernan	CT	11	Menopause 3(2):71-76, 1996
12	Factors Associated with Insurance Status among Participants in the WHI	Hsia, Sofaer, Kiefe, Zapka, Bowen, Mason, Limacher, Pettinger, Lillington	Gen.	11	Journal of Women's Health & Gender-Based Medicine 9(8):881-889, 2000
17	Sexual Orientation and Health: Comparisons in the Women's Health Initiative Sample	Valanis, Bowen, Bassford, Whitlock, Charney, Carter	CT	11	Archives of Family Medicine. 9(9):843-53, 2000 Sep-Oct
19	Ethnic, Socioeconomic, and Lifestyle Correlates of Obesity in U.S. Women: The Women's Health Initiative	Manson, Lewis, Kotchen, Allen, Johnson, Stefanick, Foreyt, Klesges, Tinker, Noonan, Perri, Hall	Gen.	11	Clinical Journal of Women's Health. 1(5):225-34, 2001 Dec
21	Hypertension and It's Treatment in Postmenopausal Women: Baseline Data from the Women's Health Initiative	Wassertheil-Smoller, Anderson, Black, Psaty, Manson, Wong, Francis, Grimm, Kotchen, Langer, Lasser	OS	11	Hypertension 2000;36:780-89
22	Pelvic Organ Prolapse: Gravity and Gravidity	Hendrix, Clark, Nygaard, Aragaki, Barnabei, McTiernan	CT	11	Am J Obstet Gynecol 2002;186:1160-6

MS ID	Title	Authors	Data Focus	Stage	Reference
24	Estimation of the Correlation between Nutrient Intake Measures Under Restricted Sampling	Wang, Anderson, Prentice	Gen.	11	Biometrics. 55, 711-717 (1999)
27	The Effects of Insurance Coverage and Ethnicity on Mammography Utilization in a Postmenopausal Population	Bush, Langer	Gen.	11	Western Journal of Medicine 168:236-40, 1998
35	Measurement Characteristics of the WHI Food Frequency Questionnaire	Patterson, Kristal, Carter, Tinker, Bolton, Agurs-Collins	Gen.	11	Annals of Epidemiology 1999;9:178-197
37	Depression as Mediated by Social Support, Life Events, and Sexual Activity in Postmenopausal Non-Hispanic White and Latina Women	Larisch, Talavera, Langer, Velasquez, Elder	Gen.	11	
40	The Health Impact of Domestic Violence in Older Women	Mouton, Furniss, Lasser, Rovi	OS	11	Journal of Women's Health & Gender-Based Medicine 1999;8(9):1173-1179
43	Sleep Complaints of Postmenopausal Women	Kripke, Freeman, Masaki, Brunner, Jackson, Hendrix, Carter	CT	11	Clinical Journal of Women's Health 1:244-252, 2001
59	Risk Factors for Kidney Stones in Postmenopausal Women in the Southern United States	Hall, Pettinger, Oberman, Watts, Johnson, Paskett, Limacher, Hays	Gen.	11	Am J Med Sci 2001;322 (1):1-7
60	WHIMS: a Trial of the Effect of Estrogen Therapy in Preventing and Slowing the Progression of Dementia	Shumaker, Bowen	WHIMS	11	Controlled Clinical Trials 19:604-621
63	Health Insurance as a Determinant of Cancer Screening in WHI OS Participants	Hsia, Kemper, Kiefe, Zapka, Sofaer, Pettinger, Bowen, Limacher, Lillington, Mason	OS	11	Preventive Medicine 2000;31:261-270
66	Walking, Vigorous Exercise, and Incidence of Cardiovascular Disease in an Ethnically Diverse Cohort of Women	Manson, Greenland, LaCroix, Stefanick, Mouton, Oberman, Perri, Sheps, Pettinger, Siscovick	OS	11	N Engl J Med, Vol. 347, No. 10
67	Yogurt Consumption is Associated with Healthy Behaviors in Post-Menopausal Women	Mossavar-Rahmani, Garland, Caan, Hebert, Wodarski, Vitolins, Himes, Parker	OS	11	In Press: Clinical Journal of Women's Health
69	Correlates of Serum Lycopene in Older Women	Casso, White, Patterson, Agurs-Collins, Kooperberg, Haines	CT	11	Nutrition and Cancer 2000;36:163-69.
70	Correlates of Serum Alpha- and Gamma-Tocopherol in the WHI	White, Masaki, Chen, Shikany, Caan, Mares-Perlman, Wilson, Kristal	CT	11	Annals of Epidemiology 2001;11:136-144
71	The Women's Health Initiative: Goals, Rationale, and Current Status	Liu	Gen.	11	Menopausal Medicine, Vol.6(2), p.1-4, 1998
86	The Effects of Physical and Emotional Status on Adherence to a Low-fat Dietary Pattern in the Women's Health Initiative	Tinker, Perri, Bowen, Patterson, Parker, Wodarski, McIntosh, Sevcik	CT	11	

MS ID	Title	Authors	Data Focus	Stage	Reference
88	Estimating Normal Hemogram Values for Postmenopausal Women	Assaf, Carleton, Miller, Coccio	Gen.	11	Clinical Journal of Women's Health Vol. 1, No. 1, December 2000, 23-28
91	Compliance with National Cholesterol Education Program Dietary and Lifestyle Guidelines Among Older Women with Self-reported Hypercholesterolemia: The Women's Health Initiative	Hsia, Rodabough, Rosal, Cochrane, Howard, Snetseelaar, Frishman, Stefanick	OS	11	In Press: American Journal of Medicine
99	Risk Factor Clustering in the Insulin Resistance Syndrome and its Relationship to Cardiovascular Disease In White, Black, Hispanic, and Asian Postmenopausal Women	Howard, Criqui, Curb, Rodabough, Safford, Santoro, Wilson, Wylie-Rosette	OS	11	In Press: Metabolism
103	The Women's Health Initiative: Recruitment Complete - Looking Back and Looking Forward (Guest Editorial)	Rossouw, Hurd	CT	11	Journal of Women's Health 8:3-5, 1999.
104	Promoting Adherence and Retention to Clinical Trials in Special Populations: A Women's Health Initiative Workshop	Wilcox, Shumaker, Bowen, Naughton, Rosal, Ludlam, Dugan, Hunt, Stevens	Gen.	11	Controlled Clinical Trials, 22 (3), 279-289
107	Vigorous Leisure Activity Through Women's Adult Life: The Women's Health Initiative	Wilcox, Heiss, Pettinger, Brunner, Daugherty, King, McTiernan	OS	11	In Press: American Journal of Epidemiology
108	Cross-Sectional Geometry and Bone Mass in the Proximal Femur in African-American and White Postmenopausal Women	Nelson, Hendrix	CT	11	
128	Inflammatory Biomarkers, Hormone Replacement Therapy, and Incident Coronary Heart Disease: A Prospective Analysis from the Women's Health Initiative Observational Study	Pradhan, Manson, Rossouw, Siscovick, Moulton, Wallace, Jackson, Pettinger, Ridker	OS	11	JAMA 2002;288:980-987
155	Changes in Food Sources of Dietary Fat in Response to an Intensive Low-Fat Dietary Intervention: Early Results from the Women's Health Initiative	Patterson, Kristal, Caan, Lillington, Mossavar-Rahmani, Simon, Snetseelaar, Van Horn, Rodabough	CT	11	
10	A Comprehensive Data Management System for Multicenter Studies	Anderson, Davis, Koch	Gen.	10	
13	Depression and Cardiovascular Sequelae in Post-Menopausal Women	Wassertheil-Smoller, Shumaker, Ockene, Talavera, Greenland, Cochrane, Robbins, Aragaki, Dunbar	Gen.	10	
30	Completeness of Purchase Mailing Lists for Identifying Older Women	Falkner, Wactawski-Wende, Trevisan	CT	10	
39	Hormone Replacement Therapy and Dietary Fat Intake Influence on Blood Lipids and Insulin in Postmenopausal Women	Chlebowski, Sparks, Stefanick, Howard, Mossavar-Rahmani, McTiernan	Gen.	10	

MS ID	Title	Authors	Data Focus	Stage	Reference
61	WHI Halfway Paper (100K Paper)	Langer, Kotchen, Daugherty, Lewis, Elmer, Trevisan, Noonan, Hendrix, Adams-Campbell	Gen.	10	
72	Post-Menopausal Bone Loss and its Relationship to Oral Bone Loss	Jeffcoat, Lewis, Reddy, Wang, Redford	Gen.	10	Periodontics 2000
76	Labeling as a Predictor of Dietary Maintenance	Hopkins, Burrows, Bowen, Tinker	CT	10	
93	Fat Intake in Husbands of Women in the Dietary Component of the Women's Health Initiative	Shikany	Gen.	10	
95	The Effects of Widowhood on Physical Health, Mental Health, and Health Behaviors: the Women's Health Initiative	Wilcox, Evenson, Aragaki, Wassertheil-Smoller, Mouton, Loevinger, Cochrane	OS	10	
98	Patterns of Antioxidant Supplement Use in Participants in the Women's Health Initiative	Shikany, Patterson, Agurs-Collins, Anderson	Gen.	10	
100	The Yield of Six-Month Recall Mammography on Screening Mammograms	Yasmeen, Romano, Pettinger, Chlebowski, Robbins, Lane, Hendrix	Gen.	10	
115	Prevalence and 3-year Incidence of Abuse in Older Women	Mouton, Rodabough, Rovi, Hunt, Brzyski		10	
120	Obesity, Body Size, and Risk of Postmenopausal Breast Cancer: The Women's Health Initiative	Morimoto, White, McTiernan, Chlebowski, Hays, Stefanick, Margolis, Manson, Kuller, Chen, Muti, Lopez	OS	10	
122	Does Statin Use Reduce Risk of Osteoporotic Fracture or Improve Bone Density in Postmenopausal Women? Results from the Women's Health Initiative Observational Study	LaCroix, Cauley, Pettinger, Hsia, Bauer, McGowan, Chen, Lewis, McNeeley, Pasaro, Jackson	OS	10	
132	Second Malignancy and Nonmelanoma Skin Cancer: The Women's Health Initiative Observational Study	Rosenberg, Greenland, Khandekar, Ascensao, Lopez	Gen.	10	
134	Alternative Self-Monitoring Tools in the Dietary Modification Component of the Women's Health Initiative	Mossavar-Rahmani, Henry, Rodabough, Bragg, Brewer, Freed, Kinzel, Pederson, Soule, Vosburg	CT	10	
142	Coronary Artery Calcification in African-American and White Women	Khurana, Rosenbaum, Howard, Adams-Campbell, Detrano, Hsia, Klouj	OS	10	
166	Is Tea Drinking Related to Bone Mineral Density and Osteoporotic Fractures? ---Results from the Women's Health Initiative Observational Study	Chen, Pettinger, Ritenbaugh, LaCroix, Robbins, Caan, Barad, Hakin	OS	10	
16	Caloric Requirements and Dietary Self-report	Hebert, Patterson, Gorfine, Ebeling, St. Jeor, Chlebowski	Gen.	9	
25	Hormone Replacement Therapy and the QT Interval	Kadish, Greenland, Limacher, Frishman, Daugherty, Parker, Schwartz	CT	9	

MS ID	Title	Authors	Data Focus	Stage	Reference
26	Special Populations Recruitment for the WHI: Success and Limitations	Fouad, Corbie-Smith, Curb, Howard, Mouton, Simon, Talavera, Thompson, Wang, White, Young	Gen.	9	
34	The Relationship between Smoking Status, Body Weight, and Waist-to-Hip Ratio: the WHI	Johnson, Klesges, Hays, Noonan, Black, Curb, Liu, Manson	Gen.	9	
55	Factor Structure and Factor Invariance of the Women's Health Initiative Insomnia Rating Scale	Levine, Shumaker, Naughton, Kaplan, Kripke, Bowen	Gen.	9	
73	Innovative Strategies for Monitoring and Enhancing Clinic Performance in the WHI Clinical Trial: The Creation of the Performance Monitoring Committee	Pottern, Naughton, Lund, Cochrane, Brinson, Kotchen, McTiernan, Shumaker	Gen.	9	
83	A Prospective Study of Physical Activity and the Risk of Breast Cancer in Women Aged 50 - 79 Years	McTiernan, Kooperberg, White, Wilcox, Coates, Adams-Campbell, Woods, Ockene	Gen.	9	
84	Research Staff Turnover and Participant Adherence in the WHI	Jackson, Berman, Snetselaar, Granek, Boe, Huber, Milas, Spivak, Chlebowski	CT	9	
85	Women's Health Initiative: Rationale, Design and Progress Report	Johnson, Anderson, Barad, Stefanick, McNaghy	CT	9	
102	Cardiovascular Outcomes Related to Anti-Hypertensive Drug Therapy in Older Women: The Women's Health Initiative Observational Study	Wassertheil-Smoller, Psaty, Greenland, Margolis, Oberman, Kotchen, Mouton, Hilker, Black, Anderson, Trevisan, Aragaki	OS	9	
105	Retention of Low Income and Minority Women in Clinical Trials: A Focus Group Study	Johnson, Williams, Fouad	CT	9	
109	NCI Monograph: Approaches to Research Trials Recruitment in Hispanic Communities: Review and Recommendations	Larkey	Gen.	9	
111	Effects of Fat Intake on Fat Hedonics: Cognition or Taste?	Bowen, Green, Vizenor, Vut, Kreuter, Rolls	OS	9	
112	Results of an Adjunct Dietary Intervention Program in the Women's Health Initiative	Bowen, Ehret, Pedersen, Snetselaar, Johnson, Tinker, Hollinger, Lichty, Sivertsen, Ocken, Staats, Beedoe	OS	9	
126	Influences on Older Women's Adherence to a Low-Fat Diet in the Women's Health Initiative	Kearney, Rosal, Ockene, Churchill	CT	9	
135	Radiographic Measurements, Bone Mineral Density and the Singh Index in the Proximal Femur of White and African-American Postmenopausal Women	Barondess, Singh, Hendrix, Nelson		9	

MS ID	Title	Authors	Data Focus	Stage	Reference
149	Health Status of Postmenopausal White Women with Back and Leg Pain Living in the Community: A Pilot Study	Vogt, Lauerma, Chirumbole, Kuller	OS	9	
187	Estrogens and Cardiovascular Disease	Rossouw	OS	9	
198	Aspects of the Management and Coordination of The Women's Health Initiative	Cochrane, Lund, Anderson, Prentice	Gen.	9	
38	Relationship of Select Dietary Components and Colorectal Cancer among Postmenopausal Women: The Women's Health Initiative	Frank, Pettinger, Paskett, Wylie-Rosett, Agurs-Collins	Gen.	8	
62	Self-reported Urogenital Symptoms in Postmenopausal Women: The Women's Health Initiative	Pastore, Carter, Hulka, Wells	Gen.	8	
29	Effects of Diet Intervention on Motivation to make other Health Related Changes	Langer, Lo	CT	7	
41	Determinants of Fasting Hyperinsulinemia	Manson, LaCroix, Haan, Rodrigues, Johnson, Allen, Hendrix	Gen.	7	
57	Regional Differences in Stroke Morbidity at Baseline in the WHI	Johnson, Hall, Oberman, Sheps, Hulka, Hays, Baum, Schenken, Burke, Limacher, Anderson, Jeppson	Gen.	7	
79	Databased Tracking and Statistical Models of the Clinical Trial Recruitment Process	Crech	CT	7	
80	Insulin Resistance and Weight Change in Postmenopausal Black and White Women	Howard, Adams-Campbell, Pasaro, Black, Stevens, Wagenknecht, Rodrigues, Safford, Allen, Snetelaar	Gen.	7	
81	The Prevalence of Urinary Incontinence in WHI Women	Hendrix, Clark, Ling, Dugan, Salmieri, Hurtado, McNeeley, Laube, McTiernan, Francis	Gen.	7	
140	Is Hysterectomy Status an Independent Determinant of Framingham Risk?	Hsia, Rossouw, Limacher, Wassertheil-Smoller, McGovern, Oberman, Barad	Gen.	7	
145	Inverse Association of Breast Cancer with the Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): Prospective Results from the Women's Health Initiative	Harris, Jackson, Frid, McTiernan, Anderson, White, Chlebowski, Ascensao	OS	7	
164	Leukocyte Count as a Predictor of Cardiovascular Events in Post-Menopausal Women	Margolis, Prentice, Greenland, Manson, Assaf, Safford, Howard, Grimm, Bray	OS	7	
177	Validity of Self-Reports of Fractures among Postmenopausal Women in a Prospective Study Results from the Women's Health Initiative	Chen, Bassford, LaCroix, Kooperberg, Jackson, Cauley, Kipersztok, Borne	Gen.	7	

MS ID	Title	Authors	Data Focus	Stage	Reference
189	Dietary Adherence in the WHI Dietary Modification Trial	Unauthored	CT	7	
31	Comparisons between Never Smokers, Former Smokers, and Current Smokers in the WHI	Ockene, Bowen, Brunner, Robbins, Shikany	OS	6	
36	Prevalence of Silent MI	Sagar, Kolchen, Wong, Graettinger, Burke, Van Vorhees, McIntosh	CT	6	
53	Dietary, Physical Activity, and Exercise Patterns Among Diabetics	Agurs-Collins, Adams-Campbell, Pasaro, Howard	Gen.	6	
68	Reliability and Physiologic Correlates of the Physical Activity Questionnaire in the WHI	Morimoto, White, Wang, Stefanick, Siscovick, Cauley, Strickland, Rebar, Rodrigues, Going, Frid	CT	6	
78	Association Between Antioxidants and BMD in an Ethnically Diverse Population of Older Women	Wolf, Cauley, Stone, Nevitt, Simon, Jackson, LaCroix, Lewis, Wactawski-Wende, LeBoff	Gen.	6	
113	Prior Use of Oral Contraceptives and Fracture Risk in Menopausal Women	Barad, Kooperberg, Wactawski-Wende, Hendrix, Watts, Liu	Gen.	6	
163	Racial/Ethnic Differences in Breast Cancer Incidence Rates	Chlebowski, Prentice, Patterson, Paskett, Lane, Hubbell, Rohan, Dolan	OS	6	
49	Patterns of Use and Characteristics Associated with HRT among Postmenopausal Women	Dunn, Greenland, Woods, Stovall, Bartholow, Francis	Gen.	5	
51	The Relationship of Quality of Social Support to Frequency of Cancer Screening Behaviors among Postmenopausal Women	Lane, Taylor, Glanz, Elam, Klaskala, Powell, Messina, Smith	Gen.	5	
52	Nutrient Intake of Women with Diabetes in the WHI Observational Study Cohort	Tinker, Gams, Lee, Smith, West, Snetselaar, Caggiula	Gen.	5	
74	Baseline Characteristics of the WHI-OS Breast Cancer Survivor Cohort	Paskett, Sherman, Anderson, Hays, McDonald, Naughton	OS	5	
87	Incidence and Correlates of Hip and Knee Replacement in the WHI	Wallace, Chang, Nevitt, LaCroix, Kaplan, Sturm	Gen.	5	
92	Comparison of Self-report, Discharge Diagnosis, and Adjudication of Cardiovascular Events in the WHI	Heckbert, Hsia, Kooperberg, McTiernan, Curb, Barbour, Gaziano, Safford, Psaty, Frishman	Gen.	5	
106	Utility of Body Mass Index (BMI) as a Proxy for Obesity Among White, Black, Asian, Native American and Hispanic Post-menopausal Women	Going, Chen, Tinker, Stefanick, St. Jeor, Lewis	Gen.	5	
127	Plasma Homocysteine Levels and Coronary Heart Disease in Women	Siscovick, Manson, Trevisan, Wallace, Howard, Burke, Ridker	OS	5	

MS ID	Title	Authors	Data Focus	Stage	Reference
129	Thrombotic Markers for Coronary Heart Disease in Women	LaCroix, Trevisan, Langer, Lewis, Hsia, Oberman, Kotchen, Ridker	OS	5	
130	Cross-sectional Analysis of Association Between Hormone Replacement Therapy and Thrombotic and Inflammatory Markers for CHD in Women	Langer, Manson, LaCroix, Lewis, Hendrix, Rossouw, Pradhan, Ridker	OS	5	
148	Outcomes of Pap Smears on Postmenopausal Women	Yasmeen, Romano, Barad, Hubbell, La Valluer, Johnson, Lane, McIntosh, Hendrix		5	
151	History of Estrogen and Oral Contraceptive Use and Cognitive Function: Results from the Women's Health Initiative Memory Study	Rapp, Dailey, Gass, Wactawski-Wende, Hendrix, Hogan, Jones, Murphy, Shumaker	WHIMS	5	
152	The Impact of Magnesium Intake on Bone Mass and Risk of Fracture in the Women's Health Initiative Observational Study	Jackson, LaCroix, Lewis, Wactawski-Wende, Cauley, Chen, Bassford	OS	5	
153	Metabolic Syndrome and Depression	Wyllie-Rosette, Cochrane, Perri, Rapp, Rosal	CT	5	
154	Does Acidogenic Diet Contribute to the Incidence of Hip Fracture?	Barzel, Wylie-Rosette, Ritenbaugh, Aickin, LeBoff	OS	5	
156	Incidence of Systemic Lupus Erythematosus in the Women's Health Initiative	Assaf, Cyr, Crowley, Coccio	OS	5	
174	HMG Co-A Reductase Inhibitor (Statin) Use and the Risk of Breast Cancer in the Women's Health Initiative Observational Study	Cauley, LaCroix, Chlebowski, Margolis, McTiernan, Vitolins, Furberg, Bauer	OS	5	
190	Predictors of LVH	Oberman, Ko, Lasser, LaCroix, Wylie	CT	5	
197	Presentation of Acute Coronary Syndromes in Women	Hsia, Rossouw, Brunner, LaCroix, Wallace	OS	5	
20	Correlates of Endogenous Sex Hormone Concentrations in WHI	McTiernan, Wactawski-Wende, Chen, Meilahn, La Valluer, Cummings, Hiatt, Baum, Hulka, Wang, McNagny	CT	4	
178	Three Year Change in BMD	Lewis, Robbins, LaCroix, Chen, Wactawski-Wende, Nevitt, Jackson, Cauley	OS	4	
193	Predictors of Adherence to the Women's Health Initiative Clinical Trial Interventions: A Conceptual Framework	Rosal, Shumaker, Snetelaar, Tinker, Cochrane, Bowen, Brunner, Ockene	CT	4	
194	Predictors of Adherence to the Hormone Replacement Therapy Clinical Trial in the Women's Health Initiative	Cochrane, Stefanick, Wallace, Granek, Lillington, Andeson, Woods, Naughton	CT	4	

MS ID	Title	Authors	Data Focus	Stage	Reference
195	Predictors of Calcium/Vitamin D Supplementation Adherence in the Women's Health Initiative	Brunner, Cauley, Snetseelaar, Jackson, LeBoff, Cochrane, Granek, Wactawski-Wende	CT	4	
196	Intrapersonal, Interpersonal, Treatment, and Organizational Adherence Predictors in the Women's Health Initiative Dietary Modification Clinical Trial	Tinker, Van Horn, Perri, Rosal, Ockene, Patterson, Assaf, Hays	CT	4	
18	The Relationship of Dietary Phytoestrogens to Menopausal Symptoms and Major Morbidity in Postmenopausal Women	Assaf, Cyr, Coccio, Hixson	CT	3	
45	Socio-demographic Determinants of Folic Acid Intake	Beresford, Kritchevsky, Vitolins	Gen.	3	
47	Is a "Too Low" Fat Diet a Marker of Health or Disease	Gilligan, Snetseelaar, St. Jeor, Van Horn, Stefanick, Kotchen, Patterson	CT	3	
54	Current Treatment Patterns in Women with Hypercholesterolemia	Manson, Freed, Chae	Gen.	3	
56	Psychometric Evaluation of the Urinary Incontinence Scale	Levine, Shumaker, Naughton, Kaplan, Bowen	Gen.	3	
90	Passive Smoke Exposure in Childhood and Adulthood and Prevalent Coronary Heart Disease in Women Enrolled in the WHI	Wagenknecht, Frishman, Wong, Ockene	OS	3	
117	Correlates of Session Completion and Self-monitoring of Food Intake among Minority Participants Enrolled in the Women's Health Initiative (WHI) Dietary Modification Intervention during the First Year of Intervention	Rosal, Ockene, Mossavar-Rahmani, Margolis, Paskett, Thomson		3	
118	Association Between Depressive Symptomatology and Physical Activity in Post-menopausal Women	Ockene, Rosal, Haan, Brunner, Mouton, Lopez, Perri, Cochrane, Matthews, Jackson	Gen.	3	
121	Quality of Life in Healthy Women and in Breast Cancer Survivors	Haan		3	
141	The Association of Food and Nutrient Intake with the Incidence of Stroke in the WHI Observational Study	Beresford, Shikany, St. Jeor, Torrens, Mossavar-Rahmani, Heiss, Patterson, Van Horn	OS	3	
157	Type 2 Diabetes and Cognitive Functioning in WHIMS	Haan	WHIMS	3	
159	Endogenous Sex Steroid Hormone and Risk of Coronary Heart Disease in Postmenopausal Women	Rexrode, Manson, Kuller, McTiernan, Stefanick, Heckbert, White	OS	3	

MS ID	Title	Authors	Data Focus	Stage	Reference
160	Correlation of Endogenous Sex Steroid Hormones with Inflammatory and Thrombotic Markers in Postmenopausal Women	Rexrode , Manson, Ridker, Cochrane, Ockene, Kotchen, Margolis, McGovern	OS	3	
173	Relationships Between Blood Pressure, Hypertension, and Hypertension Therapy and Measures of Cognition Among WHIMS Women At Baseline	Johnson , Espeland, Mouton, Margolis, Masaki, Murphy, Wassertheil-Smoller, Prineas	WHIMS	3	
186	Diabetes Prevention with Statins, ACE Inhibitors and HRT	Hsia , Howard, Limacher, Oberman, Safford, Allen, Torrens, Lawson	Gen.	3	
192	Risk Factors for Low Bone Mineral Density in American Indian and Alaska Native Women in the Women's Health Initiative	Whampl , Howard, Rossouw, Chen	Gen.	3	
200	Repression of Negative Emotion and Ambivalence about Negative Emotion: Associations with Psychosocial and Health-related Outcomes in the Women's Health Initiative	Michaels , Perrin, O'Connor, Wisdom, Ritenbaugh, Bowen, Brzyski, Cochrane	Gen.	3	

Stage

- 3=Writing group approved
- 4=Analysis proposed
- 5=Analysis in progress
- 6=Analysis completed
- 7=Draft manuscript
- 8=Final ms submitted to P&P & PO
- 9=Final ms approved
- 10=Submitted
- 11=In press/published
- 86=Dropped

Table 9.2
Ancillary Studies

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
163	Hormone Use Following the WHI E+P Trial Termination: A Pilot Study	Jennifer Hays	Jennifer Hays	yes	yes	none	CT & OS	405	no	1/03-12/04	pending
161	Bone Mass Response to Termination of Estrogen + Progestin	Jane Cauley	Lew Kuller	yes	yes	none	CT	350	no	7/10/02-10/01/02	funded
160	An Assessment of Symptoms and Symptom Self-Management for Women Abruptly stopping Hormone Replacement Study Pills	Barbara Valanis	Cheryl Ritenbaugh	yes	yes	none	CT	250	no	7/02-8/17/02	funded
159	The Insulin-like Growth Factor (IGF) System and Coronary Heart Disease	Robert Kaplan	S. Wassertheil-Smoller	no		none	2002A OS Blood Comp	650/650	no		dropped
158	Potential Mediators of the Association of Depression with CVD	Judith Wylie-Rosett	S. Wassertheil-Smoller	no		none	2002A OS Blood Comp	220/220	no		dropped
156	The Effect of Domestic Violence on Health Care Costs and Utilization	Charles Mouton	Robert Schenken	yes	yes	none	OS	217/217	no		pending
155	Carotenoids, Transforming Growth Factors, and Breast Cancer Risk	Tom Rohan	S. Wassertheil-Smoller	yes	yes	none	OS	3500/3500	yes		pending
154	Serum and DNA Precursors of Colorectal Cancer	Cedric Garland	Robert Langer	no		none	OS	400/400	yes		dropped
152	Growth Factor Genes and Female Breast, Colorectal, and Endometrial Cancers	Gloria Ho	S. Wassertheil-Smoller	yes	yes	none	2002A OS Blood Comp	1700/900	yes		pending

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
150	Effect of Airborne Particulate Matter and Other Air Pollutants on the Incidence of Cardiovascular Events in the Women's Health Initiative Observational Study	Joel Kaufman		yes	yes	none	OS	all OS women	no	5/02-4/04	funded
149	DNA Repair Genetic Polymorphisms and Breast Cancer Risk	Jennifer Hu	Electra Paskett	yes	yes	none	2001 OS Blood Comp	800/800	yes		pending
148	Relationship Between Monoclonal Hemopoiesis and other Molecular Abnormalities and the Development of Leukemia in Older Women	Harvey Priesler		yes	yes	none	2001 OS Blood Comp	59/177	yes		pending
147	Gene-gene and gene-environment interactions and breast cancer risk	Charis Eng	Rebecca Jackson	no		none	2002A OS Blood Comp	200/200	yes		dropped
146	A Prospective Study of Pancreatic Cancer Pathogenesis	Charles Fuchs	JoAnn Manson	yes	yes		2001 OS Blood Comp	93/279	yes		pending
141	Periodontal Disease and Subclinical Cardiovascular Disease in Post-Menopausal Women	Joan Dorn	Maurizio Trevisan	yes	yes	none	OS	80	no	04/01-06/01	funded
140	Environmental Epidemiology of Arrhythmogenesis in WHI	Eric Whitset		yes	yes	none	CT	all CT women	no		pending
139	Follow-up of Healthy Breast Cancer Survivors in the WHI Observational Study	Electra Paskett	Electra Paskett	yes	yes	none	OS	416	no	8/01-8/02	funded
137	Platelet Polymorphisms as Risk Factors for Myocardial Infarction in Postmenopausal Women and their Interactions with Hormone Replacement Therapy	Paul Bray	Jennifer Hays	yes	yes	none	OS	1060/2120	yes		pending
135	Natural History of Pelvic Organ Prolapse in WHI Women	Ingrid Nygaard	Robert Wallace	yes	yes	none	HRT	400	no	7/01-6/06	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
134	Serum Estrogen Hormone Metabolites, Hormone Replacement Therapy and the Risk of Breast Cancer	Francesmary Modugno	Lew Kuller	yes	yes	none	2000 OS Blood Comp	400	yes		funded
133	Biochemical and Genetic Markers of Hypertension in White and Black Women	Howard Sesso, JoAnn Manson	JoAnn Manson	yes	yes	none	2000 OS Blood Comp	800/800	yes		pending
132	A Prospective Study of Genetic and Biochemical Predictors of Type 2 Diabetes Mellitus	Simin Liu, JoAnn Manson	JoAnn Manson	yes	yes	none	2000 OS Blood Comp	3840	yes	7/02-6/07	funded
130	A Randomized Controlled Trial of Fat Reduction, Calcium/Vitamin D Supplementation, Hormone Replacement Therapy, and risk of Proliferative Forms of Benign Breast Disease	Thomas Rohan	S. Wassertheil-Smoller	yes	yes	none	DM, HRT		no	7/01-06/06	funded
129	The Association of Diabetes and Insulin-Like Growth Factor-I (IGF-I) with Risks of Colorectal, Breast, and Endometrial Cancer	Howard Strickler	S. Wassertheil-Smoller	yes	yes	none	2000 OS Blood Comp	5775	yes	2/02-2/06	funded
128	DNA Mismatch Repair Gene Associated Colorectal, Endometrial and Ovarian Cancer in Postmenopausal Women: a Novel Prospective Population-Based Study	Tom Weber	S. Wassertheil-Smoller	yes	yes	none	2000 OS Blood Comp	6500	yes		pending
127	Impact of Risk Perception on Preventive Health Behaviors, Process of Care and Outcomes Among a Diverse Cohort of Women at High Risk of Ischemic Heart Disease	Janice Barnhart	S. Wassertheil-Smoller	yes	yes	none	OS	350	no	4/1/2002-3/31/2006	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
126	Molecular and Genetic Determinants of Stroke in the Women's Health Initiative Observational Study	Sylvia Smoller	S. Wasserheil-Smoller	yes	yes	none	OS Umbrella Study	2100	yes		pending
124	Sociocultural Influences on Motivation for and Maintenance of Health-Related Dietary Change Among Women	Joylin Namie	Robert Langer	yes	yes	none	DM	90-150	no	6/00-12/00	funded
122	Feasibility Study of Computerized Tailored Dietary Feedback	Karen Glanz, David Curb	David Curb	yes	yes	none	DM	36	no	3/10/00-9/00	funded
121	Hyperinsulinemia and Ovarian Cancer	Carrie Cottrill, Lewis Kuller	Lew Kuller	yes	yes	none	OS Blood Comp	206	yes		pending
120	Epidemiology of Cervical and Lumbar Stenosis	Molly T. Vogt	Lew Kuller	yes	yes	Pittsburgh, Arizona	OS	4000	no		pending
118	Accuracy of Food Portion Estimation Among Postmenopausal Women	Christine L. Coy		yes	yes	none	DM	191	no	12/1999-4/2000	funded
117	Risk Factors for Dry Eye Syndrome in Postmenopausal Women	Kelley A. Kinney	Rebecca Jackson	yes	yes	none	OS	400	no	2/01-1/04	funded
113	Some Aspects of Mediterranean Diet in Relation to Risk of Chronic Diseases among Postmenopausal Women	Iman Hakim	Tamsen Bassford	yes	yes	none	OS	1000	yes	8/1/99 - 7/31/02	funded
110	Sex steroid hormones and risk of coronary heart disease: A nested case control study	Kathryn Rexrode/Jo Ann Manson	JoAnn Manson	yes	yes	none	1998 OS Blood Comp	700	yes	4/1/00 - 3/31/03	funded
108	Gene-environment effects and colorectal cancer	Rowan Chlebowski/Henry Lin	Rowan Chlebowski/Harbor UCLA	yes	yes	none	2001 OS Blood Comp	800/800	yes		pending
105	Carotenoids in Age-Related Eye Disease Study	Julie Mares-Perlman	Catherine Allen	yes	yes	Iowa, Portland, Wisconsin	1998 OS Blood Comp	2880	yes	4/1/00 - 3/31/04	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
104	Tamoxifen Prevention: Is it acceptable to women at risk?	Joy Melnikow	John Robbins	yes	yes	none	OS	150	no	7/1/99 - 6/30/02	funded
103	Effects of Hormone Replacement Therapy on Cognitive Aging: Women's Health Initiative Study of Cognitive Aging (WHISCA)	Sally Shumaker		yes	yes		HRT	1800	no	4/1/99 - 3/31/05	funded
102	Quality of Life Improvements and Willingness to Pay: An Investigation of Selective Estrogen Receptor Modulators	Mona Fouad	Albert Oberman	yes	yes	none	OS	120	no	10/98 - 9/98	funded
100	Genetic, Biochemical and Behavioral Determinants of Obesity	Jennifer Hays	Jennifer Hays	yes	yes		OS	775	yes	through 9/01	funded
99	GENNID Study	Rowan Chlebowski	Rowan Chlebowski Harbor UCLA	yes	yes	none	ALL	40	yes	12/1/98 - 3/31/00	funded
98	Bone mineral density as a predictor for periodontitis	Jean Wactawski-Wende	Maurizio Trevisan	yes	N/A	none	OS	1000	yes	4/2002- 4/2006	funded
97	Modeling serum markers for cost-effective ovarian cancer screening	Garnet Anderson		yes	yes	none	1998 OS Blood Comp	720	yes	4/1/00 - 3/31/04	funded
95	Work organization, psychological distress, and health among minority older women	Beatriz Rodriguez	David Curb	yes	N/A	none	OS	500	no	till 6/01	funded
93	The Epidemiology of Venous Disease	Michael Criqui	Robert Langer	yes	no		OS	725	no	3/11/98 - 6/30/99	funded
92	Fasting glucose in baseline plasma from all CT participants	Barbara Howard					CT		no	N/A	pending
90	Biomarkers and Hip Fracture	Steve Cummings	Steve Cummings	yes	yes	none	OS Umbrella Study	400/400	yes		pending

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
86	A Pilot Study to Determine the Sensitivity of Form 39 to Impaired Executive Control Function (ECF) as measured by the CLOX: an Executive Clock-Drawing Task	M.J. Polk	Robert Schenken	yes	yes	none	HRT	50	no	N/A	funded
84	Apolipoprotein E genotype, ERT use, and fat-soluble vitamin intake: Effects on Cognitive Function in Older Women	Julie E. Dunn	Philip Greenland	yes	yes	none	DM+OS	260	yes	11/98 - 12/03	funded
83	Thrombotic, Inflammatory, and Genetic Markers for Coronary Heart Disease in Postmenopausal Women: A WHI Umbrella Study	Paul Ridker	JoAnn Manson	yes	yes	none	OS Umbrella Study	1300	yes	7/1/99 - 6/30/03	funded
82	Extension of Bone Mineral Density Assessment in WHI Native American Women	Zhao Chen	Cheryl Ritenbaugh	yes	yes	none	OS	200	no	7/1/97 - 6/30/01	funded
78	Community Strategy to Retain Women Enrolled in Research	Mona Fouad	Al Oberman	yes	N/A	none	CT	40	no	7/1/97 - 9/30/97	funded
76	Tailored Messages to Enhance Adherence of Older Women to Dietary Programs for Breast Cancer control	Rowan Chlebowski	Rowan Chlebowski Harbor UCLA	yes	yes	none	DM	28	no	9/1/97 - 8/13/98	funded
75	Adherence to Dietary Modification in the WHI	Milagros C. Rosal	Judith Ochene	yes	N/A	6 (does not specify which CC's)	DM	480	no	9/1/97 - 8/30/02	funded
74	The Effectiveness of Individual Versus Group Behavioral Strategies to Increase Participants Adherence	Lois Wodarski	Maurizio Trevisan	yes	yes	none	DM	50	no	7/1/97 - 9/30/97	funded
73	Psychosocial and Cultural Determinants of NIDDM in Latinas	Deborah Parra-Medina	Robert Langer	yes	yes	La Jolla, San Antonio, Tucson	OS	228	yes	5/1/97 - 4/30/98	funded
72	Ethnicity, Body Composition, Bone Density and Breast Cancer	Zhao Chen	Cheryl Ritenbaugh	yes	yes	none	OS	800	no	9/1/97 - 8/30/02	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
70	The Prevalence & Prognostic Importance of Myocardial Ischemia During Daily Life, & its Relationship to Migraine Status:WHI	David Sheps		yes	yes	10	OS	3200	no	9/1/97 - 8/31/00	funded
68	Coronary artery calcification detected with Ultratfast CT as an indication of CAD in OS participants	Judith Hsia	Judith Hsia	yes	yes	51	OS	782	no	1/1/97 - 12/31/05	funded
67	Prevalence and Natural History of Autoimmune Thyroid Disease in Postmenopausal Women	Marjita Zakarija		yes	N/A	51	OS	1040	no	ongoing	funded
65	Incidence of Benign breast disease in the DM CT - Pilot	Tom Rohan	A. McTiernan	yes	yes	all	DM	200	no	4/1/98 - 6/30/99	funded
63	Development and Evaluation of Eating Style Index	Pam Haines		yes	yes		OS	800	no	10/1/96 - 6/30/99	funded
62	Prevention of age-related maculopathy in the WHI HRT CT: WHI-SE	Mary Haan	Mary Haan	yes	yes		HRT	3300	no	1/99 - 1/07	funded
61	Longitudinal Assessment of Memory Functioning in the WHI Clinical Trial	Beth Ober	Mary Haan	yes	yes		HRT	110	no	on-going	funded
60	Fat Intake in Husbands of WHI Dietary Arm Participants	James Shikany	Al Oberman	yes	yes	none	DM Partners		no	12/1/96	funded
57	Hispanic Women's Advocacy and Retention Strategies	Cheryl Ritenbaugh	Cheryl Ritenbaugh	yes	yes	none	OS	120	no	9/1/96 - 8/31/98	funded
56	Behavioral and psychosocial predictors of dietary change in postmenopausal women	Joan Pleuss	Alice Thomson	yes	yes	none	DM	260	no	9/1/96 - 8/31/98	funded
50	Nutrition Practice Guidelines for Maintaining Low-Fat Dietary Change in Post Menopausal Women	Beth Burrows	Ross Prentice	yes	yes	none	DM	200	no	10/1/96 - 9/30/97	funded
48	Prostate Ca Survey of Spouses of WHI Screened Women	Sylvia Smoller	Sylvia Smoller	yes	yes	none	All	1607	no	2/1/96 - 6/30/96	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
47	Effect of diet intervention on motivation to make other health-related changes	Langer/Lo	Robert Langer	yes	yes	none	DM	150	no	5/1/96 - 4/30/97	funded
40	Ethnic and age differences in use of Mammography	S. Wasserheil-Smoller	S. Wasserheil-Smoller	yes	yes	none	All	All	no	N/A	funded
39	The Effects of HRT on the Development and Progression of Dementia (WHIMS)	Sally Shumaker	Sally Shumaker	yes	yes	all except #18	HRT	4800	no	5/1/96 - 4/30/02	funded
36	Hormone Replacement Therapy and Changes in Mammographic Density	Gerardo Heiss		yes	yes		HRT	NA	no	1/98 - 12/01	funded
34	Ethnic Differences in Hip Bone Geometry by DXA and QCT	Dorothy Nelson	Susan Hendrix	yes	yes	none	HRT	330	no	12/1/96 - 12/31/02	funded
33	The Association of HRT with Abdominal and Total Body Fat in Postmenopausal Women	Charlotte Mayo	Al Oberman	yes	yes	none	OS	690	no	7/31/95 - 3/31/96	funded
31	Eye Care Use	Robert Kleinstein	Al Oberman	yes	yes	none	OS	300	no	N/A	funded
25	Ankle-Arm Blood Pressure Index Measurement	Kamal Masaki	David Curb	yes	yes	none	OS	2700	no	2/96 - 1/98	funded
24	Cross-ethnic Comparisons of Skeletal Health of Postmenopausal Women in San Diego County	Diane Schneider	Robert Langer	yes	yes	none	OS	168	no	1/3/95 - 1/2/97	funded
17	Domestic Violence in Older Women	Charles Mouton	Norm Lasser	yes	yes	none	OS	1000	no	10/25/94 - 10/24/96	funded
15	The Relationship between Osteopenia and Periodontitis	Jean Wactawski-Wende	Maurizio Trevisan	yes	yes	none	OS	1300	no	9/16/96 - 09/15/01	funded
14	High Density Lipoprotein Metabolism	Scott Going, Tamsen Bassford	Tom Moon	yes	N/A	none	OS	200	no	7/1/94 - 6/30/96	funded
13	Prevalence and Correlates of Lumbar Spinal Stenosis	Molly Vogt	Lew Kuller	yes	N/A	none	CT	150	no	on-going	funded
11	Validation and Exploration of Sleep and Mood Predictors	Daniel Kripke	Robert Langer	yes	N/A	none	OS	600	yes	8/1/95 - 7/31/99	funded

AS #	Title	Study's PI(s)	WHI Investigator	D&A Approval	PO Approval	ID#s of Other Participating Clinics	Study Population	Sample Size	Specimens?	Proposed Funding Dates	Funding Status
9	An investigation of oral hard tissue status in relation to skeletal bone mineral density measures and osteoporosis	Marjorie Jeffcoat	Al Oberman	yes	N/A	none	OS	650	no	6/1/95 - 5/31/02	funded
5	Explanations for the Development of Fat Distaste	Pamela Green	Deb Bowen	yes	N/A	none	DM	160	no	4/1/95 - 9/30/96	funded

**UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA**

IN RE: TAXOTERE (DOCETAXEL)	)	MDL No. 16-2740
PRODUCTS LIABILITY	)	
LITIGATION	)	SECTION: “H” (5)
	)	
This document relates to:	)	
All cases	)	

ORDER AND REASONS

Before the Court is a Motion for Entry of an Order Requiring Proof of Diagnosis filed by Defendants sanofi-aventis U.S. LLC and Sanofi U.S. Services Inc. (collectively, “Sanofi” or “Defendants”) (Rec. Doc. 16607). For the reasons set forth herein, Sanofi’s Motion is **GRANTED IN PART**. Accordingly, the Court enters Case Management Order No. 40, attached hereto.

BACKGROUND

Plaintiffs in this multidistrict litigation (“MDL”) are suing several pharmaceutical companies that manufactured and/or distributed a chemotherapy drug, Taxotere or docetaxel,¹ that Plaintiffs were administered for the treatment of cancer. Among these companies are Defendants sanofi-aventis U.S. LLC and Sanofi U.S. Services Inc. (collectively, “Sanofi” or “Defendants”). Plaintiffs allege that the drug caused permanent chemotherapy-induced alopecia (“PCIA”). Plaintiffs bring various claims including failure to warn, negligent misrepresentation, and fraudulent misrepresentation.

¹ Docetaxel is the generic version of Taxotere, although the Court uses the term “generic” loosely.

This litigation, which is in its eighth year, has encountered numerous roadblocks in both the bellwether selection and remand and/or transfer processes. As Sanofi points out, approximately half of the cases selected as bellwethers were removed or disqualified from the pool for, among other things, failure to establish product identification or failure to provide requisite photographs of the alleged hair loss injury.² Another four cases were voluntarily dismissed with prejudice by Plaintiffs.³ Of the 19 bellwether cases to face dispositive motion practice, all but two were dismissed.⁴ Thus, even after careful selection, the majority of selected cases could not reach trial.

Similarly, numerous cases that were initially selected to be remanded/and or transferred were subsequently found to be ineligible. The remand/transfer process was divided into multiple “waves”: “Wave 1” and “Wave 2.” On April 19, 2022, two hundred cases were identified as candidates for the Wave 1 remand.⁵ By April 3, 2023, only 93 cases remained in Wave 1.⁶ Plaintiffs in the balance of the originally nominated cases dismissed their lawsuits, asked to defer to a later wave, or were ruled or agreed to be ineligible for Wave 1. On May 22, 2023, the Court transferred 82 cases back to their designated venues in the district courts.⁷ Since that time, approximately 20 additional Wave 1 cases have resolved, and three have been dismissed on remand to the transferor courts.

On June 23, 2023, this Court identified a list of 1,000 cases selected to comprise Wave 2.⁸ After conferral, the parties identified 427 cases that were

² Rec. Doc. 16607-1 at 7.

³ *Id.* at 7.

⁴ *Id.*

⁵ Case Management Order No. 34 (“CMO 34”) (Rec. Doc. 14045) identified 200 cases selected by the Court and parties for the Wave 1 remand process set forth in Case Management Order No. 33 (“CMO 33”) (Rec. Doc. 13946).

⁶ Rec. Doc. 15761.

⁷ Rec. Doc. 15836.

⁸ Rec. Doc. 16347.

not amenable to transfer due to questions of product identification, subject matter jurisdiction, applicability of prior fencepost rulings by the Court, and other concerns related to their candidacy for prosecution.⁹ After subsequent settlements, less than 400 cases were ultimately remanded.

Sanofi alleges that, based on available data, more than 80% of the cases in this MDL involve Plaintiffs who have never been diagnosed with the alleged injury, PCIA, and/or have never sought treatment for PCIA.¹⁰ Notably, the bellwether Plaintiffs' hair loss expert and dermatologist has opined that she "cannot make [a] diagnosis [of alopecia] from pictures" because hair loss has many causes that cannot easily be distinguished.¹¹ Hair loss can be caused by estrogen-reducing hormones;¹² it may also be genetic.¹³ In fact, one plaintiff was ultimately removed from the trial pool after her expert dermapathologist diagnosed her with androgenic alopecia (female pattern hair loss), rather than her alleged injury, PCIA.¹⁴

Citing the above issues with proof, Sanofi previously raised the issue of whether this Court should implement measures for medical corroboration of the specific injury alleged in these lawsuits. Sanofi initially filed its Motion for Entry of an Order Requiring Proof of Diagnosis on July 17, 2020.¹⁵ Following a lead and liaison conference in August 2020, the Court deferred ruling on

⁹ Rec. Doc. 16511.

¹⁰ Rec. Doc. 16607-2 at 2. Notably, the PSC does not refute this point.

¹¹ Rec. Doc. 16696 at 4.

¹² *Id.* Hormone medications like Tamoxifen, which breast-cancer patients may take for a decade following chemotherapy, can cause hair loss and thinning. *Id.* According to Sanofi, nearly 40% of all Plaintiffs report taking these estrogen-reducing hormone medications, e.g., Arimidex, Tamoxifen, and Femara. *Id.* According to Sanofi, nearly 40% of all Plaintiffs report taking these estrogen-reducing hormone medications, e.g., Arimidex, Tamoxifen, and Femara. *Id.*

¹³ *Id.*

¹⁴ Rec. Doc. 16607-1 at 8. Further, Sanofi cites to a study supporting that "[r]oughly 40 percent of all women who live past middle age will develop permanent female pattern hair loss in their lifetime as a by-product of their family history." Rec. Doc. 16696 at 4.

¹⁵ Rec. Doc. 10908.

Sanofi's Motion, subject to being re-urged after the third bellwether trial.¹⁶ After the Court dismissed all of the plaintiffs selected for the third bellwether trial, Sanofi re-urged its Motion in February 2022.¹⁷ The Court declined to make an explicit ruling and entered Case Management Order No. 33, which began the Wave 1 remand process.¹⁸

Finally, the Court has recently been apprised that Sanofi and certain plaintiffs have reached an agreement in principle anticipated to dispose of approximately 2,500 cases pending before this Court and remanded previously from these proceedings. Thus, with nearly 30% of the pending cases reaching settlement, Sanofi filed the instant Re-Urged Motion for Entry of an Order Requiring Proof of Diagnosis. Plaintiffs, via the Plaintiffs' Steering Committee and Lead and Liaison Counsel, (collectively, "the PSC"), oppose.¹⁹

LAW AND ARGUMENT

Sanofi requests that this Court enter a *Lone Pine* order, the name of which derives from the New York district court decision *Lore v. Lone Pine Corp.*²⁰ The United States Court of Appeals for the Fifth Circuit has explained that "*Lone Pine* orders are designed to handle the complex issues and potential burdens on defendants and the court in mass tort litigation."²¹ "In the federal courts, such orders are issued under the wide discretion afforded district judges over the management of discovery under Fed. R. Civ. P. 16."²² *Lone Pine* orders

¹⁶ Rec. Doc. 15834 at 21.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ Rec. Doc. 16687. The PSC also submitted a competing Proposed Order at the request of the Court. Rec. Doc. 16705.

²⁰ 1986 WL 637507, No. L-33606-85 (N.J. Super. Ct. 1986).

²¹ *Acuna v. Brown*, 200 F.3d 335, 340 (5th Cir. 2000) (citing FED. R. CIV. P. 16).

²² *Id.*

generally require plaintiffs to make a prima facie showing of causation—or face dismissal.²³

The Fifth Circuit has approved the use of *Lone Pine* orders in mass tort litigation.²⁴ In *Acuna v. Brown & Root, Inc.*, the Fifth Circuit held that the district court was within its discretion to issue a pre-discovery order mandating that all plaintiffs submit expert affidavits specifying the plaintiffs’ injury and the cause; the Fifth Circuit noted that the order “essentially required that information which plaintiffs should have had before filing their claims pursuant to Fed. R. Civ. P. 11(b)(3).”²⁵

Although *Acuna* concerned a pre-discovery *Lone Pine* order, since *Acuna*, district courts, including this Court, have entered *Lone Pine* orders near the end of litigation.²⁶ Indeed, district courts implement such orders before remand to ensure either that “transferor courts receive only viable cases,”²⁷ or that “only plaintiffs with meritorious cases are compensated” if the parties ultimately reach a settlement.²⁸ Even so, a *Lone Pine* order is not appropriate

²³ See *In re Vioxx Prods. Liab. Litig.*, 557 F. Supp. 2d 741, 744 (E.D. La. 2008) (Fallon, J.); see also *In re Fosamax Prod. Liab. Litig.*, No. 06 MD 1789, 2012 WL 5877418, at *3 (S.D. N.Y. Nov. 20, 2012) (noting the plaintiffs’ “habit of dismissing cases” when called on to prove causation).

²⁴ *Acuna*, 200 F.3d at 340.

²⁵ *Id.*

²⁶ See *In re Vioxx Prods. Liab. Litig.*, 557 F. Supp. 2d at 744 (entering *Lone Pine* order requiring evidence of specific causation and citing the “advanced stage of the litigation”); see also *In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig.*, 18-md-2848, 2022 WL 952179, at *2 (E.D. Penn. Mar. 30, 2022) (same).

²⁷ *Id.*

²⁸ *In re Fosamax*, No. 06 MD 1789, 2012 WL 5877418, at *3.

in every case or suitable at every stage of litigation.²⁹ “In crafting a *Lone Pine* order, courts should strike a balance between efficiency and equity.”³⁰

Sanofi requests that the Court enter an order requiring Plaintiffs who are otherwise eligible for remand to do the following:

1. Certify her willingness to proceed,
2. Provide updated authorizations and an updated Plaintiff Fact Sheet,
3. Submit an expert medical declaration by a qualified physician diagnosing the Plaintiff with PCIA caused by Taxotere, and
4. Participate in certain, limited discovery.³¹

In response, the PSC argues that a *Lone Pine* order is an extraordinary procedure to be implemented only where “existing procedural devices explicitly at the disposal of the parties by statute and federal rule have been exhausted or where they cannot accommodate the unique issues” of the litigation.³² The PSC further argues that entering a *Lone Pine* order would be unfair and prejudicial and could potentially undermine settlement negotiations and stall the remand process.³³

²⁹ *In re Vioxx*, 557 F. Supp. 2d at 744. District Courts have likewise cited the furtherance of settlement negotiations and/or ongoing attempts to settle as factors supporting the issuance of a *Lone Pine* order. *In re Avandia Mktg., Sales Pracs., and Prods. Liab. Litig.*, No. 2007-MD-1871, 2010 WL 4720335, at *1 (E.D. Penn. Nov. 15, 2010); *see also* Rec. Doc. 16696 at 7 (citing *In re Yasmin and Yaz (Drospirenone) Mktg. Sales Pracs. and Prods. Liab. Litig.*, No. 09-md-02100, at 2 (S.D. Ill. Aug. 3, 2015) (noting that “the parties have successfully negotiated the resolution of a large number of the cases”)).

³⁰ *In re Vioxx*, 557 F.Supp.2d at 744.

³¹ Rec. Doc. 16607-1; 16607-2. Only cases involving Product Identification identifying Sanofi as the manufacturer are currently eligible for remand due to the pending appeal on preemption as to the 505(b)(2) Defendants. Rec. Doc. 13946 at 17.

³² Rec. Doc. 16687 at 4 (quoting *Nolan v. Exxon Mobil Corp.*, No. 13-439, 2016 WL 1213231, at *11 (M.D. La. Mar. 23, 2016)).

³³ The PSC’s first argument is that this Court previously ruled on Sanofi’s Motion and that the standard for reconsideration under Rule 59(e) is not satisfied. Rec. Doc. 16687 at 7–8. However, as explained above, the Court deferred ruling on Sanofi’s first Motion until after the third bellwether trial—which never took place. Rec. Doc. 10908. After the third bellwether pool Plaintiffs were dismissed, Sanofi renewed its request. Rec. Doc. 16687-2. Rather than make an explicit ruling, the Court entered CMO 33, which initiated the Wave 1

The Court finds that a *Lone Pine* order is appropriate at this stage, particularly in light of the parties' recent settlements. Any potential inequities outweigh the need for additional case management procedures as to the remaining, unsettled cases before they proceed to remand. Notably, courts in other jurisdictions have imposed *Lone Pine* orders that “require plaintiffs to furnish specific evidence like proof of a medical diagnosis, with the goal of winnowing non-compliant cases from the MDL”—which is exactly what Sanofi is requesting in the present case.³⁴

Moreover, it would not be unduly burdensome to mandate that Plaintiffs obtain basic proof of their injuries by way of a diagnosis. Although Sanofi has requested that Plaintiffs produce what appear to be complete expert reports, the Court will not require a Rule 26(f) expert report at this time. Nor will Plaintiffs be required to produce expert testimony that Taxotere caused their PCIA. Rather, Plaintiffs need only show that they actually have PCIA—rather than some other type of hair loss. After years of discovery, two bellwether trials, and initiation of the remand process, it is time for Plaintiffs to come forward with an affirmative diagnosis—which would otherwise be required to prove their injuries. Thus, as reflected in the attached Case Management Order, Plaintiffs who otherwise qualify for remand will be required to, *inter alia*, produce proof of diagnosis via expert affidavit.

remand process. Rec. Doc. 16696. Thus, there is no prior decision to alter, amend, and/or reconsider under Rules 59(e).

³⁴ *In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig.*, 18-md-2848, 2022 WL 952179, at *2 (E.D. Penn. Mar. 30, 2022) (quoting *Hamer v. LivaNova Deutschland GmbH*, 994 F.3d 173 (3d Cir. 2021)). In the *Zostavax* litigation, numerous plaintiffs appealed the dismissal of their cases after they failed to comply with the district court's *Lone Pine* order mandating that the plaintiffs produce laboratory tests linking the Zostavax vaccine to the alleged injury, shingles. *In re Zostavax*, 18-md-2848, 2022 WL 952179, at *2–3. On appeal, plaintiffs contended that, rather than require the reports at issue, the district court could have chosen alternative ways to prove specific causation, including requiring “expert reports opining that specific causation could be established within a reasonable degree of medical certainty.” Brief for Appellant at 20, *In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig.*, No. 23-1032 (3d Cir. April 14, 2023), ECF no. 20.

CONCLUSION

Accordingly, for the foregoing reasons, Sanofi's Motion for Entry of an Order Requiring Proof of Diagnosis (Rec. Doc. 16607) is **GRANTED IN PART**. The Court enters Case Management Order 40, attached hereto.

New Orleans, Louisiana, this 16th day of February, 2024.

A handwritten signature in black ink, appearing to read "Jane Triche Milazzo", is written over a horizontal line.

**JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE**

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL)	)	MDL No. 16-2740
PRODUCTS LIABILITY	)	
LITIGATION	)	SECTION: "H" (5)
	)	
THIS DOCUMENT RELATES TO:	)	
ALL CASES	)	

CASE MANAGEMENT ORDER NO. 40

Before the Court is a Motion for Entry of an Order Requiring Proof of Diagnosis filed by Defendants sanofi-aventis U.S. LLC and Sanofi U.S. Services Inc. (collectively "Sanofi") (Rec. Doc. 16607). For the reasons set forth in the foregoing Order and Reasons, Sanofi's Motion is **GRANTED IN PART**. Accordingly, the Court enters the following Case Management Order:

I. Wave 3 Plaintiffs

a. Criteria. This Order applies to all "Wave 3 Plaintiffs." Wave 3 Plaintiffs are those whose cases

- i. have not been remanded,
- ii. have not settled, and
- iii. satisfy the eligibility criteria for transfer as set forth in Case Management Order No. 33 ¶ 3(a) (Sanofi-only Product Identification) and the exclusion criteria set forth in ¶ 4(a) (CMO 12A, Single-Manufacturer Product Identification).

b. Identification of non-settling cases. On or before **June 14, 2024**, the Court will identify all cases the court-appointed mediator in this matter indicates were not settled in the agreement dated February 9, 2024.

- c. Dismissals.** After being identified as a non-settling Plaintiff, Wave 3 Plaintiffs may be removed by voluntary dismissal until **September 12, 2024**. All dismissals of Wave 3 cases shall be with prejudice, unless good cause is shown that dismissal without prejudice is warranted. The provisions of Pretrial Order No. 54 (Rec. Doc. 671) governing dismissals without prejudice otherwise remain in effect.

II. Obligations of Wave 3 Plaintiffs

- a. Certificate of Willingness to Proceed.** On or before **June 21, 2024**,¹ counsel for Wave 3 Plaintiffs must upload to MDL Centrality a certificate indicating that the plaintiff is willing to proceed.²
- b. Updated Plaintiff Fact Sheet & Updated Authorizations.** Wave 3 Plaintiffs must physically sign updated authorizations by **July 1, 2024**. Wave 3 Plaintiffs also must review and update, if necessary, the Plaintiff Fact Sheet pursuant to Pretrial Order Nos. 55 (Rec. Doc. 688), 38 (Rec. Doc. 326), and Amended 22 (Rec. Doc. 325) by **July 1, 2024**. Wave 3 Plaintiffs must physically sign verification of any update to the Plaintiff Fact Sheet.
- c. Expert Medical Declaration Confirming Permanent Alopecia on Physical Examination and, if Medically Necessary, Scalp Biopsy.** By **July 1, 2024**, Wave 3 Plaintiffs must upload to MDL Centrality a signed expert declaration, authored by a qualified physician in good standing with his or her

¹ The Court recognizes that the timeframe between identification of non-settling cases and the filing of a certificate of willingness to proceed is short. However, the Court contemplates that counsel will have sufficient time to comply with the Order, given the date of its issuance.

² A sample certification is attached to this Order as Exhibit A.

state licensing authority.³ The declaration shall state that, based on the expert's physical examination of Plaintiff, and a review of the pertinent medical records, the expert is prepared to testify that, to a reasonable degree of medical probability, Plaintiff has suffered permanent chemotherapy-induced alopecia ("PCIA") as alleged in her Complaint(s).

- i. The expert declaration must include: (i) certification that the physician physically examined the plaintiff, (in person), (not via telemedicine or other remote application), as well as a description of his or her physical findings and (ii) identification of all documents, including lab results, pathology reports, photographs, medical records, or physical examination reviewed.
- ii. Where the physician's normal practices would require the same in order to rule out other forms of alopecia, said declaration must also include the gross and microscopic pathological findings, on scalp biopsy, of the plaintiff.
- iii. The expert medical declaration must be uploaded to MDL Centrality using the "Proof of Injury – Post-Order Expert Medical Declaration" document-type field within the deadlines set forth in this Order. The medical declaration shall be physically signed by the physician under penalty of perjury.

³ The expert must meet the requirements of Rule 702. This includes possessing the appropriate specialized qualifications required to diagnose the injury and its cause (such as certain dermatologists, dermatopathologists, or potentially, certain oncologists). A general practitioner, for example, will not suffice.

- iv. No expert report pursuant to Federal Rules of Civil Procedure 26(a)(2)(B) is currently required.

III. Deceased Plaintiffs. For Wave 3 cases in which the alleged victim is deceased, counsel for Plaintiff (or succession representative) must file an affidavit from a qualified expert certifying that the expert physically examined the deceased and that, on any occasion prior to death, the deceased was diagnosed with permanent chemotherapy-induced alopecia.

IV. Wave 3 Discovery

a. Written Discovery. The parties cannot serve written discovery in Wave 3 cases at this time and without further leave.

b. Physician Depositions. Up to four depositions in each case shall be allowed: (i) the plaintiff, (ii) the plaintiff's prescribing physician, (iii) the plaintiff's diagnosing expert, and (iv) one (1) sales representative who called on the plaintiff's "Healthcare Provider" as defined in the Defendant Fact Sheet prior to the plaintiff's treatment.

- i. Pretrial Order No. 70B (Rec. Doc. 5256) allows for the ex parte scheduling of depositions by non-attorney staff. It remains in effect. All parties' prior objections to said Order and stated in defendants' Motion to Amend (Rec. Doc. 9109) are expressly preserved.

V. Enforcement. Any Wave 3 Plaintiff who fails to comply with the terms of this Order shall be listed for Non-Compliance and Show Cause Order Process following the ordinary procedures of Pretrial Order No. 22A (Rec. Doc. 3493) and her case shall be dismissed with prejudice, absent a compelling reason. Plaintiffs' objections to entry

of this Order are noted and preserved for purposes of appeal of any dismissal pursuant to it.

New Orleans, Louisiana, this 16th day of February, 2024.



HON. JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL)	)	MDL No. 16-2740
PRODUCTS LIABILITY	)	
LITIGATION	)	SECTION: "H" (5)
	)	
THIS DOCUMENT RELATES TO:	)	
<i>[insert case name and number]</i>	)	

EXHIBIT A

DECLARATION OF *[INSERT NAME OF ATTORNEY]*

I, *[attorney's name]*, am an attorney with the law firm of *[law firm's name]*. I represent *[plaintiff's name]* in the above-captioned matter. *[plaintiff's name]* has been personally contacted and has indicated *[his/her]* willingness to proceed in this litigation.

I certify under penalty of perjury that the foregoing is true and correct.

Executed on_____.

Attorney Signature: _____

Attorney Name: _____

**UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA**

IN RE: TAXOTERE (DOCETAXEL)) MDL No. 16-2740
PRODUCTS LIABILITY)
LITIGATION) SECTION: “H” (5)
)
This document relates to:)
All cases)
)
)

ORDER AND REASONS

Before the Court is the Motion for Reconsideration of the Court’s Order Granting in Part Sanofi’s Motion for Entry of an Order Requiring Proof of Diagnosis filed by Plaintiffs (Rec. Doc. 16861). For the reasons set forth herein, the Motion is **GRANTED IN PART**. The Court will amend the Order (*See* Case Management Order No. 40A) to extend the deadlines for Plaintiffs to submit an “Expert Medical Declaration” and “Certificate of Willingness to Proceed” as defined in the Order.¹ The Court denies Plaintiffs’ request to vacate or otherwise modify the Order.

BACKGROUND

Plaintiffs in this multidistrict litigation (“MDL”) are suing several pharmaceutical companies that manufactured and/or distributed a chemotherapy drug, Taxotere or docetaxel,² that Plaintiffs were administered for the treatment of cancer. Among these companies are Defendants Hospira

¹ See CMO 40A Section II(a), (c).

² Docetaxel is the generic version of Taxotere, although the Court uses the term “generic” loosely.

Worldwide, LLC f/k/a Hospira Worldwide, Inc., Hospira, Inc. (collectively, “Hospira”), Pfizer, Inc. (“Pfizer”), sanofi-aventis U.S. LLC and Sanofi US Services LLC (collectively, “Sanofi”), Sandoz Inc. (“Sandoz”), and Accord Healthcare, Inc. (“Accord”). Plaintiffs allege that the drug caused permanent chemotherapy-induced alopecia (“PCIA”). Plaintiffs bring claims of failure to warn, negligent misrepresentation, fraudulent misrepresentation, and more.

On February 21, 2024, this Court granted Sanofi’s Motion for Entry of an Order Requiring Proof of Diagnosis and issued a *Lone Pine* Order.³ The Order requires, among other things, that Plaintiffs obtain proof of the alleged injury, PCIA, via expert declaration, (the “Expert Medical Declaration”) as well as submit a certification of Plaintiffs’ willingness to proceed (the “Certificate of Willingness to Proceed”).⁴ A more comprehensive summary of the events leading up to Sanofi’s Motion may be found in the Court’s Order; however, the key points are as follows.

The parties in this case agreed to, and participated in, extensive discovery procedures. For example, pursuant to Pretrial Order No. 22, Plaintiffs were required to serve Defendants with a complete and verified Plaintiff Fact Sheet (“PFS”) providing information on Plaintiffs’ alleged injuries, the dates upon which Plaintiff was diagnosed with cancer, and the chemotherapy regimen Plaintiff received.⁵ Pursuant to Pretrial Order No. 68, Plaintiffs were required to produce dated photographs that depicted their hair within five years of starting chemotherapy, during chemotherapy (if available), within five years of completing chemotherapy, and recent photographs.⁶

³ Rec. Doc. 16778.

⁴ *Id.*

⁵ Rec. Docs. 236-1, 270.

⁶ Rec. Doc. 1085.

Despite extensive discovery, Plaintiffs do not dispute that approximately 80 percent of MDL Plaintiffs currently do not have medical evidence of their alleged hair loss injury and/or have never spoken to a doctor about their alleged injury.⁷ Citing Plaintiffs' issues with proof, Sanofi initially filed a Motion for Entry of an Order Requiring Proof of Diagnosis in July 2020.⁸ The proposed order would have required each Plaintiff to submit either evidence of a medical diagnosis of PCIA or state that Plaintiff did not intend to pursue such a diagnosis.⁹ Following a discussion with the parties at the August 2020 lead and liaison conference, the Court deferred ruling on Sanofi's Motion subject to being re-urged after the third bellwether trial.¹⁰

After the Court dismissed the third bellwether Plaintiffs, the Court, with the assistance of the parties, entered Case Management Order No. 33 ("CMO 33") governing the selection and discovery for 200 cases to comprise the "Wave 1" remand.¹¹ Four cases resolved after this Court ordered a bellwether mediation, one case resolved following mediation, and several cases were either dismissed, deferred to a later wave, or found ineligible for Wave 1.¹² Ultimately, only 82 cases were remanded back to their transferor courts.¹³

⁷ Rec. Doc. 16873 at 2. PCIA requires a differential diagnosis. Rec. Doc. 10808-1 at 6.

⁸ Rec. Doc. 10808.

⁹ *Id.* at 5.

¹⁰ Rec. Doc. 10908.

¹¹ Rec. Doc. 13946. CMO 33 required that Plaintiffs update Plaintiff Fact Sheets and possess photographs complying with Amended Pretrial Order No. 22 and Pretrial Order No. 68, among other things. *Id.* at 4. The Order also provided that the parties meet and confer regarding additional issues with photographs and product identification and provided for additional, limited discovery, including depositions of plaintiff's prescribing and treating physicians. *Id.* at 3–5. Although Sanofi requested that Plaintiffs be required to obtain proof of diagnosis as part of their Remand Proposal, the Court declined to adopt such a provision. Rec. Doc. 13912.

¹² Rec. Doc. 16607-1 at 9.

¹³ Rec. Doc. 15836. At oral argument held on May 7, 2024, Sanofi stated that 20 of these cases remain pending.

On June 23, 2023, this Court identified a list of 1,000 cases selected to comprise the “Wave 2” remand.¹⁴ After conferral, the parties identified 427 cases that were not amenable to transfer due to questions of product identification, subject matter jurisdiction, applicability of prior fencepost rulings by the Court, and “other concerns related to their candidacy for prosecution.”¹⁵ Thus, 573 cases were ultimately amenable to transfer.¹⁶

Finally, the Court was recently apprised that Sanofi and certain plaintiffs had reached an agreement in principle, which was anticipated to dispose of 30% of the pending cases. In light of these settlements and the advanced stage of this litigation, Sanofi filed a Motion for Entry of an Order Requiring Proof of Diagnosis, which the Court granted in its Order & Reasons dated February 21, 2024. Plaintiffs now request that the Court vacate that Order. Sanofi opposes.

LEGAL STANDARD

Federal Rule of Civil Procedure 54(b) states that: “[A]ny order or other decision, however designated, that adjudicates fewer than all the claims or the rights and liabilities of fewer than all the parties does not end the action as to any of the claims or parties and may be revised at any time before the entry of a judgment adjudicating all the claims and all the parties’ rights and liabilities.” “Under Rule 54(b), ‘the trial court is free to reconsider and reverse its decision for any reason it deems sufficient, even in the absence of new evidence or an intervening change in or clarification of the substantive law.’”¹⁷ “[T]he power to reconsider or modify interlocutory rulings is committed to the

¹⁴ Rec. Doc. 16778 at 3.

¹⁵ *Id.*

¹⁶ Rec. Doc. 16511. At oral argument, Sanofi stated that 200 Wave 2 cases remain pending.

¹⁷ *Austin v. Kroger Tex., L.P.*, No. 16-10502, 2017 WL 1379453, at *9 (5th Cir. 2017) (quoting *Lavespere v. Niagara Mach. & Tool Works, Inc.*, 910 F.2d 167, 185 (5th Cir. 1990)).

discretion of the district court, and that discretion is not cabined by the heightened standards for reconsideration governing final orders.”¹⁸

LAW & ANALYSIS

1. Plaintiffs’ Request to Vacate the Order

Plaintiffs argue that the *Lone Pine* Order is improper because it (1) is an “extraordinary procedure” that is unwarranted under the circumstances; (2) is unfair (in that it inequitably treats similarly situated plaintiffs); and (3) unnecessarily bifurcates expert discovery, which, in turn, will multiply costs and cause additional cross examination fodder at trial.

This Court already addressed the lion’s share of Plaintiffs’ arguments in its initial Order and found them unpersuasive. In issuing its Order, this Court, in striving to “strike a balance between efficiency and equity,” considered the advanced stage of this litigation, ongoing settlement negotiations, the burden on Plaintiffs, and the “numerous roadblocks in both the bellwether selection and remand and/or transfer processes.”¹⁹ Critically, as stated above, no party disputes that 80 percent of Plaintiffs have not obtained a diagnosis of PCIA (or that many Plaintiffs may suffer from a different type of hair loss, rather than PCIA). Additionally, many plaintiffs, when called upon to prove causation, have dismissed their claims in lieu of proceeding.²⁰

In its initial Motion, Sanofi illustrated Plaintiffs’ issues with proof by citing to specific examples, including former bellwether Plaintiff Lisa Tuyes and former trial pool Plaintiff Shelia Crayton. Plaintiff Tuyes alleged that she suffered from PCIA but never received a diagnosis, and the photographs

¹⁸ *Id.* (quoting *Saint Annes Dev. Co. v. Trabich*, 443 Fed. App’x 829, 831–32 (4th Cir. 2011)) (cleaned up).

¹⁹ Rec. Doc. 16778.

²⁰ Rec. Doc. 16873 at 2.

Plaintiff Tuyes submitted in lieu of a diagnosis showed “no discernible hair loss.”²¹ When Plaintiff Tuyes received a scalp biopsy during “phase-two discovery,” Plaintiffs’ expert dermapathologist diagnosed Plaintiff Tuyes with androgenic alopecia, rather than PCIA.²² Likewise, Plaintiff Crayton never received a diagnosis of PCIA and submitted photographs showing “no discernible hair loss.”²³ After discovery, Plaintiff Crayton chose not to secure a diagnosis and ultimately withdrew from the trial pool.²⁴

Given the above, Plaintiffs’ argument that the *Lone Pine* Order is unnecessary because this “MDL has already been through extensive procedural safeguards” falls flat. Rather, Plaintiffs illustrate precisely why the Court found at this stage—rather than earlier in this litigation, when Sanofi first moved for relief—that a *Lone Pine* Order was necessary. Discovery procedures, case-specific bellwether trial workup, and the Wave 1 and 2 remand processes have revealed evidence that many plaintiffs may be unable sustain their burden of proof.

Nevertheless, rather than requiring proof of specific causation by way of a Rule 26 expert report, as Sanofi initially requested, the Court’s Order requires only a diagnosis of PCIA in the form of an expert declaration.²⁵ The

²¹ Rec. Doc. 16607-1 at 7.

²² *Id.* at 8.

²³ *Id.*

²⁴ *Id.*

²⁵ Plaintiffs take issue with the provision of the Order stating that the expert must state that he or she “is prepared to testify that, to a reasonable degree of medical probability, Plaintiff has suffered PCIA.” Specifically, Plaintiffs argue that the “Order requires proof of a different standard than at trial . . . [u]nder most product liability law, Plaintiffs need only present proof by a preponderance of the evidence of a substantial causing factor of their injury.” Rec. Doc. 16861-1 at 6. First, although Sanofi, in its initial Motion, requested that the expert attest “within a reasonable degree of medical probability” that Plaintiff has suffered PCIA, Plaintiffs failed to raise the issue in their initial Opposition. Rec. Docs. 16607-11 at 4 and 16687. Second, generally, the “reasonable degree of medical probability” (or, in some jurisdictions, “reasonable degree of medical certainty”) standard applies in the context of medical expert testimony. *See* 2 Steven E. Pegalis, AM. L. MED. MALP. § 8:7 (July 2023); *see also* Addington v. Texas, 99 S. Ct. 1804, 1811 (1979) (noting that, “[w]ithin the medical discipline, the traditional standard for ‘factfinding’ is a ‘reasonable medical certainty’”). In

Order requires a scalp biopsy only where “the physician’s normal practices would require the same in order to rule out other forms of alopecia.”²⁶

Plaintiffs argue that even this limited declaration is inappropriate because, unlike other cases in which a *Lone Pine* Order was issued, “there is no definitive/diagnostic test” to prove a person has PCIA.²⁷ As such, Plaintiffs are disproportionately burdened by the Order because it “improperly front-loads Plaintiffs’ expert obligations to provide” a contested expert opinion by way of an in-person visit.²⁸ Plaintiffs do not argue, however, that such an opinion would not be required to prove causation if their cases are ultimately remanded.²⁹ Notably, this Court is not alone in mandating that plaintiffs produce such an expert declaration. Indeed, in issuing *Lone Pine* orders, district courts frequently require proof of causation in the form of expert affidavits and/or reports.³⁰

this instance, however, the exact difference, if any, between “medical certainty” and “medical probability” appears to be immaterial, as “medical probability” is commonly understood as equating to a preponderance of the evidence standard. *See, e.g.,* Jeff L. Lewin, *The Genesis and Evolution of Legal Uncertainty About “Reasonable Medical Certainty”*, 57 MD. L. REV. 380, 404 (1998) (explaining that the “medical probability standard” equates to a “preponderance of the evidence standard” and that the majority of courts equate “reasonable degree of medical certainty” and “reasonable degree of medical probability”). Notably, other MDL courts, presiding over products liability cases, have required plaintiffs to provide causation opinions from physicians or “other medical experts” that support their claims “to a reasonable degree of medical certainty.” *In re Zostavax Prods. Liab. Litig.*, No. 18-MD-2848, 2023 WL 8258533, at *2 (E.D. Penn. Nov. 29, 2023); *In re Fosamax Prods. Liab. Litig.*, 06 MD 1789(JFK), 2012 WL 5877418, at *5 (S.D. N.Y. Nov. 20, 2012); *In re Fresenius GranuFlo/NutraLyte Dialysate Prods. Liab. Litig.*, No. 13-02428, 2017 WL 11831712, at *3 (D. Mass Jan. 26, 2017); *In re Avandia Mktg., Sales Pracs. and Prods. Liab. Litig.*, 687 Fed. App’x 210, 215 n.3 (3d Cir. 2017). Plaintiffs fail to argue that they would not otherwise be required to produce proof of their injury via medical expert testimony. Nevertheless, to the extent that any plaintiff contends that the relevant state’s law allows Plaintiff to provide alternative proof of injury, such arguments may be presented at a show cause hearing contemplated by the Order.

²⁶ Rec. Doc. 16778 at 11. The Order further states that a plaintiff who fails to comply shall have her case dismissed with prejudice “absent a compelling reason.” *Id.* at 12.

²⁷ Rec. Doc. 16886 at 2.

²⁸ *Id.*

²⁹ In fact, Plaintiffs’ experts have opined that a diagnosis of PCIA cannot be made through photos. Rec. Doc. 16696 at 4.

³⁰ *See, e.g.,* *In re Zostavax*, 2023 WL 8258533, at *2.

At bottom, if they were ultimately remanded back to their respective transferor courts, Plaintiffs would be required to provide some proof of their alleged injury.³¹ Thus, Plaintiffs' argument that the Order is intolerable or unfair because some plaintiffs, but not others, have already settled and/or been remanded is unpersuasive.³²

As this Court has recognized, "[t]he basic purpose of a *Lone Pine* order is to identify and cull potentially meritless claims and streamline litigation in complex cases."³³ The Court finds, as it did before, that the Order comports with this basic purpose, is in line with the caselaw governing *Lone Pine* orders, and is appropriate under the circumstances.

2. Extension of Deadlines

In their briefings, Plaintiffs note that locating an expert may be difficult because of the "lack of widespread expertise" in diagnosing PCIA and suggest that the Order does not allow Plaintiffs sufficient time within which to comply.³⁴ At oral argument held on May 7, 2024, Plaintiffs reiterated their concerns and made an alternative request to stay the Order for some amount of time. Pursuant to the Federal Rules of Civil Procedure, the Court may modify the Order "for good cause."³⁵ As such, the Court will amend the Order to extend the deadlines to submit an Expert Medical Declaration and Certificate of Willingness to Proceed, as defined in Section II(a), (c) of the Order.

³¹ Rec. Doc. 16778 at 7.

³² Plaintiffs also suggest that the Order is inappropriate absent a global settlement. However, as other district courts have recognized, a global settlement is not necessary for the issuance of a *Lone Pine* order. In *re Fosamax*, 2012 WL 5877418, at *3. Further, district courts have considered settlements that are less than global as relevant (though not dispositive) to the inquiry of whether a *Lone Pine* order is warranted. See Rec. Doc. 16696 at 6–7 (collecting cases).

³³ *In re Vioxx Prods. Liab. Litig.*, 557 F. Supp. 2d 741, 744 (E.D. La. 2008) (citing *Baker v. Chevron USA, Inc.*, 2007 WL 315346, *1 (S.D. Ohio Jan. 30, 2007)).

³⁴ Rec. Docs. 16861-1 at 10 and 16886 at 1 n. 1.

³⁵ See FED. R. CIV. P. 16(b), 6(b).

CONCLUSION

For the foregoing reasons, Plaintiffs' Motion for Reconsideration is **GRANTED IN PART.**

IT IS ORDERED that the deadlines for (1) filing a certificate of willingness to proceed and (2) uploading expert affidavits are **EXTENDED** as reflected in Case Management Order No. 40A, attached hereto. All other provisions of Case Management Order No. 40 remain unchanged.

New Orleans, Louisiana, this 21st day of May, 2024.



JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE